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PREFACE

The 14th volume of Advances in Organic Synthesis presents recent exciting developments in synthetic organic chemistry. The chapters are written by authorities in the field. This volume features contributions focused on “on-water” and “in-water” synthesis strategies for heterocyclic transformations, ionic liquid based polyoxometalates as functionalized organic-inorganic hybrid materials, synthesis and bio-applications of some oxygen and sulphur containing seven membered heterocyclic compounds, applications of nitriles in the synthesis of 5-membered azaheterocycles and the role of carbon-based solid acid catalysts in organic synthesis.

This book should prove to be a valuable resource source for organic chemists, pharmaceutical scientists and postgraduate students seeking updated and critically important information on recent important developments in synthetic organic chemistry. I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new developments in the field.

I am thankful to the efficient team of Bentham Science Publishers for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), Mr. Obaid Sadiq (in-charge Books Department) and Ms. Asma Ahmed (Manager Publications).

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CHAPTER 1

"On Water" and "In Water" Strategies for Heterocyclic Transformations

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Abstract: Water is the most precious and essential element for the sustainability of life. It has emerged as a versatile solvent for various chemical transformations in recent times. It is a naturally abundant, cheap, non-toxic, inexhaustible, and non-flammable green solvent that possesses several unique physiochemical properties like hydrogen bonding, stays in a liquid state at a high range of temperatures, high dielectric constant, large surface tension, and heat capacity. These features make water a powerful domain for the eco-friendly and green synthesis of heterocycles *via* both in-water and on-water methods. Diversified heterocyclic moieties are formed in an aqueous phase through various organic reactions like multi-component reactions (MCRs), pericyclic, Wittig, Michael, Mannich, Aldol, Suzuki, Sonogashira, hydroformylation, and other organo-catalyzed reactions with high atom economy, stereo-selectivity, and sustainability. This article gives a systematic, comprehensive, and authoritative study of a range of reactions in which water is used as a solvent for the synthesis of heterocycles. This article endows an impetus to explore the synthetic and mechanistic aspects of "on" and "in" water reactions and gives insights into the divergence between on-water and in-water synthesis.

Keywords: Atom-economy, Catalysis, Green solvent, Heterocycles, Multi-component reaction, Organic synthesis, Organo catalyzed reactions, Water.

INTRODUCTION

Heterocycles are highly ubiquitous molecules in organic chemistry, having gigantic applications in diverse areas like pharmaceutical, industrial, agriculture, and many more [1 - 3]. They are widely found in nature in nucleic acids, alkaloids, vitamins, proteins, enzymes and, plant pigments, *etc.* In the past century, several imperative heterocyclic core structures have been designed and synthesized by researchers having broad synthetic utility and medicinal values

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[4, 5]. These heterocyclic transformations occurred in different environmental conditions using various reagents, catalysts, additives, and solvents *via* different strategies like conventional heating, stirring, MW irradiation, mechanochemical grinding, sonication, and so on [6 - 8]. Previously, most of the methods included harsh and toxic reaction conditions like high temperature, harmful reagents and solvents, toxic-gases, waste-generation, and tedious-workup, *etc.* However, in the past decades, after the introduction of 12 principles of green chemistry [9, 10], researchers tend towards the new and innovative eco-benign technologies *via* reducing the negative impact of organic synthesis on mother-nature. The use of safe and less-toxic solvents is one of the important aspects of green chemistry. In organic chemistry, solvents play an important role either as reaction-media or by participating themselves in the reaction [11, 12]. Various chemical-industries employ most of their energy on solvent-treatment [13], which enforces our attention towards replacing the toxic and hazardous solvents with safe and eco-benign ones. Most of the organic solvents are toxic, carcinogenic, mutagenic, corrosive, have low-flash point, deplete the ozone layer and cause many more adverse effects on human beings and the environment [14, 15]. From this point of view, scientists move towards green solvents like water, supercritical carbon dioxide, ionic-liquids, and bio-solvents [16 - 18]. Water is a natural solvent with unique chemistry and is involved in various biological processes and synthesizes diversified stereoselective bio-molecules in the living-organisms. Water is a non-flammable, non-toxic, non-pollutant, and inexpensive solvent with special characteristics like viscosity, polarity, H-bonding ability, immiscibility, high heat-capacity that improves the yield and selectivity of products [19]. The variation in the amount of salt, surfactant, and pH value in water is possible and this special feature enhances the probability of various reactions in an aqueous medium. In 1980, Rideout and Breselow disclosed water-mediated Diels-Alder reactions [20]. After a long time, in 2005, Sharpless and co-workers evolved aqueous-mediated cycloaddition reactions in the heterogeneous mixture and they term these reactions as “on-water” reactions [21]. Afterward, a number of studies performed oxidation, pericyclic, Wittig, Michael, Mannich, Aldol, Suzuki, Sonogashira, hydroformylation reactions [22 - 33], using water as a solvent for sustainable and green synthesis (Fig. **1**). Recently, many researchers worked on water-mediated organic synthesis to develop diversified bio-active molecules by following the principle of green chemistry [34 - 45].

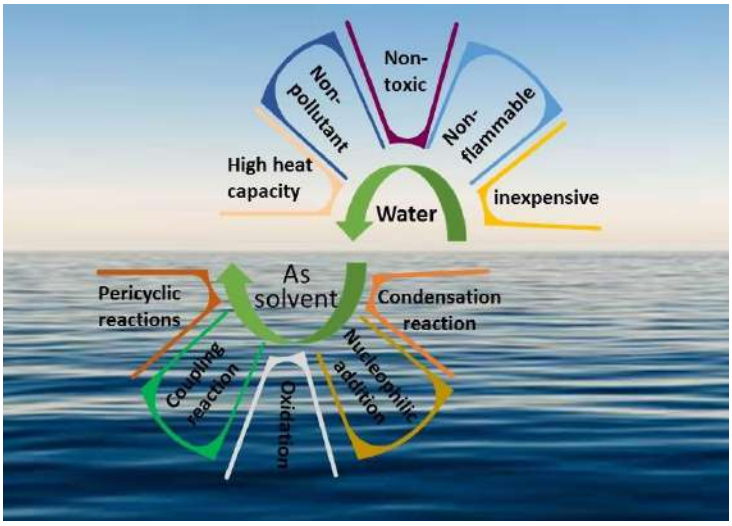


Fig. (1). Green properties of water and its applications in organic synthesis as a solvent.

Previously, various review articles have been published on this topic, which worked as introductory for readers on water-based synthesis [46 - 50]. This chapter focuses on recent aqueous-mediated heterocyclic transformations in different environmental conditions using either catalyst-free synthesis or different catalysts like acid, base, metal, nanocatalyst, and so forth, covering the literature from the year 2010 to 2020.

ON-WATER AND IN-WATER SYNTHESIS

Various water-based heterocyclic transformations are carried out in different physical and environmental conditions of water named as on-water, in-water, hot-compressed water, near-critical water, subcritical and supercritical water, *etc.* [51 - 54]. Among the aforementioned types, “on-water” and “in-water” are the most popular and common terms used in research articles. Sharpless and co-workers introduced the term “on water” and is used when reactants are insoluble in water-phase and make a bi-phasic system, oil-water emulsion without using other organic co-solvent. The rate of reaction accelerates in the oil-water emulsion by hydrophobic effect and H-bonding. Another important term “in-water” is used when the reactants are completely soluble in water (Fig. **2**) [21]. However, complete differentiation between both types from naked-eyes is a little difficult because various parameters like physical and kinetic factors affect the reaction mechanism. Therefore authors generally use the terms “synthesis in aqueous conditions”, “water-based” and “water-assisted” synthesis.

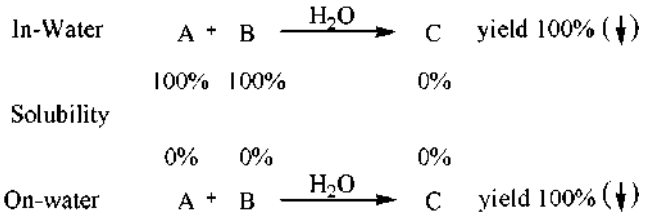


Fig. (2). Ideal green reaction conditions.

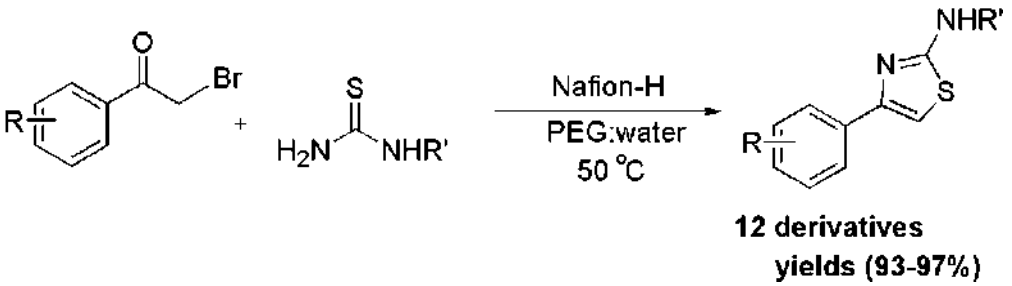
WATER-BASED HETEROCYCLIC TRANSFORMATIONS

Organocatalyzed Reactions

Organocatalysis, one of the most significant concerns in the world of synthetic chemistry, is a small organic catalytic system containing C, O, H, N, S, and P atoms. Organocatalysts have several unique characteristics including being inexpensive, easily available, non-toxic, simple preparation, easy handling, stable in air and water, and so on, which make them efficient for the catalysis of numerous reactions [55, 56].

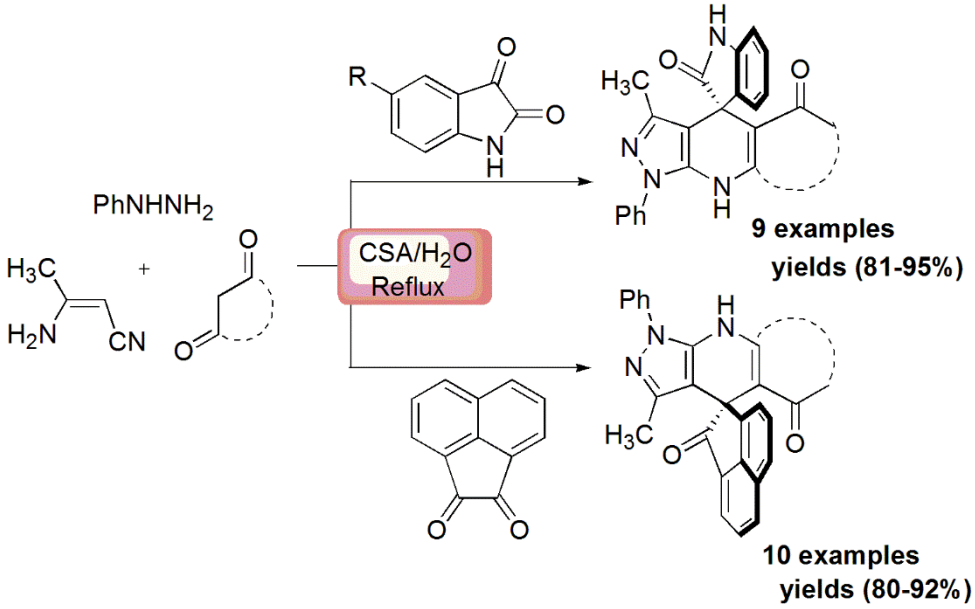
Acid-catalyzed Reactions

Perfluorinated sulfonic acid resin known as Nafion-H has high thermal and chemical inertness, selectivity, and recyclability. It bears both hydrophilic and hydrophobic part that makes it an efficient heterogeneous acid catalyst [57]. Kidwai and companions [58] demonstrated a straightforward and efficient methodology for the synthesis of substituted 2-aminothiazoles by thiourea and phenacyl bromide using PEG: H_2O (6:4) solvent and Nafion-H recyclable solid acid catalyst at 50 °C to furnish excellent yields. This synthesis is an eco-friendly approach in terms of mild conditions, high atom-economy, efficiency, and less waste-generation (Scheme **1**).



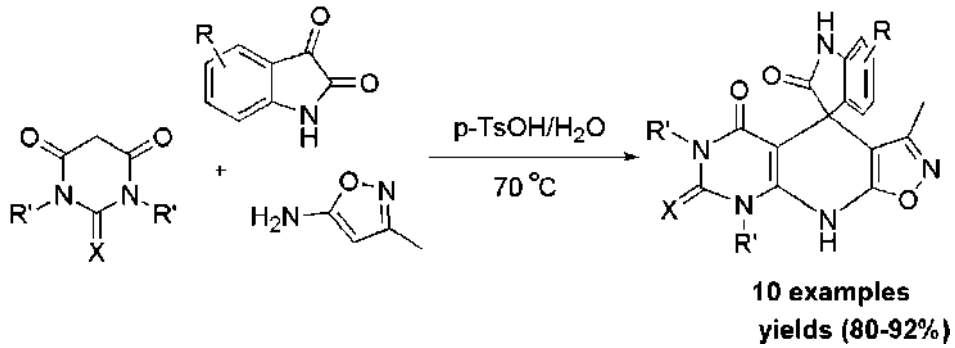
Scheme (1). Nafion-H promoted synthesis of 2-aminothiazoles.

An ingenious one-pot multi-component and camphor-10-sulfonic acid (CSA) catalyzed synthesis of spiro[indoline/acenaphthylene-3,4'-pyrazolo[3,4-b]pyridine derivatives in excellent yields was reported by Balamurugan and co-workers from the condensation of aminocrotononitrile, phenylhydrazine, acenaphthylene-1,--dione/isatin with a range of cyclic 1,3-dicarbonyl compounds such as barbituric acid, 2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione and cyclohexane-1,3-dione in water-media [59]. In this procedure, two new rings and five new (two C-N, two C-C and, one C-N) bonds were generated in one pot with high yields of products. To extend the area of research, the authors also demonstrated the synthesis of 3-(4-pyrazolyl)oxindoles from isatin, arylhydrazines, and 3-aminocrotonitrile using $InCl_3$ catalyst in an aqueous medium to yield high atom-economy in short reaction time (Scheme **2**).



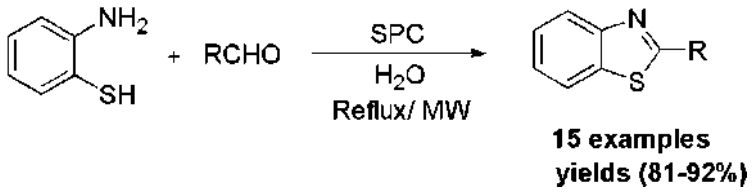
Scheme (2). CSA assisted synthesis of spirocyclic compounds.

Chasing the curiosity for the synthesis of diversified heterocycles, Rahmati and Khalesi refluxed barbituric acid, isatin and aminoisoxazole in a one-pot using p-TsOH (para-toluenesulfonic acid) and water and procured spiro[indoline-isoxazolo[4`,3`:5,6]pyrido[2,3-d]pyrimidine]triones in moderate to good yields [60]. These synthesized derivatives contain four types of heterocycles *viz*. isoxazole, pyrimidinone, oxindole, and dihydropyridine that increased their pharmacological significance. The authors also investigated the efficiency of various catalysts like $ZrCl_4$, p-TsOH, $Zr(acac)_2$ and $ZrOCl_2$, *etc*. and finally, p-TsOH gave best results in mild conditions (Scheme **3**).



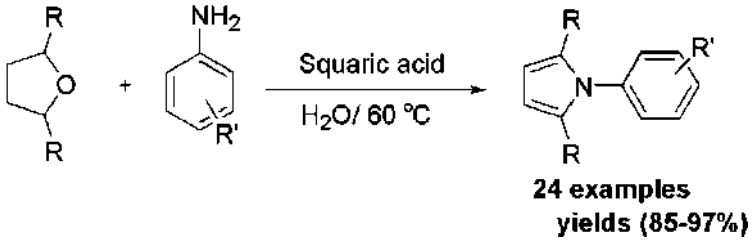
Scheme (3). Acid catalyzed synthesis of spiro[indoline-isoxazolo[4',3':5,6]pyrido[2,3-d] pyrimidine] triones.

A water-mediated SPC(Sulfonated Porous Carbon) catalyzed C=N and C-S bond formation in benzothiazole has been demonstrated by Shokrolahi and companions using 2-aminothiophenol and different aldehydes in two different conditions *viz.* conventional heating and MW irradiations [61]. The results of two comparative studies revealed that high yields were obtained in the presence of MWI in a short duration of time as compared to conventional heating. Simple and reliable method, facile workup, wide scope of substrate, excellent yields, inexpensive recyclable catalyst and use of small catalytic amount are additional features of this protocol (Scheme **4**).



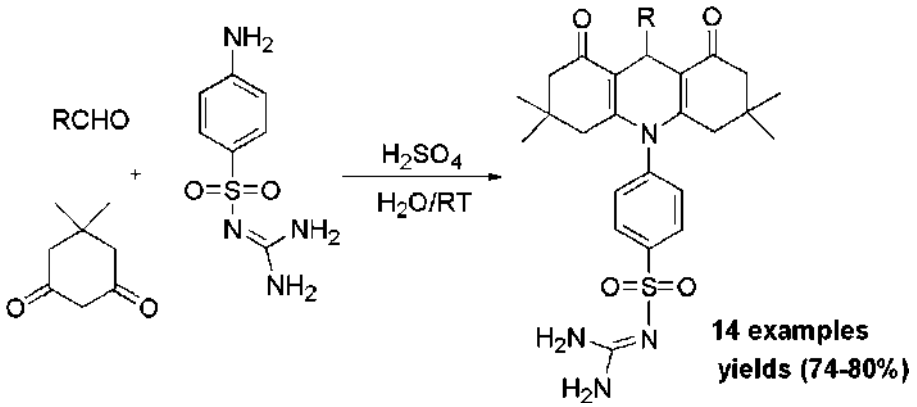
Scheme (4). SPC catalyzed synthesis of benzothiazole derivatives.

Azizi *et al.* suggested squaric acid as an efficient organocatalyst for the synthesis of N-arylpyrroles from the condensation of 2,5-dimethoxytetrahydrofuran with a varied range of aromatic amines and water as a green solvent at 60°C [62]. For the screening of catalytic efficiency, the authors applied different catalysts such as $B(OH)_3$, SiCl, TCA, $RuCl_3.7H_2O$, proline, ZnI_2, $ZrCl_4$, $HClO_4$, PTSA, CF_3SO_3H, HBF_4, squaric acid, *etc.,* on the model reaction of synthesis of N-arylpyrrole. However, squaric acid proved best in mild conditions. This method developed a library of N-arylpyrrole derivatives in excellent yields without using any long purification process (Scheme **5**).



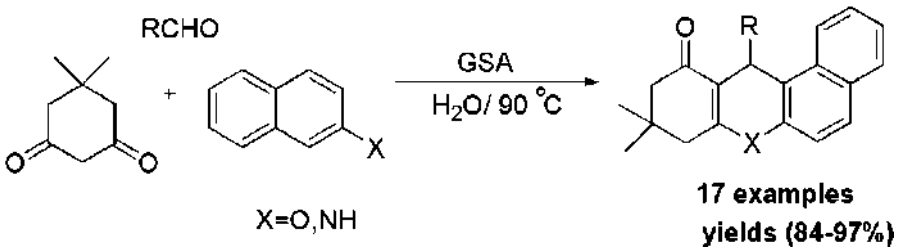
Scheme (5). Synthesis of N-substituted pyrrole derivatives.

Yesildag *et al*. demonstrated a novel, simple and one-pot multi-component synthesis of acridine sulphonamides from 4-amino-N-(diaminomethylene)benzene sulfonamide, dimedone and substituted benzaldehyde using sulfuric acid catalyst and water at room temperature to obtain moderate to good yields and screened them for the inhibition of human carbonic anhydrase isoenzyme [63]. Most of the synthesized compounds displayed moderate carbonic anhydrase inhibition (Scheme **6**).



Scheme (6). Acid catalyzed synthesis of acridines sulfonamide derivatives.

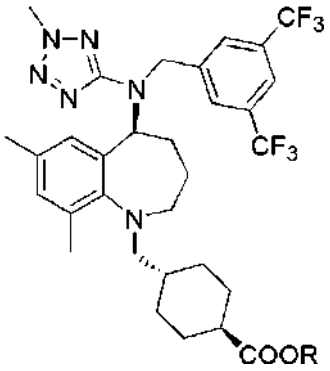
Wan and co-authors synthesized a novel glucose-containing Brønsted acid catalyst and employed them for the synthesis of tetrahydrobenzo[a]xanthenes and tetrahydrobenzo[a]acridine derivatives [64]. Condensation of dimedone, different aldehydes, and 2-naphthol/β-naphthylamine in water media and glucose sulfonic acid (GSA) catalyst was performed to acquire xanthene and acridine derivatives in high yields. A simple and one-pot method, low-priced catalyst, high acidity and activity of the catalyst and avoid by-product generation are plus points of this process (Scheme **7**).



Scheme (7). GSA assisted synthesis oftetrahydrobenzo[a]xanthens and acridines.

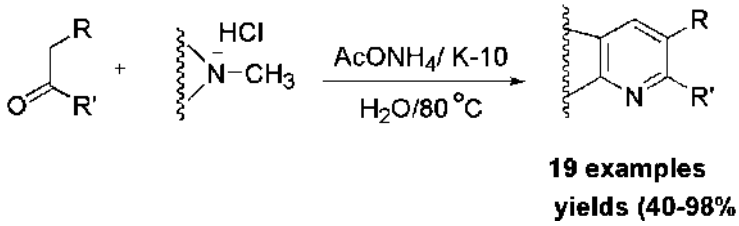
A library of 2-substituted 1,3-benzazole derivatives like benzimidazoles, benzoxazoles, and benzothiazoles was prepared using Amberlyst-15 as an economical and reusable catalyst using ultrasound in an aqueous medium by Rambabu and co-workers [65]. These heterocycles were prepared from two routes *viz.* in the first pathway, condensation of o-amino phenol/o-phenylenediamine/--amino thiophenol took place with aromatic acids and in the other one, cyclocondensation of N-acyl or benzoyl derivatives yielded desired products in moderate to high efficiency.

Evacetrapib is a synthetic drug that inhibits the CET (cholesteryl ester transfer) protein and increases dense lipoprotein cholesterol. Frederick *et al.* prepared a new route for Evacetrapib synthesis [66]. Substituted amine and sodium bisulfite adduct underwent hydrogenative reductive amination to combine benzazepine core with cyclohexyl subunit and formed Evacetrapib in multi-steps with high stereo-selectivity. Water played an indispensable role in the present mechanism *i.e.* it increased the stereo-selectivity and anti:syn ratio *via* repressed epimerization process. For industrial level applicability, the authors synthesized desired products in more than 1100 kg (Scheme **8**).



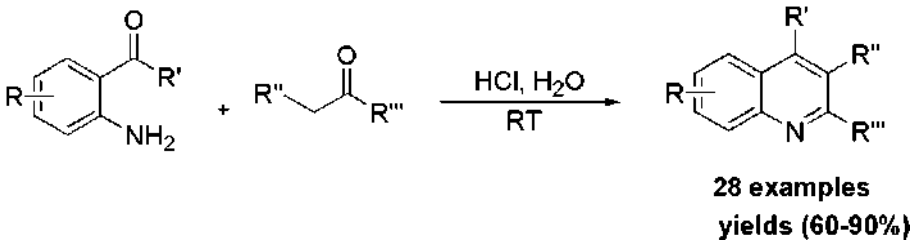
Scheme (8). Structure of Evacetrapib.

Montmorillonite K-10 assisted, regioselective one-pot MCR of mannich bases and active methylene compounds in NH_4OAc and water to furnish 5,6,7,8-tetrahydroquinolines and 2,3,6-trisubstituted pyridines in high yields was discovered by Hanashalshaha *et al.* [67] (Scheme **9**).



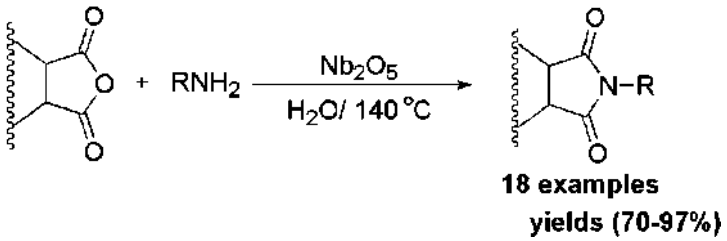
Scheme (9). Montmorillonite K-10 promoted synthesis of 2,3,6-trisubstituted pyridines and 5,6,7,8-tetrahydroquinolines.

Gopi and Sarveswari developed a facile and new protocol to develop polysubstituted quinolines *via* Friedlander annulation without the use of any conventional heating, mechanical stirring, microwave irradiation, and any other energy expenditure [68]. The authors simply kept the reaction mixture, aminoarylketones, with a range of diketones in the presence of HCl in H_2O media at room temperature for some hours and obtained the products in moderate to high yields. Here, a library of polysubstituted quinoline derivatives was prepared without use of any toxic solvent, energy expenditure and purification process with high-cost efficiency and eco-benign pathways (Scheme **10**).



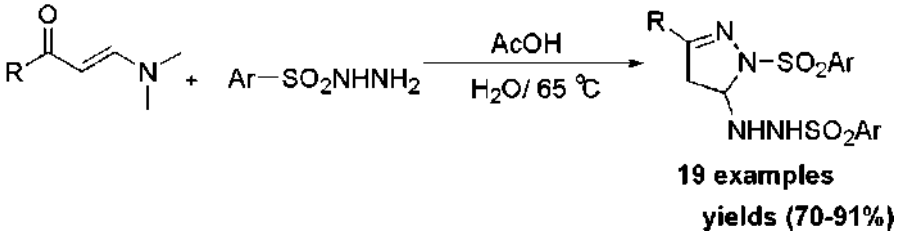
Scheme (10). Polysubstitutedquinolines synthesis from o-aminoarylketon.

Ali and companions demonstrated Nb_2O_5 as a heterogeneous reusable catalyst for the preparation of cyclic imides from carboxylic anhydrides with ammonia and different amines in a green solvent, water at 140 °C [69]. This facile and novel procedure has some remarkable features *viz.* recyclable catalyst, simple isolation, and purification, good yields, *etc.* (Scheme **11**)



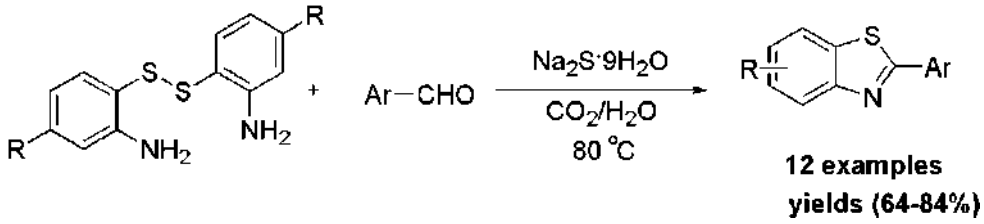
Scheme (11). Synthesis of cyclic imides from anhydrides.

Li *et al.* displayed a novel pathway for the chemoselective synthesis of substituted pyrazolines by sulfonyl hydrazines and enaminones using water medium and acetic acid promoter through multimolecular domino reactions [70]. This methodology involved inexpensive additives, green solvents, and generated three new bonds, one C=N, and two C-N bonds to produce a range of pyrazoline derivatives in excellent yields *via* a greener process (Scheme **12**).



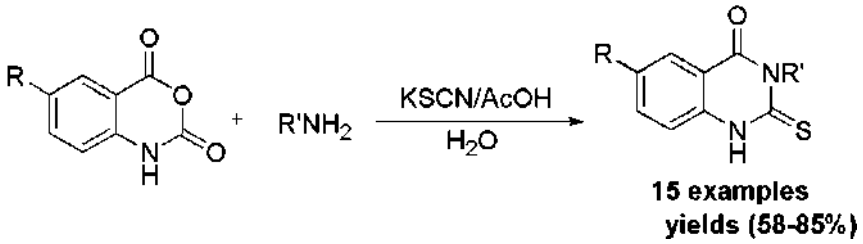
Scheme (12). Water-acetic-acid mediated synthesis of pyrazoline derivatives.

A water-mediated ingenious protocol for the synthesis of substituted benzothiazoles *via* condensation of varied aldehydes and ortho-anilinodisulfides in CO_2 and $Na_2S{\cdot}9H_2O$ system was demonstrated by Liu *et al.* [71]. Here $CO_2{\cdot}H_2O$ worked as self-neutralizing acid, formed H_2CO_3 and further ionized to produce H^+ ions. This eco-friendly method displayed simplicity, selectivity, good atom-economy, wide applicability, and avoid waste-generation too (Scheme **13**).



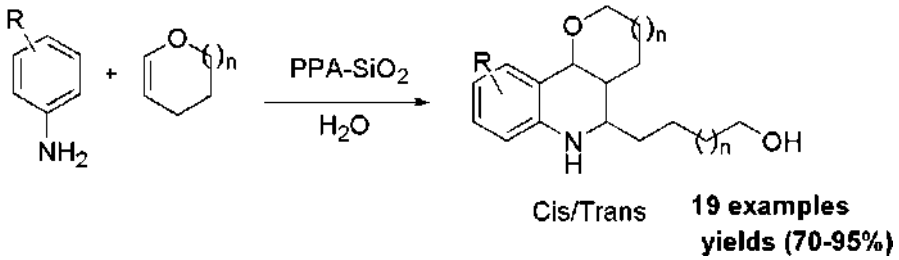
Scheme (13). Synthesis of 2-substituted benzothiazole derivatives.

Bardajee *et al*. discovered a facile pathway for the synthesis of 2-thioxoquinazolinone from potassium thiocyanate, amine and isatoic anhydride in AcOH and water in moderate to excellent yields [72]. The impact of solvent and catalyst was also studied by authors where AcOH and water exhibited the best results and was inexpensive and less toxic as compared to previously reported methods (Scheme **14**).



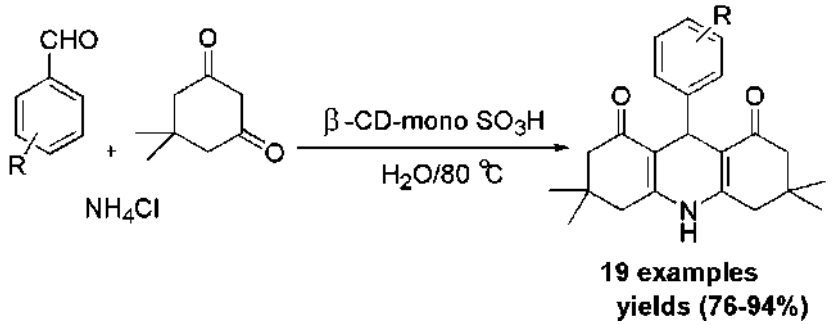
Scheme (14). Synthesis of 2-thioxoquinazolinone using KSCN.

The synthesis of substituted tetrahydroquinolines and quinazolinones with high efficiency by the reaction of 3,4-dihydropyran and substituted aniline, using a catalytic amount of PPA-SiO_2 in water was reported by Ansari and co-workers [73]. The authors also conducted comparative studies using different cyclic ethers like DHF, DHP and catalysts such as $BiBr_3$, $InCl_3$, PPA, PPA-SiO_2, and cation exchange resin for understanding the feasibility of reaction. Here, both cis and trans isomers were obtained, yet, in the presence of electron releasing substituents, cis-isomer was found pre-dominantly and the configuration was confirmed by ^{1}H NMR spectra and NOESY studies (Scheme **15**).



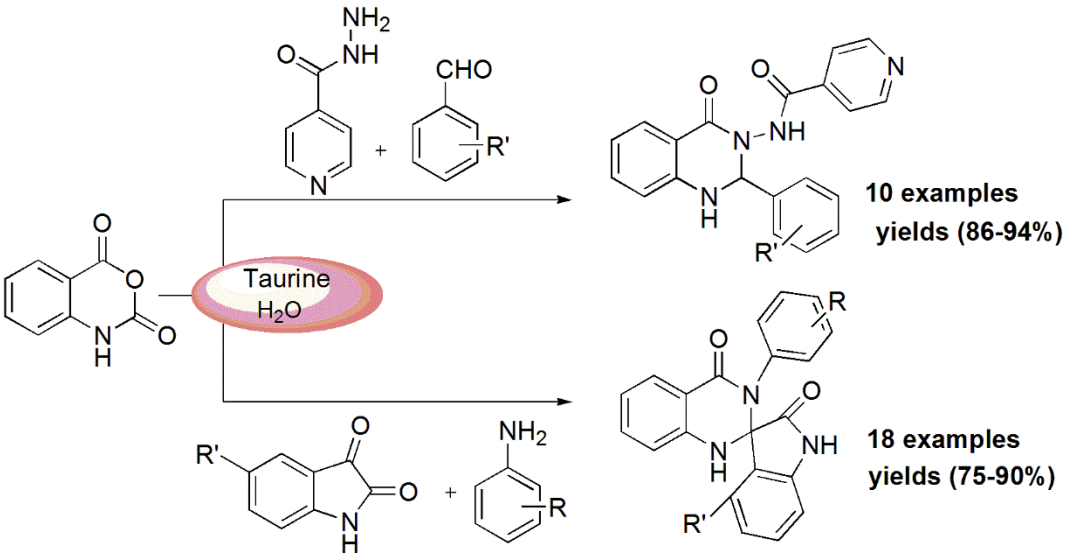
Scheme (15). PPA-SiO_2 catalyzed synthesis of furano and pyranotetrahydroquinolines.

β-Cyclodextrin monosulphonic acid and water-assisted one-pot multi-component synthesis of acridine derivatives from ammonium chloride, dimedone, and a range of aromatic aldehydes with high yields was established by Madankumar *et al.* [74]. The present protocol is simple, having a broad range of derivatives, mild conditions, facile workup, and reusability of catalyst up to five consecutive cycles compared to previously reported methods (Scheme **16**).



Scheme (16). β-CDmonoulphonic acid promoted synthesis of acridine derivatives.

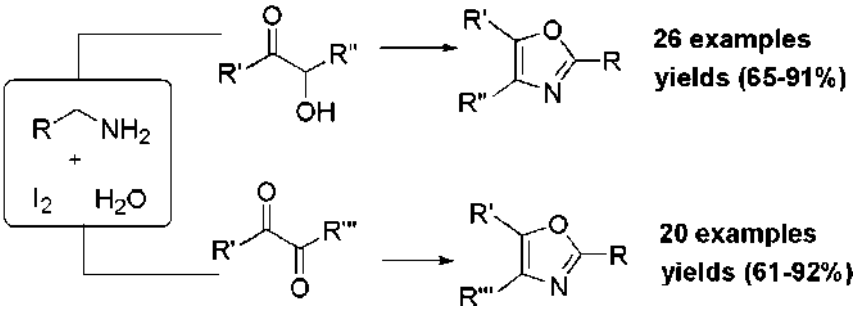
Chate and companions enclosed 2-aminoethanesulfonic acid (taurine) as an efficient, green and reusable catalyst for the preparation of a library of 1,2-(dihydroquinazolin-3(4*H*)isonicotinamides and spirooxindole-dihydroquinazoli nones by the reaction of isatoic anhydride, substituted aniline and anhydride in water medium *via* one-pot multi-component reaction to afford high yields [75]. The authors also studied the impact of various solvents and catalysts on this model reaction (Scheme **17**).



Scheme (17). Synthesis of dihydroquinazolinones derivatives.

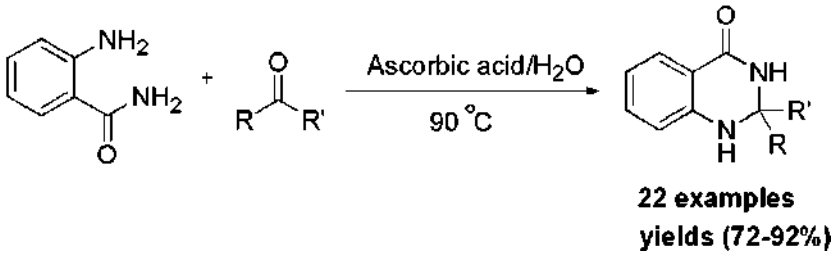
Banerji and group developed an efficient, simple, and rapid method for the synthesis of oxazole by the condensation of benzil with a range of benzylamine using iodine catalyst and K_2CO_3 base in water to obtain high yields [76]. In order to find the optimal conditions, the authors applied various catalysts (I_2, TBAI,

TBAB, TBAC, KI, and PIDA), bases (K_2CO_3, $NaHCO_3$, TEA, DBU and pyridine), solvents (H_2O, MeCN, THF, toluene, DMF and EtOH) and oxidants (air, O_2, N_2 and TBHP) in the reaction and finally, catalyst I_2 with K_2CO_3 base and H_2O at 60 °C in air showed good results (Scheme **18**).



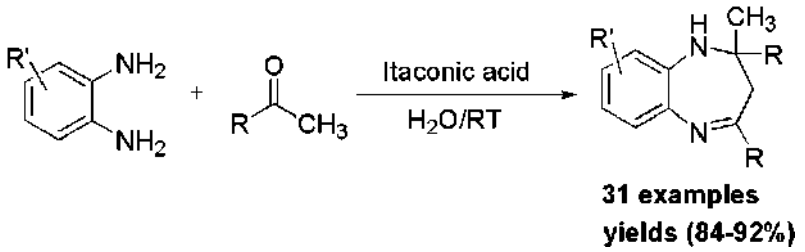
Scheme (18). Synthesis of polyarylatedoxazoles using iodine.

L-ascorbic acid catalyzed the formation of substituted quinazoline in high yields *via* condensation of o-aminobenzamide with a wide range of carbonyl groups (aldehydes and ketones) [77]. The authors studied this reaction in various conditions *i.e.,* different solvents, catalyst loading, and temperature. However, 20 mol% of ascorbic acid in water at 90 °C gave the best results (Scheme **19**).



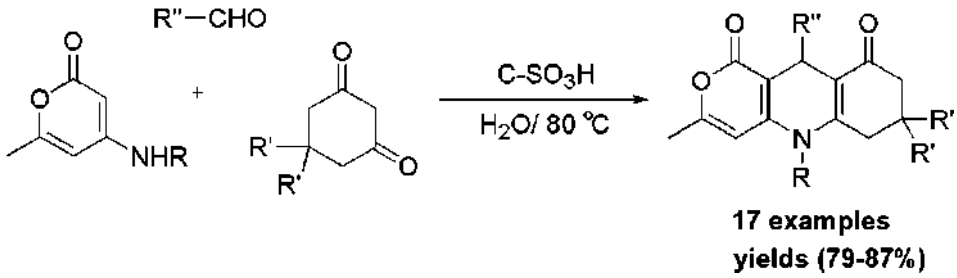
Scheme (19). Synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives.

Tamuli *et al.* demonstrated the role of naturally occurring itaconic acid in the generation of C-N bond between *o*-phenylene diamine and substituted acetophenone using water at room temperature and produced respective 1,5-benzodiazepines in high yields [78]. This green and efficient protocol has several advantages like metal-free synthesis, use of a high range of substrates, avoiding long purification, short reaction time, biodegradable and reusable catalyst (Scheme **20**).



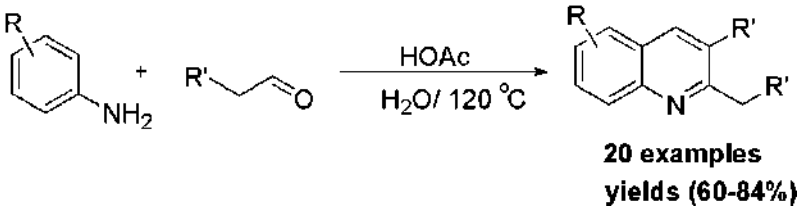
Scheme (20). Synthesis of 1,5-benzodiazepines derivatives using itaconic acid.

Very recently, Yang and co-workers disclosed carbon-sulfonic acid catalyzed one-pot domino synthesis of poly-substituted pyrano [4,3-b] quinoline-1,9-(5H) dione from 1,3-cyclohexanedione, aldehydes and 6-methyl-4-(arylamino--2H-pyran-2-ones in water at 80 °C in high yields [79]. This effective heterogeneous catalyst was reusable up to six consecutive cycles without significant loss in activity. According to the reaction mechanism, the solid acid catalyst activated aldehydes and formed the condensation intermediate, followed by cyclization and produced pyranone derivatives (Scheme **21**).



Scheme (21). Synthesis of poly-substituted pyrano[4,3-b]quinoline-1,9-(5H)-dione derivatives.

Recently, Zhang *et al.* developed an ingenious, water based route for the synthesis of disubstituted quinolines by arylamines and aldehydes using HOAc catalyst in good yields. However, phenylacetaldehyde gave comparatively low yields [80] (Scheme **22**).

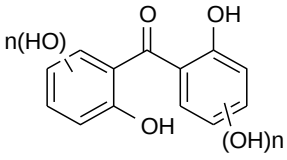
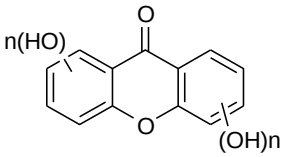
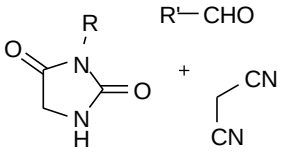
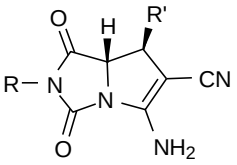
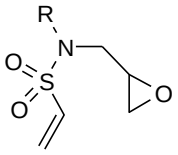
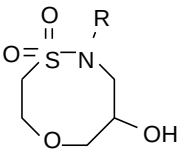
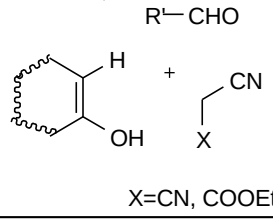
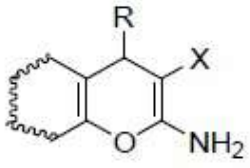
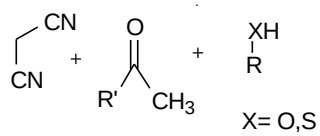
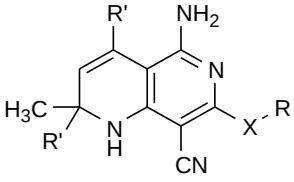


Scheme (22). HOAc mediated synthesis of 2,3-disubstituted quinolones.

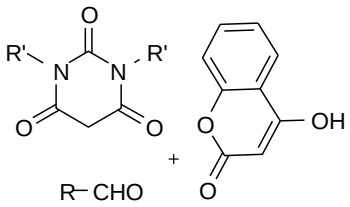
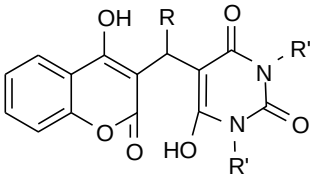
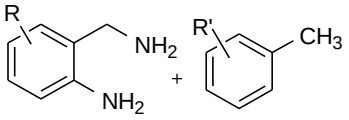
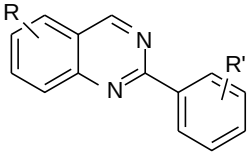
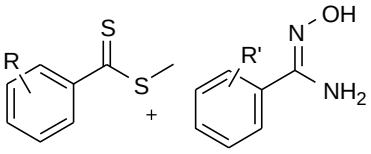
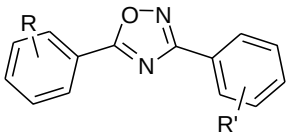
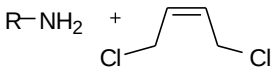
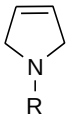
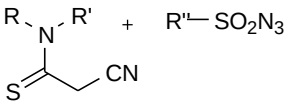
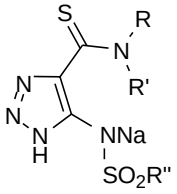
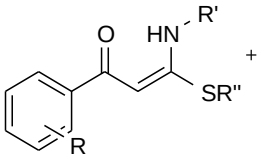
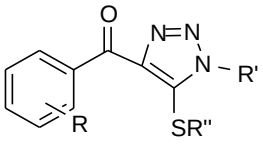
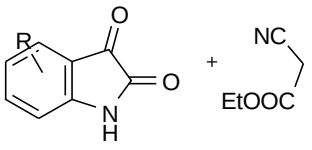
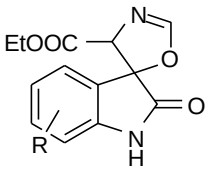
Base-catalyzed Reactions

A weak base, sodium acetate (NaOAc) and water supported cyclization of 2,2'-dihydroxybenzophenone under MW irradiations to synthesize hydroxy xanthones in excellent yields was reported by Zhang *et al.* [81]. The authors revealed that no significant yield of the desired product was found in the absence of MWI or in the presence of simple heating (Table **1, Entry 1).**

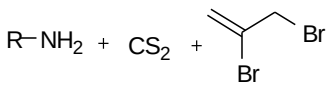
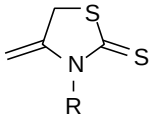
Table 1. Various water-based heterocyclic transformations using base-catalyst.

Entry	Reactant	Product	Reaction Conditions [Examples/ (yields %)]	References
1			H_2O/ NaOAC/ MW **[6/(94-99)]**	[81]
2			H_2O/ piperidines/ 70 °C [**24/(55-94)**]	[82]
3			H_2O/ NaOH or NaHS/ 90 °C [**14/(63-85)**]	[83]
4			H_2O/ POPINO/ Reflux [**63/(87-98)**]	[84]
5			H_2O/ Et_3N/ Reflux [**54/(87-95)**]	[85]

(Table 1) cont.....

Entry	Reactant	Product	Reaction Conditions [Examples/ (yields %)]	References
6			H_2O/ SSC/ 80 °C [**12/(72-86)**]	[86]
7			H_2O/ NaOH/ 100 °C [**41/(60-78)**]	[87]
8			H_2O/ NaOH/ 90 °C [**28/(91-97)**]	[88]
9			H_2O/ K_2CO_3, Na_2CO_3/ MW [**20/(66-98)**]	[89]
10			H_2O/ NaOH, EtOH/EtONa/ 0-60 °C [**39/(50-80)**]	[90]
11			H_2O/ TMEDA/ 120 °C [**22/(62-89)**]	[91]
12			H_2O/ DABCO/ RT [**15/(60-75)**]	[92]

(Table 1) cont.....

Entry	Reactant	Product	Reaction Conditions [Examples/ (yields %)]	References
13			H_2O/ K_2CO_3/ RT [**10/(62-92)**]	[93]

An ingenious, multi-component, and highly regio-, chemo-, and diastereoselective synthesis of 2-azapyrrolizidine in moderate to high yields from the reaction of malononitrile, hydantoin, and benzaldehydes using piperidine in water was demonstrated by Rajarathinam and co-authors [82]. This diversity-oriented synthesis offered two contiguous stereocenters embedded pyrrolizidine alkaloid and the reaction proceeded *via* Knoevenagel condensation, Michael addition, and 5-exo-dig cyclization (Table **1, Entry 2).**

Ji and his companions discovered a facile and efficient route to synthesize sultam with novel core structure *via* intermolecular Michael addition, 8-endo-tet intramolecular epoxide ring-opening and cyclization [83]. Cyclic eight-member sultams were prepared from the cascade reaction of vinyl sulfonamide epoxides with NaOH and NaHS in the water at 90 °C with good product yields (Table **1, Entry 3)**.

A library of 2-amino-4*H*-chromene was prepared from the condensation of malononitrile/ethyl acetoacetate, aldehydes and active methylene compounds in the presence of organocatalyst, potassium phthalimide-N-oxyl (POPINO) and solvent H_2O by Dekamin *et al.* [84]. This one-pot three-component reaction has special features like a clean and simple process, inexpensive starting material, high yields in short reaction time and no need for tedious column-chromatography, *etc.* (Table **1, Entry 4).**

Das and co-workers discovered a novel “on water” approach for the synthesis of [1, 6]-naphthyridines without the use of any N-heterocyclic moiety as a substrate [85]. The combination of malononitrile, ketones and phenol/thiols in Et_3N base produced a range of new functionally rich heterocycles in a single step, which contains six new bonds, three C-C, two C-N and one C-S/C-O. The authors also revealed the impact of water on the rate of acceleration and the pathway of the reaction was confirmed by DFT calculations (Table **1, Entry 5)**.

Barbituric acid and 4-hydroxycoumarins are highly potent in numerous biological activities. Eskandari and group developed a combination of pharmacologically active components, barbituric acid and 4-hydroxycoumarin with aldehydes using

base catalyst, silica sodium carbonate (SSC) in a green solvent, water and obtained high yields [86]. For the optimization of reaction conditions, the authors employed different catalysts such as $MgSO_4$, $AlCl_3$, $FeCl_3$, $In(OTf)_3$, Na_3PO_4, SSC in variation with reaction temperature and SSC led to highest yields at 80 °C (Table **1, Entry 6)**.

In 2018, Chatterjee and companions demonstrated a base mediated synthesis of 2-aryl quinazolines in green medium, water from α,α,α-trihalotoluene and 2-aminobenzylamines with O_2 oxidant at 100 °C [87]. This transformation proceeded through intramolecular cyclization followed by elimination, and finally oxidation *via* 3,4-dihydroquinazolines intermediacy. Kinetic isotopic effect (KIE) experiment showed the value of relative rate constant (k_H/k_D) as 6.67, which corroborated the final oxidation step as a rate determining step (RDS). The hidden properties of this method are use of cheap and easily available base, use of green solvent and oxidant and simple purification (Table **1, Entry 7)**.

Swarup and coauthors discovered a facile strategy for the synthesis of 3,5-disubstituted 1,2,4-oxadiazole derivatives by amidoximes and dithioesters in NaOH at 90 °C *via* nucleophilic substitution, dehydration and intramolecular cyclization to produce good yields [88]. After optimization of the feasibility of the reaction, the authors concluded that the reaction proceeded slowly in organic solvents (EtOH, DMSO, DMF, MeCN, MeOH, *etc.*) and other bases (Na_2CO_3, K_2CO_3, TEA, DIPEA and so on) as compared to water medium and NaOH base (Table **1, Entry 8)**.

De Souza and co-workers explored a versatile method for the synthesis of N-substituted-2,5-dihydro-1*H*-pyrroles and N-substituted-1 *H*-pyrroles from cis-1,4-dichloro-2-butene with aromatic and aliphatic amines using K_2CO_3 base and Na_2SO_3 or KI/I_2 additives in water under microwave irradiations *via* oxidative aromatization [89]. This method includes high selectivity, atom-economy, ample scope of amine substituents, and mild reaction conditions (Table **1, Entry 9)**.

Filimonov and companions studied the base-mediated reaction of azides with thioamides in water to prepare monocyclic and bicyclic thiadiazole-4-carbimidamides and triazole-4-car bothioamides in moderate to high yields [90]. The simple, reliable, transition-metal free, and efficient protocol has a good approach towards the synthesis of functionalized heterocycles (Table **1, Entry 10)**.

A metal-free and base promoted condensation of tosyl hydrazine and β-thiolated enaminones in the aqueous medium to synthesize substituted 1,2,3-triazoles in good yields was explained by Deng *et al.* [91]. The authors also employed various bases and organic solvents to investigate their efficiency for the designed

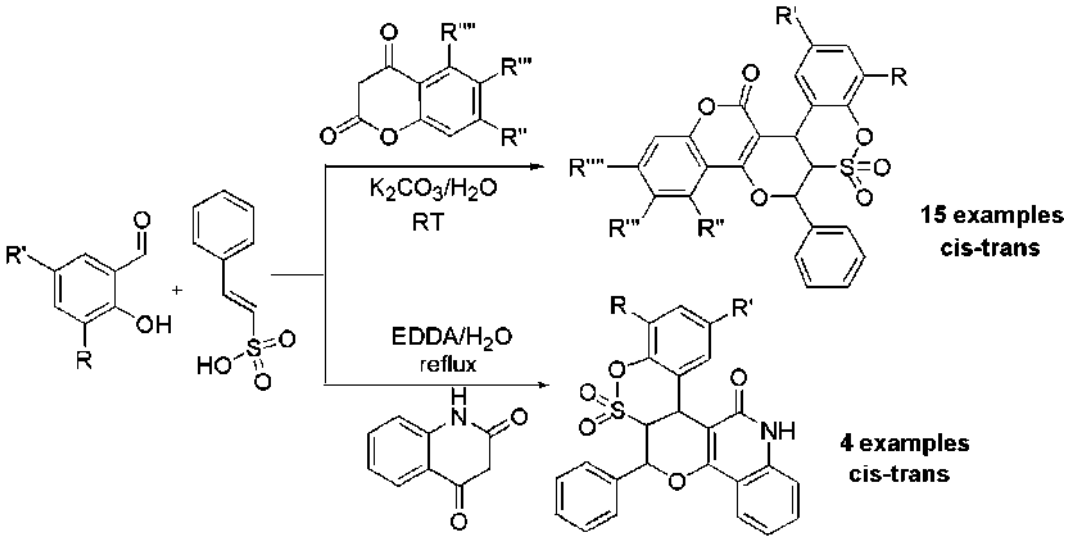
protocol. According to the plausible mechanism, initially, an anionic intermediate formed *via* deprotonation of β-thioenaminone in the presence of a base. This intermediate underwent nucleophilic addition with tosyl azide and then Regitz diazo transfer roıse to another intermediate, and finally, intramolecular annulation gave desired products (Table **1, Entry 11)**.

Very recently, Rankan and group described the synthesis of "on water" regioselective spirooxindole oxazolines from isocyanoacetate and isatin using DABCO base at ambient temperature through [3 + 2] cycloaddition reaction [92]. This methodology has various advantages, *i.e*., wide-range of functionality, mild conditions, high yields, facile process as compared to previously reported methods (Table **1, Entry 12).**

Recently, Hou *et al.* reported a facile and efficient strategy for the synthesis of 4-methylene-2-thiazolidinethiones in a one-pot process through *in situ* generation of dithiocarbamate from the reaction of primary amine, CS_2 and 2,3-dibromopropene in K_2CO_3 base and water *via* condensation, S-allylation and cyclization process [93]. They noted the effect of different bases (Et_3N, NaOH, KOH, K_3PO_4, and K_2CO_3) in various solvents (THF, CH_3CN, DMF, EtOH, H_2O) but, use of K_2CO_3 base and H_2O showed best results at ambient temperature (Table **1, Entry 13)**

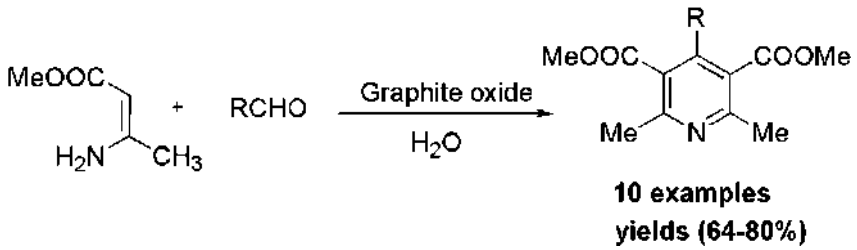
Other Organocatalysis Reaction

Fused pyrano-quinolinone and chromenone derivatives have gained much attention because of their diverse biological activity. Therefore, Ghandi and co-workers developed a facile, one-pot multi-component method for the synthesis of substituted pentacyclic-fused pyrano [3, 2] chromenone or quinolinone benzosultone from the reaction of aldehyde, styrene sulfonyl chloride with coumarin and quinolinone derivatives using water as a green solvent in different reaction conditions [94]. According to the reaction mechanism, the desired product was generated *via o*-sulfonylation, Knoevenagel condensation, and hetero Diels-Alder reaction that confirmed this cascade reaction and cis-trans formation. The salient features of this process are clean and simple method, high efficiency, good atom-economy, diversified product, and molecular complexity, *etc.* (Scheme **23**).



Scheme (23). Synthesis of pentacyclic-fused pyrano [3, 2,c]chromenone or quinolinone benzosultone derivatives.

Graphite oxide was found to display high efficiency in Hantzsch one-pot three component synthesis of 1,4-dihydropyridines and was reported by Mirza-Aghayan and coauthors from the reaction of methyl 3-aminocrotonate and aldehydes in water media and furnished products in moderate to good yields [95]. Reasonable catalyst, mild conditions, facile workup, and simple pathways are plus points of the present methodology (Scheme **24**).

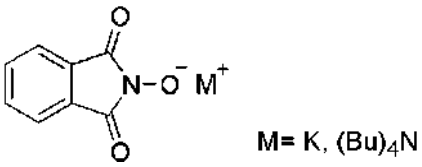


Scheme (24). Synthesis of 1,4-dihydropyridinesusing GO.

Vitamin B1 (VB1) possesses micronutrients that help in various body functions of human beings and are also used for catalysis in organic transformations. In 2015, Işık *et al*. discovered water-based one-pot multi-component synthesis of substituted acridinediones using aldehydes, dimedone and amines as substrates in the presence of non-hazardous VB1 catalyst [96]. The authors also checked the efficiency of other catalysts like amberlyst-15, *p*-dodecylbenzenesulfonic acid, and 5-(2-hydroxyethyl)-4-methyl-3-phenylthiazol-3-ium chloride *etc.,* as compar-

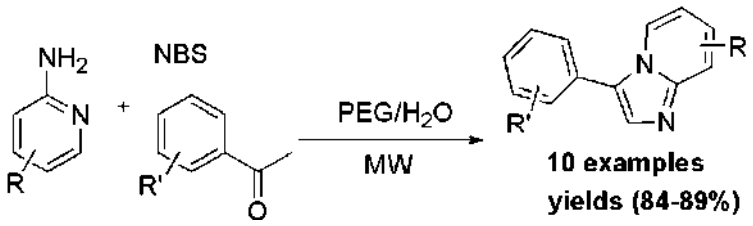
ed to VB1, though none of these could demonstrate better efficiency for the synthesis of acridinedione. A straightforward and efficient method, high yield, effortless purification, low-cost and eco-friendly catalyst are additional advantages of this protocol.

Dekamin and co-authors explored phthalimide-N-oxyl salts as organocatalysts for MCR of ethyl acetoacetate, vanillin, and hydroxylamine hydrochloride in water to prepare (Z)-3-methyl-4-(arylmethylene)-isoxazole-5(4H)-one derivative at room temperature [97]. Cheap catalyst, clean-reaction, high range of substrate, and high yields make this protocol greener and environment-friendly (Scheme **25**).



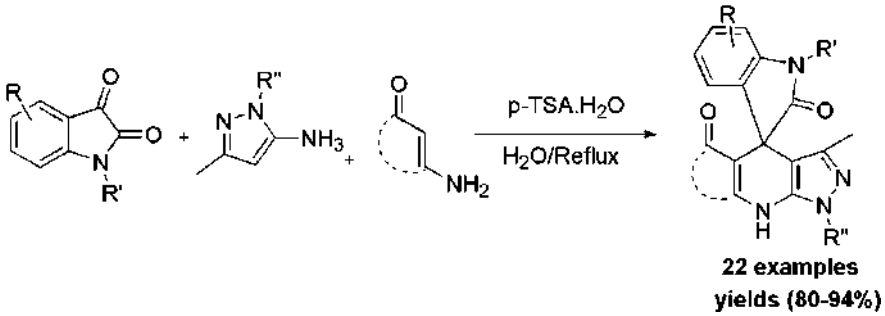
Scheme (25). Structure of phthalimide-N-oxyl salts.

A microwave-assisted one-pot three-component condensation of N-bromosuc cinimide, 2-amino pyridines, and acetophenones in PEG-400: water (1:2) with high yields at 300W and 80–85 °C was reported by Wagare *et al.* [98]. The authors revealed that the presence of an electron-withdrawing group (EWG) on starting materials increased the rate of reaction and yield of products. According to the investigation of the reaction mechanism, N-bromosuccinimide released bromine cation and this cation attached to acetophenone and formed α-bromoacetophenones. Then it underwent coupling reactions with 2-aminopyridine, and finally, cyclization furnished the desired products. This convenient and economical protocol avert the usage of lachrymatric α-haloketones, toxic reagents, and decreased reaction time as compared to previously reported methods (Scheme **26**).



Scheme (26). One-pot synthesis of imidazo[1,2-a]pyridine under MWI.

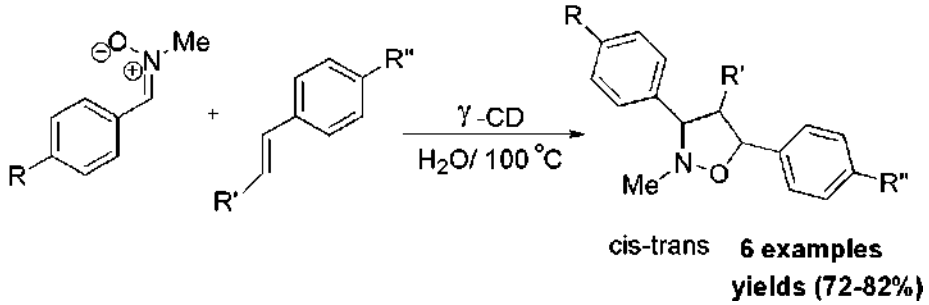
Kalita and companions discovered an efficient, facile, and water-based one-pot MCR of 5-aminopyrazole, isatin, and 2,6-diaminopyrimidin- 4-one/6-aminouracil using para-toluene sulfonic acid monohydrate (PTSA.H_2O) catalyst to obtain spiro (indoline-3,4'-pyrazolo[4',3':5,6] pyrido[2,3-d]pyrimidines) with high throughput in short reaction time [99]. All the synthesized derivatives were characterized by ^1H, ^{13}C NMR spectra, and crystal structure data. This eco-benign and mild methodology eliminated the use of a long chromatographic process, and increased substrate scope using versatile and cheap catalyst (Scheme **27**).



Scheme (27). *p*-TSA mediated synthesis of spiro (indoline-3,4'-pyrazolo[4',3':5,6] pyrido[2,3-d] pyrimidines).

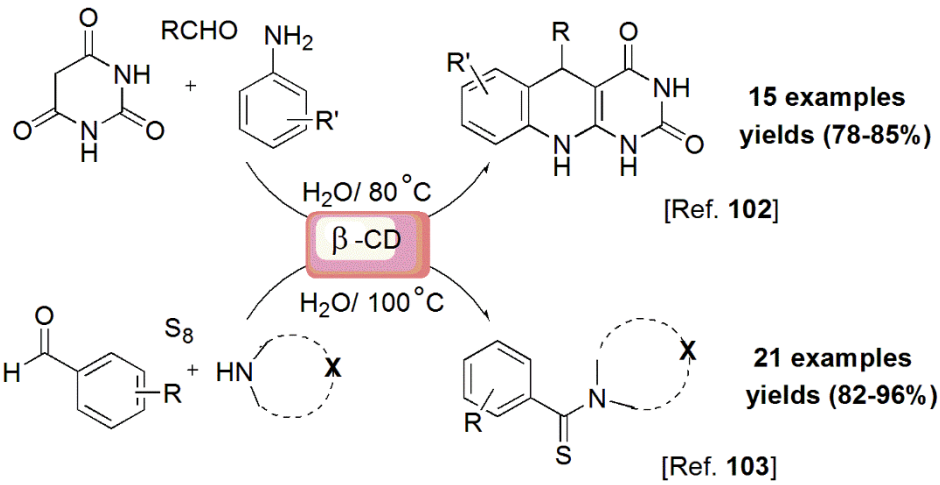
L-proline has been applied as an organocatalyst in various organic transformations like Aldol reaction, Michael addition reaction, Mannich reaction, *etc.*, owing to their dual action as catalyst and ligand. Bhattacharjee *et al.* explained the efficiency of L-proline catalyst for the synthesis of xanthenes and chromeno [2,3-d]pyrimidine-trione derivatives in the water at ambient temperature from the reaction of aromatic aldehydes, cyclic 1,3-dione, and barbituric acid [100]. Natural, economical, and water-soluble catalyst, facile purification, good yields, and high enantioselectivity make this process eco-friendly. The authors also explained geometric parameters and molecular orbital diagram of some selected derivatives *via* time-dependent DFT calculations.

Cyclodextrins (CD) are cyclic oligosaccharides having α-1,4-glycosidic bonds between the outer hydrophilic surface and central hydrophobic hole, so they easily connect with any hydrophobic molecule in water solvent like host-guest phenomenon of enzymes. Therefore, Floresta and companions reported γ-CD catalyzed stereoselective synthesis of isoxazolidine derivatives using a range of cinnamates and styrenes in the water at 100 °C *via* 1,3-dipolar cycloaddition [101]. Here, the catalyst is highly efficient, displayed excellent diastereomeric excess (>95%) and recyclability. The structure of synthesized derivatives was screened using ^1H, ^{13}C NMR, and cis/trans configuration revealed from 1D NOESY spectra (Scheme **28**).



Scheme (28). Synthesis of isoxazolidine derivatives.

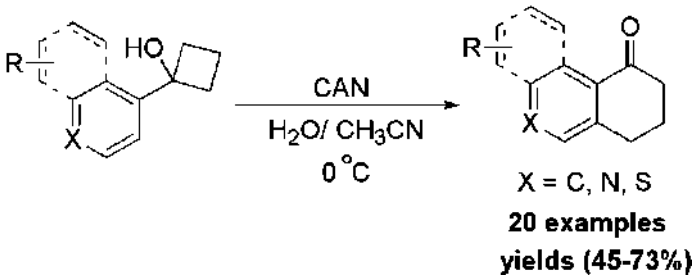
Reddy and coauthors employed β-cyclodextrin supramolecules for the catalytic synthesis of pyrimido[4,5-b]quinoline-diones from barbituric acid, aniline and substituted aldehydes in water and afforded moderate to good yields *via* guest-host complexion approach [102]. The mechanism displayed that, firstly, β-C--aldehyde complex was formed, which was further combined with barbituric acid and produced enone. Then, Michael addition between enone and aniline took place and finally, cyclization furnished the desired product **(**Scheme **29)**. In addition, Tayade and group used β-CD and water for the synthesis of thioamide derivatives through one-pot MCR reaction of cyclic secondary amines, sulfur, and substituted aldehydes and obtained high yields [103]. β-CD was easily recovered and reusable in further reactions without significant loss of activity (Scheme **29**).



Scheme (29). Synthesis of heterocyclic derivatives using β-CD.

Ce^{4+} mediated catalyst-free synthesis of 1-tetralones from cyclobutanol in water-acetonitrile solvent within 30 sec at 0 °C was reported by Fang *et al*. *via* oxidative ring-opening and cyclization reaction [104]. This facile and ingenious process

gave good yields in short reaction time and was also applicable in gram-scale synthesis. These final products were found to easily undergo various transformations. The reaction proceeded through a free-radical intermediate, which was generated *via* a single electron transfer (SET) process controlled by CAN ($Ce(NH_4)_2(NO_3)_6$) (Scheme **30**).



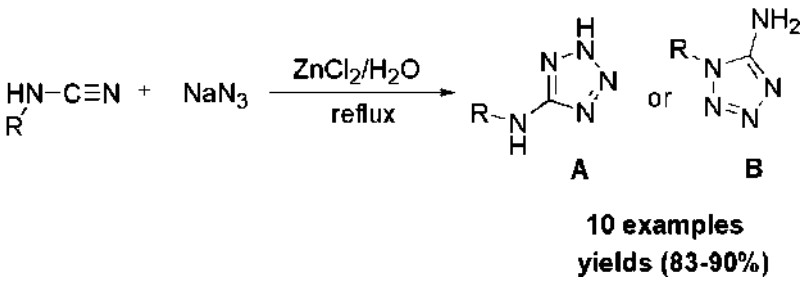
Scheme (30). CAN-promoted synthesis of 1-tetalones.

Dandia and coauthors reported an inventive protocol for the synthesis of quinazolinones through the combined effect of water (solvent) and NaCl (salting-out agent) *via* "ambiphilic dual activation" and "kosmotropes perturbation" which increased the space for reaction and brought reactants close together [105]. The regioselective C-N bond was generated from the reaction of benzyl alcohols and aminobenzamides using NaCl, H_2O, and TBHP under MWI, to obtain high yields and also precluded the use of metal, base, and organic solvents. The authors also displayed that the presence of an electron-donating group and ortho substitution decreased the yields that were controlled by H-bonding and steric effect. The credit of the presented protocol includes simple procedure, mild conditions, and high functional group tolerance.

A domino one-pot three-component synthesis of substituted chromeno[4,3-b]quinoline using guanidine hydrochloride organocatalyst and water as a green solvent by the condensation of dimedone, 4-aminocoumarin, and benzaldehyde has been demonstrated by Olyaei and co-workers [106]. This eco-benign synthesis provided high yields using efficient catalysts through a simple procedure and circumventing a long chromatographic process. According to the investigation of plausible mechanism, initially, aldehydes and dimedone displayed Knoevenagel condensation to form Michael acceptors and further showed Michael's reaction with 4-aminocoumarin. Finally, cyclization and dehydration provided the desired product.

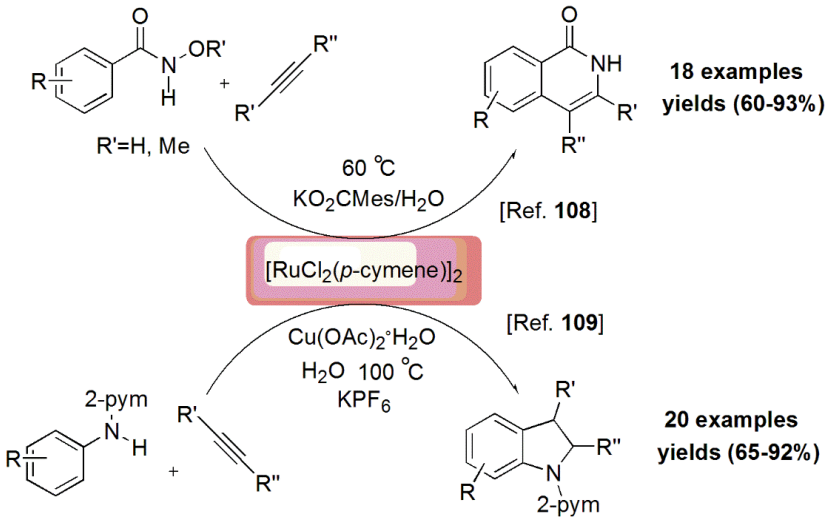
Metal Catalyzed Reactions

Habibi and co-authors employed $ZnCl_2$ for the regiospecific synthesis of arylaminotetrazole from sodium azide and arylcyanamides in a water medium to furnish good yields [107]. Electrical and steric factors play a crucial role in product formation. When the aryl ring of arylcyanamides was substituted with ERG, then the aryl substituent carrying nitrogen got involved in the cyclization step and formed 1-aryl-5-amino-1*H*-tetrazoles **(A),** but when EWG was present, then terminal unsubstituted nitrogen underwent cyclization process and formed 5-arylamino-1*H*-tetrazoles **(B)**. The position of the halogen group at ortho position and para position favored the formation of **(B)** and **(A),** respectively, from the consequence of intramolecular hydrogen bonding at *o*-position. Ingenious process, good atom-economy, green-solvent, simple purification are favorable points of this methodology (Scheme **31**).



Scheme (31). Synthesis of arylaminotetrazoles.

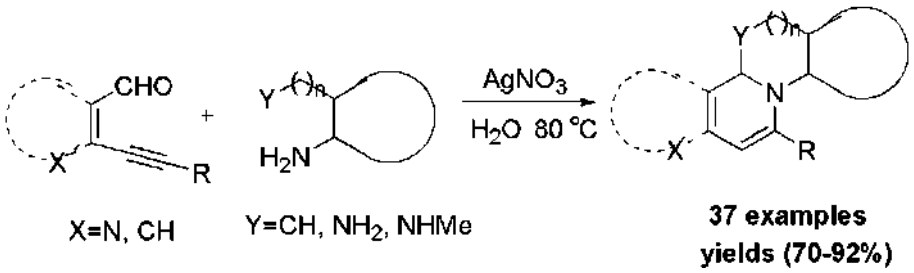
A new ruthenium-based system was found as an efficient catalyst in water for the synthesis of N-heterocycles. $[RuCl_2(p\text{-cymene})]_2$ was synthesized by Ackermann and group and was utilized for C-H/N-O bond generation from the reaction of alkynes and N-methoxybenzamide in the presence of KO_2CMes additives and furnished isoquinolones in moderate to good yields [108]. The kinetic isotope effect (KIE) revealed that carboxylate-assisted ruthenation was the rate-limiting step **(**Scheme **32)**. After successful application of $[RuCl_2(p\text{-cymene})]_2$ as an efficient, robust, and chemoselective catalyst, Ackermann and Lygin employed them for N-substituted indole synthesis *via* oxidative C-H/N-H bond functionalization of anilines with alkynes in the presence of PF_6 additives and water solvent [109] (Scheme **32**).



Scheme (32). Ruthenium-catalyzed synthesis of isoquinolone and indoles.

Das *et al.* discovered an ingenious, facile and indium catalyzed synthesis of N-substituted pyrroles in high yields from 2,5-dimethoxytetrahydrofuran and nitro compounds in HCl at room temperature *via* Paal–Knorr reaction [110].

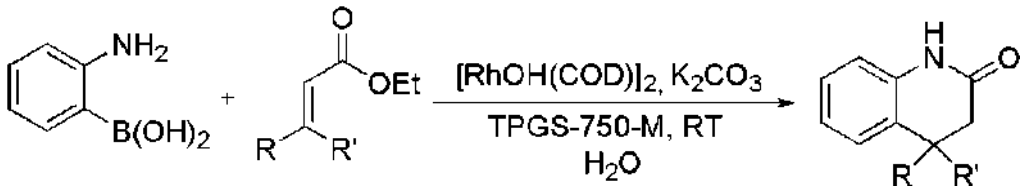
Verma *et al*. discovered a newer, efficient, and regioselective on-water approach for the synthesis of isoquinolines and naphthyridines fused with oxazine from the reaction of amines and ortho-alkynylaldehyde using silver-catalyst at 80 °C in moderate to good yields. Here, the reaction proceeded *via* intermolecular imine formation followed by the intramolecular nucleophilic attack and proton transfer and finally produced 6-endo-dig cyclized fused heterocyclic products [111] (Scheme **33**).



Scheme (33). Silver-catalyzed synthesis of oxazine/benoxazine fused isoquinolines and naphthyridines.

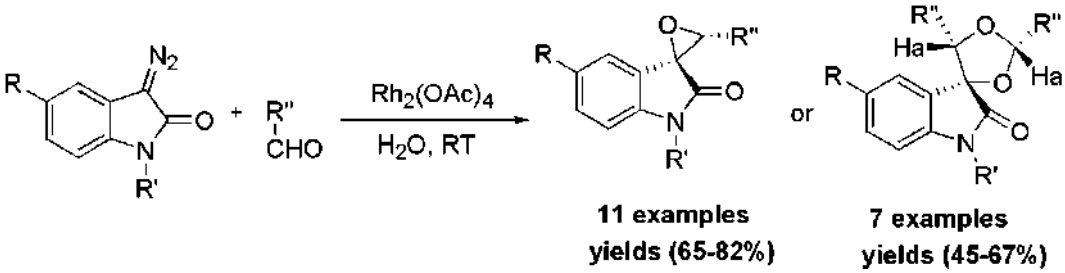
Cocaa and co-workers reported microwave assisted $BiCl_3$ catalyzed [2 + 3] cycloaddition reaction of various nitriles with sodium azide in isopropanol/water (3:1) to synthesize 5-substituted-1*H*-tetrazoles in moderate to good yields [112].

Linsenmeier and Braje introduced a facile pathway for the synthesis of dihydroquinolinone derivatives at ambient temperature from 1,4-addition of α,β-unsaturated esters with 2-aminoboronic acid in $[RhOH(COD)]_2$, K_2CO_3, and TPGS-750-M surfactant. Additionally, the authors also investigated the reaction of substituted boronic acids and α,β-unsaturated esters to evaluate the scope of reaction [113] (Scheme **34**).



Scheme (34). Synthesis of dihydroquinolinones.

Muthusamy and Ramkumar explained diastereoselective 'on-water' $Rh_2(OAc)_4$ catalyzed synthesis of spiroindolo-oxiranes and –dioxolanes from the reaction of diazo amides and various aromatic aldehydes at ambient temperature. Here, the product formation was dependent on the substitution pattern of aldehydes, *i.e.*, in the presence of EWG, carbonyl ylide was formed and ERG's presence commenced dipolar cycloaddition reactions [114] (Scheme **35**).

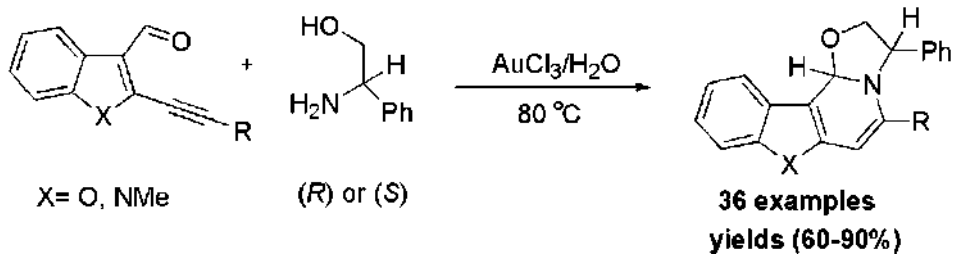


Scheme (35). Rhodium(II)catalyzed synthesis of spiroindolo-oxiranes and –dioxolanes.

CuI/polystyrene-supported pyrrole-2-carbohydrazide(PSP) catalyzed water-assisted cyclization of 2-alkynylaniline derivatives using TBAB (tetrabutylammonium bromide) was disclosed by Song and companions to form indoles with high atom-economy. This heterogeneous catalyst was easily recovered and reusable up to several cycles [115].

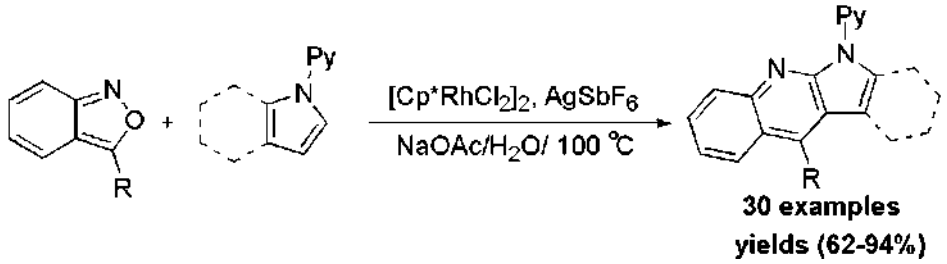
Pal and co-workers reported a simple, one step Au(III)-catalyzed regio- and stereoselective synthesis of benzofurooxazolo pyridines and pyridoindoles fused with oxazolo moiety from the reaction of (S) and (R)-phenylglycinol with o-alkynyl aldehydes in water at 80 °C *via* selective C −N bond generation at more

electrophilic alkynyl carbon [116]. This methodology allowed a vast range of functionality to produce fused heterocyclic system with 6-endo-dig regioselectivity (Scheme **36**).



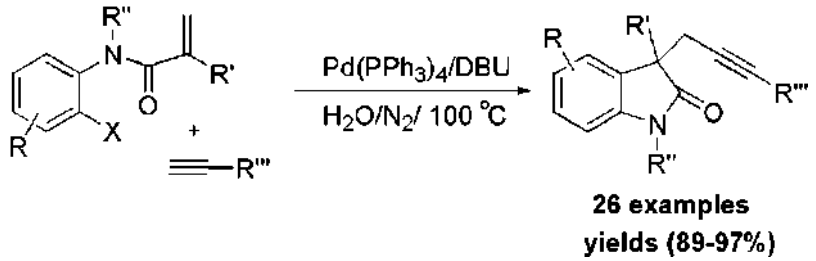
Scheme (36). Regio- and stereoselective synthesis of oxazolofused pyridoindoles and benzofurooxazolo pyridines.

Water-mediated C−H amination/annulation of substituted isoxazoles and indoles using $[Cp^*RhCl_2]_2/AgSbF_6$ catalytic system with NaOAc additive at 100 °C to prepare a wide range of indoloquinoline derivatives with good atom-economy was demonstrated by Shi and Wang [117] (Scheme **37**).



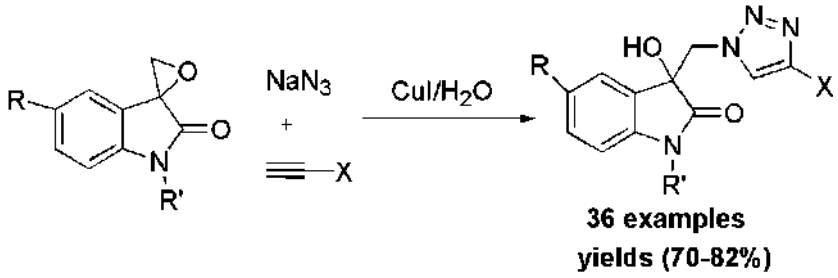
Scheme (37). Rh(III) catalyzed synthesis of indoloquinoline derivatives.

Wang *et al*. designed a domino Heck–Sonogashira reaction between substituted methacrylamide and N-propargylaniline using $Pd(PPh_3)_4$ catalyst, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) base and N_2 in water to synthesize 3-(--aminobut-2-ynyl)oxindole derivatives in excellent yields [118]. These synthesized analogs worked as precursors for the synthesis of a bio-active drug, which was applied as a neurokinin receptor antagonist and 5-HT7 receptor antagonist (Scheme **38**).



Scheme (38). Synthesis of 3-(4-aminobut-2ynyl)oxindole derivatives.

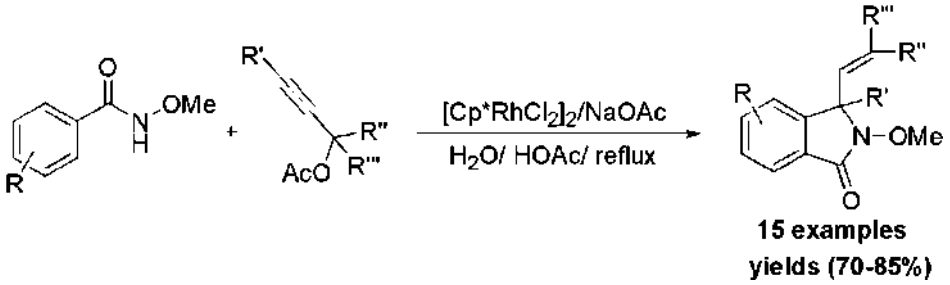
Jadhav *et al.* reported a one-pot MCR of 2-amino pyridine, aromatic carbonyl compounds, and succinamide in AgI, I_2, and water-PEG-400 solvent system under MWI to develop 2-phenylimidazo[1,2-a] quinoline and 2-phenylimidazo[1,--a]pyridine in excellent yields [119]. Keivanloo and group introduced water-assisted one-pot MCR of propargyl alcohol, 3-substituted-2-chloroquinoxalines, and secondary amines in K_2CO_3, sodium dodecyl sulfate (SDS) and $Pd(PPh_3)_2Cl_2$-CuI catalyst to prepare 1,4-disubstituted pyrrolo[1,2-a] quinoxalines *via* Sonogashira coupling/isomerization/intramolecular cyclization/base-induced aromatization [120]. Kumar and companions displayed water-based azidolysis of 1-methylspiro[indoline-3,2′-oxiran]-2-one with NaN_3 and further azide-alkyne cycloaddition with phenylacetylene using CuI catalyst to form 3-hydroxy-1-allyl-3-[(4-aryl/alkyl-1H-1,2,3-triazol-1-yl)methyl]indolin-2-ones with high regioselectivity. Authors envisioned that water decreased the energy barrier and tend the reactant towards forwarding reaction *via* H-bonding [121] (Scheme **39**).



Scheme (39). Copper-catalyzed azide-alkyne cycloaddition reaction.

Hybrid conjugates play an important role in diverse areas like synthetic, pharmaceutical, and industrial, *etc.,* due to their combined and synergistic effects. From this point of view, Wadhwa and the group developed an eco-benign and novel route for the synthesis of thiadiazoloquinazolinone-coumarin hybrids using water as a green medium [122]. One pot-MCR of 1,3-dicarbonyls, 2-oxo-2*H*-chromene-3-carbaldehyde and 5-aryl-1,3,4-thiadiazol-2-amines in the presence of $Bi(NO_3)_3.5H_2O$ in aqueous media under MWI to afford good yields of hybrid

heterocycles *via* Knoevenagel condensation, Michael addition and intramolecular cyclization. Wu and companions discovered an efficient regioselective rhodium-catalyzed synthesis of isoindolin-1-ones from N-methoxybenzamide, 2-alkynylic acetates, and NaOAc base using HOAc in water solvent at 55 °C temperature [123]. After isolation of intermediate, control experiment, and KIE studies, the authors described the plausible reaction mechanism and found that the reaction proceeded *via* C−H activation, allene formation, cyclization, and protonation (Scheme **40**).



Scheme (40). Rhodium-catalyzed synthesis of isoindolin-1-ones.

Banerjee and co-workers designed and synthesized $CuCl_2$ supported graphitic polymeric C_3N_4 (Cu@g-C_3N_4) and utilized them in on-water regioselective [2+3] cycloaddition of sodium azide and substituted nitroolefins/alkynes to produce NH-1,2,3-triazoles in excellent yields [124]. Cu@g-C_3N_4 worked as an efficient and robust catalyst with wide functional group applicability and recyclability up to ten cycles without considerable loss of catalytic activity.

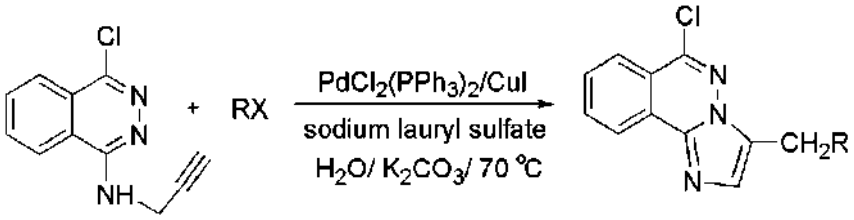
A library of substituted quinazolinones was prepared from the catalytic condensation of various benzaldehydes and *o*-bromobenzonitrile in the presence of $CuCl_2$ catalyst, Cs_2CO_3 base, and L-proline in an aqueous medium by Liu *et al.* [125]. The authors also explored the versatility of this methodology by variation in the starting material like *o*-aminobenzamide, *o*-bromobenzamide, and *o*-aminobenzonitrile. Dihydroquinazolinones were also synthesized *via* the protection of N_2. Liu *et al.* demonstrated a facile route for the synthesis of succinimide using unsupported nanoporous nickel material (NiNPore) in water from succinic anhydride and $NH_3 \cdot H_2O$ with high efficiency [126]. Additionally, glutaric anhydride (GA) was also converted into glutarimide with a 71% yield using this procedure. Here, the NiNPore catalyst has good catalytic activity with reusability up to three runs.

Bakherad and co-workers disclosed a novel and efficient route for the preparation of 1-aryl-4-(2-phenylethynyl) [1, 2, 4]triazolo[4,3-a]-quinoxalines in good yields *via* sonogashira coupling [127]. 2,3-dichloroquinoxaline, phenylacetylene,

bromine, hydrazine hydrate, and different aldehydes were refluxed in the presence of K_2CO_3, Pd/C catalyst, and water at 70 °C to furnish the desired products.

After this success, in 2018, a range of phthalazine-1,4-dione linked with 1,2,3-triazole was synthesized by Bakherad *et al.* and screened for *in vitro* antibacterial activity *against P. aeruginosa, B. subtilis, and M. luteus* and their in-silico molecular docking study was also revealed for their bio-activity [128]. The azide-alkyne cycloaddition reaction of aromatic azides with mono and di-substituted 2,3-dihydro-phthalazine-1,4-dione using $Cu(OAc)_2$ catalyst, sodium ascorbate, and metformine additives in an aqueous medium at 80 °C displayed excellent yields. *In vitro* study results exhibited that some of the compounds showed good potency for antibacterial activity against the standard drug, tetracycline, and the bio-activity of molecules was also influenced with substitution pattern of different functional groups.

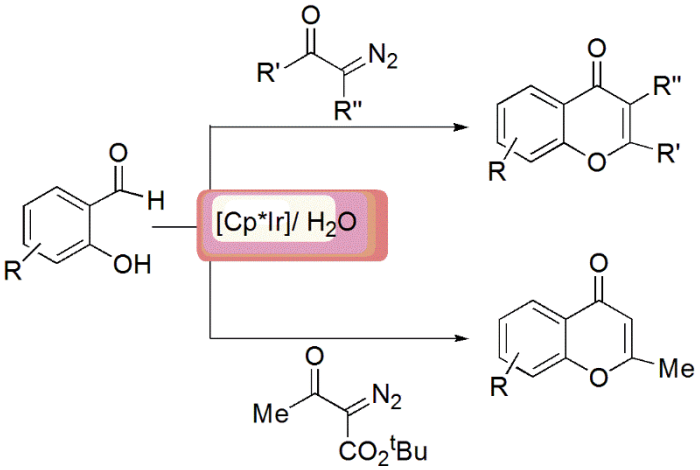
Bakherad and groups demonstrated that $PdCl_2(PPh_3)_2$ could be utilized for the synthesis of antibacterial heterocycles, 3-aryl-substituted 6-chloroimidazo[2, 1-a]phthalazines in water [129]. 1-chloro-4-propargylaminophthalazine and aryl iodides/bromides were refluxed in the presence of $PdCl_2(PPh_3)_2$/CuI catalyst, sodium lauryl sulfate surfactant, and K_2CO_3 base in a water solvent to obtain high yields of products. The *in vitro* anti-microbial study against bacterial strains *B. subtilis* and *M. luteus* (gram +ve) and *P. aeruginosa* (gram -ve) results revealed that most of the compounds displayed promising activity as compared to reference drug penicillin in liquid dilution method (Scheme **41**).



Scheme (41). Synthesis of substituted 6-chloroimidazo[2, 1-a]phthalazines.

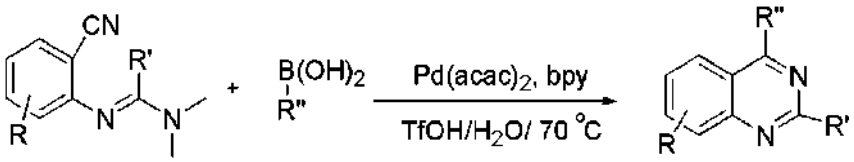
Copper-catalyzed and water-mediated one-pot MCR of 3-(2-halophenyl--3-oxopropane, aq. NH_3 and different aldehydes in the presence of additive L-proline and base K_2CO_3, to develop a library of 4-quinolone derivatives in moderate to good yields, was developed by Gore *et al.* [130]. After various control experiments, the authors concluded that the formation of desirable products was completed *via* aldol condensation and intramolecular Michael addition. The authors also demonstrated the synthetic utility of synthesized products *via* the formation of BQCA drugs and oxolinic acid. Ir(III)-catalyzed C −H bond functionalization *via* annulation of diazoketones and salicylaldehydes in

water was explained by Debbarma and co-workers to produce substituted chromones. This synthesis was also explored through decarboxylation using tert-butyl diazoester [131] (Scheme **42**).



Scheme (42). Cp*Ir(III)-catalyzed synthesis of chromones.

Yuan *et al.* discovered a facile and high yielded on-water palladium-catalyzed synthesis of substituted 4-arylquinazolines from the condensation of benzonitriles and arylboronic acids using bpy(2,2'-bipyridine) ligands and TfOH additive [132]. For further exploration, the authors derivatized some of the synthesized compounds, which were found highly selective PI3Kδ inhibitors against inflammatory diseases previously. According to possible reaction mechanism, initially, arylboronic acid and palladium catalyst formed arylpalladium species, which displayed carbopalladation of a cyano group and imine protonation and generated a palladium ketamine complex, followed by intramolecular nucleophilic addition and finally aromatization gave 4-arylquinazolines (Scheme **43**).



Scheme (43). Synthesis of 4-arylquinazolines.

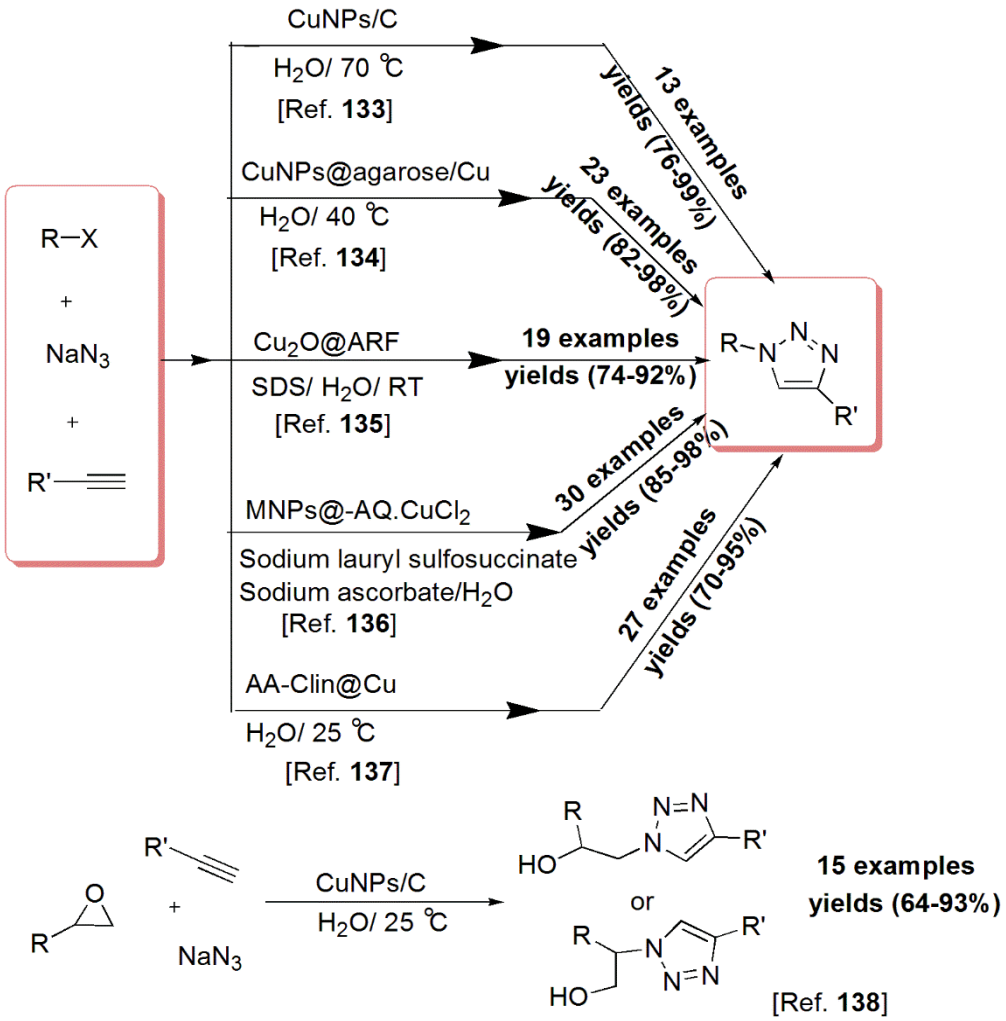
Nanocatalyst Supported Reactions

Alonso and group prepared activated carbon-supported copper nanoparticles (CuNPs/C) and utilized them for water-based Huisgen 1,3-dipolar cycloaddition of alkynes with organic halide/diazonium salt/epoxide/aniline/alkenes as

precursors of sodium azide at elevated temperature and furnished 1,2,3-triazoles in high yields [133]. Versatility on substrate selection, heterogeneous reusable catalyst, excellent yields without tedious work-up expressed the eco-friendliness and sustainability of the present method.

Agarose-supported Cu nanoparticles also displayed similar results for the synthesis of 1,2,3-triazoles and were reported by Gholinejad *et al.* [134]. In this method, a wide scope of substrates with excellent yields demonstrated the generality of the reaction and the catalyst was also reusable up to five consecutive cycles without significant loss of activity. Similarly, Ghosh and companions also prepared unique Amberlite resin formate immobilized Cu_2O nanoparticle (Cu_2O@ARF) and applied it as a robust catalyst for the synthesis of 1,2,3-triazoles using SDS as a phase transfer catalyst in water media at room temperature [135]. Simultaneously, Mogaddam and companions discovered a new magnetic nano-composite MNPs@8-AQ.$CuCl_2$ for the catalysis of the above-mentioned protocol with SLS (sodium lauryl sulfosuccinate) and sodium ascorbate in water medium at room temperature [136]. This catalyst was highly efficient because of the production of high yields in shorter reaction time and high recyclability compared to the previous method. From the success of previous work, in 2019, Gholinejad and group introduced a new acid-activated clinochlore supported copper nanoparticles (AA-Clin@Cu) as an eco-friendly catalyst for the synthesis of 1,2,3-triazoles under mild conditions [137]. This catalyst was highly efficient, reusable, gave excellent yields, and supported a wide range of substituents for the product formation. In continuation of previous water-mediated 1,2,3-triazoles synthesis, Alonso and group explored their research using substituted epoxides/alkynes and CuNPs/C catalyst to prepare β-hydroxy-1,2-3-triazoles with high atom-economy [138]. Regio- and stereochemistry of the products were evaluated from X-ray crystallographic analyzes and NMR spectra (Scheme **44**).

Copper oxide nanocatalyst was employed by Ahmadi *et al.* in a one-pot three-component synthesis of 4-amino-5-pyrimidine carbonitriles in aqueous conditions from N-unsubstituted amidines, aldehydes, and malononitrile at room temperature [139]. Using water solvent, the yields of the product was significantly higher as compared to other organic solvents *viz.* CH_2Cl_2, THF, EtOH, MeCN, and so on. The remarkable features of this protocol are a facile method, easy accessibility, inexpensive, eco-benign, excellent yields in short reaction time, simple purification and recoverable catalyst *etc.*



Scheme (44). Various nano-particle catalyzed synthesis of substituted 1,2,3-triazoles.

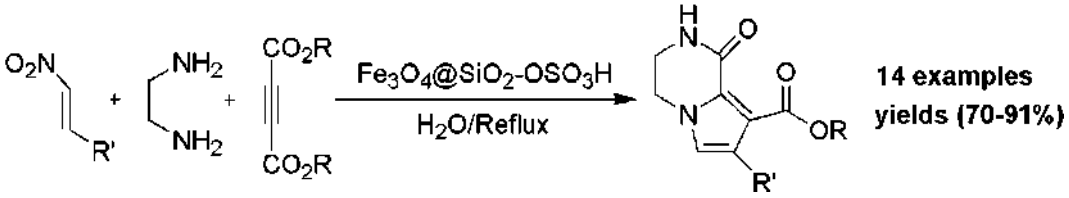
High biological and pharmaceutical activities of pyrimido[4,5-b]quinolines derivatives inspired Edjlali and group to develop an eco-friendly "in water" synthetic approach [140]. For this purpose, cellulose supported Fe_3O_4 nano-particles were used as a heterogeneous reusable catalyst in one-pot multi-component reaction of 6-amino-1,3-dimethyluracil and dimedone with a range of aldehydes and furnished high yields of pyrimido[4,5-b]quinolines in water-media.

An efficient, inexpensive and reusable catalyst ZnO nanoparticle promoted the synthesis of a library of dihydropyrimidinones/thiones from ethyl acetoacetate, urea/thiourea, and various aldehydes in high yields and was displayed by Hassanpoura and co-authors [141]. This heterogeneous catalyst was reusable up to

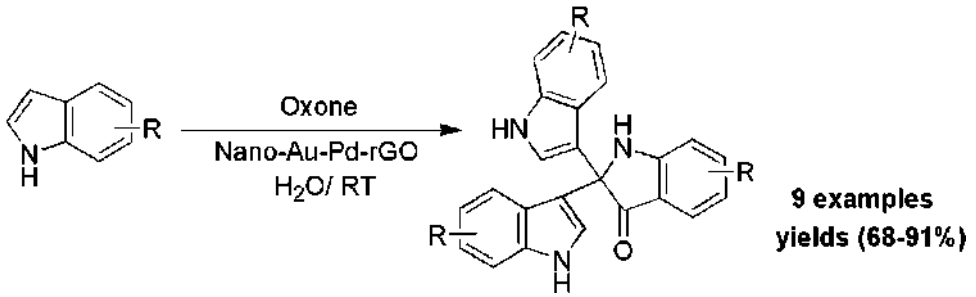
three runs and the product was formed in a short reaction time without using the long-workup process. Sharma *et al.* discovered a novel $NiFe_2O_4$ catalyzed water-mediated one-pot three-component synthesis of pyrimidine-thiazole and screened them for the anticancer activity against different cancer cell lines MCF-7, HeLa, and A375 using erlotinib, as standard drug and also studied their interaction with different proteins *via in silico* molecular docking studies [142]. The reaction between various aldehydes, thiosemicarbazide, and N-(3-(2-bromo-2-(2-chloro pyrimidin-4-yl)acetyl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide, afforded regio-selective multi-functionalized pyrimidine-thiazole derivatives. The bio-activity of molecules was also validated from the results of *in-silico* studies and ADME analysis.

Rostami and Shiri developed Fe_3O_4@SiO_2-OSO_3H magnetic nanocomposites, well-characterized from FT-IR, VSM, SEM, EDX, and XRD spectral analysis and their catalytic efficiency were also evaluated for the synthesis of pyrrolo [1,2-*a*]pyrazines. One-pot multi-component condensation of β-nitrostyrene, dialkylacetylenedicarboxylates and ethylenediamine in water using 0.06 gm of the catalyst was used to afford a high yield of products [143]. The catalyst was simply recovered from the external magnet and reused up to five consecutive cycles without significant loss in catalytic activity (Scheme **45**).

Gohain *et al.* discovered the "on-water" assisted synthetic route for 2,2-bis (indoly-3-yl)indoline-3-ones using two nanocomposites Au/Pd-rGO and Au–Pd-rGO and also compared their catalytic efficiency [144]. 3C-functionalized oxindoles were prepared from N–H protection-free indole using both catalysts in water and oxone at ambient temperature *via* oxidative homo trimerization and furnished good yields. Au–Pd-rGO produced high yields taking more time compared to Au/Pd-rGO. The key step of the reaction was *in situ* generation of isatin, which was more electrophilic and easily showed nucleophilic reaction with indole moiety (Scheme **46**).



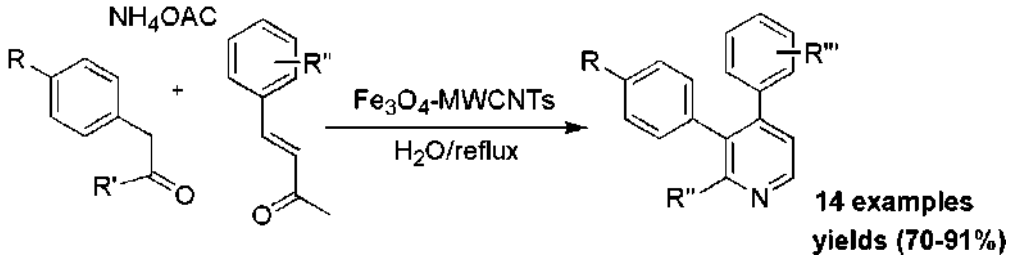
Scheme (45). Synthesis of pyrolo[1,2-a]pyrazines using nano-catalyst.



Scheme (46). Synthesis of 2,2-bis(indol-3-yl)indolin-3-ones.

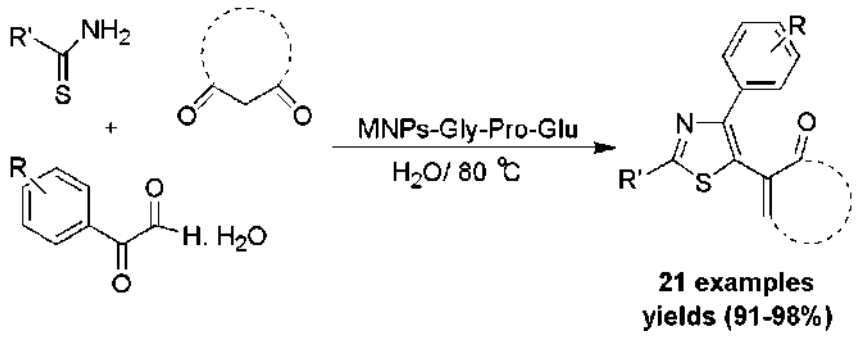
Very recently, Hemmat and companions reported the viability of $CoFe_2O_4$@SiO_2@Co(III) salen complex as a heterogeneous catalyst for the preparation of quinoline derivatives in water *via* a coupling reaction of 2-aminobenzophenone and varied carbonyl compounds to furnish high yields with chemoselectivity [145]. This protocol has unique characteristics *viz.* novel catalysis, facile process, simple workup, easy catalyst recovery from the magnet and displayed insignificant loss in catalytic activity after five runs.

Basavegowda and co-workers prepared Fe_3O_4-multiwalled carbon nanotubes (Fe_3O_4−MWCNTs) from the root extract of *Astragalus membranaceus* and applied it as a robust, eco-friendly and magnetically recyclable catalyst for water-mediated condensation of cinnamaldehyde, ketone and ammonium acetate at room temperature to synthesize poly-functionalized pyridines in high yields [146] (Scheme **47**).



Scheme (47). Synthesis of polyfunctionalizedpyridines derivatives.

Arabpoor *et al.* immobilized Gly-Pro-Glu (tripeptide) on silica-encapsulated γ-Fe_2O_3 magnetic nanoparticles and employed them for one-pot three component synthesis of tri-substituted 1,3-thiazole using thiobenzamides, cyclic-1,--dicarbonyls and arylglyoxals as starting materials and water as a green solvent [147]. Excellent yields, less reaction time, convenient workup, mild conditions, effortless recovery, and ten times reusability of catalyst validates the catalytic activity and efficiency of magnetic nanocatalyst (Scheme **48**).

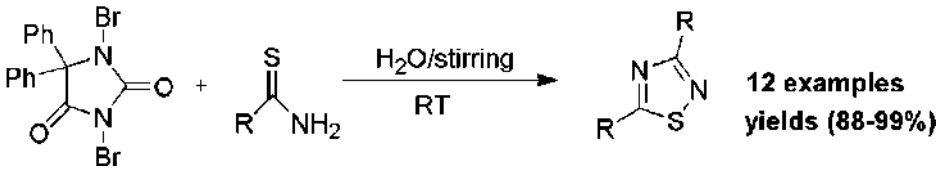


Scheme (48). Synthesis of trisubstituted 1,3-thiazole derivatives.

Catalyst-free Reactions

Singal and coauthors introduced an efficient and facile water-mediated synthesis of 3,4-dihydropyrimidinones in various conditions *viz.* heating, ultrasound, and MWI from the reaction of urea, β-dicarbonyl compounds and a range of aldehydes to afford excellent yields [148]. Here, water played a significant role *via* hydrogen bonding and increased the rate of reaction. The authors compared the effect of various conditions on the rate of reaction and yields and found that MWI displayed the highest yields within two minutes, whereas ultrasound and conventional heating took more time and gave comparatively low yields.

Wide studies have been carried out over many years in the field of thioamides. An approach toward this area was developed by Boeini and group from thiobenzamides and N,N'-dibromophenytoin in water *via* oxidative cyclization without the use of any catalyst and toxic reagents to obtain excellent yields of 3,5-diaryl-1,2,4-thiadiazoles within 5-10 minutes and without bromination at aromatic ring [149] (Scheme **49**).



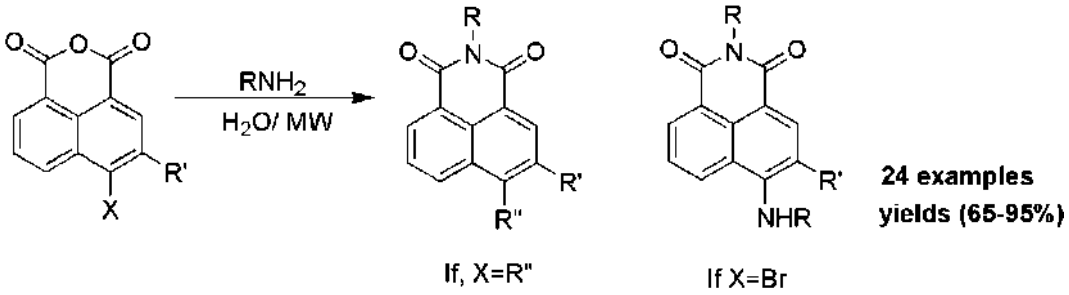
Scheme (49). Synthesis of 3,5-diaryl-1,2,4-thiadiazoles.

Panda and Jain reported a facile and eco-benign synthesis for developing a range of 2-aryl benzimidazoles from the reaction of various aldehydes and *o*-phenylenediamines in water with high atom economy [150]. Panda *et al.* introduced an on-water-based synthesis of spiro-indoles from 1*H*-indol-2,3-dione, various range of aromatic amines and thioglycolic acid at room temperature under

MW irradiation *via* generation of Schiff base, which was confirmed by ^{1}H and ^{13}C NMR spectral analysis [151]. The additional advantages of this method are the synthesis of new compounds, excellent yields in mild conditions, avoid the use of toxic reagents, removal of waste generation, and side-product formation.

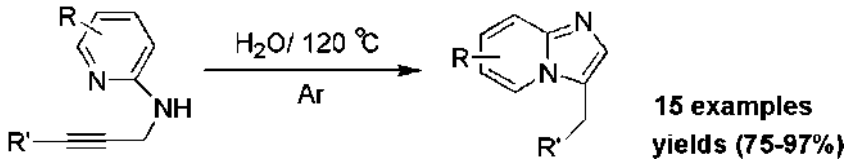
Azizi and group developed a new and rapid one-pot three-component ultrasound-assisted synthesis of dithiocarbamates in water in moderate to high yields from primary/secondary amines, unsaturated carbonyl compounds, or alkyl halides with carbon disulfide. This method has an economical and eco-benign approach because of its low-cost, high selectivity, use of ultrasound irradiations, catalyst-free, toxic reagent free synthesis [152]. Pramanik and co-authors demonstrated an "on-water" synthesis of Hantzsch dihydropyridines from readily available ammonium acetate, aldehydes, and ethyl acetoacetate in good yields with high purity along with circumventing the use of organic solvents and harsh reagents and conditions [153].

Water mediated condensation of primary amine and substituted 1,8-naphthalic anhydride under MW irradiation to prepare substituted 1,8-naphthalimide derivatives in good yields with short reaction time *via* simple workup was reported by Zhang *et al.* [154] (Scheme **50**).



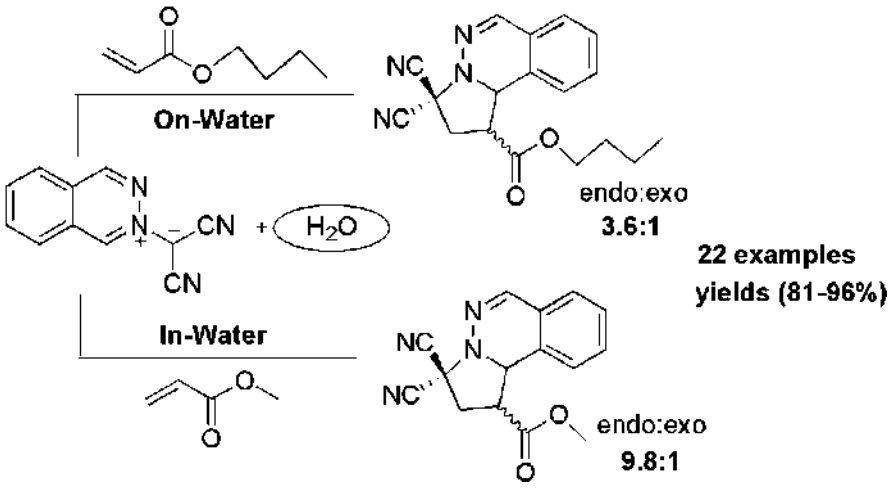
Scheme (50). Synthesis of N-and N-,4-substituted 1,8-napthalimides.

For the first time, in 2013, Chandramohan and co-workers developed a novel, organic-solvent and catalyst-free synthesis of imidazo[1,2-a]pyridines from intramolecular hydroamination [155]. In water medium, substituted N-(prop-2-yn-1-yl)pyridin-2-amines got transformed in corresponding imidazo[1,2-a]pyridines in argon environment *via* 5-exo-dig cyclization and 1,3-prototropic shift. Despite this, the use of thiazole substrate did not give positive results and was decomposed during the reaction (Scheme **51**).



Scheme (51). Synthesis of imidazo[1,2-a]pyridines.

In 1981, Breslow and companions explained the Diels−Alder cycloaddition reaction of cyclopentadiene and dienophiles in the presence of water and also evaluated endo: exo ratios of products [156]. After that, Butler *et al.* studied the Huisgen cycloaddition reaction of phthalazinium-2-dicyanomethanide with various electron-poor and electron rich dipolarophiles like substituted styrene, vinyl ketones and alkyl acrylates in both "in water" and "on-water" conditions [157]. Here, the authors displayed the switching and the border of "in water" and "on-water" reaction in reference to Huisgen cycloaddition and revealed that this phenomenon was controlled by solubility, H-bonding and hydrophobic character of reaction mixture. When hydrophobic characters are reduced, the reaction moved from "in-water" to "on-water" and sometimes got reversed. Generally, "in-water" reaction gave a high endo/exo ratio as compared to "on-water" and displayed endo-effect. The stereochemistry of isomers was demonstrated from NMR, NOE difference spectra (NOEDS), DEPT, and COSY (Scheme **52**).

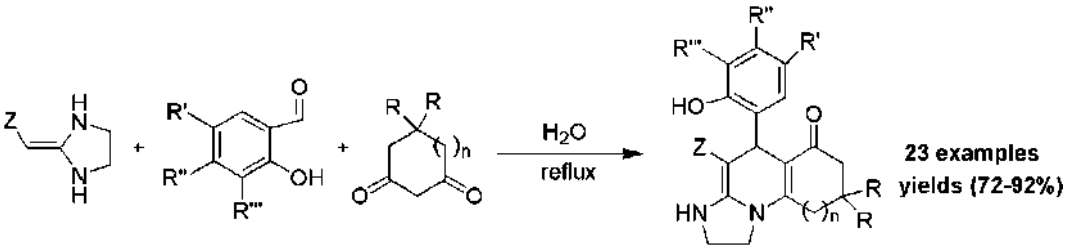


Scheme (52). Water-based Huisgen cycloaddition reactions.

Yang *et al.* demonstrated a novel and simple catalyst-free strategy for the synthesis of a library of 1,4- dihydropyridines from the stirring of sealed vessels, charged with nitrogen and filled with aldehydes and β-keto esters, ammonium salts $(NH_4)_2CO_3$ and water steam at 70-75 °C to produce excellent yields *via*

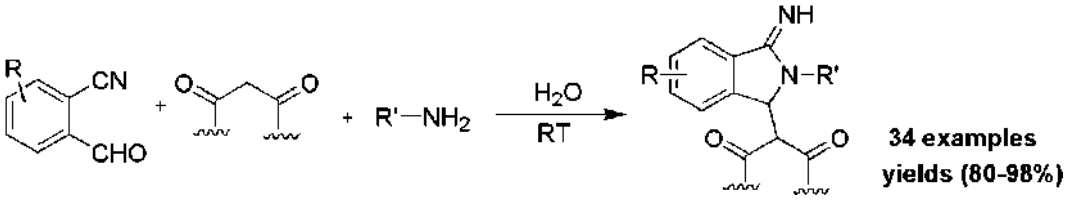
Hantzsch reaction [158]. Using different ammonium salts, the authors revealed the importance of buffered pH of the medium. Operation simplicity, cost-efficient, facile workup, high reusability of the solvent system are remarkable features of this protocol. Akbaslar and companions introduced an eco-friendly, catalyst-free, water-mediated Paal Knorr pyrrole synthesis using hexa-2,5-dione and a primary amine, and achieved excellent yields of N-substituted 2,5-dimethyl pyrrole [159]. Through variations in the substrate, the authors found that aliphatic amines gave more yields as compared to aromatic amines.

Ma *et al*. presented a one-pot three-component cascade reaction to develop a range of fused polycyclic 1,4-dihydropyridine compounds using 1,3-cyclohexanedione, heterocyclic ketene aminals, and salicylaldehyde as substrates with water as a green solvent and found moderate to good yields [160]. According to reaction mechanism initially, Knoevenagel condensation between 1,3-cyclohexanedione and salicylaldehyde took place and formed an intermediate, which reacted with ketene aminals *via* aza-ene reaction followed by fast imine-enamine tautomerization, which resulted in the formation of a new intermediate. Furthermore, the intermediate displayed N-cyclization, and finally, dehydration furnished the desired product (Scheme **53**).



Scheme (53). Synthesis of polycyclic 1,4-dihydropyridine derivatives.

A library of 3-arylsulfinylindoles was prepared under ambient conditions from substituted indoles and arylsulfinic acid in water *via* electrophilic sulfenylation in good to excellent yields by Miao and companions [161]. According to the investigation, it was found that the reaction proceeded *via* sulfinyl cation. Facile process, mild conditions, high functionality, avert the use of toxic additives and solvents are plus points of the present protocol. Shen and co-authors reported an efficient water-mediated one-pot three-component synthesis of isoindolin-1-imine by the reaction of active methylene compounds, amine and 2-cyanobenzaldehyde at room temperature with high atom economy [162]. Here, 5,5-dimethylcyclohexane-1,3-dione, Meldrum's acid, 1,3-cyclohexanedione and 1,3-dimethylbarbituric acid were used as active methylene compounds, which displayed the versatility of this method and excellent yields were obtained using a simple purification process (Scheme **54**).



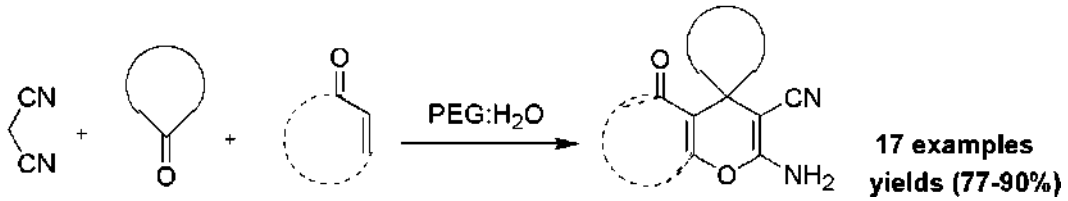
Scheme (54). Synthesis of isoindole-1-imine derivatives.

Bozdoğan *et al.* demonstrated a facile and economical synthesis of n-alkyl and n-aryl succinimides from the stirring of succinic acid and primary amines in the water at 100 °C [163]. The authors also studied the effect of different solvents on the rate of reaction; hence water proved best under model conditions. The superior characteristics of the present method are simple process, catalyst-free, ample substrate scope, eco-friendly, excellent yields, and effortless work-up as compared to previous researches.

Zhu and companions demonstrated an efficient "in water" synthesis of quinazolinones by anthranilamides and 1,1-dichloro-2-nitroethene at 80 °C [164]. According to the investigation of the reaction mechanism, anthranilamides displayed double nucleophilic substitution reaction to 1,1-dichloro-2-nitroethene with the removal of HCl and further isomerized to produce the desired final product. High functionalities, good yields, and simple purification are additional merits of this methodology.

Singla *et al*. reported an eco-friendly MW-assisted synthesis of substituted thiazolidin-4-ones by the reaction of dimethylacetylenedicarboxylate (DMAD) and diverse thiosemicarbazone in water to produce adequate to good yields [165]. The authors also proceeded with this synthesis in thermal heating and found low yields in high reaction time as compared to MW process.

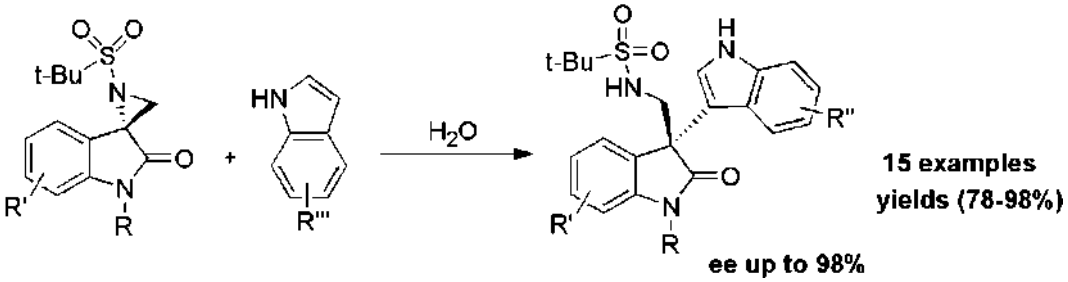
The synthesis of 4-phenyl-4*H*-pyrans, spirochromenes, and dihydropyrano[3,2-c]chromenes in good yields from the reaction of malononitrile, aromatic aldehydes and 4-hydroxy coumarin/cyclic 1,3-dione in PEG-600:H_2O solvent system was explained by Survase and companions [166]. The authors studied the impact of different solvents like toluene, DMF, EtOH, ethylene glycol, glycerol, PEG-600:H_2O *etc.,* on the rate of reaction and yields, however, PEG-600:H_2O displayed the best results. This one-pot MCR has simplicity, clean reaction, recyclability of reaction media, and produced the products in moderate to excellent yields (Scheme **55**).



Scheme (55). Synthesis of 4H-pyran derivatives under catalyst-free conditions.

Further, Survase *et al.* reported a facile one-pot water-based synthesis of two different moieties, first, pyrano[2,3-c]pyrazole by aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate and another, pyrimido[1,2-*a*]benzimidazole synthesized from the reaction aldehydes, malononitrile and benzimidazole in PEG-400:water solvent system to obtain high yields [167]. The solvent system was easily recovered and reused after three runs, and the products obtained were purified using easy crystallization techniques without the use of column chromatography.

Hajra and co-authors displayed on-water regio- and stereospecific synthesis of unsymmetrical bisindoles *via* ring-opening reaction of spiro aziridineoxindoles and indoles with excellent yields and high enantioselectivity [168]. Here, the authors gave detailed information of the molecular mechanism and H-bonding of different solvents, which activated the substrate in the reaction medium and accelerated the rate of reaction. Other solvents did not give promising results for the enantiopure synthesis of bisindoles (Scheme **56**).

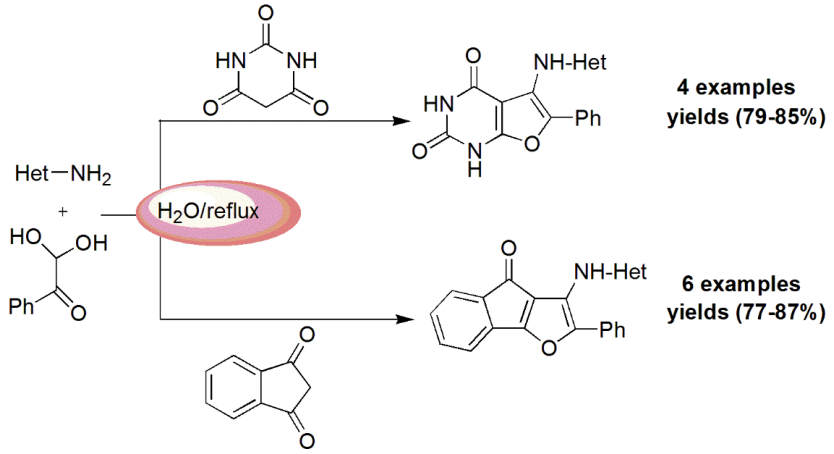


Scheme (56). Synthesis of unsymmetrical 3,3'-bisindoles with high enantioselectivity.

A novel, catalyst-free, and green-solvent mediated pseudo-six component one-pot synthesis of diversified pyrimidines from barbituric acid, aldehydes and anilines with various functionalities *via* simple stirring at room temperature was developed by Brahmachari *et al.* [169]. In this protocol, the authors prepared fifty derivatives of pyrimidines and generated six new bonds, *i.e.,* four C-C bonds and two C-N bonds including σ and π-bonds. For the validation of the reaction mechanism, intermediate enamine and chalcone were isolated and characterized. Simple

procedure, low-cost substrate, high yields, gram-scale synthesis, simple purification, low E-factor, and high atom-economy made this protocol green and eco-friendly.

Recently, indeno-fused furan core has gained much interest owing to their immense bio-applications in various diseases. Considering their potential in diverse areas, Khoeiniha and co-authors disclosed the synthetic route for furo[2,3-d]pyrimidines and 4H-indeno[1,2-b]furan-4-ones from the reaction of phenylglyoxal monohydrate, 1,3-indandione/barbituric acid and 2-aminopyridines using water and obtained the products in high yields [170]. According to the investigation of probable mechanism, initially, aldol condensation of 1,3-indandione, phenylglyoxal monohydrate produced an intermediate which underwent Michael addition and provided another intermediate followed by intramolecular cyclization and finally, dehydration furnished desired product. This simple procedure produced high yields in a short span of time, avoiding long and tiresome purification methods (Scheme **57**).

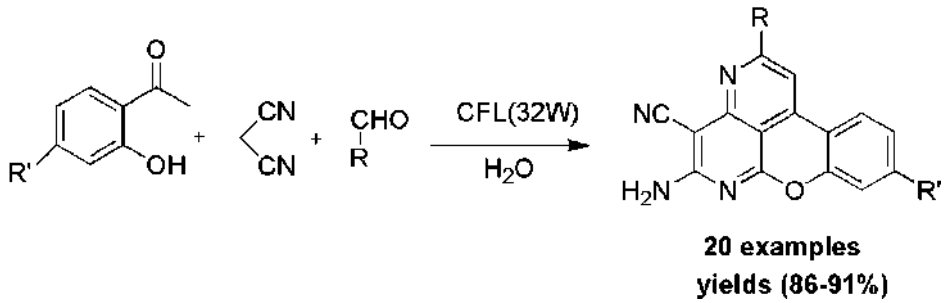


Scheme (57). Synthesis of 4H-indeno[1,2-b]furan-4-one and furo[2,3-d]pyrimidine derivatives.

Zeng and companions demonstrated "on-water" one-pot four-component synthesis of pyrazolo [3,4-b] pyridinones and screened their activity against the influenza virus (H5N1 pseudovirus) [171]. The condensation of substituted benzoyl acetonitriles, various benzaldehydes, hydrazine hydrate/1-phenyl hydrazine, 5,5-dimethylcyclohexane-1,3-dione/Meldrum acid using PEG-2000/H_2O as a reaction medium took place to furnish the products in moderate to high yields. The presence of EWG on benzaldehydes and benzoyl acetonitriles increased the yield of products and hydrazine hydrate also gave better results compared to phenylhydrazine. Here, the authors displayed the importance of the PEG/H_2O system in mechanistic ways *i.e.* at high temperature, water could be

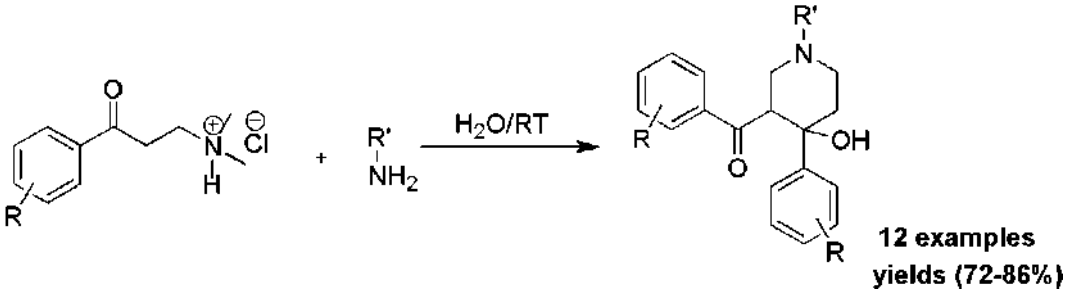
ionized and generated more H^+ ions which penetrated between two immiscible layers and PEG helped them *via* increasing the number of collisions in the reaction. The superior characteristics of this methodology are the novel process, formation of five new bonds and two new rings, reaction-medium was recyclable and reusable up to five times, *etc.*

Mohammadi and Shaterian introduced visible light assisted one-pot multi-component synthesis of chromeno [4,3,2-de] [1, 6]naphthyridines by malono-nitrile, 2'-dihydroxyacetophenones with a range of aldehydes in water to obtain excellent yields [172]. Other organic solvents like EtOH, DCM, THF, CH_3CN, CH_2Cl_2 did not give satisfactory yields compared to H_2O. The reaction proceeded *via* photochemical activation of malononitrile-benzaldehyde conjugate, radical generation, tautomerization, and intramolecular cyclization. Facile and economical process, effortless work-up, cost-effectiveness, greener conditions and good purity made this protocol sustainable and eco-benign (Scheme **58**).



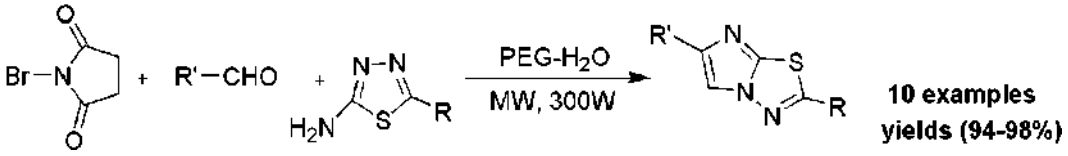
Scheme (58). Synthesis of chromeno [4,3,2-de] [1, 6]naphthyridine derivatives.

The synthesis of disubstituted 5-aminopyrimidines in high yields by the reaction of vinyl azides and urea/thiourea using water and microwave irradiation was presented by Dehbi and group [173]. Clean and simple procedure, inexpensive, high conversion, good functional group tolerance, avoids the use of column-chromatography, and less reaction time are the advantages of this method. Jagadale and coworkers developed a novel and simple protocol for the synthesis of piperidinols from Mannich base and primary amine using water and also screened them for anthelmintic activity against Indian earthworm *Pheretima posthuma* [174]. The *in-vitro* studies showed that most of the synthesized compounds showed high anthelmintic activity against reference drug albendazole (Scheme **59**).



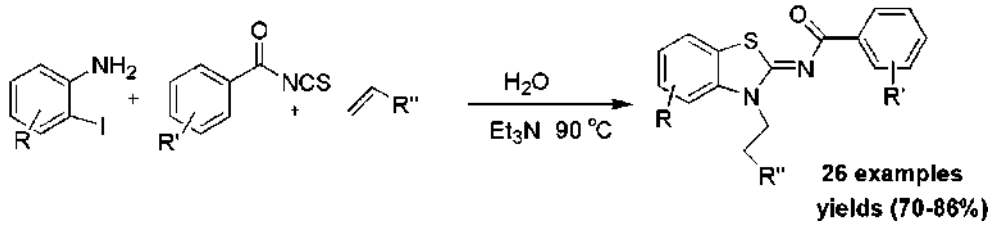
Scheme (59). Synthesis of piperidinols.

A reliable, ingenious one-pot MW assisted synthesis of benzo[d]imidazo[2,1-b] thiazoles from the reaction of NBS (N-bromosuccinimide), 5(biphenyl-4-yl)-1, 3,4-thiadiazol-2-amine and a range of ketones in the presence of PEG-400 and water at 80–85 °C with high atom-economy was demonstrated by Wagare *et al*. [175]. PEG-400 and water behaved as high efficient solvents in contrast to other organic solvents (Scheme **60**).



Scheme (60). Synthesis of substituted imidazo[2,1-b] [1, 3, 4]thiadiazole.

Saini and co-authors reported a catalyst-free and base-supported one-pot multi-component synthesis of benzothiazolylidene-benzamides by acrylates, aroylisothiocyanates, and ortho-iodoanilines in a water reaction medium with good yields and high regioselectivity [176]. Here, the mechanism showed that initially, urea intermediate was formed, then intramolecular nucleophilic reaction occurred with iodobenzene, and finally, S_NAr reaction led to the formation of products. To increase the scope of the present methodology, benzo[d]thiazolyl was produced using benzoyl isothiocyanate and 2-iodoaniline *via* initial amidation and further aromatic nucleophilic substitution at ambient conditions (Scheme **61**).

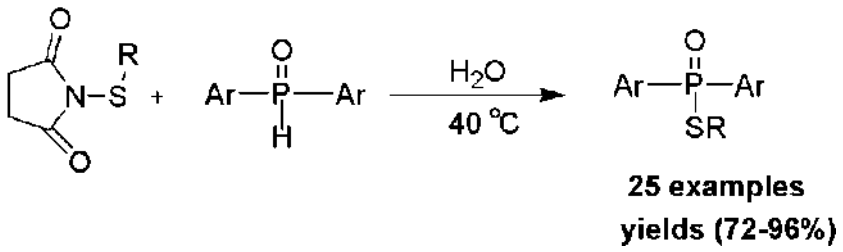


Scheme (61). Synthesis of benzothiazolylidene derivatives.

In 2019, Ghadiri and coauthors reported one-pot three-component reaction of substituted barbituric acid, N-alkyl-1-(methylthio)-2-nitroethenamine and isatin in water to produce spiro[indoline-3,5′-pyrano[2,3-d]pyrimidine] in good yields *via* a combination of Knoevenagel condensation, Michael addition, and o-cyclization process [177].

Vesamicol, its analogs, and β-blockers have high biological potential and have attracted active researchers towards this area. Therefore, Agarwal and group developed a convenient, eco-friendly chemo-selective protocol for the synthesis of Vesamicol analogs from different epoxides *viz.* cyclohexene oxide/1,4-dihydr--2,3-epoxynaphthalene/styrene oxide/1,2-epoxy-3-phenoxypropane with 4-phenyl piperidine in the water at room temperature in excellent yields [178]. Here, water worked as a key component that displayed dual behavior, as a catalyst and a solvent. This approach eluded the use of toxic reagents and catalysts, removed chemical waste generation with high selectivity of products, 100% atom economy and also applied gram scale synthesis, which made this approach green and sustainable.

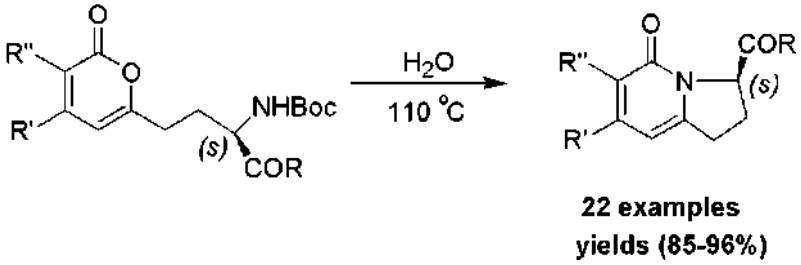
Wang and companions reported a simple, metal-free, and water-mediated P-S coupling reaction of *N*-(aryl/alkylthio)succinimide with H-phosphonate esters/ diarylphosphines and H-phosphine oxides at 40 °C in excellent yields [179]. This reaction was also carried out in the presence of varied catalysts like CuI, $Cu(OAc)_2$, $Ni(COD)_2$ with different bases, t-BuOK, Na, K_2CO_3, Cs_2CO_3, K_3PO_4, Et_3N, *etc.* and considerable yields were not obtained in the presence of catalyst and base. The reaction mechanism most likely involved free radical reactions and nucleophilic substitution. Moreover, this method has wide functional group tolerance, catalyst-free green synthesis and capable for gram-scale synthesis (Scheme **62**).



Scheme (62). Synthesis of thiophoshinates, thiophosphates, and thiophosphinites.

Disadee and companions investigated a water-mediated, one-pot, catalyst-free cascade annulation of 2-pyrenes for producing a chiral center bearing bicyclic 2-pyridines [180]. This process involved the combination of various transformations such as N-Boc deprotection, cyclic enamine generation, isomerization,

esterification, and lactamization to produce peptidomimetic core comprised bicyclic 2-pyridines. After applying diverse substituents, two different conditions were revealed and the authors found some selectivity in decarboxylation and esterification reaction profile. Here, α-carbon of the amino acid displayed retention of chirality. This method removed the use of acidic, basic and metallic reagents, and special arrangements as compared to previous methods (Scheme **63**).



Scheme (63). Synthesis of bicyclic 2-pyridones with retention of chirality.

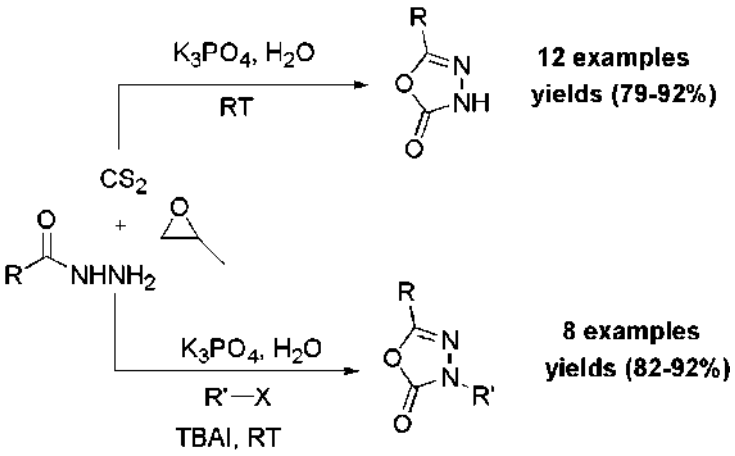
Recently, Isomura *et al.* discovered Chennat-type synthesis of 4-aryl-1-4-dihydropyridine-3,5-dicarboxylic acid dimethyl esters in water medium from the reaction of aldehydes, amine, and methyl propiolate and furnished the products in moderate to good yields [181]. The mechanistic study displayed the role of hydrogen-bonding network, which increased the rate of –OH elimination to obtain intermediate, which provided the final product.

Miscellaneous Synthesis

Salt-mediated Reactions

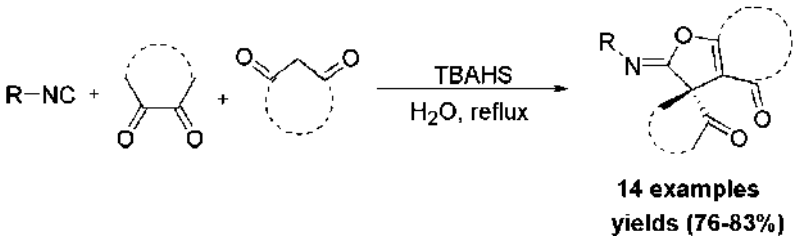
A simple one-step eco-benign synthesis of 1,5-benzothiazepines from 2-aminothiophenol and 1,3-diaryl-2-propenones using TAATB (tetrabutylammoni-umtribromide) catalyst in aqueous solution was reported by Yan and co-authors [182].

Yan *et al*. enclosed water-based K_3PO_4 mediated one-pot multicomponent synthesis of mono and di-substituted-1,3,4-oxadiazole-2-(3*H*)-one from the reaction of propylene oxide, acylhydrazines, carbon disulfide, and organic halides to obtain excellent yields at ambient conditions *via* formation of intermediate β-hydroxysulfide [183] (Scheme **64**).



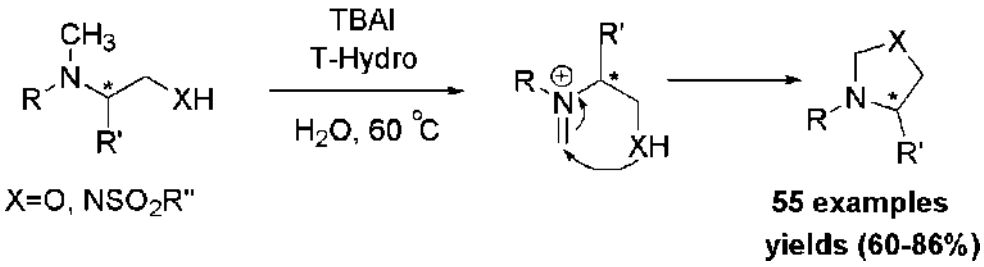
Scheme (64). Synthesis of substituted-1,3,4-oxadiazole-2(3*H*)-one.

Condensation of isocyanides, 1,3-diones and cyclic carbonyl compounds using tetrabutylammoniumhydrogensulfate (TBAHS) in aqueous solution to afford spiroiminolactone derivatives *via* one-pot MCR was discovered by Safaei and companions. Simple procedure, high yields, cheap and efficient catalyst, and good atom-economy are plus points of the present method [184] (Scheme **65**).



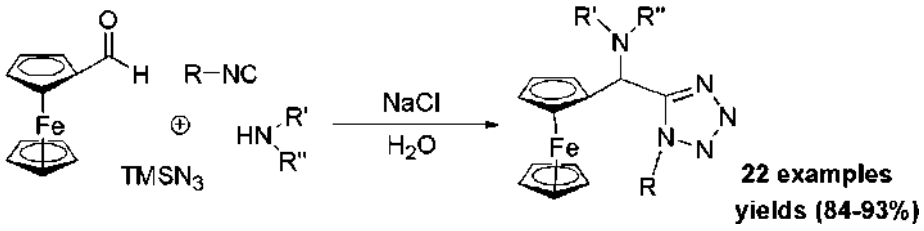
Scheme (65). Synthesis of spiroiminolactone derivative.

Samanta *et al.* explored an efficient on-water synthesis of substituted quinoxalines from 1,2-diamines and 1,2-diketones in NaCl at 95 °C. In present methodology, a library of quinoxaline derivatives was prepared in excellent yields using easy purification [185]. Satheesh and coauthors demonstrated an on water and tetrabutylammonium iodide catalyzed C(sp^3)−H functionalization/C−O/C−N bond generation using 1,2-diamines/1,2-aminoalcohols in the presence of tert-butyl hydroperoxide oxidant (T-Hydro) and produced imidazolidines/oxazolidines in good yields through regioselective oxidative cross-coupling and formation of a radical intermediate. Enantiospecific products were obtained in the case of optically active reagents [186] (Scheme **66**).



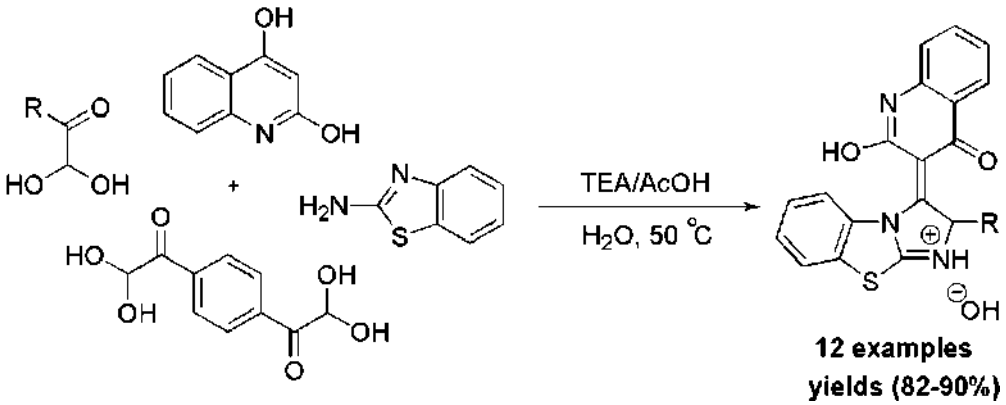
Scheme (66). Synthesis of oxazolidines and imidazolidines.

Combined effect of NaCl and water on Ugi-Azide reaction for the synthesis of 1,5-disubstituted tetrazoles from the reaction of aldehyde, azidotrimethylsilanes, isocyanides and amines *via* formation of kosmotropes was studied by Dandia *et al*. Among all the derivatives, some of them revealed high potency for inhibition of β–hematin and also underwent different transformations [187] (Scheme **67**).



Scheme (67). Synthesis of 1,5-disubstituted tetrazoles.

Isomura and co-authors devised an efficient and facile synthesis of 1,4-dihydropyridine from the reaction of methyl propiolate and amine salt, ammonium acetate in a water medium to afford moderate yields. The reaction proceeded *via* Michael addition and dimer formation, where free amine and liberated proton acted as nucleophile and electrophile respectively [188]. Etiv and group designed and synthesized a novel route for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole-1-ium hydroxide from 2-aminobenzothiazole, quinoline-2,4-diol and arylglyoxals using TEA/AcOH catalyst in aqueous medium and simple purification afforded high yields *via* Knoevenagel condensation, Baldwin's 5-exo-trig cyclization and keto-enol rearrangement [189] (Scheme **68**).



Scheme (68). Synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole-1-ium hydroxide.

A novel DABCO based tetracationic acidic organic salt was prepared and utilized for the condensation of aldehydes with active methylene compounds (dimedone/1,3-dimethylbarbituric acid) and synthesized tetraketones and Knoevenagel adducts by ZiyaeiHalimehjani *et al*. [190]. This catalyst has two $–SO_3H$ groups in the cationic part and four HSO_4^- groups in the anionic part of the structure and displayed various special features, high-acidity, air stability, environment-friendly, which can be helpful for near future reactions.

Others

Beheshtiha and co-workers demonstrated an eco-friendly, simple, and efficient ionic liquid assisted synthesis of benzimidazoles and quinoxalines, using *o*-phenylenediamine with aromatic aldehydes and 1,2- diaminoaren in the water at room temperature [191]. Here, ionic liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ is an inexpensive, eco-benign, and reusable catalyst possessing high reactivity and gave excellent yields in short reaction time. Wan and coworkers applied PTC $(n\text{-}Bu)_4NBr$ for the condensation of tosyl hydrazide and varied α,β-unsaturated carbonyl compounds with NaOH in an aqueous medium to afford a high yield of 1-*H*-pyrazoles [192].

Ghosh and Mandal introduced sodium dodecyl sulfate (SDS) catalyzed water-based quinoxaline derivatives in moderate to high yields from 1,2-diamines and α–bromoketones [193]. A general mechanism for SDS mediated synthesis showed that SDS and water made micellar solution and both hydrophobic reactants came into the central hydrophobic core of micelle and displayed condensation and *in situ* aromatization to furnish final product. Here, water increased the rate of reaction *via* increasing the solubility of the catalyst compared to organic solvents.

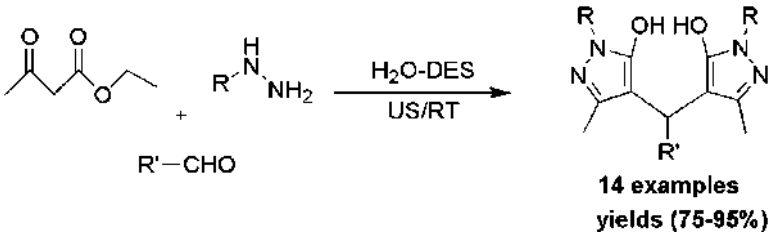
Zhao and co-authors demonstrated a facile synthesis of nitro heteroaromatics from nitrogen-rich heterocyclic amines in a water medium *via* oxidation by potassium peroxymonosulfate [194]. Here, some important compounds, such as 5-amino-3-nitro-1*H*-1,2,4-triazole and 3,4,5-trinitro-1*H*-pyrazole, were also produced. The facile and safe method, inexpensive reagents, mild conditions are the salient features of the present protocol compared to the previous method.

Protein collagen of Caspian Sea's swim bladders, Isinglass, was used for the efficient and sustainable synthesis of spiroacenaphthylenes and spirooxindoles and was reported by Javanshir and companions [195]. Condensation of 1,3-dicarbonyl and activated methylene compounds with acenaphthenequinone/isatin in the water at room temperature furnished moderate to excellent yields in less reaction time *via* one-pot MCR. High group functionality, easily available reagents, simple purification, high purity, short reaction time, and recyclable and green catalyst are the important features of this methodology.

Konwar and coauthors utilized a waste material, egg-shell powder, for the efficient synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles from azide-alkyne cycloaddition reaction of benzyl azide and phenylacetylene in $CuSO_4{\cdot}5H_2O$ in an aqueous medium, avoiding the use of extra-base/additive/ligands at ambient temperature [196]. Lee and Cheon demonstrated the synthesis of 2-substituted quinolines from 2-aminochalcones catalyzed by benzylamine in an aqueous solution. A wide range of functionality, facile workup, inexpensive and reusable catalyst are additional advantages of the present protocol [197]. Parvizi *et al.* displayed a novel Lewis acid-surfactant catalyzed water-based synthesis of bis-aminothiazoles from the reaction of *α*-bromo derivatives of bis-acetophenones with thiourea using $Fe(SD)_3$ *via* ultrasound radiations and also screened their antibacterial activity against four bacterial strains, including *E. coli*, *B. subtilis*, *M. luteus*, and *P. aeruginosa* [198].

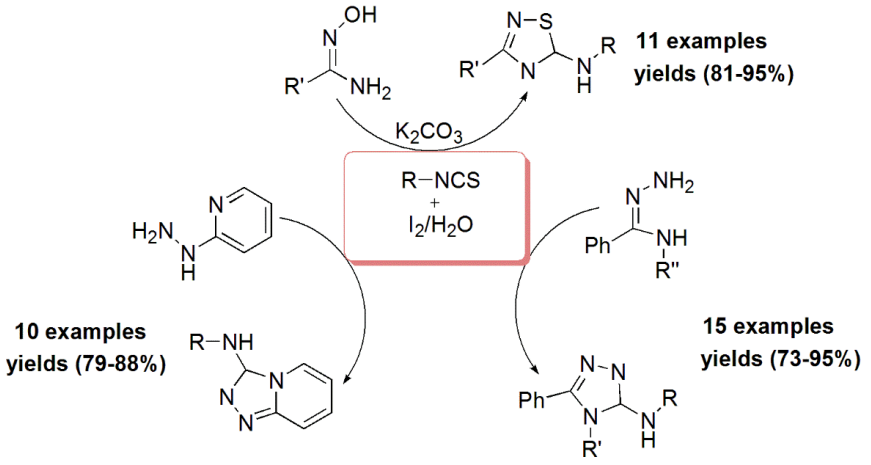
Another approach using anionic surfactants sodium dioctyl sulfosuccinate (SDOSS) for the synthesis of tetrahydropyridines *via* Mannich reaction was disclosed by Parikh *et al.* [199]. One-pot MCR of amine aldehydes and 1,3-dicarbonyl compounds in water using SDOSS catalyst resulted in the formation of microreactors to accelerate the rate of reaction. The effect of various organic solvents and other surfactants were also studied and afforded lower yields, which revealed the significance of water and SDOSS surfactant. In 2017, Zhang and companions reported sunlight promoted photocatalyst-free synthesis of pyrazoles from α, β-unsaturated hydrazines, MeCN, and K_2CO_3 in water through direct irradiation of N- centered anion [200].

In 2018, Kamble *et al.* presented a one-pot water-mediated and deep eutectic solvent (ChCl:tartaric acid) catalyzed Knorr pyrazole synthesis of 4,4-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s. The reaction of phenylhydrazine and ethyl acetoacetate with various aldehydes took place using ultrasound irradiations (US) at ambient temperature to obtain the products in excellent yields in short reaction time *via* Knovenagel-Michael reaction [201]. Greener techniques, wide applicability, mild reaction environment, gram-scale synthesis, and an efficient and reusable catalyst made this protocol eco-benign (Scheme **69**).



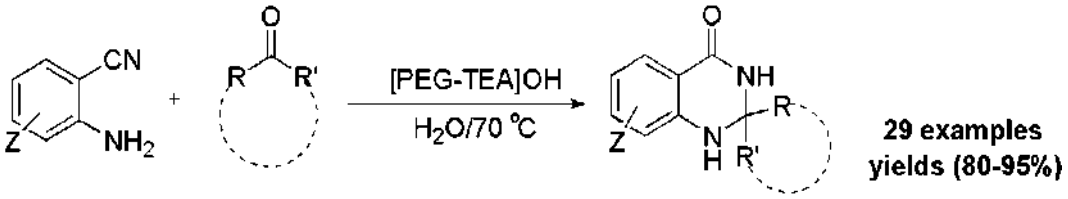
Scheme (69). Synthesis of 4,4-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s derivatives.

Jatangi and coauthors developed a strategy for C-N and N-S bond formation between isothiocyanates and substituted amines in water *via* molecular iodine mediated oxidation and produced substituted triazoles and thiadiazoles with high atom-economy [202]. When amidrazone and 2-hydrazinopyridine were used with isothiocyantes as substrates at room temperature in I_2 and water, substituted triazoles were formed. While isothiocyanates reacted with amidoximes in I_2 and water using K_2CO_3 at 60 °C and produced respective thiadiazoles. This protocol allowed a wide range of functional group tolerance with high yields and gram-scale applicability to synthesize a library of heterocyclic compounds (Scheme **70**).



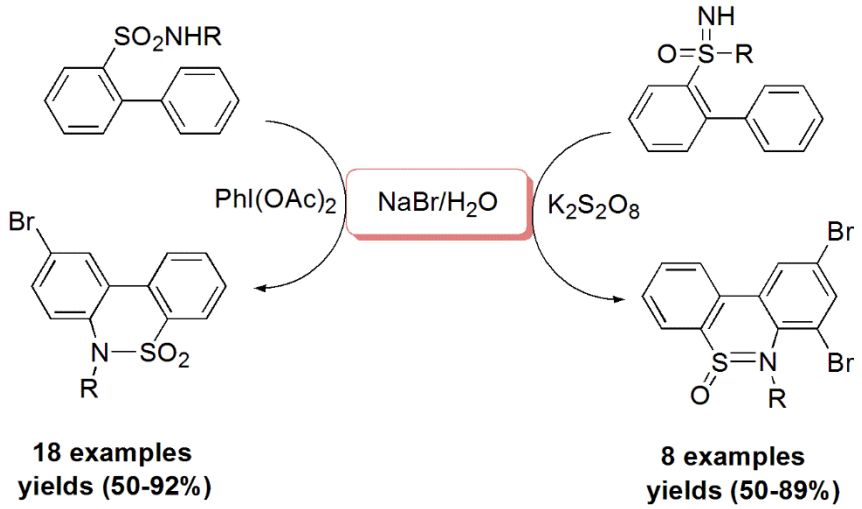
Scheme (70). Synthesis of polysubstituted triazoles and thiadiazoles.

A novel surfactant based catalyst polyethylene glycol-bonded tetraethyl ammonium hydroxide ([PEG-TEA]OH) was synthesized by Safaei and co-authors and was employed for the water-based catalytic preparation of 2,3-dihydroquinazolin-4(1*H*)-ones from varied carbonyl compounds and 2-aminobenzonitrile in high yields in short reaction time [203]. This efficient and biodegradable catalyst was easily recoverable and reused up to six runs (Scheme **71**).



Scheme (71). Synthesis of 2,3-dihydroquinazolin-4(1 H)-ones *via* surfactant based catalyst.

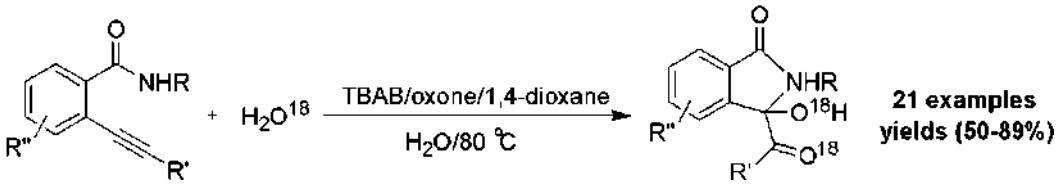
Li and group reported a catalyst-free water-assisted synthesis of bromobenzothiazines using N-methyl-2-biphenylsulfonamide, readily available bromo source, NaBr and oxidant, $PhI(OAc)_2$ /$K_2S_2O_8$ *via* tandem C-H amination and site-selective bromination [204]. Here, the reaction proceeded through intermediate BrOAc and the products were purified using a simple procedure (Scheme **72**).



Scheme (72). Synthesis of bromobenzothiazines derivatives.

Liu *et al*. demonstrated an efficient water-based synthesis of 1,4-dioxane facilitated 3-hydroxyl isoindolin-1-ones from 2-alkynylbenzamide in the presence

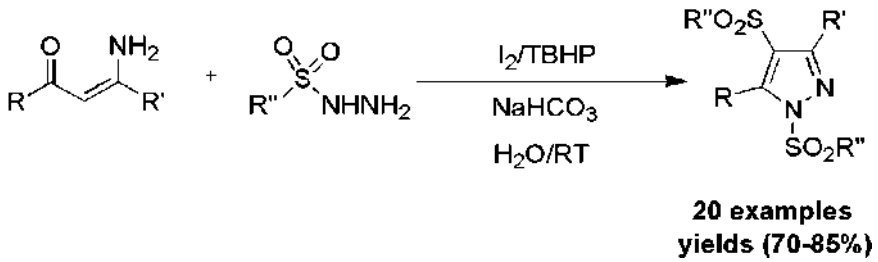
of TBAB and oxone *via* hydroxyl hydrative aza-cyclization with broad functionalities [205]. After various control experiments, the authors revealed the possible mechanism, which followed regioselective brominative 5-exo-dig aza-cyclization/ bromohydration/ hydrolysis (Scheme **73**).



Scheme (73). Synthesis of 3-hydroxylisoindolin-1-ones.

Xu and co-authors discovered regioselective DMSO/H_2O_2 assisted reaction of various ketones and 2-mercaptobenzimidazoles using HCl in aqueous solution to prepare benzoimidazo[2,1-b] thiazoles *via* formation of carbon radical [206].

A range of substituted pyrazoles was synthesized from the cascade reaction of sulfonyl hydrazines and enaminones using I_2/TBHP and $NaHCO_3$ through C-H sulfonylation/pyrazole annulations by Guo *et al.* [207]. Isotope labeling studies validated that the C-N bond of enaminone was cleaved during the reaction and also validated that the amino group worked as a hydrogen bond donor and supported the reaction in the aqueous medium (Scheme **74**).



Scheme (74). Synthesis of substituted pyrazole derivatives.

Jain and co-authors reported an ecobenign regioselective Cu(I) –NaCl catalyzed azide-alkyne cycloaddition reaction of terminal alkynes and benzyl azides/coumarin azides under ultrasonication to furnish fluorogenic 1,4-disubstituted triazoles at room temperature *via* formation of kosmotropes and increasing the interaction of reactants with high TOF(turn over frequency) 88.18 min^{-1} and TON(turn-over number) 4850 [208].

CONCLUSION AND OUTLOOK

In the present chapter, we have summarized various water-mediated heterocyclic syntheses of the past ten years. In the current scenario, researchers are adhering towards green and sustainable synthesis *via* diminishing the adverse effects of organic reactions. Water is the green and highly abundant solvent of our planet with special chemical and physical properties like high heat capacity, non-toxicity, small size, high surface tension, high polarity, and low compressibility, *etc.*, which are responsible for making it viable for diversified organic reactions. The article has been focused on water-promoted heterocyclic transformations in different environments and the reactions are categorized on the basis of catalysis *viz.* organocatalyzed, metal-catalyzed synthesis, nano-particle catalyzed, metal-catalyzed, bio-catalyzed, catalyst-free synthesis, and other fields of catalysis. Most of the reactions involved the formation of C-O, C-N, C=O, C=S, and C=N bonds with multiple ring generation in one-pot MCR. Moreover, these heterocycles play an important role in different areas of our everyday life, like agriculture, food industries, polymers, drug designing, and so on. A mild and safe environment, inexpensive synthesis, high yields, excellent selectivity, less waste-generation, facile separation of catalyst, and reusable reaction media are the benefits of water-based heterocyclic reactions. Therefore, from the concern of economic, greener, safe and sustainable synthesis, water plays a momentous role as a solvent for a vast array of reactions.

However, a closer look at the synthetic outcomes has displayed that a detailed insight of the mechanism, thermodynamics, and kinetics of water-mediated transformations are urgently required to disclose numerous facts and concepts. Researchers should urge for in-depth study of different aspects of water for improving the basic understanding of different reactions. Moreover, researchers should also find out the presence of other solvents, surfactants, ligands, and additives to control the progress of the reaction. Concerning these issues, it seems that the area of organic-synthesis in water is still immature and a lot of research is still awaited to demonstrate the role of water in varied special cases. It is hoped that our chapter shall put an invincible contribution for promoting and designing newer synthetic approaches to develop multifarious applicable molecules in the eco-benign environment.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 2

Ionic Liquid Based Polyoxometalates as Functionalized Organic-Inorganic Hybrid Materials for Catalytic Organic Reactions

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Abstract: Functionalized organic-inorganic hybrids of ionic liquids (ILs) with Keggin polyoxometalate (POM) anions of heteropolyacids have received considerable attention in the catalytic study as homogeneous/heterogeneous catalysts owing to their combined unique structural flexibility of the POM anions and tunable behavior imparted by the ionic liquids to the organic-inorganic hybrid of POMs (IL-POM). This includes enhancement of thermal and chemical stability, acidity, surface activity, redox properties, *etc.* The attachment of Brønsted acidic sites such as -COOH or $–SO_3H$ on organic cations of the hybrid materials provides a strong acidic character that can make them appropriate for the replacement of non-recyclable liquid Brønsted acid catalysts in organic reactions. Hydrophobicity, reusability, recyclability, and productivity of these materials certainly satisfy the need for advanced organic synthesis. A large number of designable target-oriented hybrids have been studied as recyclable homogeneous/heterogeneous catalytic systems to explore their industrial values for oxidation and acid-catalyzed organic reactions. This chapter gives a brief introduction to the development of acidic ionic liquid-based POMs hybrid material with varied organic cations tethered with Brønsted acidic sites and their beneficial effects in catalytic organic reactions. The content of this report may provide enormous scope for the development of industrial-scale organic processes based on the IL-POMs hybrid catalysts.

Keywords: Brønsted acidic, Functionalized, IL-POMs, Organic-inorganic hybrid, Organic reaction, POMs.

INTRODUCTION

Polyoxometalates (POMs) and Their Structural Significance

"Polyoxometalates" can be defined as discrete anionic metal-oxygen clusters [1] of oxo metal polyhedra of MO_x (x = 5, 6) as basic construction unit where M re-

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presents early transition metals (M) in their high oxidation states (*e.g.,* W, Mo, V, Nb, Ta) and also partly substituted other metals (*e.g.*, Al, Ti, Cr, Mn, Fe, Co, Ni, Zn, Zr, Ru, Pd, Ln, *etc.*) [2 - 4]. Incorporation of the heteroatom in the anionic metal-oxygen clusters of polyoxometalates generates heteropolyacids (HPAs) in association with proton as their cation. The significance of POMs is observed from their diverse structural variation of polyhedral clusters with unique properties in terms of thermal stabilities, Brønsted acidities, nucleophilicity, crystalline nature, excellent redox behavior, and solubility in polar solvents, *etc.* The structural modification of the POMs framework can be possible in the presence of organic moieties. The unification of varied inorganic and organic parts at the molecular level produces a diverse type of organic-inorganic hybrids with provision for variation of the required properties. It thus furnishes new opportunities for designing target-specific hybrid material. The nature of the organic part may be biostructures such as enzymes, proteins, amino acids, or other functionalized organic molecules that undergo immobilization on the inorganic part through physical or chemical interactions to get the organic-inorganic hybrid with advanced properties of both the components. For example, Zara *et al.* introduced functional organic-inorganic hybrid nanoflowers (FNFs) of immobilized enzymes using proteins/enzymes as the organic parts and Cu^{2+} as the inorganic part in a phosphate-buffered saline solution with remarkable activities and stabilities as compared to free and conventionally immobilized enzymes [5]. From then onwards, a number of protein/enzymes containing flower-shaped organic-inorganic hybrid nanostructures have been developed as biomaterials that take advantage of nanomaterials in terms of both functional and structural availability. This offers new routes for improving the biological functions of enzymes and expands their applications in areas such as biosensors, bioanalytical devices, and industrial biocatalysis [6 - 16].

In the case of organic-inorganic hybrids of POMs, a large number of ionic liquids-based materials have been developed to get target specific systems involving incorporation of different organic cations from ionic liquids to the anionic clusters of POMs with added advantages of enhanced hydrophobic nature, rising solubility in nonpolar solvent, higher thermal and chemical stabilities, increasing Brønsted acidic strength, modification of redox properties, *etc*., [17 - 19]. These ionic liquid-based hybrids of POMs are designable and flexible enough to tune with the diverse physicochemical properties of ionic liquids through variation of organic cations, which deal in multiple ways to introduce different functionality in the POMs hybrid. The limited numbers of inorganic cations, mainly H^+, Na^+, K^+, Cs^+, $NH^{4+,}$ Ag^+, *etc*., are less likely to undergo any modification. Polyhedral framework in POMs has the ability of artificial tuning based on their structural variation, which instigates nature like acidity, basicity, redox stability, and chirality. Several classical structural types of POM anions

such as Keggin, Wells–Dawson, Lindqvist, Anderson–Evans, Weakley, Finke, Silverton, Stranberg, *etc*., can be used for the same [20]. Among them, Keggin-, Dawson- and Lindqvist-type species have earned a special place in POM chemistry as they function as excellent candidates for the multistep elaboration of POM based materials. The Keggin type structures are the most desirable structures in catalysis due to their unique stability and they have been broadly studied for decades (Fig. **1**) [21].

The tuned properties of POMs have been extensively explored in various areas (Fig. **2**), including catalysis, medicine, materials science, nanotechnology, molecular magnetism and photochemistry, *etc*. [22 - 34].

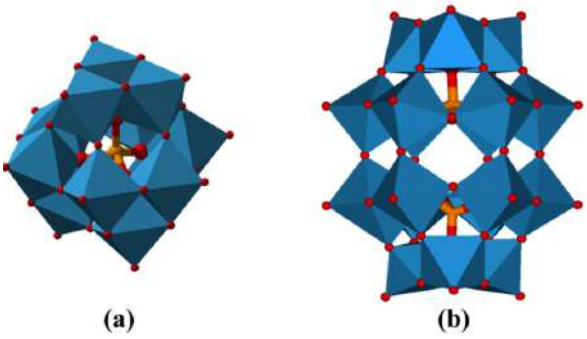


Fig. (1). (a) Keggin structure ($XM_{12}O_{40}^{n-}$) & **(b)** Dawson structure ($X_2M_{18}O_{62}^{n-}$).

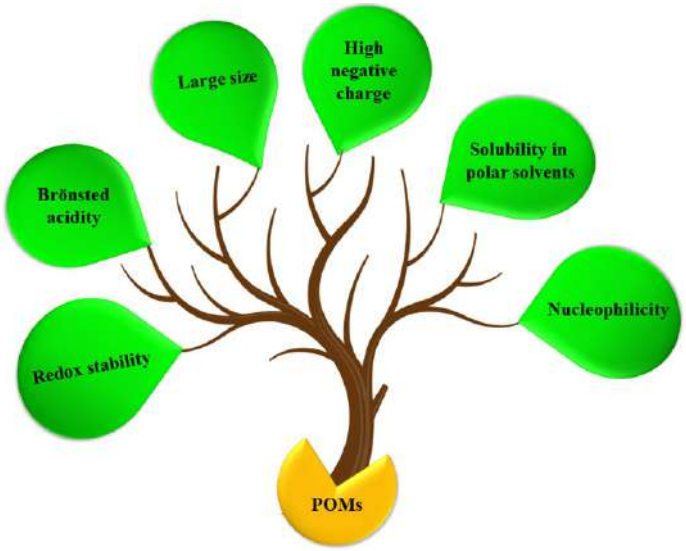


Fig. (2). Properties of POMs.

Katsoulis *et al.* (1998) published one review article including patent literature and uses of the POM in different applications like coatings, analytical chemistry, processing radioactive waste, separations, sorbents of gases, membranes, sensors, dyes/pigments, electrooptics, electrochemistry/electrodes, capacitors, dopants in non-conductive polymers, dopants in conductive polymers, dopants in sol-gel matrixes, cation exchangers, flammability control, bleaching of paper pulp, clinical analysis, food chemistry other than catalysis and medicine [35].

Ionic Liquids Based Functionalized POMs

Based on their ion-pair composition, ionic liquids (ILs) own diverse physical properties such as viscosity, thermal stability, vapor pressure, non-flammability, *etc.* and therefore, most of the ionic liquids have been studied as excellent homogeneous catalytic systems with greater catalytic ability and efficiency in the field of organic synthesis [22 - 24]. Many heterogeneous catalytic systems have been developed to improve the thermal, air, and water sensitivity of the ILs using specific predefined designs or the modified ones [25 - 27]. Thus, a vast array of IL-based catalysts has been growing since the last few decades and extending its feasibility through the unlimited scopes they possess. Modification of POMs to functionalized POMs using ionic liquids has been studied extensively to reduce solubility in polar solvents, and control the use of redox properties and acidic sites. A combination of remarkably active polyoxometalate anions with ionic liquids results in very stable organic cation-based POM salt, which could be used in all the three types of catalytic processes mentioned in Fig. (**3**).

Detailed literature study reveals the development of functionalized POMs involving task-specific ionic liquids and their use to achieve the target with utmost efficiency. As an outcome of the concept of organic-inorganic hybrid, POMs have been utilized to synthesize new class of task-specific ionic liquid-based POM salts by pairing of anionic POM with or without functional group tethered organic cations [36]. Enhanced Brønsted-acidic character of these ionic salts may be acquired from the presence of Brønsted acidic functional groups (*e.g.*-COOH, -SO_3H) with the organic cation of hybrid POMs. Additionally, the hydrophobicity of the task-specific POM salts can be improved through variation of chain length of alkyl substituents of the organic cations. These hybrid POMs ionic salts can be utilized as solvent/temperature-responsive self-separable heterogeneous catalysts for a variety of oxidation and acid-catalyzed organic reactions.

Advantages as Catalysts: Importance of Organic-Inorganic Hybrids

Super acidic nature and excellent structural stability of the POMs accelerate their catalytic efficiencies as photocatalyst or electrocatalyst to undergo multi-electron

redox cycles in homogeneous or heterogeneous catalytic reactions. A huge number of POMs are involved in acid and oxidation catalysis [21, 37, 38]. Preferable candidates for several industrial-scale catalytic processes are the highly efficient homogeneous POMs catalytic systems with low toxicity and less corrosive properties. However, the major problems arise from difficulties in recycling and purification of product in case of POM catalysts. To turn these obvious disadvantages of homogeneous POMs into advantages, researchers have been designed heterogeneous POM catalysts which have received much attention in the area. Being the most common and better idea for the preparation of heterogeneous catalytic systems for many reactions, immobilization of POMs on porous support also suffers from drawbacks like weak interaction of the POMs with the inert support, aggregation and leaching of the POMs on the support material during catalysis as well as in work-up step. As a solution to this problem, the development of organic-inorganic hybrids of POMs have emerged as powerful route for creation of multifunctional POMs in combination with various organic components by covalent bond, electrostatic or other weak interactions that produce more efficient recyclable heterogeneous catalysts. On the contrary to simple POM/HPA homogeneous catalysis, more complicated heterogeneous catalysis can be divided into three types which are surface type, pseudoliquid bulk type and bulk type respectively (Fig. **3**) [39].

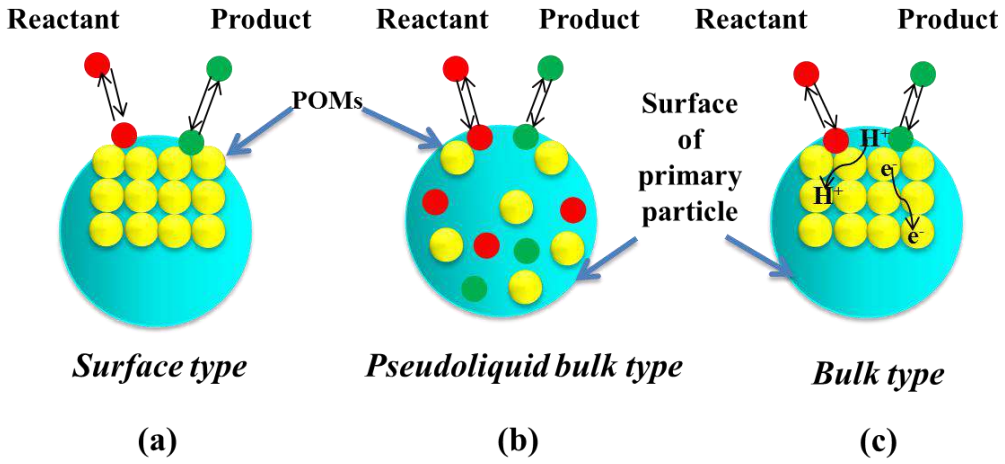


Fig. (3). Three catalysis models of solid POM catalysts.

Literature study reveals two types of organic-inorganic hybrids of POMs where **type-I** material involves only electrostatic, H-bonds, or van der Waals interactions in between the organic and inorganic moieties, while **type-II** binds *via* strong covalent or iono-covalent bonds [40]. In **type-I** hybrids, the anionic nature of

POM clusters permits strong association with the organic counter cation whereas substitution of oxo group of the POMs by organic ligands directly links them to the metal center in **type-II** material. Binding of organic ligands may effectively form expanded structure of the hybrid in various directions and dimensions through connection of metal ions. Uniform distribution at molecular level and firm anchoring through covalent bonds or extensive H-bonds are the characteristics of POMs moieties in these hybrid structures. The polarity of POMs framework is modified according to the increasing porosity and hydrophobicity of hybrid structure in presence of organic ligands [41]. The acidic sites of hybrids material depend on the POMs framework with different metal cation and also the presence of acidic functionality in organic cations. Thus, combination of newly added unique physical/chemical properties with all their structural changes makes the POMs as water insoluble heterogeneous catalysts with greater thermal stability and modified catalytic activities as redox and acidic catalysts.

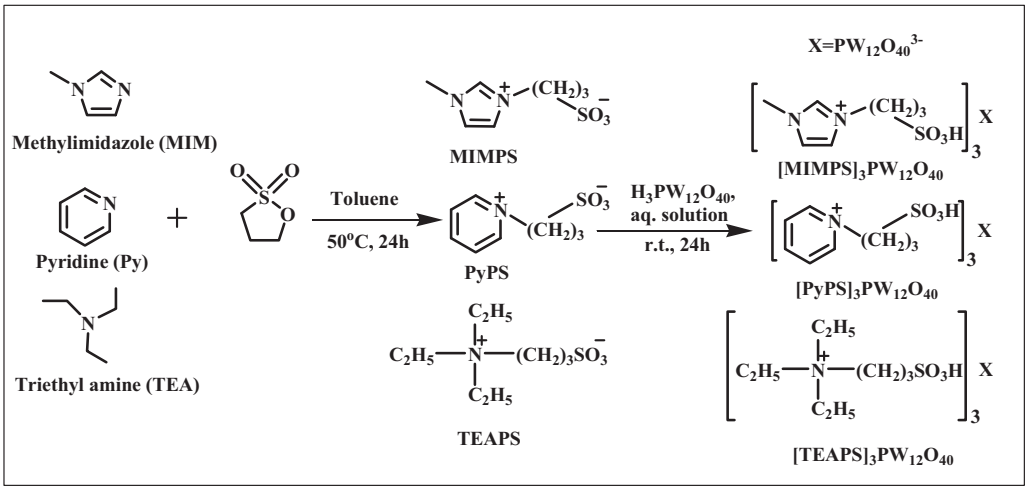
Catalytic Variation of Ionic Liquid-Polyoxometalates (IL-POMs)

Due to the variations in solvent-catalyst interactions, the IL-POM materials may act as homogeneous catalysts, heterogeneous catalyst, or self-precipitated catalysts from homogeneous solution through change of solvents, temperatures, or other external additive chemicals. Based on their uses they can be further subdivided into oxidation-reduction catalyst, photocatalyst, electrocatalyst, acidic catalyst, supported ionic liquid phase catalyst *etc*. The next section includes a brief discussion of catalytic applications of functionalized IL-POMs in organic reactions till date.

IMPORTANCE OF FUNCTIONALIZED IL-POMS IN VARIOUS ORGANIC REACTIONS

Functionality derived from task specific ionic liquids imparts immense importance to IL-POMs which initiates various applications efficiently. Among the widespread field of activities performed by IL-POM materials, their catalytic ability occupies the major area which involves wide range of organic transformations. Literature search indicates a number of N-alkylsulfonic acid functionalized POM salts of imidazolium, ammonium and pyridinium cations as task-specific acidic ionic liquid materials with their catalytic uses in various organic reactions. Leng and his group (2009) prepared three members of solid organic-inorganic POM hybrid materials $[MIMPS]_3PW_{12}O_{40}$, $[PyPS]_3PW_{12}O_{40}$, and $[TEAPS]_3PW_{12}O_{40}$ from ion-pairing of propane sulfonate functionalized ionic liquid containing imidazolium, pyridinium and triethylammonium cations with Keggin-structured heteropolyanions (Scheme **1**). Their catalytic abilities were explored [42] as “reaction-induced self-separation catalysts” for various

esterification reactions in presence of polycarboxylic acid or polyol as one of the reactants and also for a liquid–liquid biphasic esterification system, presenting high yield and selectivity for target esters with easy recyclability up to seven cycles [43]. They compared the catalytic activities of propane sulfonate functionalized imidazole (MIMPS) salts of $PW_{12}O_{40}^{3-}$, $PMo_{12}O_{40}^{3-}$, $SiW_{12}O_{40}^{4-}$, and the conventional IL-forming anion HSO_4^- in the esterification of acetic acid with *n*-butanol [43]. Results showed higher catalytic activities of the hybrid POM catalysts than $[MIMPS]HSO_4$ ionic liquid as well as the respective HPAs. They also observed reaction-induced phase-separation nature of the POMs catalysts of propane sulfonate functionalized imidazole with heteropolyanions of $SiW_{12}O_{40}$ and $PMo_{12}O_{40}$ with higher catalytic activities [42].



Scheme (1). Synthesis of heteropolyacid (HPA) salts.

Huang *et al. also* tested the activity of $[PyPS]_3PW_{12}O_{40}$ as redox catalyst for desulfurization of fuels in $[omim][PF_6]$ using aqueous H_2O_2 as oxidant [44]. They used a simple, highly efficient catalysis procedure involving flexible recyclability. Zhu and his coworkers (2011) explored the $–SO_3H$ functionalized imidazolium POM salt $[MIMPS]_3PW_{12}O_{40}$ along with three other POMs $[Bmim]_3PW_{12}O_{40}$ (1-butyl-3-methyl imidazolium phosphotungstate), $[Bmim]_3PMo_{12}O_{40}$ (1-butyl-3-methyl imidazolium phosphomolybdate) and $[Bmim]_4SiW_{12}O_{40}$ (1-butyl-3-methyl imidazolium silicotungstate) for desulfurization of fuel (Fig. **4**) [45]. The reaction was completed in one hour at 30°C with 100% S-removal and recyclability up to 8th cycles maintaining the same activity. Both the reports proved the higher activity of heteropolyanion based ionic liquids as compared to others in desulfurization of sulfur compound dibenzothiophene (DBT). The catalytic oxidative desulfurization rate of organic sulfur was observed in

descending order of dibenzothiophene (DBT) > 4, 6-dimethyldibenzothiophene (4, 6-DMDBT) > benzothiophene (BT).

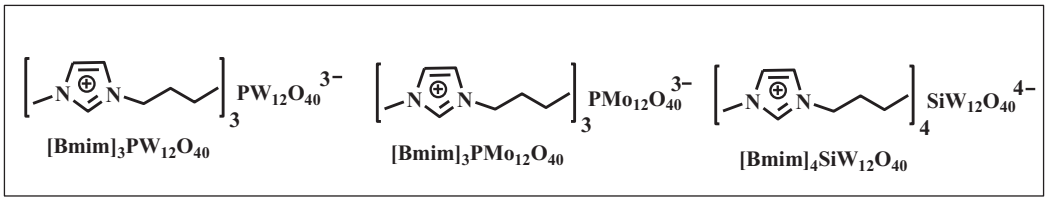
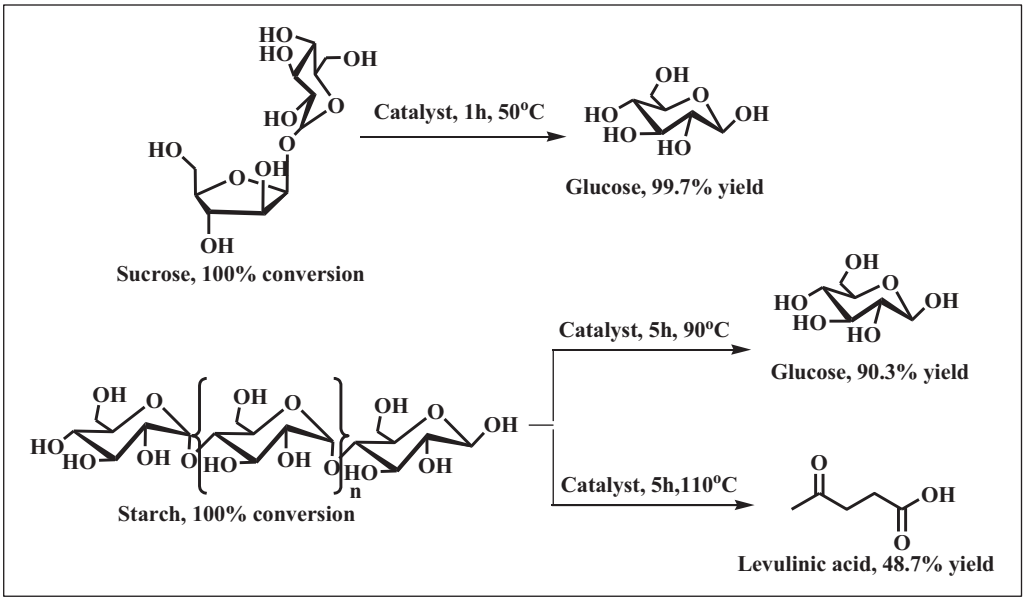


Fig. (4). Structures of $[Bmim]_3PW_{12}O_{40}$, $[Bmim]_3PMo_{12}O_{40}$ and $[Bmim]_4SiW_{12}O_{40}$.

Sun and his group synthesized similar members of imidazolium heteropolyacid ionic liquids $[C_4H_6N_2(CH_2)_3SO_3H]_{3-n}H_nPW_{12}O_{40}$ (Fig. **5**) using the optimized method reported previously by Leng *et al.* [42]. The new members were successfully utilized as catalyst for one pot depolymerization of cellulose into glucose, conversion of sucrose and starch into glucose and also one pot preparation of levulinic acid (LA) directly from cellulose [46] (Scheme **2**). The yields of levulinic acid were found as 63.1% and 48.7% for the same catalytic degradation of cellulose and starch for 12h and 5h reactions respectively. They worked as easily separable catalysts and displayed negligible loss of catalytic activity.



Scheme (2). Transformation of polysaccharides by $[MIMPS]H_2PW_{12}O_{40}$.

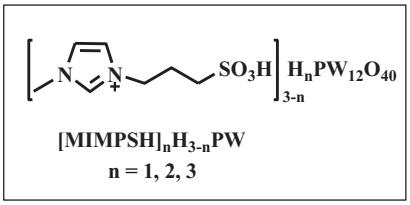
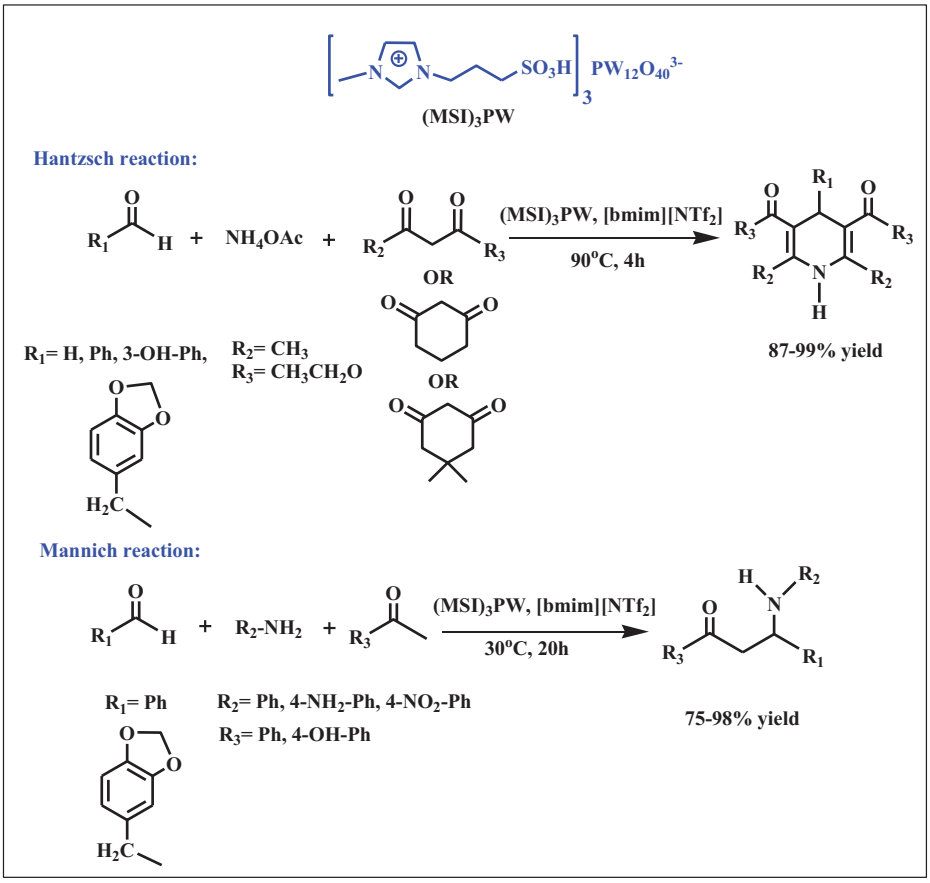


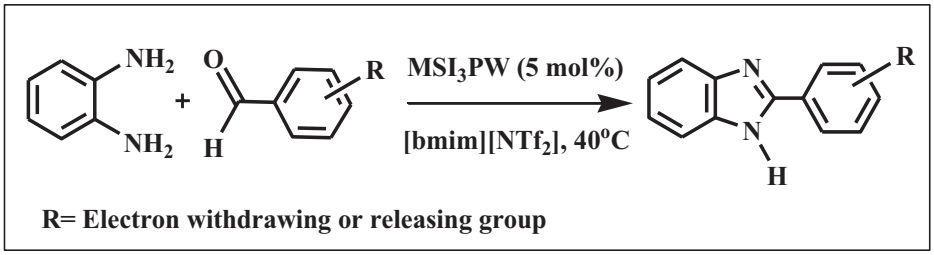
Fig. (5). Structure of $[MIMPSH]_nH_{3-n}PW$.

Zhu *et al.* [46] developed (1-(3-sulfopropyl)-3-methylimidazolium phosphotungstate as hybrid material and later on it was studied as reusable catalyst for three-component Mannich and Hantzsch reactions in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide $[bmim][NTf_2]$ ionic liquid by Alvim and his group [47] (Scheme **3**). This POM–ionic salt was labeled as $(MSI)_3PW$ instead of $[MIMPS]_3PW_{12}O_{40}$. In 2015, the same group employed MSI_3PW (5 mol%) in $[bmim][NTf_2]$ ionic liquid for condensation between aldehydes and *o*-phenylenediamines to afford 2-arylbenzimidazole derivatives (Scheme **4**) [48] at 40°C for 10h reaction to give 80-99% yields of products. Super acidic behavior of the catalyst was monitored by ESI-MS (electrospray ionization-mass spectrometry) and theoretical calculation also supported the super acidic behavior of the catalyst along with the pronounced ionic liquid effect of $[bmim][NTf_2]$.

Another series of POM salts abbreviated as $[MIM\text{-}PSH]_xH_{3-x}PW_{12}O_{40}$ reported by Han *et al.* [49] in 2013 (x indicates the molar ratio of MIM-PS/TPA changing from 1.0 to 3) was fabricated by combining tungstophosphoric acid (TPA) and -SO_3H-functionalized zwitterions ionic complex 3-(1-methylimidazolium-3-yl) propane-1-sulfonate (MIM-PS). Among the five composite materials, namely $[MIM\text{-}PSH]_{3.0}PW_{12}O_{40}$ (84.8% yield), $[MIM\text{-}PSH]_{2.5}H_{0.5}PW_{12}O_{40}$ (88.4% yield), $[MIM\text{-}PSH]_{2.0}HPW_{12}O_{40}$ (90.4% yield), $[MIM\text{-}PSH]_{1.5}H_{1.5}PW_{12}O_{40}$ (87.5% yield), and $[MIM\text{-}PSH]H_{2.0}PW_{12}O_{40}$ (85.1% yield), the $[MIM\text{-}PSH]_{2.0}HPW_{12}O_{40}$ catalyst showed best catalytic ability with production of 90.4% biodiesel from palmitic acid through esterification reaction. This catalyst displayed efficient recyclability up to six cycles under the optimized condition. This group again followed the same method as Leng *et al.* [42] and extended their study for the preparation of pyridinium cation containing POM salts [50], $[PPSH]_xH_{3-x}PW_{12}O_{40}$ (x = 1.0–3.0) by incorporating varied amounts of tungstophosphoric acid (TPA) and pyridinium propyl sulfobetaine (PPS) zwitterionic precursor. Owing to their strong acidity, the PPS-TPA hybrid catalysts followed decreasing activity order as $[PPSH]_2HPW_{12}O_{40}$> $[PPSH]_{2.5}H_{0.5}PW_{12}O_{40}$> $H_3PW_{12}O_{40}$> $[PPSH]_{1.5}H_{1.5}PW_{12}O_{40}$> $[PPSH]_3PW_{12}O_{40}$> $[PPSH]H_2PW_{12}O_{40}$. These were evaluated as self–separated catalysts for acetalization of benzaldehyde with glycol which resulted in an optimal acetal yield over 85%.



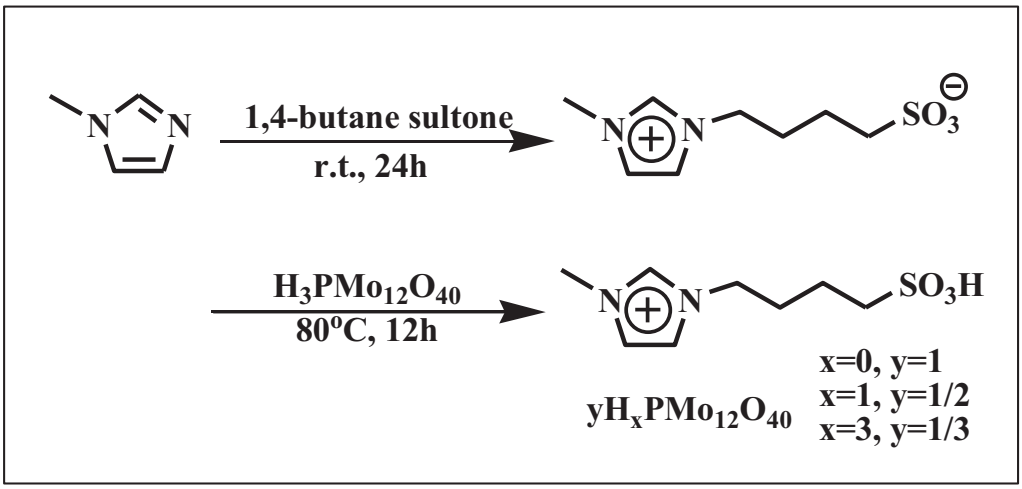
Scheme (3). Three component Mannich and Hantzsch reactions catalyzed by $(MSI)_3PW$ supported in $[bmim][NTf_2]$ ionic liquid.



Scheme (4). Synthesis of 2-arylbenzimidazoles using MSI_3PW.

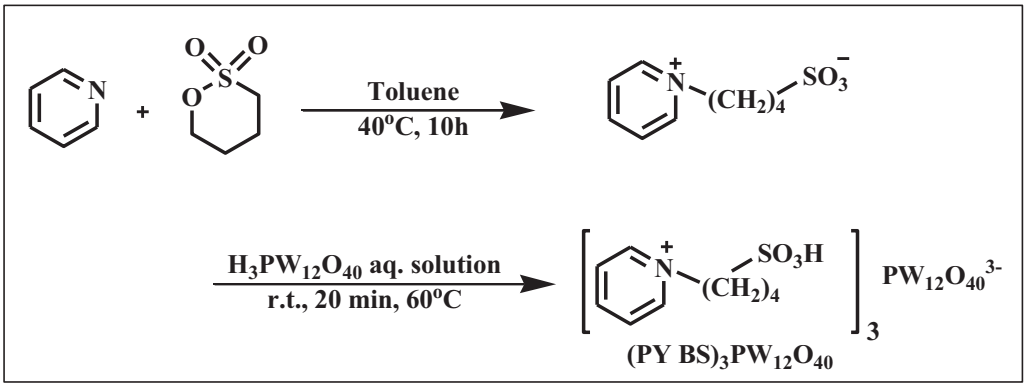
A series of Brønsted acidic Keggin structured POM ionic salts $[SO_3H(CH_2)_4Mim]_nH_{3-n}PMo_{12}O_{40}$ (n = 1, 2, 3) (Scheme **5**) was synthesized by Yang *et al.* [51] and their catalytic activity was screened for regioselective mono

nitration of aromatic compounds (*e.g.* toluene, benzene and chlorobenzene *etc.*) in HNO_3 (67%) for 10 hour at varied temperature. Three catalysts showed better catalytic activity than the corresponding system with zwitterion $[Mim(CH_2)_4SO_3]$ or Keggin heteropolyacid $H_3PMo_{12}O_{40}$ at same reaction condition. Considering the same quantity of acidic protons offered by the catalysts, the activities of five compounds were obtained as descending order of $(CH_2)_4SO_3HMim]_3PMo_{12}O_{40}$ >$[(CH_2)_4SO_3HMim]_2HPMo_{12}O_{40}$>$[(CH_2)_4SO_3HMim]H_2PMo_{12}O_{40}$>$Mim(CH_2)_4SO_3$ >H_3 $PMo_{12}O_{40}$ against the decreasing yields for nitration of toluene as model reaction under the optimized condition. The optimized catalyst $[(CH_2)_4SO_3HMim]_3PMo_{12}O_{40}$ was tested for reusability and found to be effective up to three cycles with 87.7-79.5% yield after which formation of side products inhibit the reactivity.

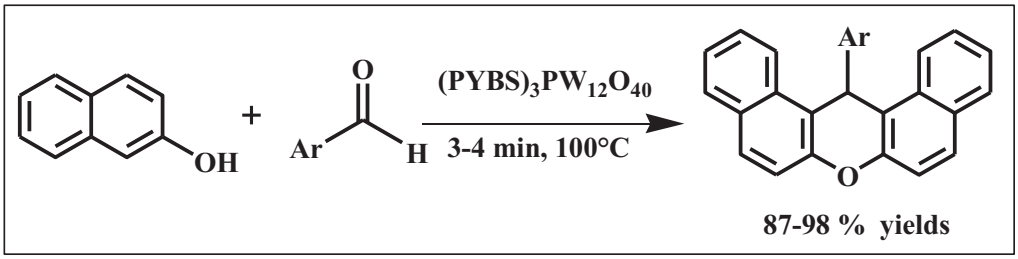


Scheme (5). Synthesis of $[SO_3H(CH_2)_4Mim]_nH_{3-n}PMo_{12}O_{40}$ (n = 1, 2, 3).

The POM hybrid of $–SO_3H$ functionalized pyridinium cation and $PW_{12}O_{40}^{3-}$ Keggin anion was introduced by Heravi *et al.* [52] (Scheme **6**) and used as reusable catalyst for preparation of 14-aryl-14*H* dibenzo[a, j]xanthenes at 100°C in 3-14 min with excellent yield (87-98%) (Scheme **7**). They compared the catalytic behavior of this IL-POM material with reported methods involving H_2SO_4, *p*-toluene sulfonic acid, sulfamic acid, I_2, Amberlyst-15, $NaHSO_4$, Preyssler catalyst $[NaP_5W_{30}O_{110}]$, $[MIMPS]HSO_4$ and also with heteropolyacid $[H_3PW_{12}O_{40}]$ as catalyst. And these methods required very high time (0.5-73h) to afford satisfactory yield (50-99% yield) as compared to the IL-POM catalyst.



Scheme 6. Synthesis of $(PYBS)_3PW_{12}O_{40}$.

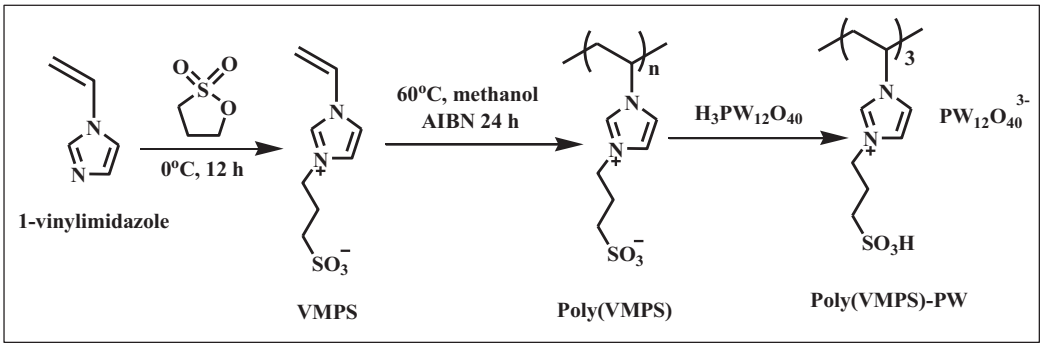


Scheme (7). $(PYBS)_3PW_{12}O_{40}$ catalyzed synthesis of 14-aryl-14*H* dibenzo[a,j] xanthenes.

In 2012, this POM-IL was further modified to a supported ionic liquid (IL) mediated sol–gel hybrid organic–inorganic material by Ebrahimi *et al.* and explained their effective use in hollow fiber solid phase micro extraction (HF-SPME) [53]. They successfully overcame the hurdle of slowing down of the sol-gel reaction due to high viscosity of ionic liquid by providing heteropolyacid-based supported IL mediated advanced sol–gel materials for HF-SPME. The material was effectively utilized for determination of the organophosphorus pesticides in hair matrices.

In continuation to the synthesis of functionalized POMs, Leng and his group (2012) again developed polymeric hybrid of $-SO_3H$ based POM Brønsted acidic ionic salts from the reaction of $H_3PW_{12}O_{40}$ with polymeric 1-vinyl-3-propane sulfonate imidazolium [Poly(VMPS)] to yield the solid polymeric hybrid (Scheme **8**) [54]. This work involved comparison of activities of Poly(VMPS)-PW, MimPS-PW, Poly(VMPS)-HSO_4, $H_3PW_{12}O_{40}$ and without catalyst in esterification of acetic acid with n-butanol using the reaction conditions: catalyst (0.2g), acetic acid 30 mmol, molar ratio of acetic to n-butanol 1:1.2, 110°C for 1.5h. Among which the highly active and selective solid catalyst showed 97.4% conversion of

acetic acid and was easily recovered and steadily reused. Their stable and solid nature was attributed to the polymeric unit present in the frame.



Scheme (8). Synthesis of Poly(VMPS)-PW.

In 2012, $SiW_{12}O_{40}$-based ionic liquid (SWIL) (Fig. **6**) and silica supported $SiW_{12}O_{40}$-based ionic liquid (SWIL/SiO_2) with different contents of SWIL [55] were synthesized by Zhen *et al.* Scheme **9** indicates the preparation of two different compositions of SWIL/SiO_2 which involves reaction intermediates MPS-SiO_2-1 (SWIL/SiO_2-1) and MPS-SiO_2-2 (SWIL/SiO_2-2) produced by feeding the two weight ratios of silica to MPTMS ((3-mercaptopropyl) trimethoxysilane) such as 40:1 and 20:1, respectively. The hybrid sample SWIL/SiO_2 showed high initial catalytic activity similar to the SWIL and was separated from the product through simple filtration. But increase in the SWIL amount in SWIL/SiO_2 decreases the reusability of the catalyst. Loss of the SWILs that immobilized on SiO_2 during the reaction reduced SWIL content of SWIL/SiO_2-1 and SWIL/SiO_2-2 by 26.85% and 57.59% after 7 cycles as compared to fresh SWIL/SiO_2. Even though the two catalytic systems SWIL and SWIL/SiO_2 showed better catalytic activity in esterification of oleic acid for biodiesel production, the leaching of SWIL from silica support deactivated the SWIL/SiO_2 catalyst. The SWIL/SiO_2 obtained higher thermal stability and better reusability than that of SWIL.

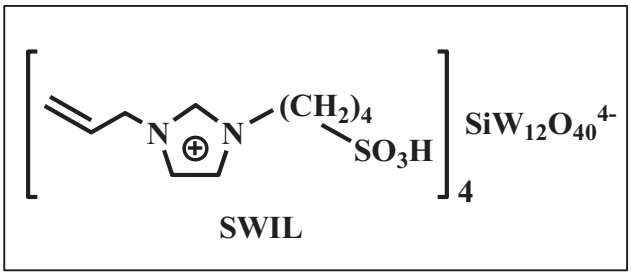
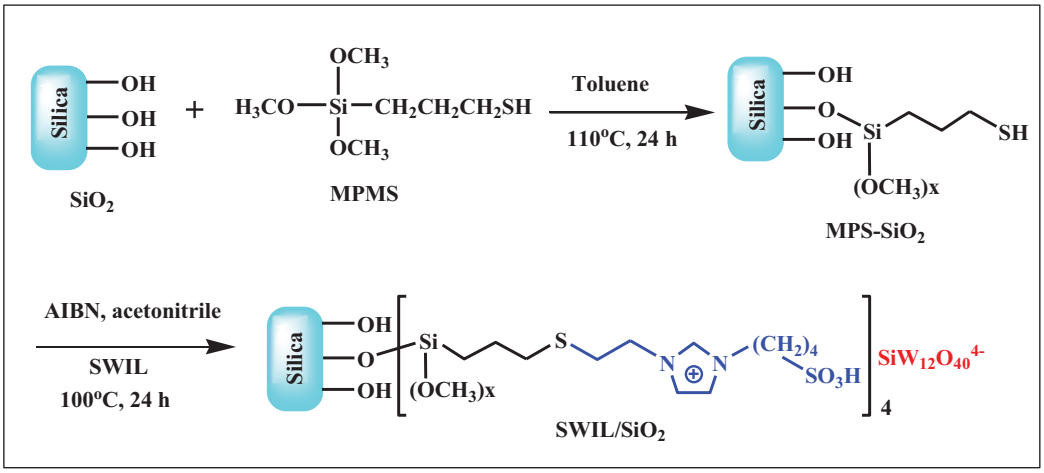


Fig. (6). Structure of SWIL.

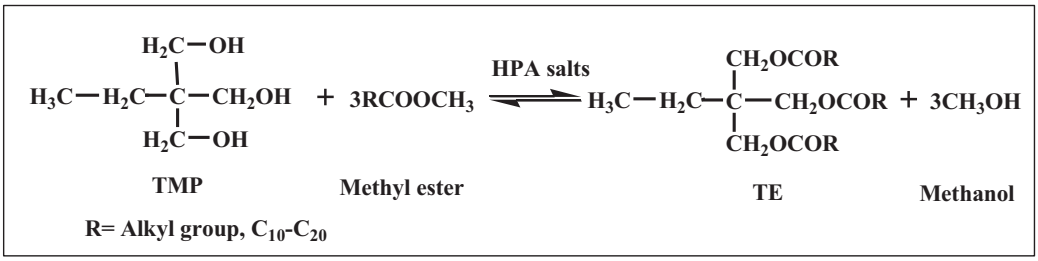


Scheme (9). Synthesis of SWIL/SiO_2.

Huang and his group (2014) [56] prepared a series of homogeneous water-tolerable PPS-TPA-HOAc catalysts consisting of pyridinium propyl sulfobetaine (PPS), tungstophosphoric acid, and acetic acid. These catalysts were examined in catalytic acetylation of glycerol (GL) and separated from glycerol acetate product as distinct liquid phase *via* self-segregate process after completion of the reaction. Varying TPA calcination temperature and continuous removal of excessive H_2O in the reaction system manifested strong correlations between the catalytic activity of the catalyst with acidic strength, HOAc/glycerol molar ratio, and reaction temperature. Under optimal reaction conditions acetylation reaction with 100% GL conversion and GTA selectivity as high as 98.9% were achieved for the PPS–TPA–100–2.0 catalyst. The newly synthesized PPS–TPA–HOAc samples were highly efficient, durable, and reusable homogeneous catalyst system readily feasible for continuous operation and practical industrial applications in biochemical processes.

Another series of self-separable POM salts of $[PyBS]^+$, $[TEABS]^+$ and $[MIMBS]^+$ cations paired with $PW_{12}O_{40}^{3-}$, $PMo_{12}O_{40}^{3-}$, $SiW_{12}O_{40}^{4-}$ heteropolyacid anions (Fig. **7**) was developed by Li *et al.* [57] and were used as reusable catalysts for (Scheme **10**) trans esterification of trimethylolpropane (TMP). Their catalytic activities were investigated in the transesterification of TMP with methyl oleate and compared with the bare heteropolyacids, conventional ionic liquids as well. Results indicated that the cations were more responsible for reactivity than the heteropolyanions. Also cations without functionalized group offered low reactivity which proved the higher efficiency of butane sulfonate functionalized group in organic cation. The catalysts were self-separable and highly recyclable. They also designed [58] a series of Keggin and Dawson structured POM liquid

catalysts consisting of $[PyBS]_n^+$, $[TEABS]_n^+$, $[ImBS]_n^+$ (n = 3, 4 and 5) cations and $H_2PV_2Mo_{10}O_{40}^{3-}$, $P_2Mo_{18}O_{62}^{6-}$, $P_2W_{18}O_{62}^{6-}$, $PV_2Mo_{10}O_{40}^{5-}$, $HPV_2Mo_{10}O_{40}^{4-}$, $SiW_{12}O_{40}^{4-}$, $PMo_{12}O_{40}^{3-}$, $PMo_{12}O_{40}^{3-}$ anions. These recyclable multifunctional catalysts were applied in one-pot transformation of cellobiose/cellulose to valuable chemicals, such as formic acid (FA) and levulinic acid (LA). Among them vanadium containing POM-IL catalyst offered significantly higher selectivity of LA (46.3%) and FA (26.1%) than the other catalysts, together with 100% conversion of cellobiose.



Scheme (10). Transesterification of trimethylolpropane.

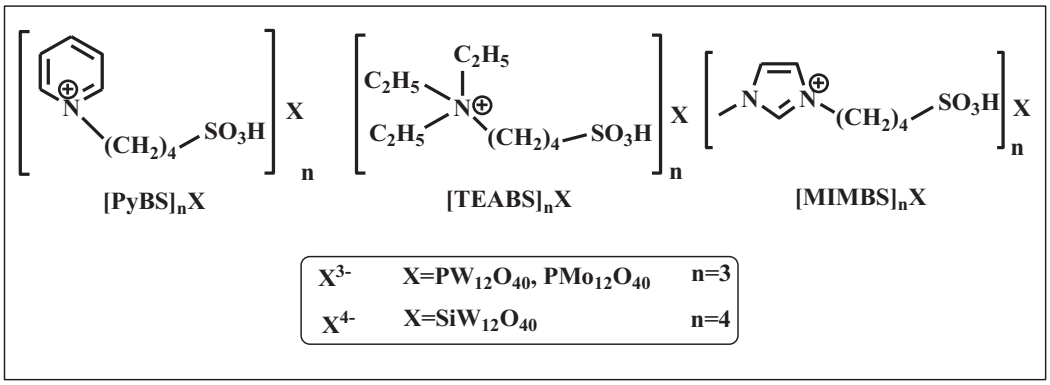
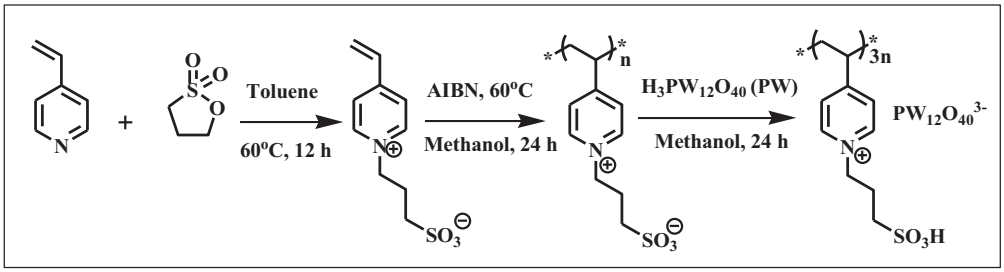


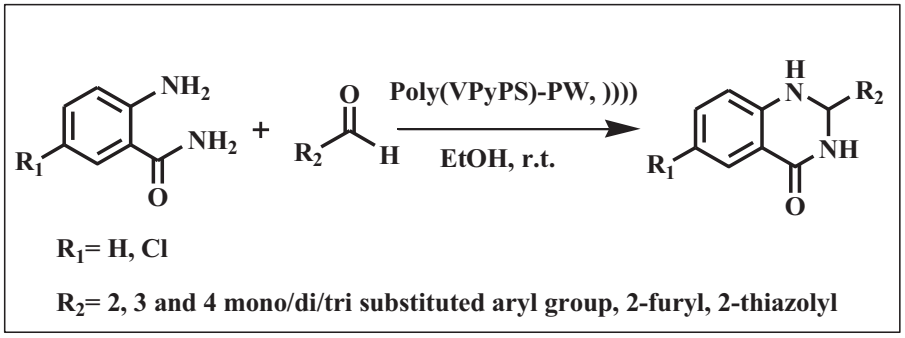
Fig. (7). Structures of heteropolyacid based ionic salts.

Liu *et al.* (2014) explored excellent catalytic activity of two of the above-mentioned sulfonated imidazolium and ammonium based HPA-IL namely $[MIMBS]_3$ $PW_{12}O_{40}$ and $[TEABS]_nPW_{12}O_{40}$ along with other HPA-ILs for the esterification reaction of diethylene glycolmonobutyl ether with acetic acid. They further studied their kinetic behavior and observed excellent catalytic activities as compared to HPA-ILs, H_2SO_4, $H_3PW_{12}O_{40}$, and Amberlyst-15 resin [59]. Activation energies of 57.97 and 58.96 kJ mol^{-1} were obtained by the Arrhenius equation for $[TEABS]_3PW_{12}O_{40}$ and $[MIMBS]_3PW_{12}O_{40}$ respectively and both the catalysts could be easily recovered and reused six times without any significant decrease in catalytic activity.

Wang *et al*. performed the reaction of 4-vinylpyridine with 1, 3-propanesultone, followed by the polymerization and addition of the heteropolyacid to develop another sulfonated poly(4-vinylpyridine) heteropolyacid salt poly(VPyPS)-PW (Scheme **11**) [60]. This polymeric salt was efficiently examined as reusable catalyst for synthesis of 2, 3-dihydro-4(1H)-quinazolinones derivatives under sonication irradiation (Scheme **12**). Compared to the low conversion of conventional anion based Poly(VPyPS)-HSO_4 catalyzed reaction and poor recyclability of $H_3PW_{12}O_{40}$, the easily recyclable solid poly(VPyPS)-PW catalyst satisfactorily gave high yield of 87% within shorter reaction time. Combination of SO_3H functional groups, the polymeric framework of IL-cation and the large heteropolyanion effectively conducted the reaction.



Scheme (11). Preparation of poly(VPyPS)-PW.



Scheme (12). Poly(VPyPS)-PW catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Later on, they applied this catalyst as reusable heterogeneous catalyst for one-pot synthesis of β-amino carbonyl compounds *via* Mannich reaction of aromatic aldehydes, aromatic ketones and aromatic amines in ethanol at room temperature [61].

Anion-exchange of 1, 3-propanesulfonate poly (N-vinylimidazole-co-diviny lbenzene) with Keggin structured phosphotungstic acid resulted in similar type of sulfonated heteropolyacid salt P(VB-VMS)PW [62] (Fig. **8**) which was assessed

as catalyst in Friedel-Crafts benzylation reaction between single-ring aromatic compounds with benzyl alcohol under solvent-free condition. The mesoporous ionic copolymer P(VB-VMS)PW represented a liquid-solid heterogeneous reaction system which can be contributed to the featured structure of the ionic copolymeric cation. This insoluble solid hybrid catalyst presented a superior yield of 96.7% with consistent selectivity of 54.3%/45.7% corresponding to p-/o- major products.

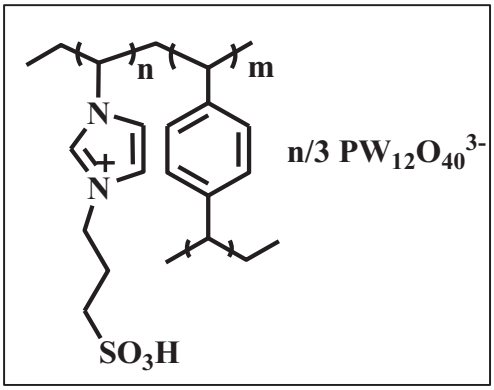
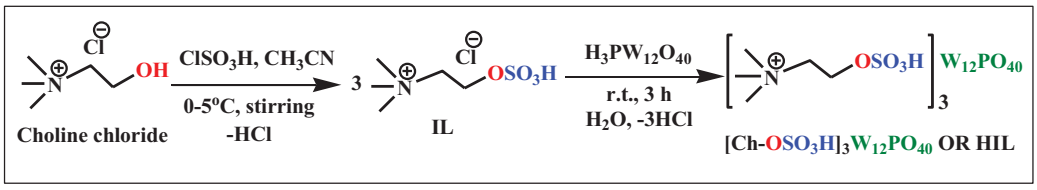


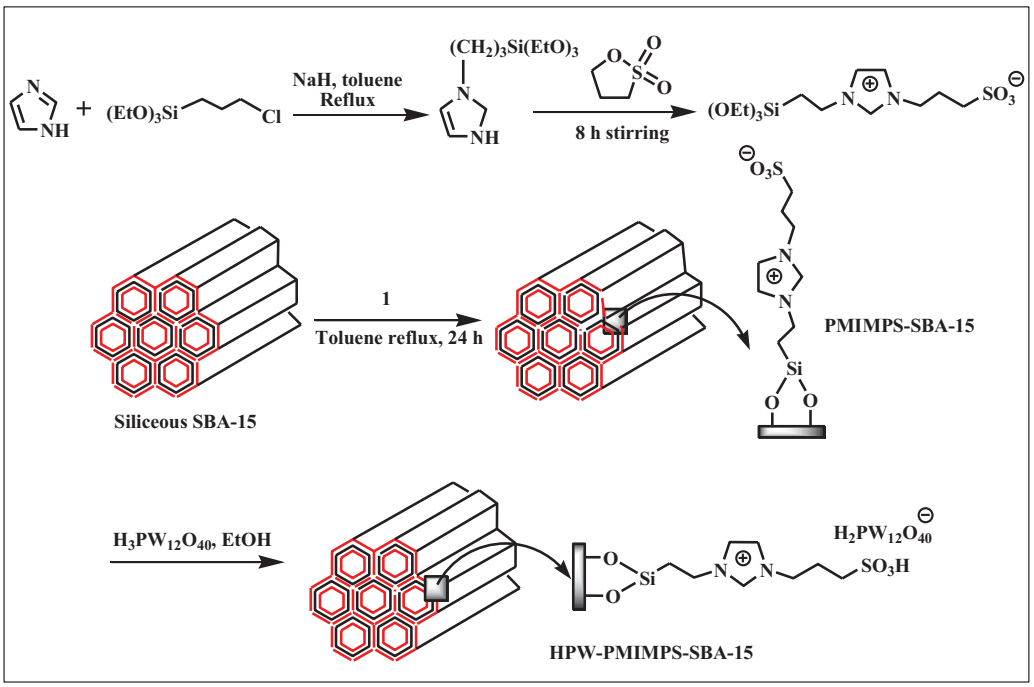
Fig. (8). Structure of P(VB-VMS)PW.

Satasia and his group [63] prepared one heteropolyanion-based sulfated ionic liquid (HIL-[Ch-OSO_3H]$_3W_{12}PO_{40}$) by pairing sulfate functionalized cholinium cation [N, N, N-trimethyl-2-(sulfooxy)ethanaminium] with catalytically active phosphotungstate anion ($W_{12}PO_{40}^{3-}$) (Scheme **13**). The newly developed ionic liquid was examined for N-formylation of amines under solvent-free grinding condition. This methodology offered cleaner conversion over 5-15 min reaction for primary and 40-95 min for secondary amines with high turnover frequency (TOF) and chemoselectivity. Comparison of data with reported catalysts suggested that Keggin type structure of heteropolyanion might have increased the activity of POM-IL catalyst. The catalyst was easily recovered by simple filtration and could be reused without any significant loss of activity up to six cycles.



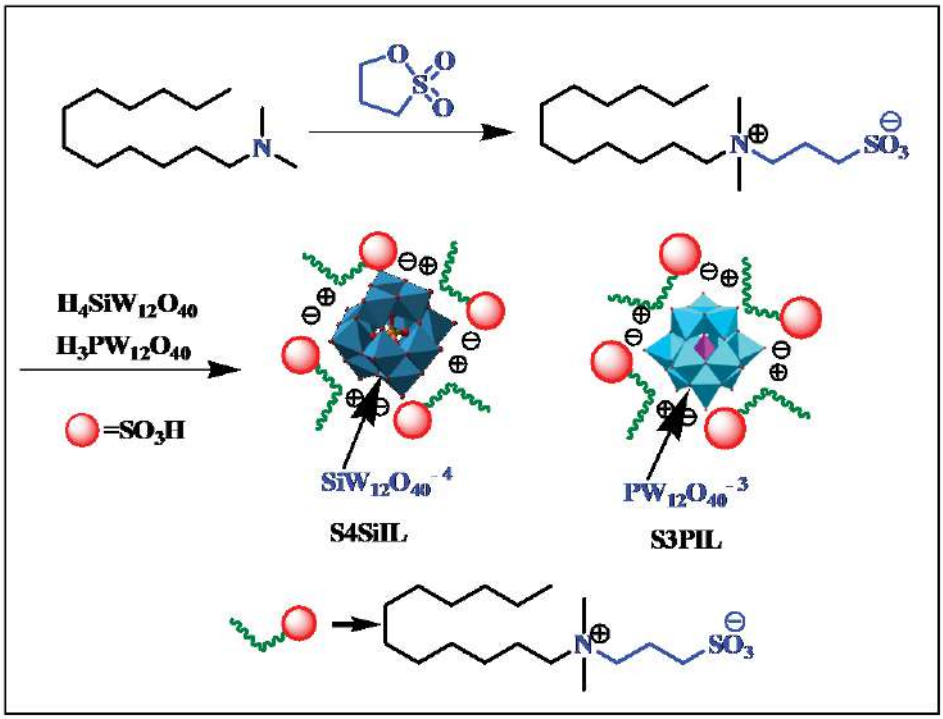
Scheme (13). Synthesis of [Ch-OSO_3H]$_3W_{12}PO_{40}$.

Sheng *et al.* [64] utilized sulfonate-functionalized ionic liquid-modified mesoporous silica SBA-15 to load various compositions of phosphotungstic acid ($H_3PW_{12}O_{40}$) by total anion-exchange (HPW-PMIMPS-SBA-15) method (Scheme **14**). This work inferred that the support material maintained its structure even after surface modification and the subsequent anion-exchange step of $[PW_{12}O_{40}]^{3-}$ (PW). The 30% composite showed higher efficiency (97.8% styrene conversion with 93.9% yield of phenylxylyl ethane) in alkylation of o-xylene with styrene as compared to the task-specific basic ionic liquid (1-(propyl-3-sulfonate) 3-methy--imidazolium phosphotungstate) (90.8% phenylxylyl ethane).



Scheme (14). Synthesis of immobilized HPW-PMIMPS-SBA-15 materials.

Li *et al.* in 2015 [65], introduced two long chain multi-SO_3H functionalized heteropolyanion-based ionic liquids S4SiIL and S3PIL (Scheme **15**). These two ionic liquids displayed their efficiency as homogeneous catalysts in solvent free selective oxidation of alcohols with 35% aqueous hydrogen peroxide without adding any phase transfer catalyst. They were readily recoverable and efficiently reusable for five times.



Scheme (15). Synthesis of S4SiIL and S3PIL.

In the same year, the same group [66] again developed three multi -SO_3H functionalized heteropolyanion-based ionic hybrids S2SiIH, S2PIH and S4SiIH (Fig. **9**) using N, N, N′, N′-tetramethylethylene diamine or N, N, N′, N”, N”-pentamethyldiethylenetriamine with 1, 3-propanesultone followed by addition of $H_4SiW_{12}O_{40}$ or $H_3PW_{12}O_{40}$. The obtained hybrids were screened as recyclable heterogeneous catalysts for Baeyer–Villager oxidation using 35% aqueous H_2O_2 as oxidant and showed high catalytic activity under solvent-free conditions. The target lactones were obtained with yields of 69% to 88% in 3h at 50°C using ketone:H_2O_2: ionic hybrids in the ratio of 1:2.5:0.05 (mol). Appropriate acidity and acid content of catalytic system are crucial for the high yield of lactones.

Tong and his coworkers [67] synthesized two POMs-based IL gels (Fig. **10**) exhibiting typical thermotropic liquid-crystalline properties through grafting of two Keggin-type heteropoly anions such as $\{PMo_{11}VO_{40}\}^{4-}$ and $\{PW_{11}MoO_{40}\}^{3-}$ by using N-methyl imidazolium-1-(3-sulfonic group) propyl (MIMPS) ionic liquid. Their properties like electrochemical stability, ionic conductivity were studied and compared with various known IL-based electrolytes which proved higher electrochemical stability as well as conductivity of the gel electrolytes.

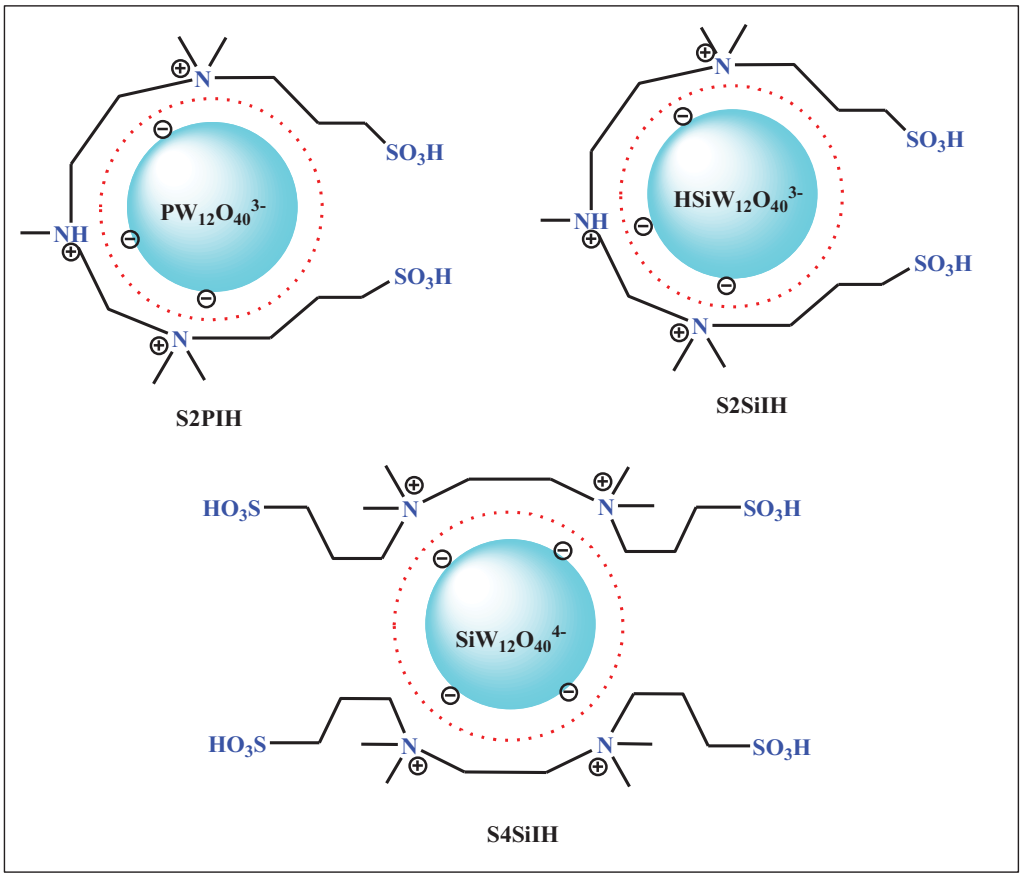


Fig. (9). Structures of heteropolyanion-based ionic hybrids S2SiIH, S2PIH and S4SiIH.

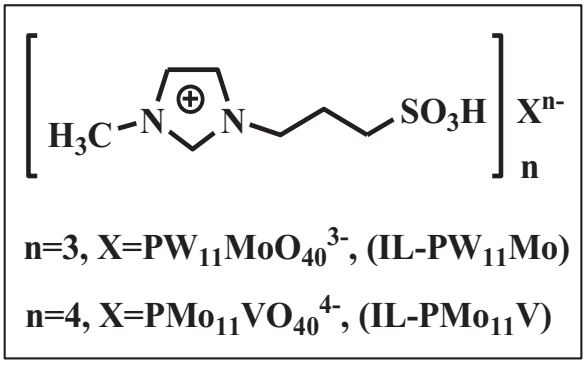
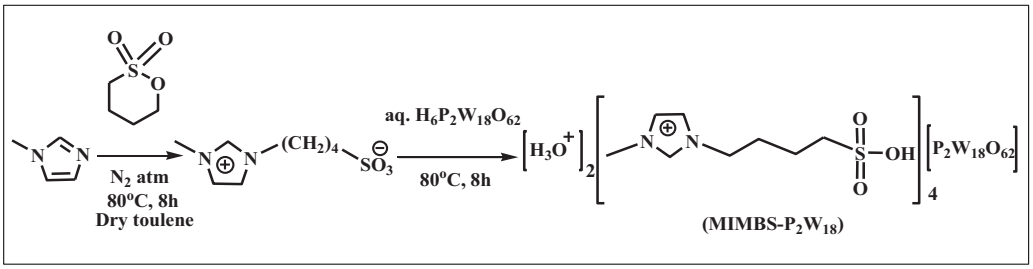


Fig. (10). Structures of gel electrolyte POM.

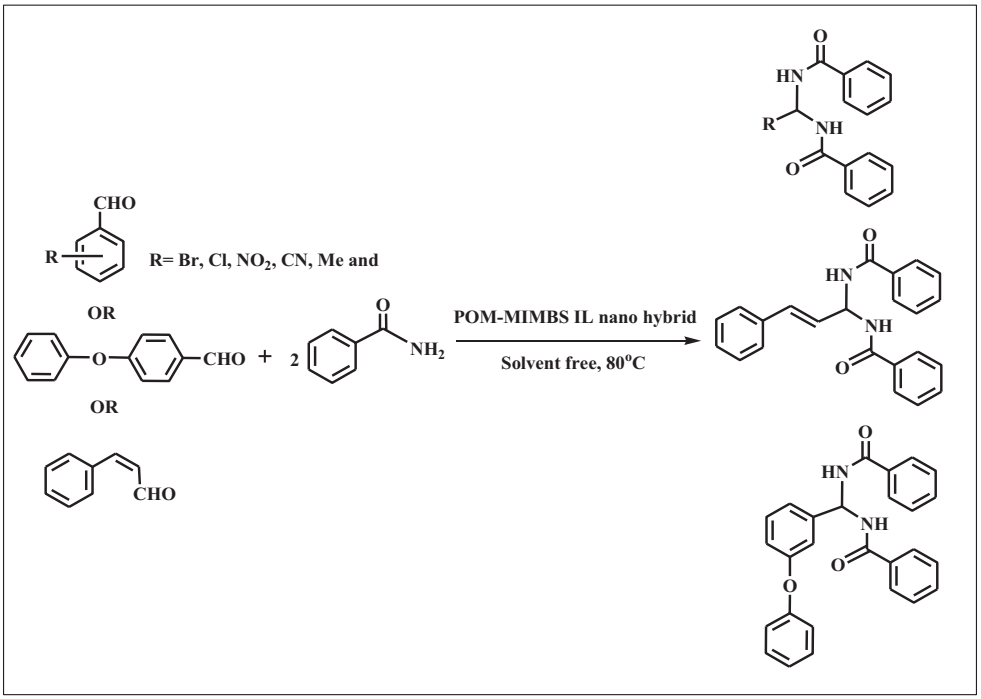
Han *et al*. [68] employed the zwitterion 3-(1-methylimidazolium-3-yl)propne-1-sulfonate ionic liquid (MIM-PS) and molybdovanadophosphoric acid ($H_4PVMo_{11}O_{40}$) to design a series of Keggin-type HPA-based ionic liquid catalysts ($[MIM\text{-}PSH]_xH_{4-x}PVMo_{11}O_{40}$, x = 1-4). Their catalytic performances were evaluated in esterification of n-caprylic acid to methylcaprylate, among which the $[MIM\text{-}PSH]_{2.0}H_{2.0}PVMo_{11}O_{40}$ catalyst resulted an optimal reaction activity. An experimental design was exploited *via* response surface methodology (RSM) on the basis of the Box–Behnken design (BBD). Accordingly, a maximum methylcaprylate yield of 95.6% was obtained over the $[MIM\text{-}PSH]_{2.0}H_{2.0}PVMo_{11}O_{40}$ catalyst under the optimal conditions. Such HIL-composites possessing unique self-separation properties and durability that are favorable for product separation and catalyst recycle show prospective industrial applications as practical catalysts for conversion of biomass to valuable chemicals and biodiesels.

In 2018, Ali *et al.* developed a new organic-inorganic nano hybrid ionic liquid based on polyoxometalate $H_2[MIMBS]_4[P_2W_{18}O_{62}].11H_2O$ (MIMBS-P_2W_{18}), originated from self-assembling of Dawson-type polyoxometalate $[P_2W_{18}O_{62}]^{6-}$ and organic ionic liquid [1-(3-sulfonic group) butyl-3-methyl imidazolium (MIMBS)] component according to **16** [69]. The easily recyclable heterogeneous catalyst showed efficiency for the synthesis of symmetrical N, N´-alkylidene bisamides under solvent-free conditions at 80°C with 68-93% yield in 15-40 min reaction time (Scheme **17**). Comparison of the performance of POM-MIMBS IL with the Keggin and Dawson HPA proved that the presence of organic groups (MIMBS) along with the POMs has significant effect on the catalytic activity of the catalyst and imparted good reusability up to five cycles.

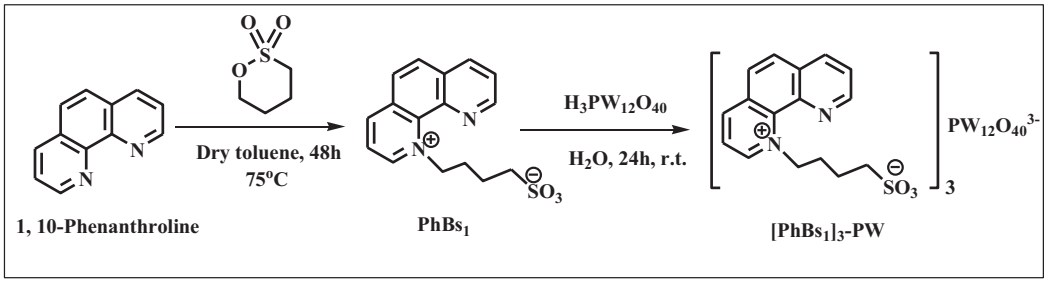
In 2019, Keshavarz and his group developed three novel heteropolyanion-based Brønsted acidic ionic liquids (BAILs), butane mono sulfonic acid functionalized 1, 10-phenanthrolium, butane mono and bis sulfoacid-functionalized 1, 4-dimethylpiperazinium salts of phosphotungstate catalyst $PhBs_1$-PW (Scheme **18**), $[PipBs_1]_3$-PW and $[PipBs_2]_3$-$(PW)_2$ [70] (Scheme **19**). They tested their activity in the esterification reactions of monocarboxylic acids with monohydric alcohols. The newly designed catalysts showed a self-separation performance after reaction, which can be easily recovered and quite steadily reused as confirmed by six-run recycling test. Among the three, only 0.15g of $[PipBs_2]_3$-$(PW)_2$ displayed the best catalytic performance by giving 87-96% yield with 100% selectivity within 1.5-2h reaction time. In absence of HPA anion, trace amount of yield was formed similar to that of neat condition.



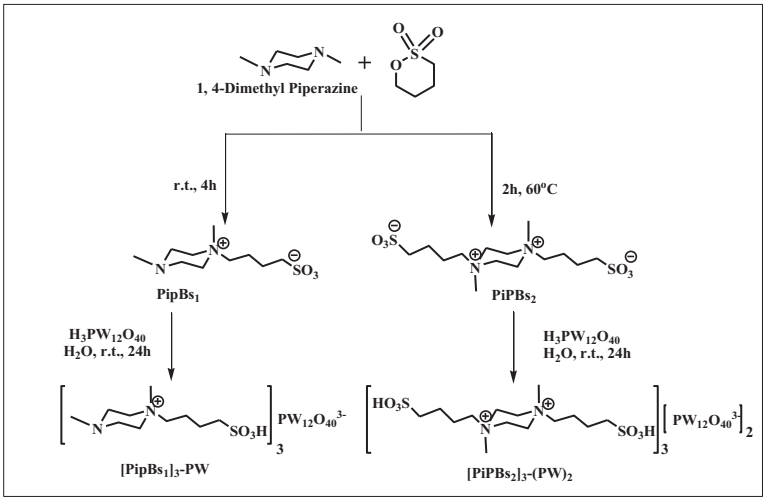
Scheme (16). Synthesis of MIMBS-P_2W_{18} nano-hybrid.



Scheme (17). Synthesis of symmetrical N, N´-alkylidene bisamide derivatives using POM-MIMBS IL nano-hybrid.



Scheme (18). Synthesis of $[PhBs_1]_3$-PW.



Scheme (19). Synthesis of $[PipBs_1]_3$-PW and $[PipBs_2]_3$-$(PW)_2$.

Again, in the same year, they utilized [4-(1, 10-phenanthrolium-1-yl) butane-1 sulfonate]$_3PW_{12}O_{40}^{3-}$ ($PhBs_1$-PW) (Scheme **18**) [71] for the efficient synthesis of 3, 3-diaryloxindole derivatives from the condensation of indole with isatins in water under reflux condition. The catalyst showed high yields of the products up to 97% and good recyclability up to eight reusability runs.

A series of polyoxometalate-based ionic liquid (POM-IL) catalysts with functional sulfonic acid groups, $[TEAPS]_{3+n}PW_{12-n}V_nO_{40}$ (n=1, 2, 3) were synthesized (Fig. **11**) [72] and their catalytic ability and reusability were evaluated on esterification of chloroacetic acid and n-amyl alcohol. With an esterification rate of 98.75% only 0.2g of $[TEAPS]_5PW_{10}V_2O_{40}$ was found to be the best active catalyst and reusable up to five times without significant decrease in activity. It acted as a temperature-responsive catalyst, forming a homogeneous mixture with the reactants at reaction temperature of 140°C.

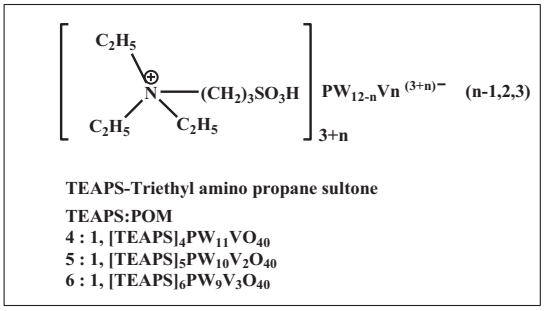
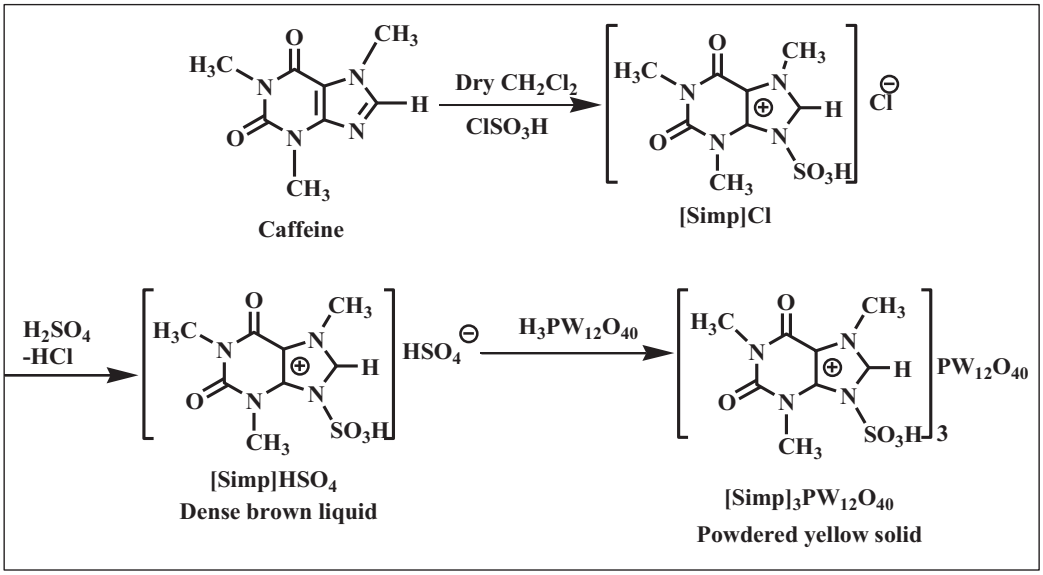


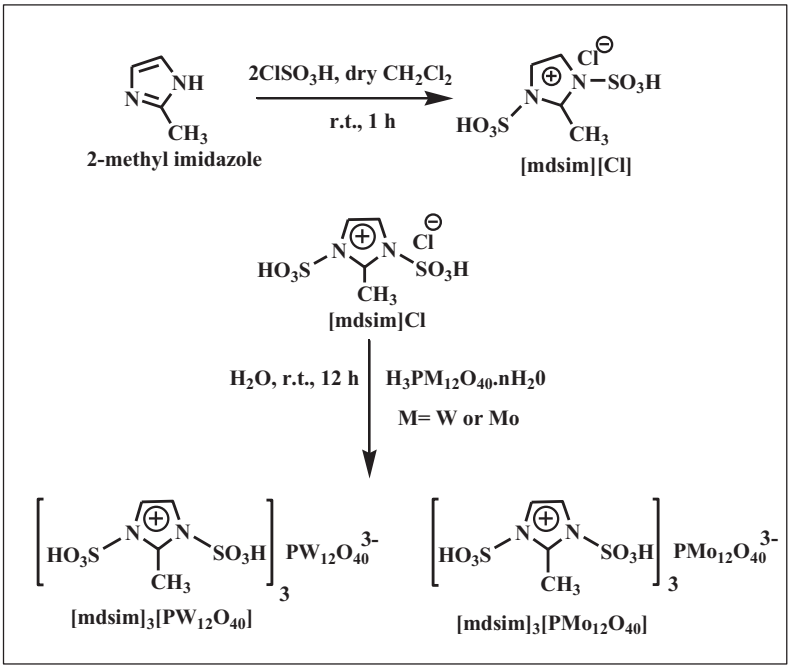
Fig. (11). Structure of the IL-POMs $[TEAPS]_{3+n}PW_{12-n}V_nO_{40}$ (n=1, 2, 3).

The above-mentioned literatures describe only development and catalytic uses of the acidic POM-ionic salts as solid or liquid material with various organic cations containing –N alkyl sulfonic groups for different organic reactions. The first direct N-sulfonic acid functionalized heteropolyacid-based ionic hybrid $[Simp]_3PW_{12}O_{40}$ was prepared in nano-form from the reaction of 3-sulfonic acid 1-imidazolopyridinium hydrogen sulfate $[Simp]HSO_4$ with $H_3PW_{12}O_{40}$ in aqueous solution involving solvothermal process as reported by Tayebee *et al.* (Scheme **20**) [73]. The synthesized compound was applied as heterogeneous nanocatalyst in one-pot, multi-component reaction of aldehydes, phthalhydrazide and dimedone under solvent free condition at 100°C to give 2H-indazolo[2, 1-b]phthalazine-1, 6, 11(13H)-trione within short time. The new ionic material gave 85% yield in 20 min which was more efficient as compared to other reported catalysts (30-120 min, 85-94% yield).



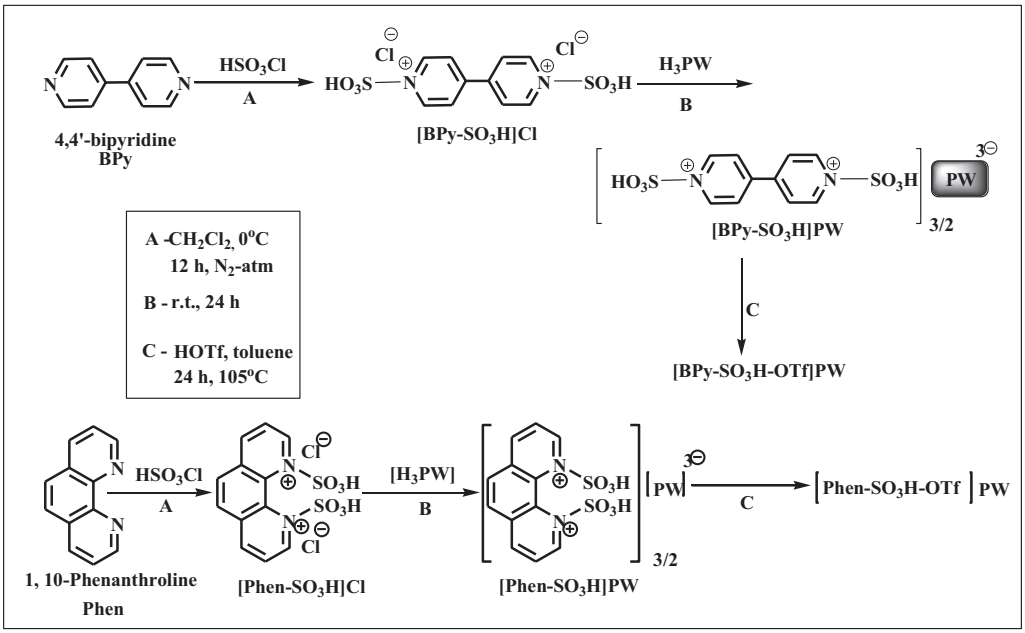
Scheme (20). Synthesis of $[Simp]_3PW_{12}O_{40}$.

Followed by this, Saikia *et al.* reported direct N-SO_3H functionalized 1, 3-disulfoimidazolium POM-salts of phosphotungstic acid and phosphomolybdic acid as reusable heterogeneous catalysts for nitration of aromatic hydrocarbons at ambient temperature within short time (Scheme **21**) [74]. In this work, direct N-SO_3H group replaced the traditional conc.H_2SO_4 in nitration reaction. The extra stability, reusability and milder reaction conditions were obtained from the HPA anion present in the catalyst. It minimized the adverse effects of the reaction and contributed towards a greener protocol for nitration reaction.



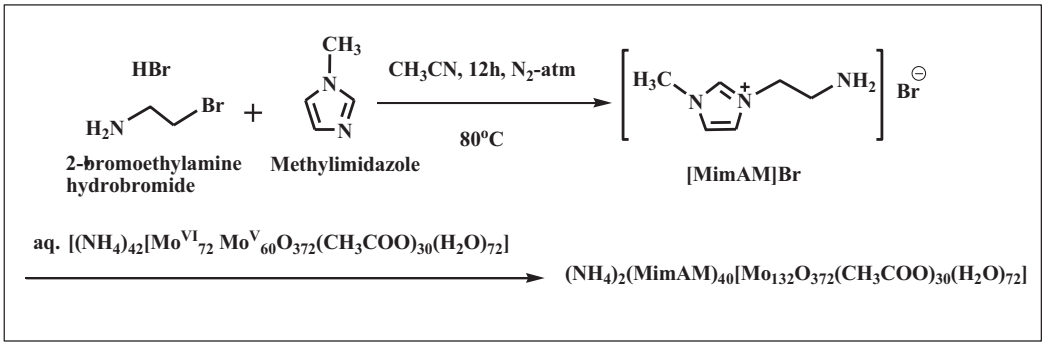
Scheme (21). Synthesis of N-SO_3H functionalized 1, 3-disulfoimidazolium POM-salts $[mdsim]_3[PW_{12}O_{40}]$ and $[mdsim]_3[PMo_{12}O_{40}]$.

Again in 2018, Cao and his group [75] prepared a series of novel superacidic polyoxometalate-based ionic hybrids by grafting polyoxometalate and sulfonic acid group on 4, 4'-bipyridine (BPy) and 1, 10-phenanthroline (Phen) (Scheme **22**) as highly efficient catalysts for indirect hydration of olefin to alcohol. The synthesized ionic hybrids [BPy-SO_3H]PW, [Phen-SO_3H]PW, [BPy-SO_3H-OTf]PW and [Phen-SO_3H-OTf]PW were examined along with other catalysts to assess their strength in esterification of cyclopentene with acetic acid using molar ratio of acetate acid to cyclopentene (3:1), catalyst dosage (20 wt.%), reaction temperature (80°C), reaction time (15h) with >99% selectivity. After performing the esterification of various carboxylate acids with different olefins over [BPy-SO_3H-OTf]PW catalyst with same reaction condition, direct and indirect hydration was conducted in 17.5 h time. The result showed the higher efficiency of the catalyst in indirect hydration with 96-98% yield in the second step of hydrolysis retaining its activity up to five consecutive runs.



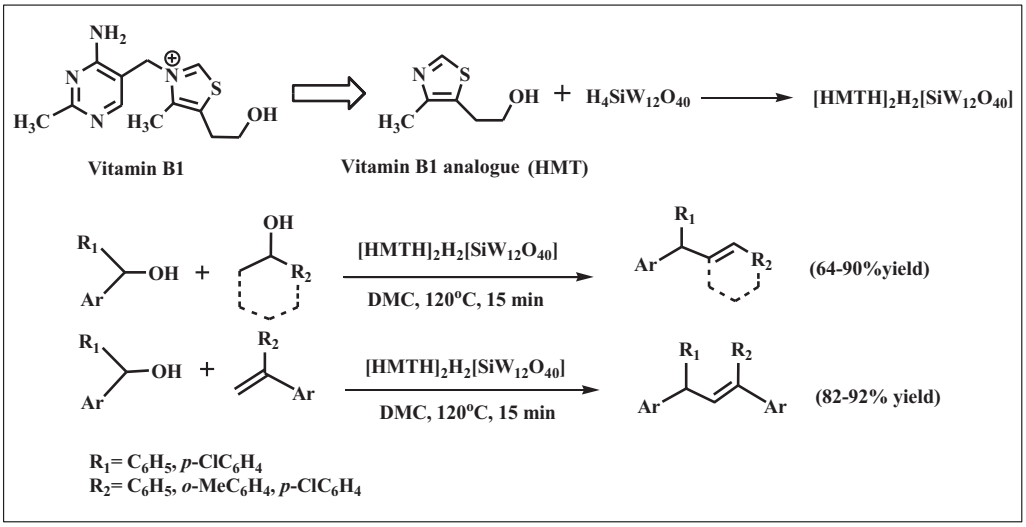
Scheme (22). Synthesis of ionic hybrids [BPy-SO_3H-OTf]PW and [Phen-SO_3H-OTf]PW.

Besides these –SO_3H functionalized ionic liquids, one-NH_2 functionalized ionic liquid was also synthesized and utilized by Fareghi-Alamdari *et al.* in 2017 to prepare an organic-inorganic material $(NH_4)_2(MimAM)_{40}[Mo_{132}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$ (Scheme **23**) [76]. They used this material as catalyst in the oxidation of dibenzothiophene (DBT) derivatives with H_2O_2 (35%) as a safe and green oxidant. The catalyst was easily separated from the reaction solution by simple filtration and recycled for several times without loss of activity.



Scheme (23). Synthesis of Mo132-MimAm by Fareghi-Alamdari *et al.*

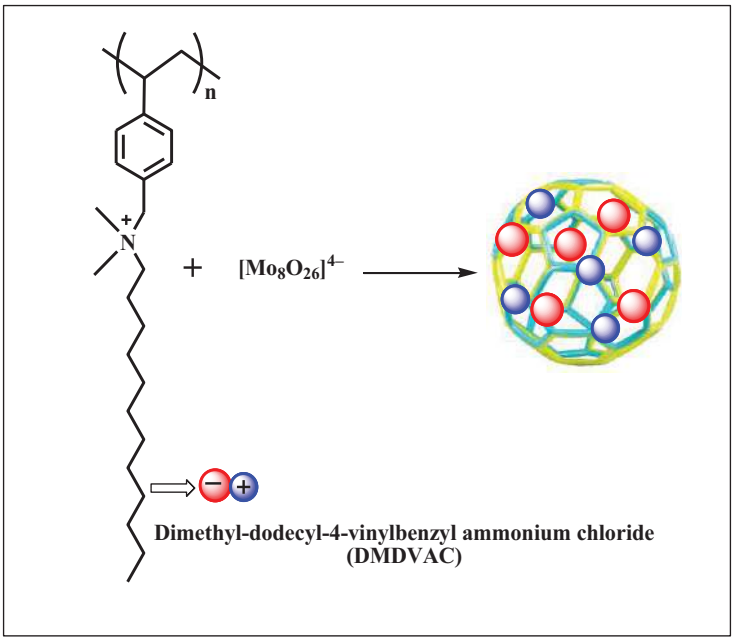
Yang and his coworkers (2019) designed an acidic heterogeneous ionic liquid $[HMTH]_2H_2[SiW_{12}O_{40}]$ from the inexpensive, nontoxic vitamin B1-like compound, *i.e.*, 5-(2-hydroxyethyl)-4-methylthiazole (HMT), and the noncorrosive heteropolyacid ($H_4SiW_{12}O_{40}$) (Scheme **24**) [77]. This catalyst was effectively used for the direct dehydrative coupling of alcohols with alcohols (or alkenes) to synthesize various polysubstituted olefins in good to excellent yields with dimethyl carbonate (DMC) as a green solvent. 3 mol% of the catalyst was able to catalyze the reaction in gram scale with satisfactory yield at 120°C within 1h in DMC. Up to eight cycles the catalyst was used without significant loss of its activity.



Scheme (24). $[HMTH]_2H_2[SiW_{12}O_{40}]$ catalyzed dehydrative reaction in dimethyl carbonate.

In the same year, Yang *et al.* developed poly(ionic liquid)-based porous hybrid materials through ionic self-assembly method and proposed as adsorbents for removal and separation of ionic dyes [78]. The ionic liquid poly-[N, N-dimethyldodecyl-(4-vinylbenzyl)ammonium chloride] was synthesized by simple radical polymerization and directly assembled with the multi-charged anionic cluster of polyoxometalate (POM) to form PIL/POM hybrid materials without involving any toxic organic solvents and tedious modification processes (Scheme **25**). The synthesized materials were utilized as adsorbents for removal of a variety of ionic dyes from water. The selectivity and adsorption ability towards cationic and anionic dyes could be effectively controlled by adjusting the proportion of PIL and POM in the hybrid materials. The PIL/POM hybrid possesses flexible interlinked framework, which contributed to the accessibility of adsorption sites, and thus exhibited excellent adsorption capacity unlike common cross-linked

polymer. The used adsorbent was easily collected and regenerated after completion of the process which proved the efficiency, durability and sustainability of the material in water purification treatment.



Scheme (25). Synthesis of PIL/POM hybrids.

All the above-mentioned works on IL-POMs highlighted their tremendous catalytic efficiency as heterogeneous self-separable catalyst in various reactions.

CONCLUSION AND FUTURE SCOPES

In conclusion, it was observed that the functionalized ionic liquids played an important role in polyoxometalate based catalytic systems by contributing their functionality to the materials. The significance of these IL-POM systems lies in the stability, efficiency, recyclability, and reusability of the catalysts. Transition from homogeneous to heterogeneous state brings the ultimate advantages of the materials. Literature reveals the limited functional groups tethered ionic liquid involved in the synthesis of IL-POMs. Ionic liquids containing Brønsted acidic functional group $–SO_3H$ have been utilized by researchers in the synthesis of $–SO_3H$ functionalized IL-POMs. Ionic liquids other than this have not been used for the development of functionalized IL-POMs except for one $–NH_2$ functionalized IL. From the detailed discussion of the reported methods and materials it is found that the scope of new strategies employing different task

specific ionic liquids with various functional groups may have the great potential in the field of organic synthesis. With the enhancement of properties such as stability, reusability and activity towards vast area of organic reactions, designing of new IL-POM materials would be a better choice to explore. This chapter claims to include all the functionalized IL-POMs used in various organic processes and brings out the opportunities for future development in this area.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 3

Recent Advances in the Synthesis and Bio-applications of Some Oxygen and Sulphur Containing Seven Membered Heterocyclic Compounds

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Abstract: Most of the heterocyclic compounds are pharmaceutically active and have numerous applications in various industries. Rigorous effects have been done and still going on in the search for more dynamic and advantageous compounds. Many researchers have focused their work on the synthesis of lower member heterocyclic compounds. However, not many efforts have been made for the higher membered compounds, though having equipotency. The aim of the current study is to collect and document the data available in the seven-membered heterocyclic compounds *i.e*. oxepin and thiepine compounds. The present study includes natural sources, drugs, synthetic methods, reactions, and biological activities of these compounds and their derivatives. Various seven-membered heterocyclic compounds have been synthesized *via* Friedel-craft Cyclization, Ullmann cross-coupling, Sonogashira coupling, and *etc*. However, biological potencies have still not been explored much by the researchers. This encouraged us to write this book chapter, as it has too much scope for future research.

Keywords: Anti-fungal, *Bauhinia purpurea*, *Bauhinia variegata*, Benzothiepine, Benzoxepin, C-O coupling, C-S coupling, Dibenzoxocinone, Dibenzoxepinone, Friedel-craft Cyclization, Intermolecular Cyclization, Intramolecular Cyclization, *Juncus effuses*, Michel Addition, Oxepine, Ptaeroxylin, Pterulinic acid, Sonogashira coupling, Thiepine, Ullmann cross-coupling.

INTRODUCTION TO O & S CONTAINING SEVEN MEMBER HETEROCYCLICS

Heterocyclic compounds are based on a variety of synthetic [1] and natural mole-

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cules [2]. In certain cases, hetero(poly) cyclic rings of different sizes form the backbone of drugs [3], bioactive molecules, and even specialized materials. Heterocycles are of vast significance for industrial, biological, and for the well working of human beings. Heterocycles are there in numerous natural products as well as pharmaceutically active compounds [4 - 8]. During recent years, there has been an intense investigation of different classes of heterocycles. Industrial researchers worldwide have synthesized heterocyclic compounds under ordinary and exceptional conditions, because these reactions are reliably and economically effective. Several different techniques have been developed in the past for the synthesis of different heterocycles, and this advancement is still in ceaseless demand [9 - 11]. The construction of heterocycles is highly considerable in organic synthesis [12]. The chemistry of heterocyclic compounds in organic chemistry continues to be an important field because of their variety of applications. Considering the fact that most of the pharmaceutical and agrochemical items contain at least one heterocyclic ring, we can assuredly see the significance of heterocyclic compounds. Also, a number of natural products depend on heterocyclic units only as a portion of the biologically active compound, for example, vitamins, antibiotics, and hormones [13, 14]. Heterocyclic compounds have become immensely important in human life, especially since these compounds have been successfully tested against several diseases and therefore needed medicinal imports. Heterocyclic compounds are common in nature and necessary to live. They play a key role in every living cell's metabolism. Heterocyclic compounds containing nitrogen, oxygen, and sulfur are essential building blocks used to construct different chemical compounds of immense biological or medical importance [15].

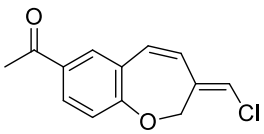
Medium-sized heterocyclic rings are the key in modern organic chemistry because of their ubiquity in Nature [16, 17]. Therefore, the synthesis of medium-sized rings is an important yet challenging goal in modern organic chemistry [18, 19]. An extensive research attempt has focused on the advancement of various methods for preparing a medium-sized rings, including macrocyclization [20], annulations [21], and ring expansion [22]. However, medium-sized heterocyclic rings are measured as complex structures to access because of their adverse transannular interactions to facilitate the synthesis of the desired product and entropic factors that disfavor cyclization. Benzene fused heterocycles become the center of attraction because of its wide scope of pharmacological activities [23]. Few methods exist for their synthesis. Furthermore, many well-designed strategies for the construction of these rings depend upon metal catalysis [24, 25]. Therefore, various novel methods for the synthesis of these heterocyclic rings are highly desirable.

From the literature study of the last 10 years, it was concluded that there is no such report present, which can portray the present situation going on in the synthesis and biological properties of O & S-containing seven-membered heterocycles. Although very few reviews are accounted for to date [26a-e, 27]. So this motivates us to write a report from 2010 to date which can describe the present situation of O & S-containing seven-membered heterocycles. In this review, we have mainly focused our interest on the synthesis and reaction of O & S-containing seven-membered heterocycles.

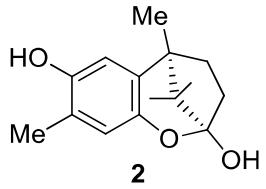
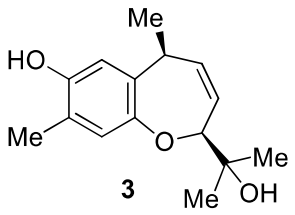
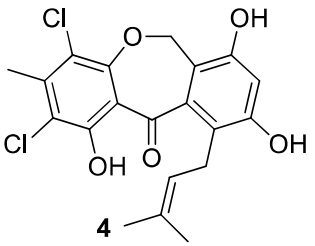
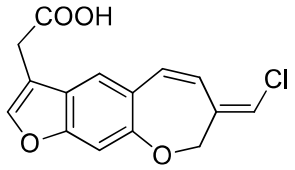
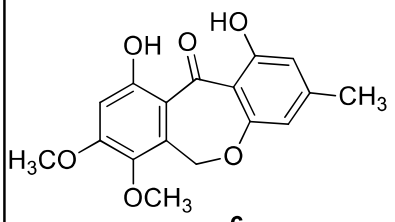
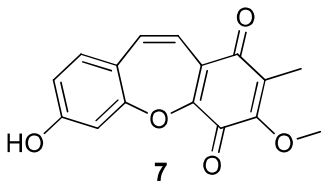
O-CONTAINING SEVEN-MEMBERED HETEROCYCLES

Oxepin is the seven-membered heterocycles containing Oxygen as a heteroatom. Oxepin and hydrooxepin homologous are core skeletons in many naturally occurring biologically active compounds. These compounds can also be used as an intermediate in the heterocycle synthesis [28] because of which their synthesis gained much attention. The carbon-oxygen bond formation is the simplest method for synthesizing oxygen-containing heterocyclic rings in organic synthesis [29]. Benzoxepines are broadly dispersed in a variety of pharmacologically active compounds and natural products [30], for example, pterulinic acid [30a] **(5)**, and ptaeroxylin [30b]. The dibenzo[b,f]oxepins moiety is somewhat rare in nature, and a maximum of them possess exciting medicinal properties [31]. In contrast to any other oxepin derivative, dibenz[b,d]oxepine derivatives synthesis has always been challenging for the researchers. Recently, dibenzo-[b,f]oxepins moiety have been isolated from the natural product by chemists, mainly from plants such as *Juncus effuses*, *Bauhinia variegata*, and *Bauhinia purpurea* [32] (Table **1**). Dibenzoxocinone and dibenzoxepinone are the basic moieties that are used in biologically active molecules, for example, Isoxepac **(16)** (for anti-inflammatory) [33], Arugosin F**(19)** (for Antifungal) [34], and Fluradoline **(20)** (for Analgesic drug) [35] (Table **2**). Dibenzo[b,d]oxepinones derivatives are of great significance.

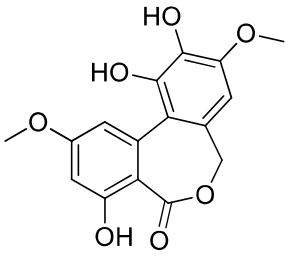
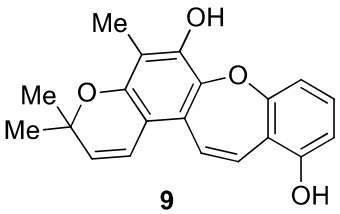
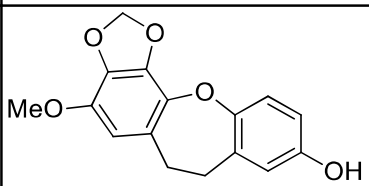
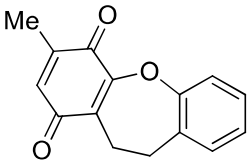
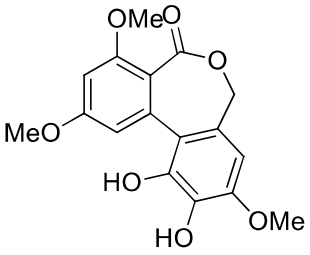
Table 1. The natural product containing fused oxepin moiety.

S.No.	Name	Structure	Sources	Biological Activity
1.	Pterulone [36]	 1	Isolated from mycelium and liquid cultures of wood-decay fungus in the genus Pterula.	Antibacterial, Antifungal properties

(Table 1) cont.....

S.No.	Name	Structure	Sources	Biological Activity
2	Enokipodin A [37]	 **2**	It is a sesquiterpenoid from enokitake	Antimicrobial activity.
3	Heliannuol B [38]	 **3**	Isolated from sunflower	Allelopathic activity
4	Pestalachloride B [39]	 **4**	Endophytic fungus	Antifungal activity
5	Pterulinic acid [36a]	 **5**	From fruit-derived fungi Pterula sp. 82168	Antifungal activity
6	Chaetone G [40]	 **6**	From Insect Pathogenic fungus Aschersonialuteola BCC 31749.	Antitumor
7	Bauhiniastatin 1 [41]	 **7**	From the aerial parts of Bauhinia purpurea	Anticancer

(Table 1) cont.....

S.No.	Name	Structure	Sources	Biological Activity
8	Ulocladol [41]	 **8**	From the marine sponge-derived fungi Ulocladium botrytis	Tyrosine kinase (p561ck) inhibitory
9	Bauhinoxepin A [42]	 **9**	Isolated from B. Saccocalyx	Antimycobacterial Activities
10	Bulbophyol B [43]	 **10**	Isolated from Bulbophyllum Kwangtungense	Inhibit human epithelial carcinoma and human erythomyeloblastoid leukemia cell lines
11	Bauhinoxepin J [43]	 **11**	Isolated B. Purpurea	Antimycobacterial activity, ant malarial activity, anti-tumor
12	Graphislactone d [44]	 **12**	From the cultured lichen mycobiont of Graphis scripta var. pulverulenta	Antitumor

(Table 1) cont.....

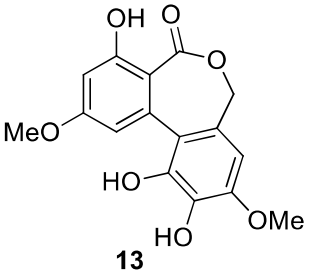
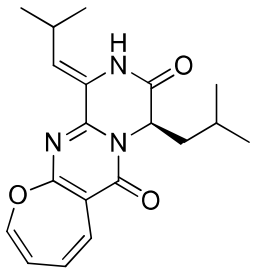
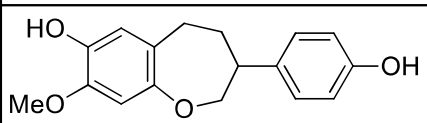
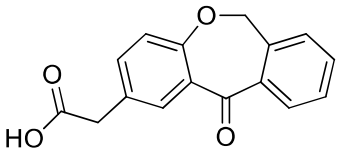
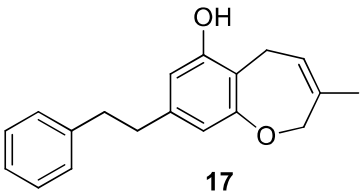
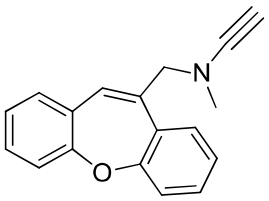
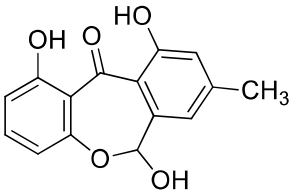
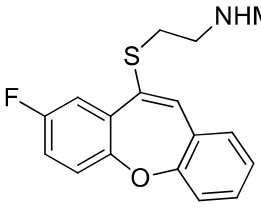
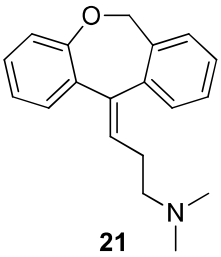
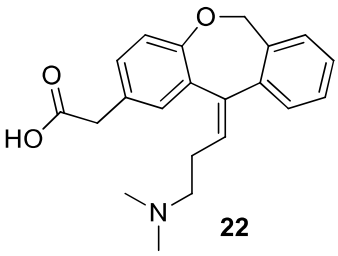
S.No.	Name	Structure	Sources	Biological Activity
13	Ulocladol [45]	 **13**	from a culture of the Ulocladium botrytis	Tyrosine kinase inhibitor
14	Aranotin [46]	 **14**	From the fungus Aspergillus Janus	Antiplasmodial activity against the malaria parasite

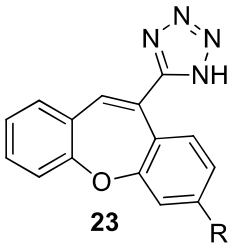
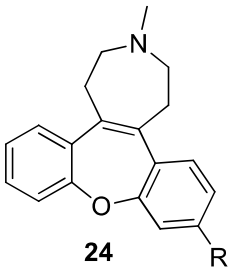
Table 2. Drugs containing O, Seven membered heterocyclic ring, and their derivatives.

S.No.	Name	Structure	Biological Activity
1.	Ruscozepine [47]	 **15**	Anti-inflammatory
2.	Isoxepac [33]	 **16**	Anti-inflammatory
3.	Radulanin A [48]	 **17**	Antibiotic activity

(Table 2) cont.....

S.No.	Name	Structure	Biological Activity
4.	CGP 3466 [49]	 **18**	Apoptosis inhibitor
5.	Arugosin F [34]	 **19**	Anti-fungal
6.	Fluradoline [35]	 **20**	Analgesic drug
7.	Doxepine [50]	 **21**	Anti-depressant
8.	Olopatadine [51]	 **22**	Anti-allergic

(Table 2) cont.....

S.No.	Name	Structure	Biological Activity
9.	Angiotensin-II [52]	 **23**	Receptor antagonist
10.	Maroxepine [53]	 **24**	Antipsychotic drug

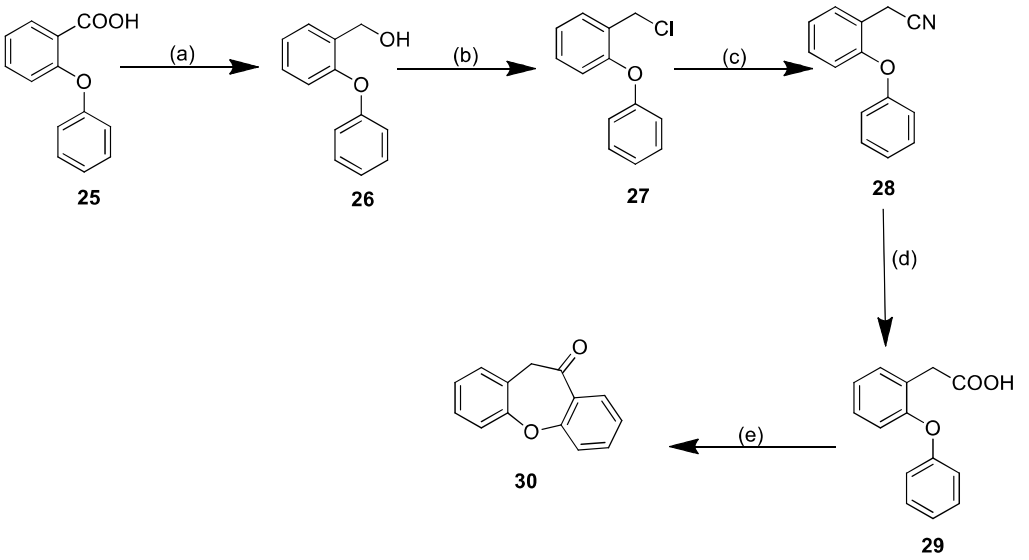
Synthesis of Oxepin and its Homologous

In recent years, various scientists have worked on synthesizing oxepin derivatives and have explored their biological part. Although the synthesis of the seven-membered oxepin has always been a tough task for researchers. Synthesis of oxepin ring has been gained by an intramolecular or intermolecular cycloaddition followed by ring cyclization.

Intramolecular Ring Cyclization

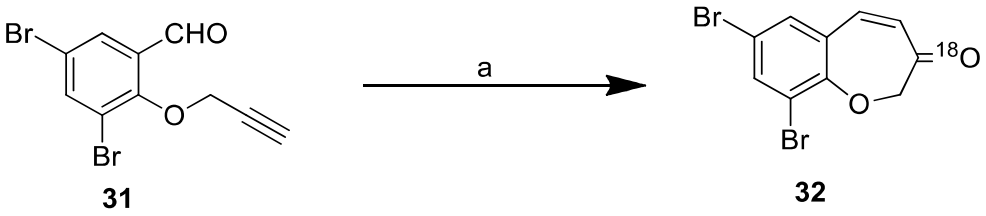
C-C Bond Formation

Dorn *et al.* [54] showed their interest in synthesizing dibenz[b,f]oxepinone *via* a multi-step reaction. The first step proceeds by the reduction of 2-phenoxybenzoic acid **(25)** with $LiAlH_4$ in THF to give (2-phenoxy phenyl)methanol **(26),** which further reacts with thionyl chloride to give 1-(chloromethyl)-2-phenoxy benzene **(27),** which was further converted to nitriles **(28)** with potassium cyanide followed by oxidation with KOH to give 2-(2-phenoxy phenyl)acetic acid **(29)**. Further, the acids undergo ring-closure by the intramolecular Friedel–Crafts metathesis to give the product **(30)** under the optimized reaction conditions, which act as a p38 MAP kinase enzyme (Scheme **1**).



Scheme (1). Synthesis of dibenz[b,f]oxepinone. Reagents: **a)** $LiAlH_4$, THF, 0 °C, reflux, temperature, 4h; **b)** $SOCl_2$, toluene, 80 °C, 1.5h; **c)** Potassium cyanide, H_2O, ethanol, reflux, temperature, 5h; **d)** Potassium hydroxide, H_2O, ethanol, reflux, temperature, 4h; **e) (i)** Dichloromethane, 1.5h; **(ii)** $AlCl_3$, Dichloromethane, rt, 2.5h.

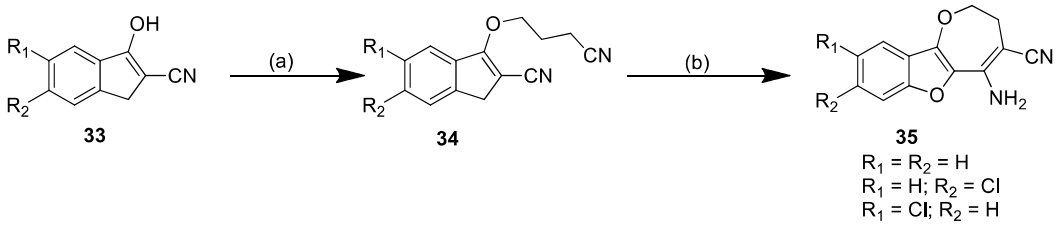
Sze *et al.* [55] in 2011 portrayed a new method for the gold-catalyzed synthesis of fused oxepinone **(32)** *via* Petasis–Ferries rearrangement/ tandem intramolecular heterocyclization. The substituted benzaldehyde **(31)** undergoes Petasis–Ferries rearrangement/ Tandem intramolecular heterocyclization under the mild reaction condition to give the reported product **(32)** in a maximum yield of 99% (Scheme **2**).



Scheme (2). Gold catalyzed synthesis of fused oxepinone. Reagents: **a)** (i) BnOH (1.2equiv), DCM, air, RT, 1h; (ii) *p*TsOH.H_2O (20 mol%), 40 °C, 6h.

Okuda and *et al.* [56] in 2012 portrayed the synthesis of compound **(35)** *via* Thorpe-Ziegler reaction. The 3-hydroxy-1H-indene-2-carbonitrile **(33)** was reacted with C_6H_4ClN in the presence of K_2CO_3 and potassium iodide in dimethylformamide to give 3-(3-cyanopropoxy)-1H-indene-2-carbonitrile **(34),**

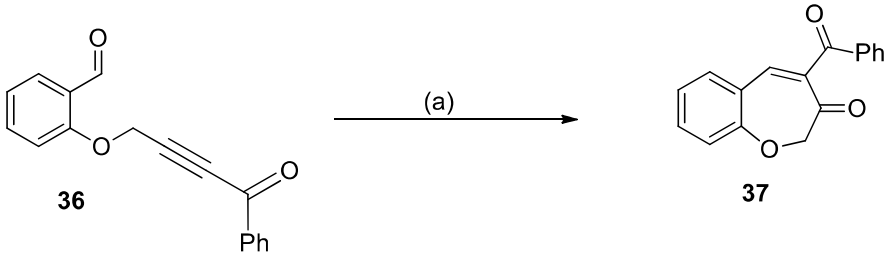
which was further reacted with *t*- BuOK in dry tetrahydrofuran to give compound **(35)** in very low yield (Scheme **3**).



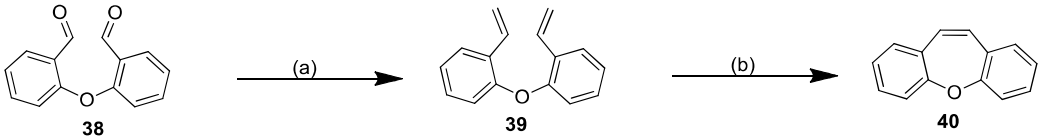
Scheme (3). Synthesis of benzofuro [3,2-b]oxepin derivative *via* Thorpe-Ziegler reaction. Reagents: **a)** 4-chlorobutylnitrile, K_2CO_3, KI, DMF; **b)***t*-BuOK, THF.

Mangina *et al.* [57] examined the gold (III) catalyzed intramolecular cyclization of benzaldehyde **(36)** using ACN and water as a solvent at 70 °C to get the expected product **(37)** in medium yield (Scheme **4**).

Matsuda and Sato [58] in 2013 demonstrated the synthesis of dibenzo[b,f]oxepine derivative **(40)** *via* Wittig methylenation of bis(2-formylphenyl)ether **(38)**, to furnish Bis(2-vinylphenyl) ether **(39)** followed by Ru catalyzed subsequent ring-cyclization metathesis to afford the synthesis of dibenzo[b,f]oxepine **(40)** in high yield (Scheme **5**).



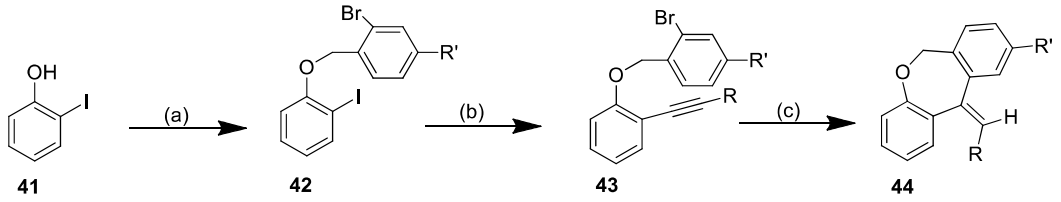
Scheme (4). Gold catalyzed synthesis of 4-benzoylbenzo[b]oxepin-3(2H)-one. Reagents: **a)** $AuCl_3$ (10%), CH_3CN/H_2O (2:0.1), 70 °C, 3h.



Scheme (5). Synthesis of dibenzo[b,f]oxepine derivative *via* Wittig methylenation. Reagents: **a)** $Ph_3P{=}CH_2$; b) [Ru].

Majumdar *et al.* [59] study the scope of Mizoroki-Heck cyclization reaction for the synthesis of (Z)-11-butylidene-6,11-dihydrodibenzo[b,e]oxepine **(44)** its

homologous. The 2-iodophenol **(41)** undergoes a coupling reaction with 2-bromobenzylbromide under the required condition to give the compound **(42)**. Further, the iodine compound **(42)** undergoes the Sonogashira cross-coupling reaction with an alkyne to synthesize a compound **(43),** which further undergoes the Mizoroki-Heck cyclization reaction to give the required product **(44)** in moderate yield (Scheme **6**).

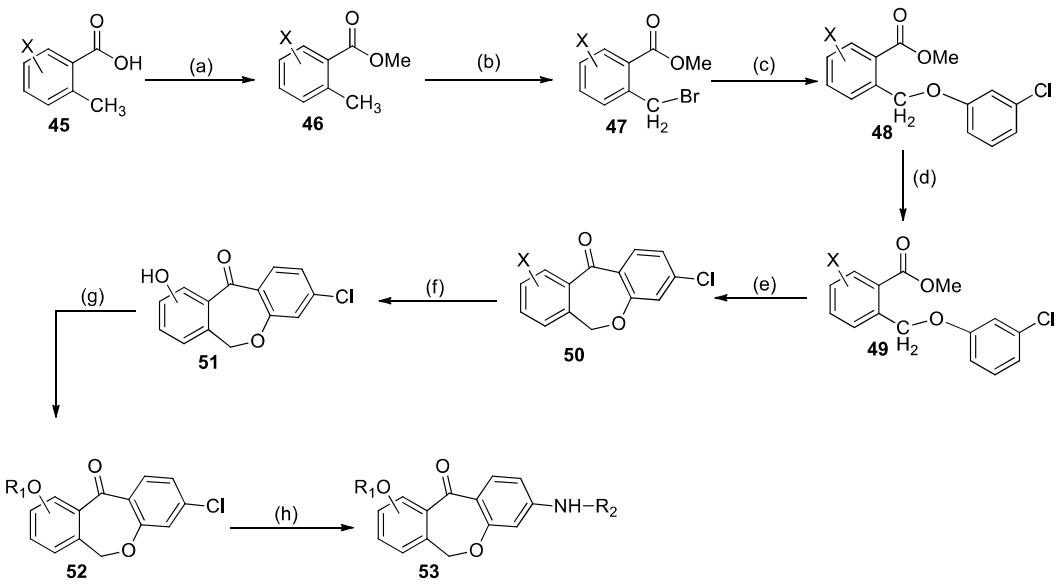


R = C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, Ph, $CMe_2(OH)$, $CHMe(OH)$, CH_2OH, $SiMe_3$, *p*-MeC_6, *m*-$OMeC_6H_4$, *p*-$CMe_3C_6H_4$; R' = H
R = C_4H_9, C_5H_{11}; R' = OMe

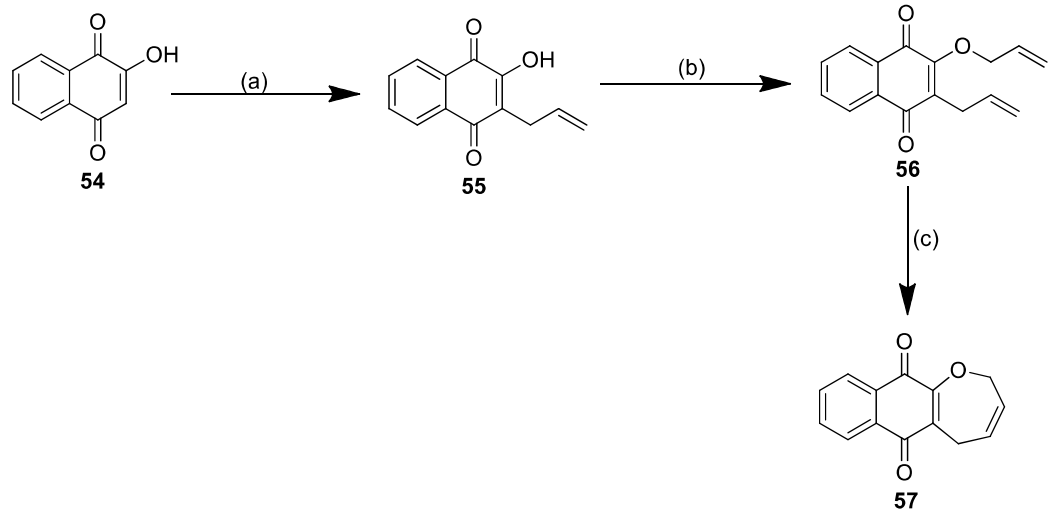
Scheme (6). Synthesis of (Z)-11-butylidene-6,11-dihydrodibenzo[b,e]oxepine derivatives *via* Mizoroki-Heck cyclization reaction. Reagents: **a)** $C_7H_6Br_2/C_6H_2Br_2O$, acetone, potassium carbonate, reflux, 4h; **b)** Alkyne, $Pd(PPh_3)_2Cl_2$, CuI,dimethylformamide(DMF), triethylamine, rt, 4h; **c)** $Pd(PPh_3)_4$, HCOONa, DMF/H_2O (5:2), 100 °C, 2-4h.

Kassiou and co-workers [60] in 2013, demonstrated the synthesis of dibenzooxepinone derivative **(53)** *via* a multi-step reaction under different reaction conditions (Scheme **7**) which acts as a P2X7 receptor antagonist. The first step proceeds *via* esterification of 3- or 4-methoxy-substituted 2-methylbenzoic acid derivatives **(45)** to give the compound **(46),** which further undergoes bromination of benzyl group **(47)** followed by esterification with 2-chlorophenol to give the corresponding ester as an intermediate product **(48)** which was further hydrolyzed to give acid **(49)** followed by intramolecular Friedel-craft acylation under the required reaction condition to give a ring cyclized product as an intermediate **(50)** which is then reacted with boron tribromide at low temperature in DCM in order to obtain the phenol derivative **(51)**. The tricyclic oxepin ring **(52)** was further reacted with substituted aniline derivatives to get the target product **(53)**.

Rocha *et al.* [61] in 2014 worked on the synthesis of Oxepin derivative **(57)** *via* intramolecular ring cyclization. 2-hydroxynaphthalene-1,4-dione **(54)** undergoes O-allylation with allyl bromide under microwave irradiation at 150 °C using K_2CO_3 and DMF as a base followed by [3, 3]-sigmatropic rearrangement to give 3-allyl intermediate **(55)** in 55% yield. The intermediate **(55)** further undergoes *O*-allylation with allyl bromide **(56)** followed by ring-closing metathesis using Grubb's catalyst to give oxepin as a final product **(57)** in medium yield (Scheme **8**).

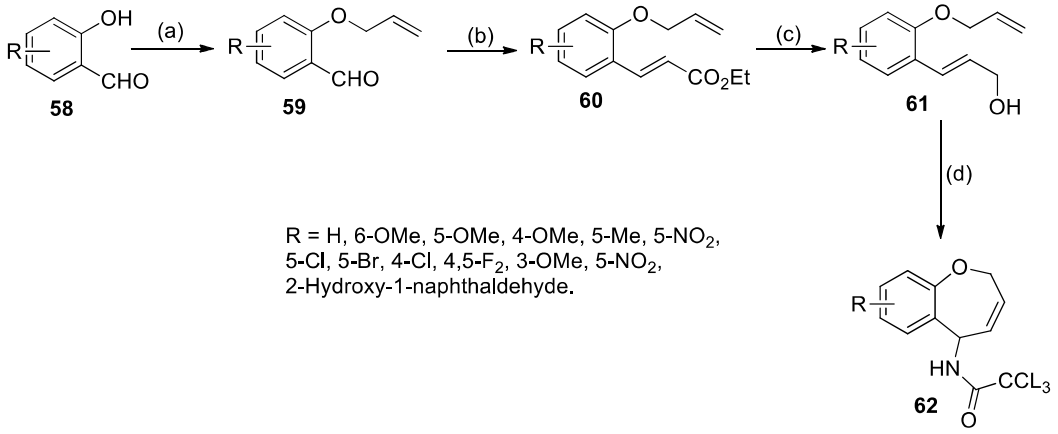


Scheme (7). Synthesis of dibenzooxepinone derivative Reagents: **a)** H_2SO_4, MeOH, reflux; **b)** NBS, CCl_4, 72 °C; **c)** K_2CO_3, 3-chlorophenole, Me_2CO, reflux; **d)** KOH, MeOH/H_2O, 40^{0}C; **e)** $SOCl_2$, $AlCl_3$, DCM, room temperature, TFAA, BF_3-Et_2O, DCM, rt; **f)** BBr_3, DCM, -20 °C; **g)** K_2CO_3, R_1-X, Me_2CO/DMF, reflux; **h)** Substituted aniline derivatives, Cs_2CO_3, X-Phos, Pd(OA **c)**$_2$, 1,4-dioxane, *t*-BuOH, reflux, For the nature of R_1 and R_2.



Scheme (8). Synthesis of Oxepin derivative *via* intramolecular ring cyclization. Reagents: **a)** allyl bromide, MW, 150 °C, DMF, potassium carbonate; **b)** allyl bromide, dry acetone, potassium carbonate; **c)** refluxing DCM, Grubb's catalyst.

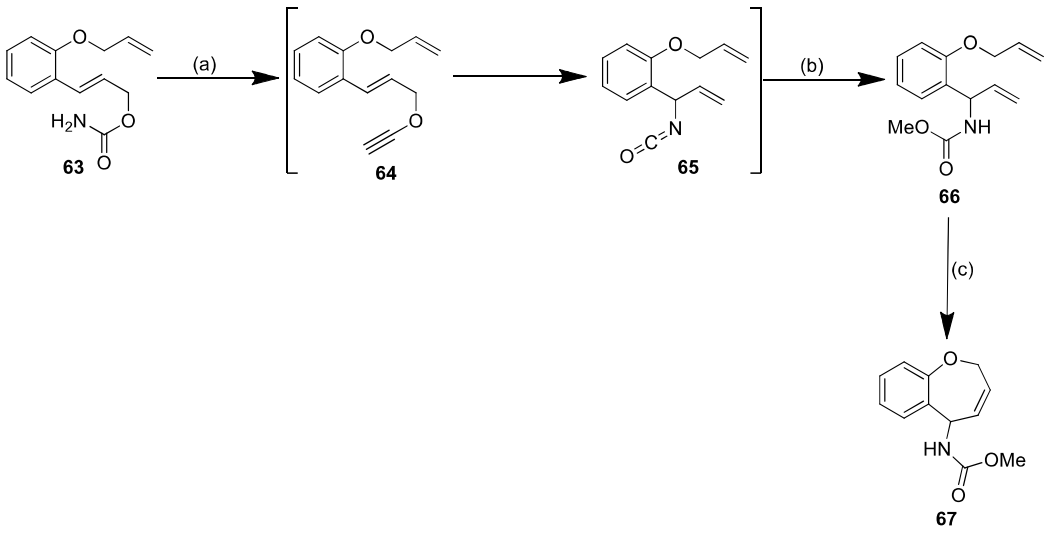
Calder and co-workers [62] worked on the organic synthesis of oxepin derivative **(62),** starting with salicylaldehydes **(58)** (Scheme **9**). The salicylaldehydes **(58)** undergo *o*-allylation with allyl bromide in the presence of K_2CO_3 in DMF to give 2-allyloxybenzaldehydes **(59),** which further undergoes Horner– Wadsworth–Emmons reaction with TEPA under mild Masamune– Roush conditions to give the compound **(60)** which was further reduced with DIBAL-H to give the resulting alcohol **(61)**. The resulting alcohol **(61)** was subjected to ring cyclization under standard reaction conditions to give the required product **(62),** which shows significant biological properties as an ACAT inhibitor.



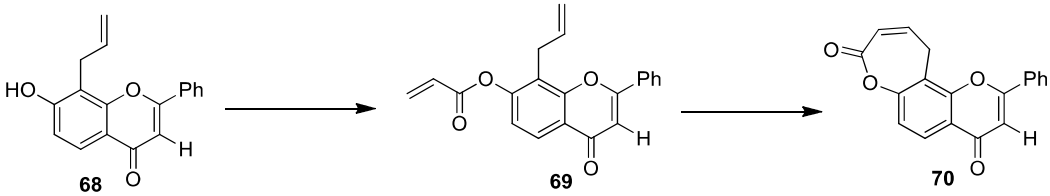
Scheme (9). Synthesis of Benzoxepin derivative. Reagents: **a)** allyl bromide, K_2CO_3, DMF, 70 °C, 2h; **b)** LiBr, TEPA, DBU, MeCN, rt, 18h; **c)** DIBAL-H, Et_2O, -78 °C to rt, 18h; **d) (i)** Cl_3CCN, DBU, DCM, rt, 1h; **(ii)** 140 °C, K_2CO_3, *p*-Xylene, 18h; **(iii)** grubbs II (5 mol%), 50 °C, 20h.

Chwastek *et al.* [63] in 2016 reported Carbamate **(63)** as a reactant for the synthesis of benzoxepin derivative **(67)** (Scheme **10**). The Carbamate **(63)** was reacted with 2,2,2-trifluoroacetic anhydride (TFAA) in the presence of triethylamine to give allyl cyanate **(64)** followed by [3, 3] sigmatropic rearrangement to give allyl isocyanate **(65)**, which further gets converts to allyl carbamate **(66)** followed by ring cyclization to give the final product **(67)** under the optimized reaction condition.

Rao *et al*. [64] in 2016, portrayed a two-step reaction for the synthesis of oxepin derivatives **(70)**. The compound **(68)** undergoes Claisen rearrangement **(69)** followed by intramolecular ring-closing to give the target product **(70)** under the optimized reaction condition (Scheme **11**) which possesses the anti-mycobacterial property.

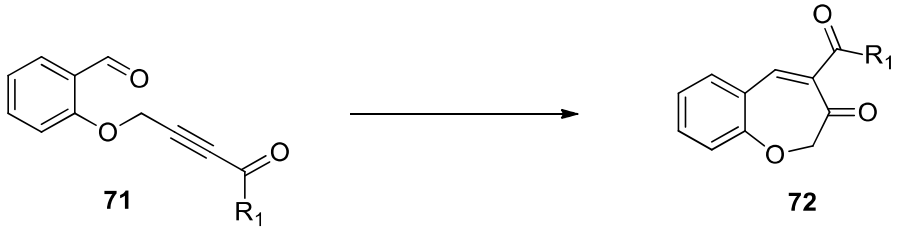


Scheme (10). Synthesis of benzoxepin derivative. Reagents: **a)** TFAA, Et_3N, THF, 0 °C to rt, 1h; **b)** MeOH, Bu_3SnOMe, tetrahydrofuran, room temperature (overall 3 steps); **c)** Grubbs II catalyst (5 mol%), Dichloroethane (DCE), 50 °C.



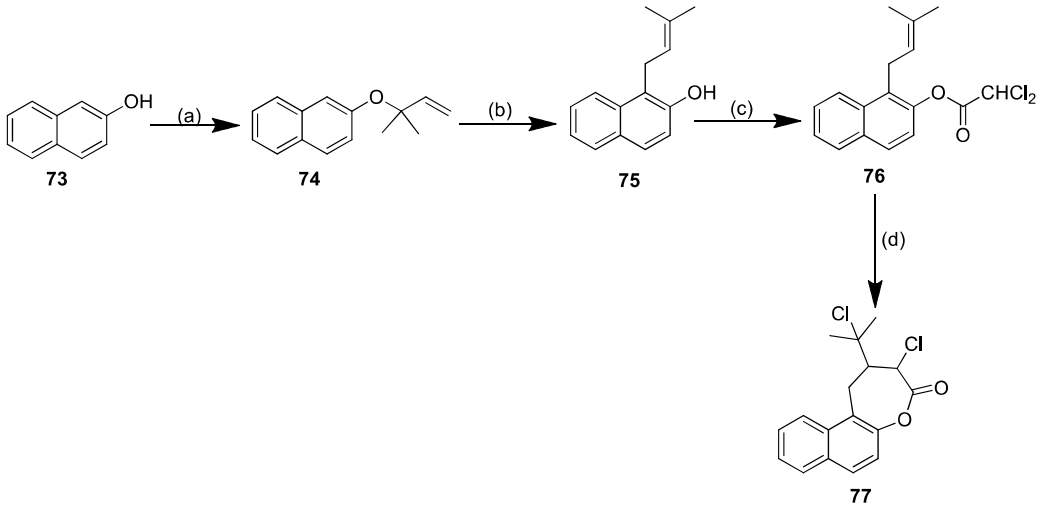
Scheme (11). Synthesis of oxepin derivative *via* Claisen rearrangement.

Mangina *et al.* [57] in 2016 worked on the Au-catalyzed intramolecular cyclization of substituted aryl aldehydes **(71)**. The alkyne of compound **(71)** undergoes oxidation, which further undergoes intramolecular condensation to give benzo fused oxepin **(72)** as a major product (Scheme **12**).



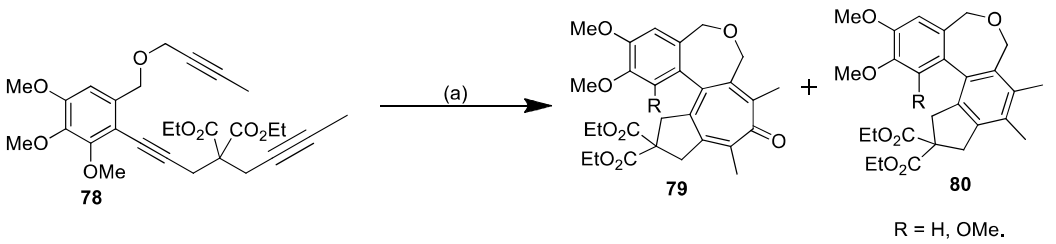
Scheme (12). Synthesis of oxepinone derivative *via* ring cyclization.

Tittal [65] in 2017 described a novel route for the synthesis of 3-chloro-2-(2-chloropropan-2yl)-2,3-dihydronaphtho[2,1-b]oxepin-4(1H)-one **(77)** starting from 2-napthol **(73)**. The 2-napthol **(73)** on reaction with 3-bromo-3-methyl-but-1-ene under mild reaction condition give compound **(74)**, which further undergoes thermal Claisen rearrangement reaction in DMA to afford the synthesis of compound **(75)** followed by protection of hydroxyl group with dichloroacetyl chloride ($CHCl_2COCl$) in the presence of base Et_3N (triethyl amine) to give compound **(76)**, which was further reacted with CuCl/bpy in dry DCE under inert N_2 to synthesize the target product *i.e.,* 3-chloro-2-(2-chloropropan-2-yl)-2, 3-dihydronaphtho[2,1-b]oxepin-4(1H)-one **(77)** in medium yield (Scheme **13**).



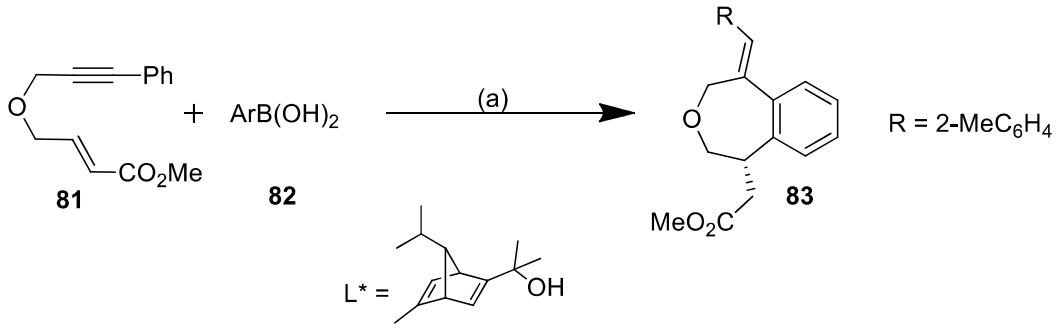
Scheme (13). Multi-step reaction patheay for the synthesis of oxepin derivative. Reagents: **a)** 3-bromo-3-methyl-but-1-ene/K_2CO_3; **b)** Claisen rearrangement DMA/120-130 °C; **c)** Dichloroacetylation in Et_3N/0-5 °C; **d)** CuCl/TMEDA (1:1 molar ratio), dry DCE, reflux for 5 hours.

Chien [66] in 2018 worked on the synthesis of tetracyclic oxepine moiety **(80)** *via* intramolecular cycloaddition. The compound **(78)** undergoes intramolecular [2+2+2+1] or [2+2+2] cycloaddition using $[Rh(CO)_2Cl]_2$ as a catalyst in toluene to give the target product **(79) & (80)** in excellent yield (Scheme **14**). The product was tested against various biological activities [67].



Scheme (14). Synthesis of oxepine derivative *via* intramolecular [2+2+2+1] or [2+2+2] cycloaddition. Reagents: **a)** $[Rh(CO)_2Cl]_2$ (5 mol%). CO (1atm), toluene [0.1M], 60 °C, 120h.

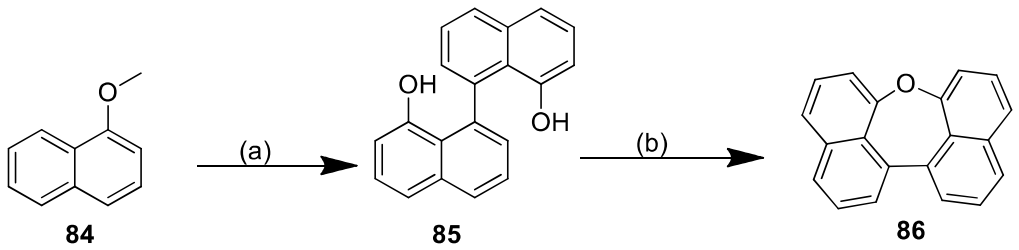
Selmani *et al.* [68] worked on the synthesis of Rh catalyzed tetrahydrobenzo [d]oxepines **(83)** derivative. The compound **(81)** reacts with arylboronic acids **(83)** in the basic medium at 60 °C using $[RhCl(CH_2CH_2)_2]_2$ as a catalyst in the presence of chiral Dane L* to afford the synthesis of the cyclized product with high enantioselectivities (Scheme **15**).



Scheme (15). Synthesis of Rh catalyzed tetrahydrobenzo[d] oxepines derivative. Reagents; **a)** $[RhCl(CH_2CH_2)_2]_2$ (1.5 equiv), L* (3.3 mol%), KOH (3.3 mol%), MeOH, 60 °C.

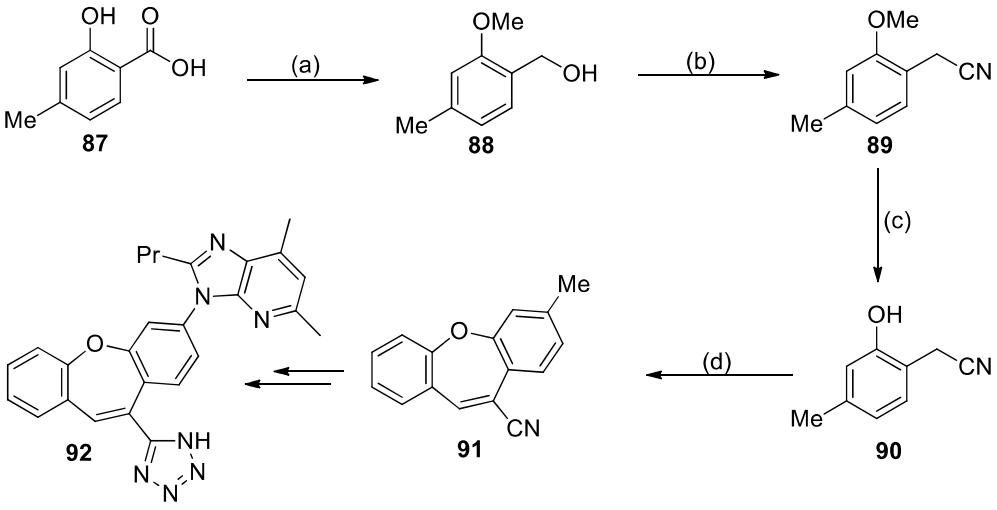
C-O Bond Formation

Dobelmann *et al.* [69] carried out their work for the Synthesis of dinaphtho-oxepine derivative **(86)**. The 1-methoxynaphthalene **(84)** undergoes C-C bond formation using Fe(aca **c**)$_3$ followed by the deprotection of the methoxy group using BBr_3 in DCM at 0 °C to give diol [70] **(85)** in excellent yield, which further undergoes intramolecular ring cyclization using *p*-TsOH in refluxing toluene [71] to afford the synthesis of compound **(86)** in 87% yield (Scheme **16**).



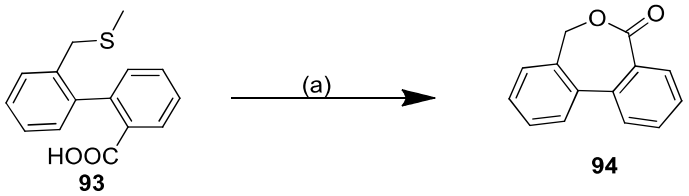
Scheme (16). Synthesis of dinaphtho[1,8-bc:1',8'-ef]oxepine. Reagents: **a)** (i) n-BuLi (1.1 eq.), 0 °C, Fe(aca **c)**$_3$ (1.1 eq.), rt, 2 h; (ii) BBr_3 (2.2 eq.), CH_2Cl_2, 0 °C, 3 h; **b)** *p*-TsOH, toluene, reflux.

Choi *et al.* [72] worked on the synthesis of organic compounds **(92)**. The 2-hydroxy-4-methylbenzoic acid **(87)** undergoes methylation of the alcohol group followed by acidic reduction to give the corresponding (2-methoxy-4-methylphenyl) methanol **(88)** in excellent yield. Further, the compound **(88)** undergoes bromination-cyanidation under the optimized condition to give 2 (2-methoxy-4 methylphenyl) acetonitrile **(89)** in 87% yield, which further undergoes demethylation to give the corresponding 2-(2-hydroxy-4-methylphenyl) acetonitrile **(90)** followed by ring-cyclization to give 7-methyldibenzo[b,f] oxepine-10-carbonitrile **(91)**. They further worked out their interest in the synthesis of angiotensin II antagonist **(92)** (Scheme **17**).



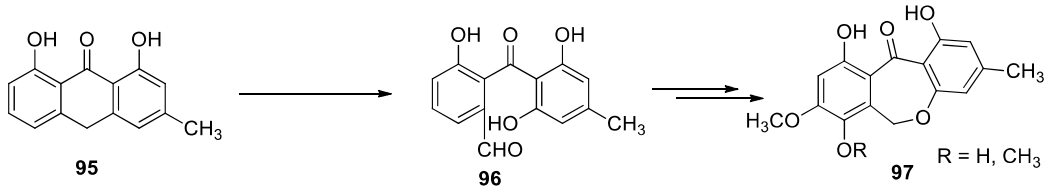
Scheme (17). Synthesis of dibenzo[b,f]oxepin derivative. Reagents: **a) (i)** MeI, K_2CO_3, acetone, reflux, 18h; **(ii)** $LiAlH_4$, THF, 0 °C, 10min; **b) (i)** PBr_3, pyridine, Et_2O, 50 °C, 2h; **(ii)** NaCN, TBAB, DCM/H_2O (1:1), 25 °C, 5h; **c)** NaCN, DMSO, 180 °C, 5h; **d)** Cs_2CO_3, MS, toluene, 130 °C, 48h.

Zhang *et al.* [73] in 2015 also carried out their research on the synthesis of compound **(94)** in excellent yield *via* intramolecular ring cyclization of 2'-(methylthio)methyl)-[1,1'-biphenyl]-2-carboxylic acid **(93)** under the optimized reaction condition (Scheme **18**).



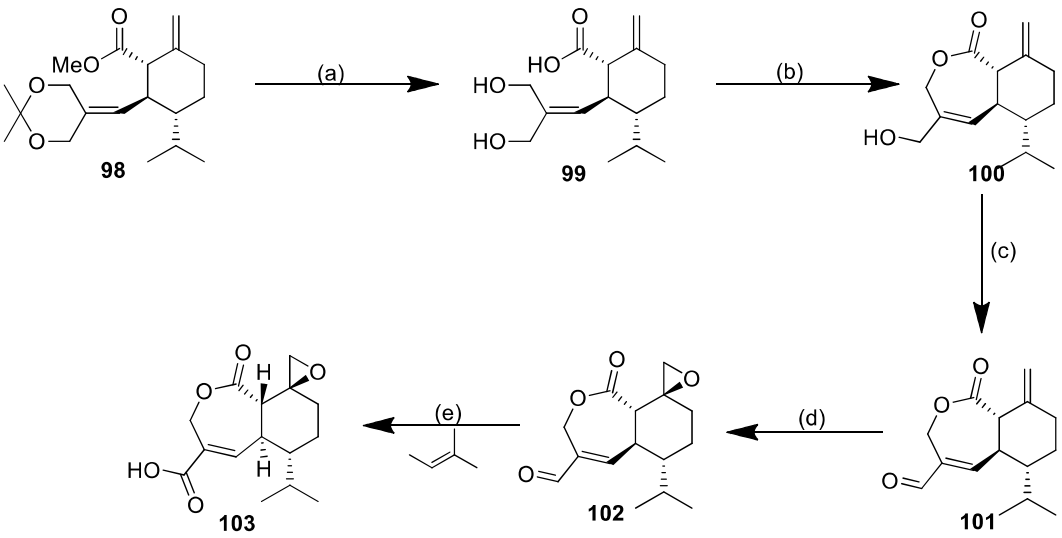
Scheme (18). Synthesis of dibenzo[c,e]oxepin-5(7H)-one. Reagents: **a)** $[Cp^*Rh(CH_3CN)_3][SbF_6]$ (5 mol%), 1-AmylOH (1 ml), air, 120 °C, AgOAc (2.0 equiv).

Kornsakulkarn *et al.* [74] in 2015 reported the scope of oxidative cleavage of compound **(95)** to give 2-(2,6-dihydroxy-4-methylbenzoyl)-3-hydroxybenzaldehyde **(96)** as an intermediate product followed by ring cyclization to give Compound **(97)** as a final product, which is rich in antibacterial property and possess cytotoxic activities against MCF-7, KB, and NCI-H187 (Scheme **19**).



Scheme (19). Oxidative cleavage of anthracene derivative.

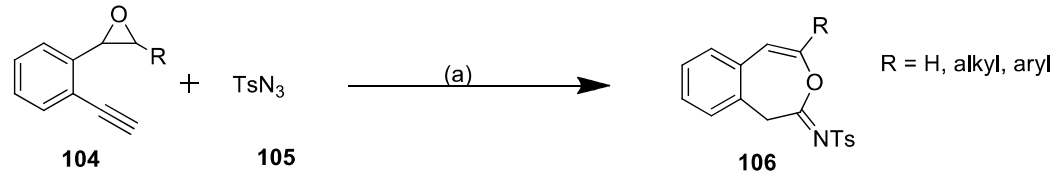
Barbe *et al.* [75] in 2020 demonstrated the scope of a multi-step reaction for the synthesis of compound **(103)**. The compound **(98)** undergoes hydrolysis under the labeled conditions to give the corresponding diol **(99)** in 92% yield, which further undergoes lactonization conditions followed by the removal of triethylammonium salts to give the cyclized product **(99)**. The compound **(100)** further undergoes allylic oxidation using MnO_2 as an oxidizing agent to give a corresponding aldehyde **(101)** followed by epoxidation using $MoO_3.H_2O$ as a catalyst to give compound **(102)**. The final step proceeds by the generation of acid **(103)** using Pinnick oxidation conditions (Scheme **20**).



Scheme (20). Synthesis of spiro [benzo[c]oxepin derivative. Reagents: **a) (i)** HCl, H_2O; **(ii)** NaOH, H_2O; **b)** BOP-Cl, DMAP, Et_3N, DCM; **c)** MnO_2, DCM; **d)** TBHP, $MoO_3.H_2O$, toluene; **e)** NaOCl, NaH_2PO_4, *t*-BuOH:H_2O.

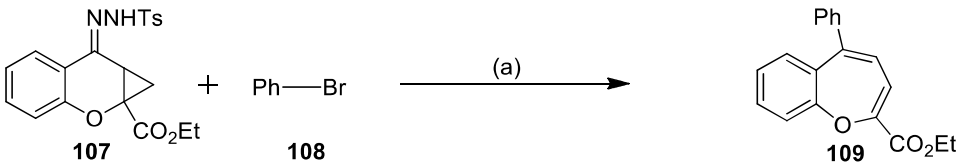
Ring Expansion

Li *et al.* [76] in 2012 worked on the Cu (II) catalyzed reaction of 2-(--ethynylphenyl)oxiranes **(104)** with 4-methylbenzenesulfonyl azide **(105)** using 1,4-dioxane as a solvent and *i*-Pr_2 NEt as a base to give the target product *i.e.* 3-benzoxepine derivative **(106)** in moderate yield (Scheme **21**).



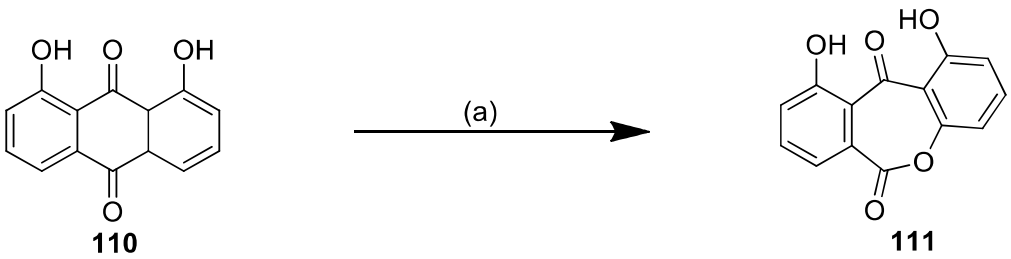
Scheme (21). Synthesis of 3-benzoxepine derivative. Reagents: **a)** CuCl (10 mol%), *i*-Pr_2NEt (1.5 equiv), 1,4-dioxane, rt, 0.5-2h.

Xie *et al.* [77] in 2016 represented a reaction pathway for the synthesis of compound **(109)** (Scheme **22**). The compound **(107)** undergoes Pd-catalyzed carbene insertion and β-carbon elimination, followed by ring expansion of the highly strained cyclopropane ring **(109)** under the basic reaction conditions.



Scheme (22). Ring expansion of cyclopropane. Reagents: **a)** Pd/L, base, solvent, T °C.

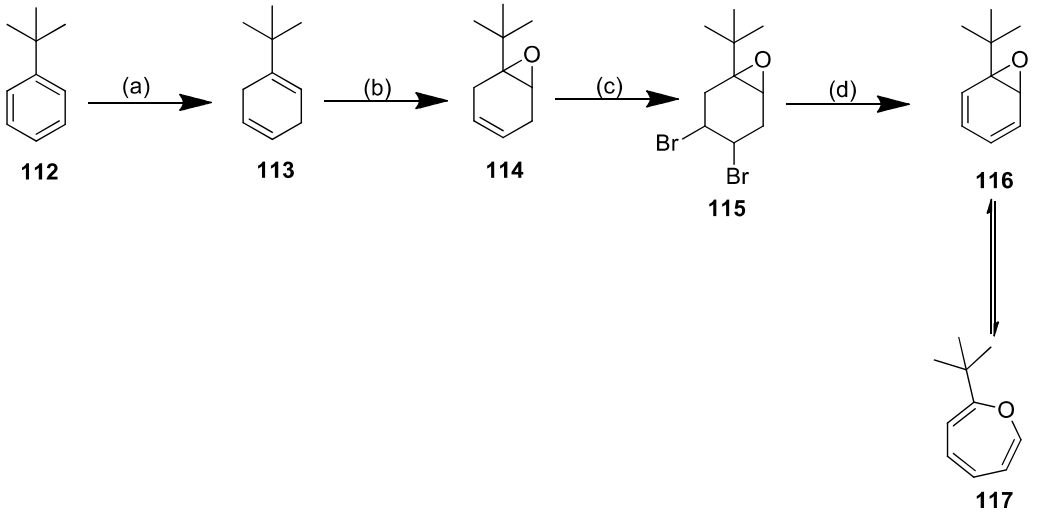
Newson *et al.* [78] studied the scope of Baeyer−Villiger reaction for the synthesis of Oxepin moiety **(111)**. 1,8-dihydroxy anthracene-9,10(4aH,9aH)-dione **(110)** was reacted with peroxytrifluoroacetic acid in DCM followed by Baeyer−Villiger reaction mechanism to synthesize 1,10-dihydroxydibenzo[b,e]oxepine-6,11-dione **(111)** in very low yield [79, 80] (Scheme **23**).



Scheme (23). Synthesis of 1,10-dihydroxydibenzo[b,e]oxepine-6,11-dione *via* Baeyer−Villiger reaction. Reagents: **a)** F_3CCO_3H, DCM.

Stok *et al.* [79] in 2016 worked on the synthesis of substituted oxepine derivatives **(117)** by the reported procedure [80]. The tert-butylbenzene **(112)** undergoes birch reduction to give 1-(tert-butyl)cyclohexa-1,4-diene [81] **(113)** followed by epoxidation with *m*-CPBA to give the corresponding epoxide ring **(114)**, which was further reacted with bromine to give dibromo product **(115)**. The bromide product **(115)** is treated with DBU to give an aromatic ring **(116)** followed by epoxide ring opening to furnish the synthesis of the target oxepin ring **(117)** (Scheme **24**).

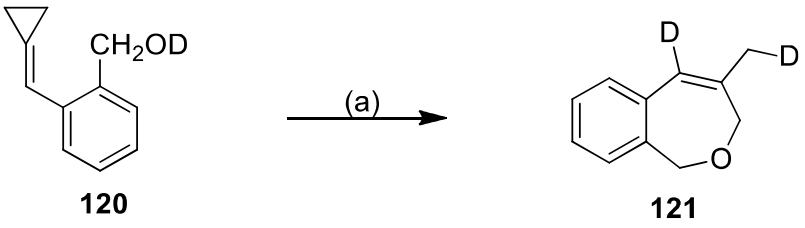
Gini and Mancheño [82] in 2016, showed their keen interest in the synthesis of dibenzoxepines derivatives **(119)** in medium to high yield. Xanthones **(118)** were taken as the main reactant which undergoes Wagner–Meerwein-type rearrangement under the required reaction condition at room temperature to give the target dibenzoxepin product **(119)** (Scheme **25**).



Scheme (24). Synthesis of substituted oxepine derivative. Reagents: **a)** Li/NH_3, -78 °C; **b)** m-CPBA, H_2O/DCM; **c)** Br_2, $CHCl_3$/ C_5H_{12}, -78 °C; **d)** DBU, Et_2O.

Scheme (25). Synthesis of dibenzoxepines *via* Wagner–Meerwein-type reaccrangement. Reagents: $Cu(OTf)_2$ (10 mol%), 2,2'-bypiridine (30 mol%), $TMSCNH_2$ (2.4 equiv), $(PhCO_2)_2$ (1.2 equiv), MeCN (2.0 Ml), rt, 18h.

Chen *et al.* [83] worked on the Rh-catalyzed synthesis of benzoxepine derivative **(121)**. The compound **(120)** undergoes ring-opening of the highly strained cyclopropane ring followed by ring-closing using $Rh(cod)_2BF_4$ as a catalyst under refluxing with dioxane (Scheme **26**).

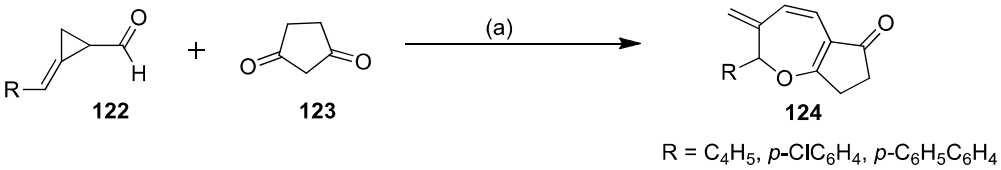


Scheme (26). Rh-catalyzed synthesis of benzoxepin derivative. Reagents: **a)** $Rh(cod)_2BF_4$, dioxane, reflux.

Intermolecular Reaction

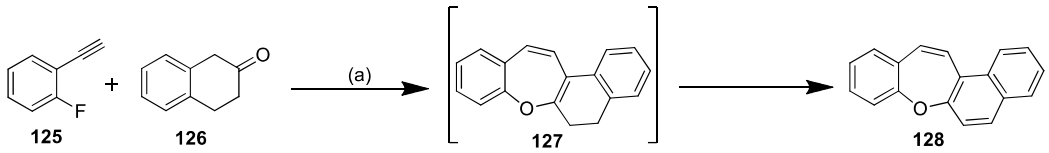
Cycloaddition Reactions

Tang *et al.* [84] in 2010worked on the synthesis of the oxepin derivative **(124)**. The cyclopropane carbaldehyde **(122)** undergoes cycloaddition cyclopentane-1,--dione **(123)** undergoes cycloaddition followed by ring-opening in toluene at 100 °C to give the desired oxepin derivative **(124)** in very low yield (Scheme **27**).



Scheme (27). Synthesis of 3-methylene-7,8-dihydro-2H-cyclopenta[b]oxepin-6(3H)-one. Reagents: **a)** L-proline (10 mole%), toluene, 100 °C, 1.5h.

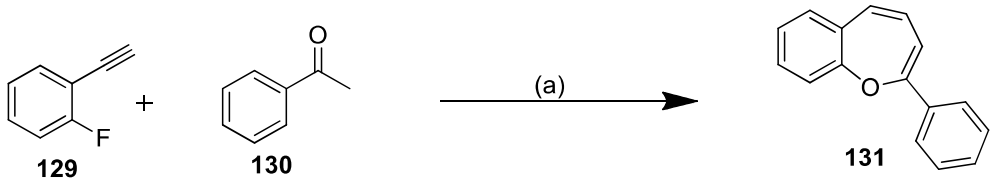
Ouyang and coworkers [85] represented a new strategy for the synthesis of compound **(128)** *via* [4+3] cycloaddition. The 1-ethynyl-2-fluorobenzene **(125)** undergoes cycloaddition with 3,4-dihydronaphthalen-2(1H)-one **(126)** under the standard reaction condition to give the expected product **(127),** which further undergoes aromatization to give the unexpected product **(128)** in excellent yield (Scheme **28**).



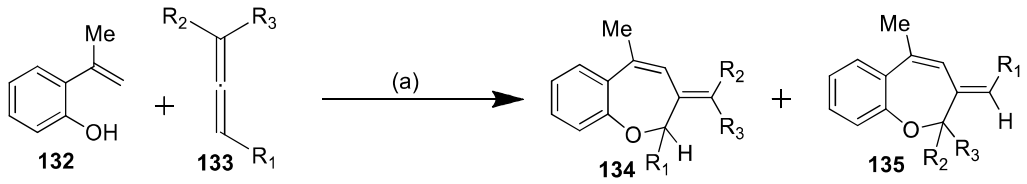
Scheme (28). Synthesis of naphtho[1,2-f]oxepine derivative *via* [4+3] cycloadditon. Reagents; **a)***t*-BuOK (1 equiv), DMSO (10 ml), 120 °C, N_2 12h.

Ouyang *et al.* [85] demonstrated a reaction pathway for the synthesis of benzoxepine derivative **(131)** *via* [4+3] annulation. The 1-ethynyl-2-fluorobenzene **(129)** undergoes cycloaddition with acetophenone **(130)** in DMSO to give 2-phenylbenzo[b]oxepine **(131)** in 75% yield (Scheme **29**).

Casanova *et al.* [86] worked on the [5+2] Pd- catalyzed cycloaddition of alkenylphenols **(132)** and allenes **(133)**. The benzooxepine derivatives **(134 & 135)** were obtained in excellent yield by the [5+2] cycloaddition of alkenylphenols **(132)** and allenes **(133)** under the standard reaction condition with excellent regio- and diastereoselectivties (E/Z) (Scheme **30**).

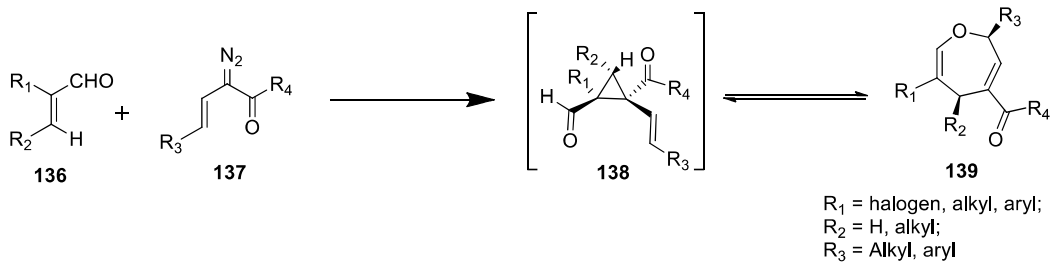


Scheme (29). Synthesis of benzoxepine derivative *via* [4+3] annulations. Reagents; **a)** *t*-BuOK (1 equiv), DMSO (10 ml), 120 °C, N_2 12h.



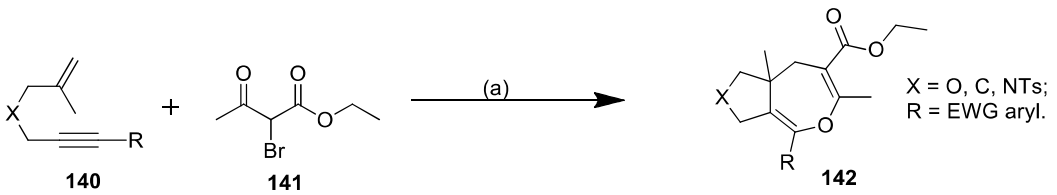
Scheme (30). Pd-catalyzed [5+2] cycloaddition of alkenylphenols and allenes. Reagents: **a)** 7.5 mol% Pd(OA **c**)$_2$, 0.5 equiv Cu(OA **c**)$_2$, H_2O, CH_3CN, 85 °C, air, 15h.

Shim *et al.* [87] in 2017, worked on the catalytic asymmetric synthesis of 2,5-dihydrooxepines **(139)**. The acrolein derivatives **(136)** and vinyldiazo compound **(137)** undergo Michael addition reaction initiated by a cyclopropanations using COBI Lewis acid to give chiral *cis*-1-formyl-2-vinylcyclopropanes (*cis*-FV **C) (138)** followed by retro-Claisen rearrangement to give compound **(139)** which in equilibrium with *cis*-FVC (Scheme **31**).



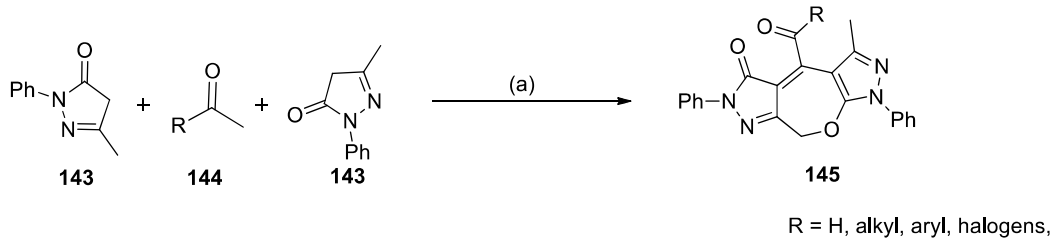
Scheme (31). Catalytic asymmetric synthesis of 2,5-dihydrooxepines.

Zheng and co-workers [88] in 2017 showed their interest in the synthesis of dihydrooxepines derivative **(142)** *via* a one-pot cascade radical cyclization (Scheme **32**). The 1,6 enynes **(140)** undergoes Cu catalyzed [2+2+3] radical cyclization with ethyl 2-bromo-3-oxobutanoate **(141)** under the optimized reaction condition to give the target product in low to high yield.



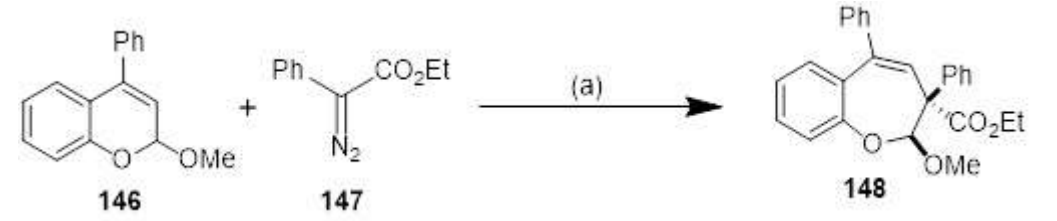
Scheme (32). Synthesis of dihydrooxepines derivative *via* [2+2+3] radical cyclization. Reagents: **a)** $[Cu(CH_3CN)_4]ClO_4$ (10 mol%), sodium carbonate (4.0 equiv), DIAD (10 mol%), toluene, 120 °C, N_2, 24h.

Wu *et al.* [16] in 2017 showed their interest in the synthesis of Iodine-catalyzed fused oxepin compound **(145)** and it's homologous in moderate to excellent yield. The substituted pyrazol-5(4H)-one **(143)** undergoes a condensation reaction with substituted aldehyde or ketone **(144)** using DMSO as a solvent at 140 °C to give the required product **(145)** in maximum yield (Scheme **33**).



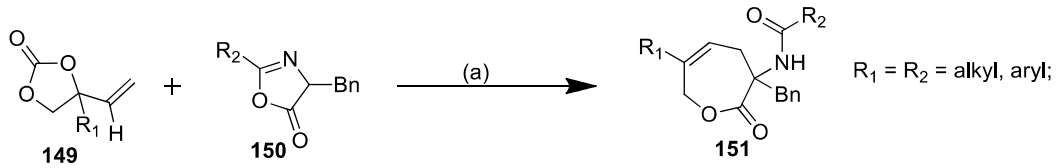
Scheme (33). The reaction of substituted pyrazole with aldehyde or ketone. Reagents: **a)** I_2, CF_3SO_3H, DMSO, 140 °C.

Courant *et al.* [89] in 2018 portrayed the synthesis of dihydrobenzo[b]oxepine derivative **(148)**. The compound **(146)** undergoes addition reaction with substituted phenylacetate **(147)** in the solution of TMSOTf, methanol, and dichloromethane followed by the ring-opening to give the final product *i.e.* (2S,3R)-ethyl 2-methoxy-3,5-diphenyl-2,3-dihydrobenzo[b]oxepine-3-carboxyl ate **(148)** in high yield (Scheme **34**).



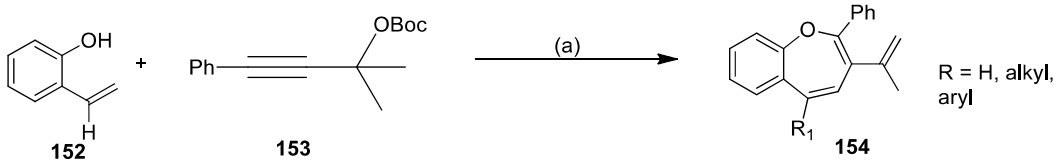
Scheme (34). Synthesis of dihydrobenzo[b]oxepine carboxylate derivative. Reagents: **a) (i)** TMSOTf (30 mol%); **(ii)** MeOH, DCM, -15 °C.

Zhao *et al.* [90] in 2018 demonstrated the synthesis of Oxepin derivative *via* Pd-catalyzed [5+2] cycloaddition reaction. The vinyl ethylene carbonates **(149)** undergo [5+2] cycloaddition reaction with oxazol-5-(4H)-ones **(150)** and their homologous using $Pd_2(dba)_3$ as a catalyst in THF to afford 3,4-Dihydrooxepi--2(7H)-ones **(151)** in moderate to high yield (Scheme **35**).



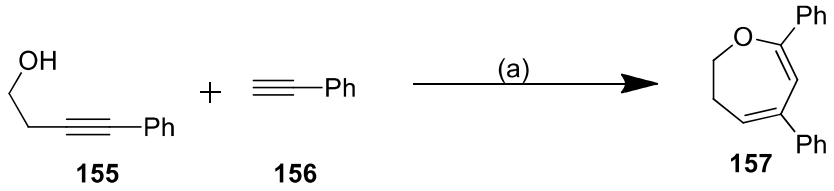
Scheme (35). [5+2] cycloaddition of vinyl ethylene with oxazol-5-(4H) -ones. Reagents: $Pd_2(dba)_3$ (2.5 mol%), (10.0 mol%), additives (1.0 eq.), THF,rt.

Yi *et al.* [91]demonstrated the synthesis of benzoxepine derivative **(154)** by intermolecular [5+2] cycloaddition (Scheme **36**). 2-vinylphenol derivatives **(152)** undergo Rh-catalyzed intermolecular [5+2] cycloaddition with compound **(153)** in DMF to yield benzoxepine derivative **(154)** in moderate to excellent yield.



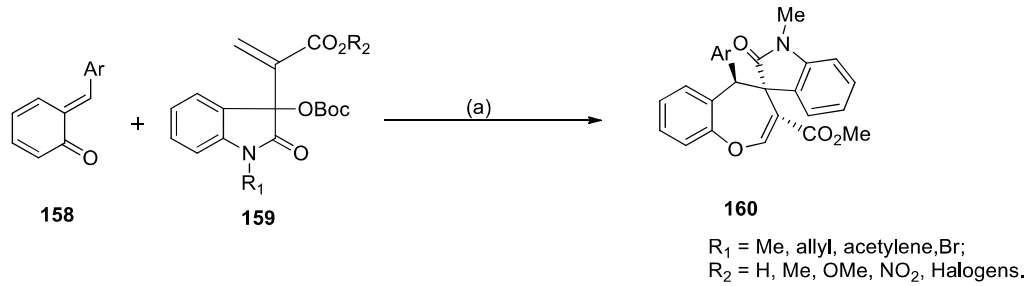
Scheme (36). One-pot synthesis of Rh- catalyzed benzoxepine derivative. Reagents: $[Cp^*RhCl_2]_2$ (2.5 mol%), Cu(OA **c**)$_2$ (2 equiv), Cs(OA **c**) (1 equiv), DMF, 120 °C, 24h.

Yang *et al.* [92] in 2019 showed their interest in the synthesis of a dihydro-oxepine derivative **(157)**. The 4-phenylbut-3-yn-1-ol **(155)** and ethynylbenzene **(156)** undergo gold-catalyzed intermolecular ring cyclization followed by catalytic cyclomerization to give the dihydro-oxepines **(157)** in excellent yield (Scheme **37**).



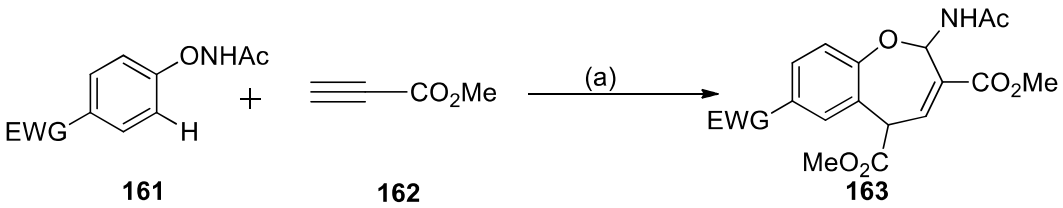
Scheme (37). Synthesis of dihydro-oxepines derivative *via* intermolecular cycloaddition. Reagents: **a)** 5% *I*PrAuNTf$_2$, $CHCl_3$, 40 °C, 11h.

Du *et al.* [93] represented the scope of Morita−Baylis−Hillman carbonates under the moderate reaction condition. The compound **(158)** undergoes [4+2] cycloaddition with compound **(159)** using MeCN and DABCO as a reagent at 25 °C to give the Spiro seven-membered benzo[b]oxepines **(160)** in excellent yield with high diastereoselectivity (Scheme **38**).



Scheme (38). Synthesis of Spiro seven-membered benzo [b] oxepines *via* [4+2] cycloaddition. Reagents: **a)** DABCO (20 mol%), MeCN, 25 °C.

Liu *et al.* [94] in 2019 proposed a new strategy for the synthesis of EWG-substituted 2,5-dihydrobenzo[b]oxepines derivatives **(163)** in excellent yield. The EWG-substituted N-phenoxyacetamides **(161)** undergoes [3+2] cycloaddition reaction with methyl propiolate**(162)** under the optimized reaction condition at 50 °C to give the product **(163)** in maximum yield (Scheme **39**).

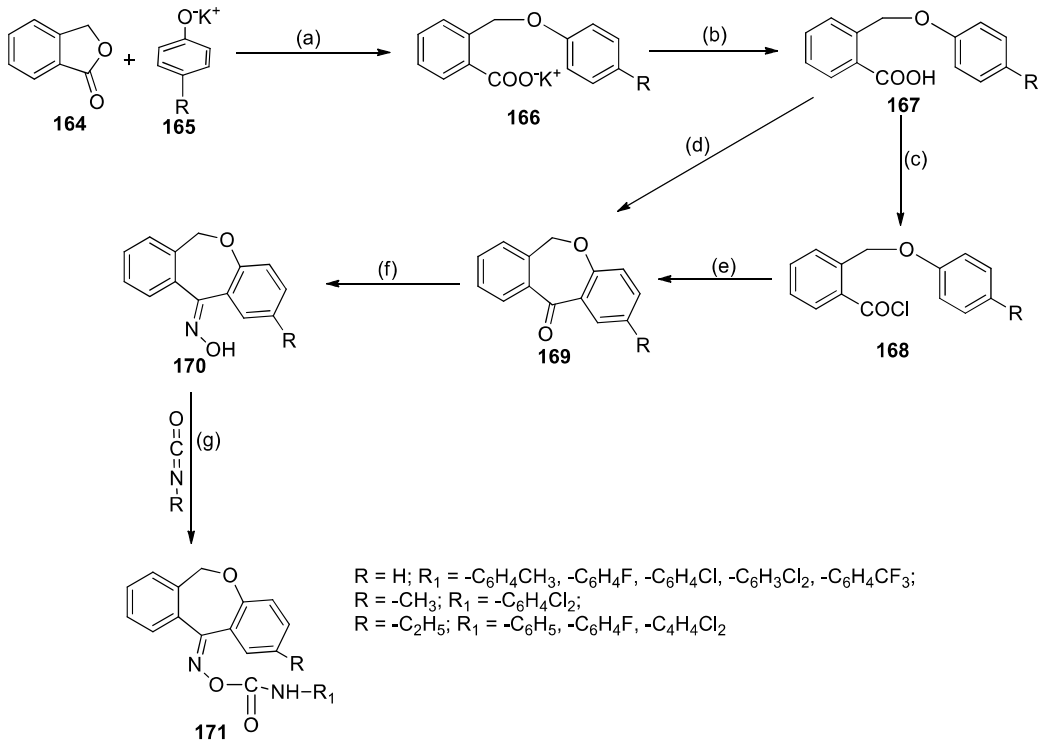


Scheme (39). [3+2] cycloaddition of N-phenoxyacetamides with alkyne. Reagents: 2M-NH_3. MeOH (1 equiv), MeOH, 50 °C, under air.

Intermolecular Ring Cyclization

Vlad *et al.* [95] demonstrated a new Multi-step reaction pathway for the synthesis of compound **(171)** and its homologous which are rich in antimicrobial properties. The first step proceeds by the condensation of fused ketone **(164)** with *p*-R-$C_6H_5O^-K^+$, potassium p-ethylphenoxide, or potassium *p*-cresolate **(165)** in xylene to give the potassium salt **(166),** which were further separated from the reaction mixture to give the corresponding acid **(167)**. In the next step, the acid **(167)** undergoes two different reaction pathways to form the corresponding

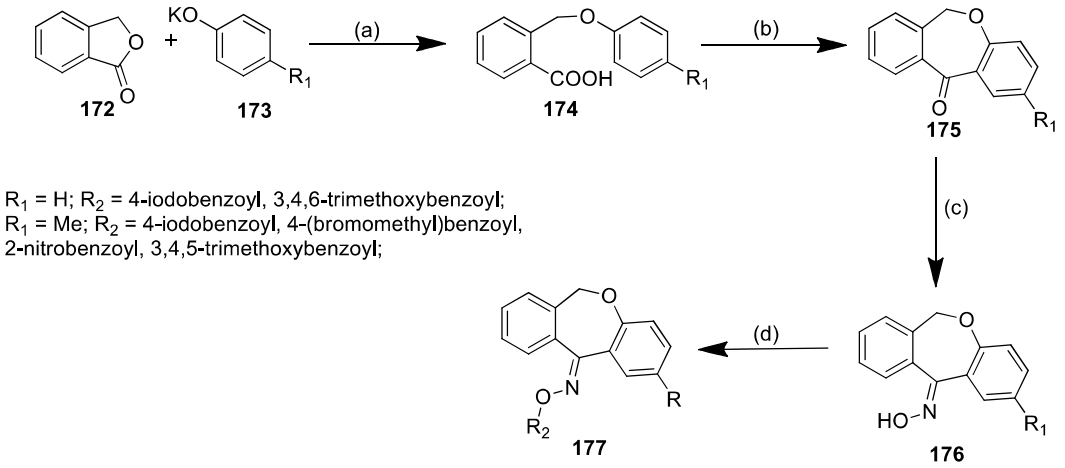
ketone **(169)**. The first method involves the direct heating of acid with polyphosphoric acids to give the corresponding ketone **(169)** in poor yield, and another method involves the Friedel-craft Cyclization of acid with $SOCl_2$ in dry dichloroethane to get the acid chloride **(168)** in medium yield. The compound **(169)** undergoes a reaction with $NH_2OH.HCl$ to give the oxime **(170),** which further reacts with aryl isocyanates in THF to give the required product **(171)** in acceptable yield (Scheme **40**).



Scheme (40). Synthesis of dibenzo[b,e]oxepin-11(6H)-one *O*-carbamoyl oxime and its homologous. Reagents: **a)** Xylene, reflux; **b)** HCl, -KCl; **c)** $SOCl_2$, DCE, reflux, 3h; **d)** APP, $-H_2O$; **e)** $AlCl_3$, DCE, -HCl; **f)** NH_3OH^+, Py, reflux; **g)** O=C=N-R_1, THF, reflux.

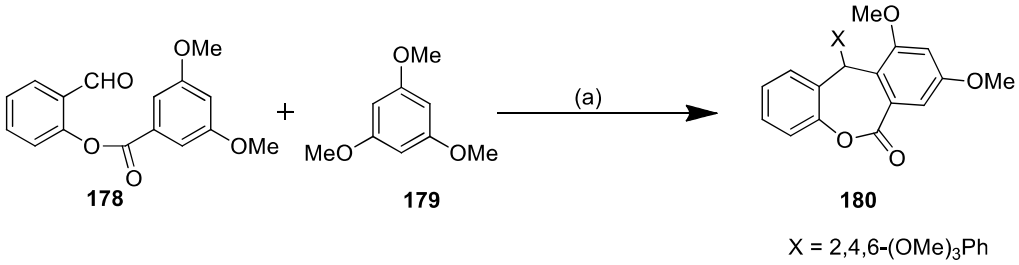
Sadek and co-workers [96] in 2011 describe a novel route for the synthesis of *O*-benzoyloximes derivatives **(177)** which possess antimicrobial properties. The compound **(172)** was treated with substituted potassium phenoxide **(173)** in Xylene to synthesize the corresponding 2-(phenoxymethyl)benzoic acid derivative **(174)** which further undergoes Friedel-Crafts cyclization followed by cyclization to give substituted dibenzoxepinone **(175)**. The compound **(175)** was reacted with $NH_2OH.HCl$ in the presence of pyridine to give oxime **(176)** as an intermediate which further undergoes acylation with benzoyl chlorides under the required

reaction condition to give compound **(177)** as a final product (Scheme **41**).



Scheme (41). Synthesis of dibenzooxepine derivative. Reagents: **a)** Xylene, reflux, 5h, 1 N NaOH, 1 M HCl; **b)** (i) $SOCl_2$, reflux, 3h; (ii) $AlCl_3$, 0-5 °C; (iii) stirring, 5-20 °C, 1h; **c)** Pyridine, NH_2OH: HCl, reflux, 96h; **d)** anhyd. Benzene, pyridine, corresp. Substituted benzoylchloride, reflux, 2h.

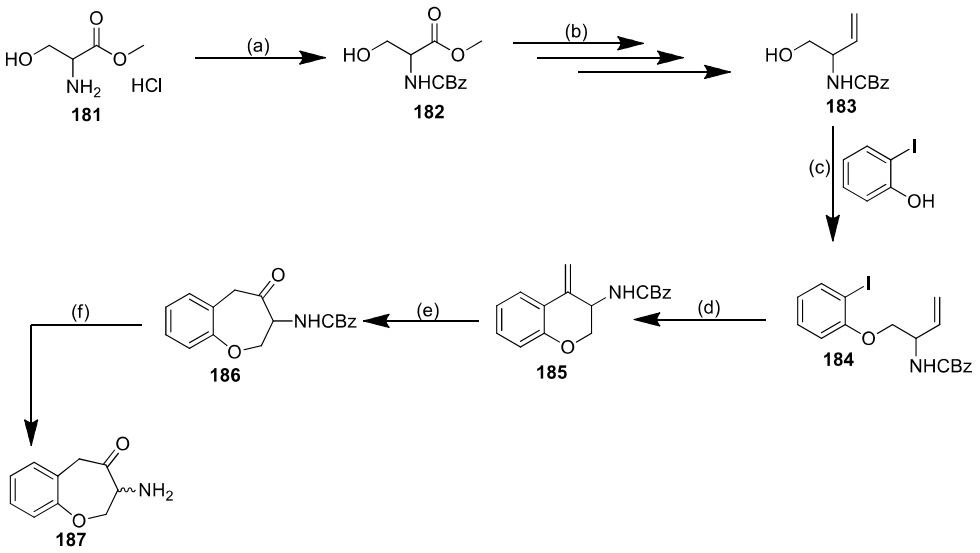
Reddy and co-workers in 2012 [97] worked on the intermolecular cyclization of 2-formylphenyl 3,5-dimethoxybenzoate **(178)** with trimethoxybenzene **(179)** using ACN as a volatile solvent at room temperature to give the synthesis of compound **(180)** as a final product in 52% yield (Scheme **42**).



Scheme (42). Intermolecular cyclization of 2-formylphenyl 3,5-dimethoxybenzoate with trimethoxybenzene. Reagents: **a)** I_2 (10 mol%), CH_3CN, rt, 12h.

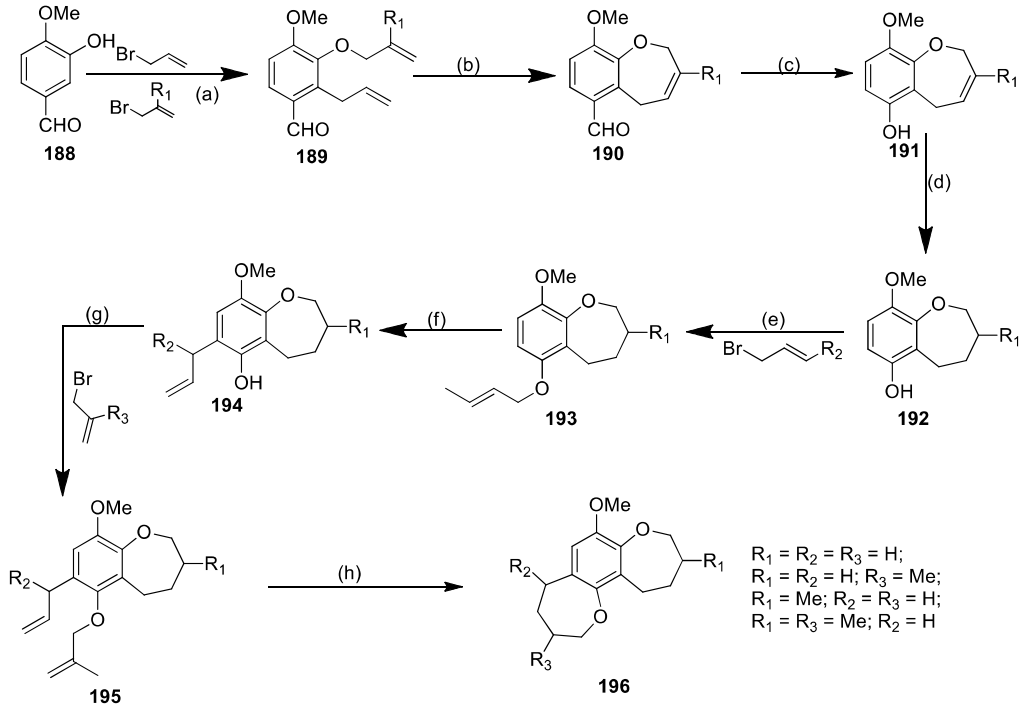
Roux *et al.* [98] in 2011 demonstrated a novel reaction route for the synthesis of 3-amino-2,3-dihydrobenzo[b]oxepin-4(5H)-one **(187),** which are recognized as aminopeptidase N (APN)/CD13 inhibitors. The methyl 2-amino-3-hydroxy propanoate **(181)** undergoes the protection of the amino group and hydroxyl group to give corresponding *N*-protected and *O*-protected intermediate **(182)** followed by reduction with DIBAl-H to give alcohol, the alcohol further undergoes

oxidation with Dess-Martin periodinane to give aldehyde, which was further converted to alkene **(183)** followed by deprotection of alcohol. The **(183)** undergoes Mitsunobu reaction with 2-iodophenol to give **(184)** followed by an intramolecular heck reaction to give cyclized intermediate **(185)** which was further treated with [hydroxy(tosyloxy)iodo]benzene (HTIB) in methanol **(186)** followed by the removal of N-protected group to give the desired oxepin derivative **(187)** in acidic medium (Scheme **43**).



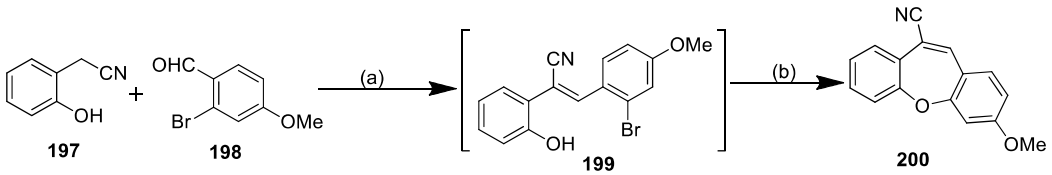
Scheme (43). Synthesis of 3-amino-2,3-dihydrobenzo[b]oxepin-4(5H)-one. Reagents: **a)** CbzCl, Na_2CO_3, THF, rt, 12h; **b)** (i) TBDMSCl, Imidazole, DCM, 50 °C, 12h; (ii) DIBAL-H, THF, -78 °C, 2h; (iii) DMP, DCM, rt, 2h; (iv) KHDMS, $BrCH_3P(C_6H_5)_3$, THF, 3h, 0 °C, THF, -78 °C to rt, 2h; (v) TBAF, THF, 0 °C, 3h; **c)** DEAD, PPh_3, toluene, 0 °C to rt, 12h; **d)** Pd(OA **c**)$_2$, PPh_3, Ag_2CO_3, MeCN, 12h, 80 °C; **e)** PhI(OH)OTs, MeOH, 20 min, rt; **f)** HBr, 33% AcOH, 12h, rt.

Chang *et al.* [99] in 2012 portrayed a new reaction pathway to afford the multi-step synthesis of benzodioxepanes homologous (Scheme **44**). The reaction proceeds with the double allylation of 3-hydroxy-4-methoxybenzaldehyde **(188)** using the general reaction condition followed by ring-cyclization using Grubbs catalyst in DCM to give carbaldehyde derivative [100, 101] **(190)**. Further, the aldehyde group undergoes Baeyer-Villiger reaction with K_2CO_3 and *m*-CPBA in DCM to give compound [102] **(191)** followed by a reduction of oxepin double bond to give compound **(192)**. The compound **(192)** further undergoes O-Allylation with allyl bromide, which further undergoes Claisen rearrangement under the optimized reaction condition to give **(194)**. The **(194)** again undergoes O-allylation followed by ring-closing to give the target compound *i.e.,* benzodioxepanes **(196),** in medium to high yield.



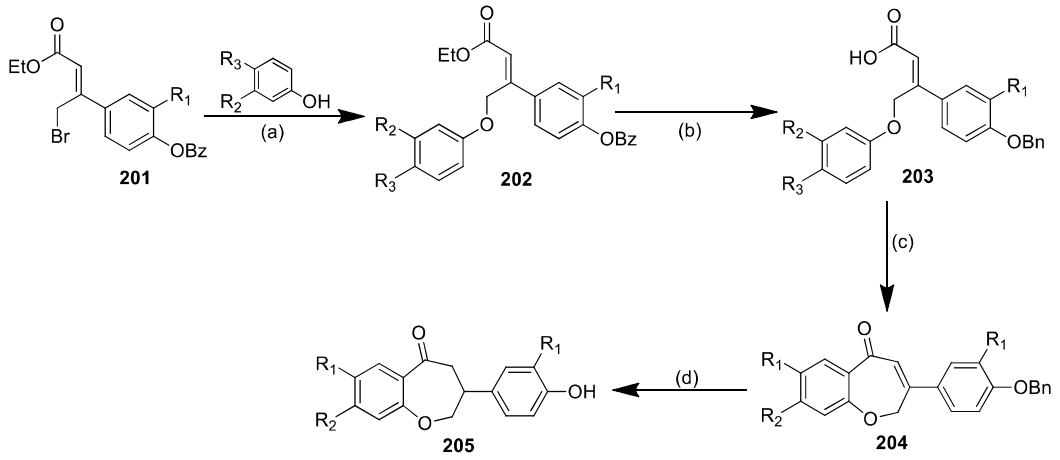
Scheme (44). Synthesis of benzodioxepanes derivatives. Reagents: **a)** LDA, $PhBCl_2$; **b)** Grubbs II, DCM; **c)** K_2CO_3, *m*-CPBA, DCM; **d)** H_2, Pd/C, EtOAc; **e)** K_2CO_3, acetone; **f)** decalin; **g)** K_2CO_3, acetone; **h)** Grubbs II, Pd/C, DCM, H_2.

Wang *et al.* [103] in 2013 studied the impact of Knoevenagel condensation reaction followed by the Ullmann-ether formation reaction to give the cyclized product **(200)** in moderate yield (Scheme **45**). The 2-(2-hydroxyphenyl) acetonitrile **(197)** undergoes Knoevenagel Condensation reaction with 2-bromo-4-methoxybenzaldehyde **(198)** in Cs_2CO_3 using DMF as a solvent to give intermediate **(199),** which further undergoes intramolecular ring cyclization to give dibenzo[b,f]oxepin *via* two pathways. Either in the absence of CuI, *via* the aromatic nucleophilic substitution reaction, or by Ullmann-ether formation in the presence of CuI to give the predominant product **(200)** in 92% yield.



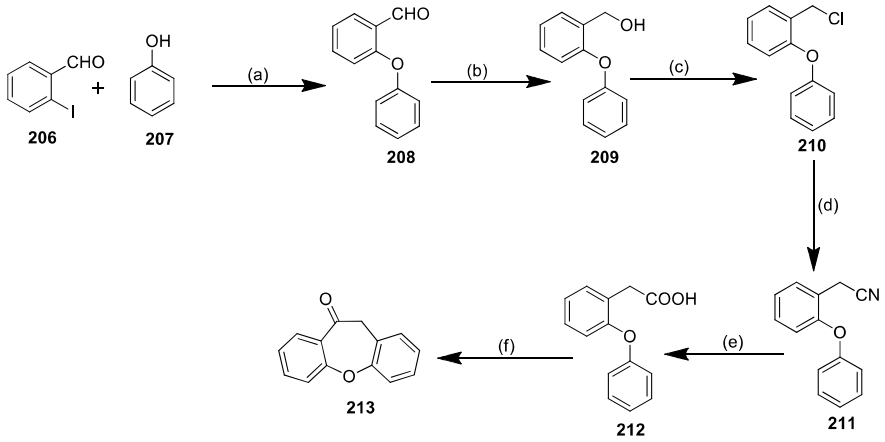
Scheme (45). Synthesis of dibenzo[b,f]oxepin *via* Ullmann-ether formation. Reagets: **a)** Cs_2CO_3. DMF, 100 °C.

Herrmann and co-workers [47] in 2014 described a novel route for the synthesis of oxepin **(205)**. The esters **(201)** couples with phenol derivatives under the basic condition to afford the synthesis of enoates **(202)** followed by saponification of an ester with LiOH in a mixture of THF/H_2O to give enoic acids **(203)**, which further undergoes Friedel crafts acylation under the mild reaction conditions. The acid group of compound **(203)** was activated by using cyanuric chloride $(NCCl)_3$ and pyridine with $AlCl_3$ followed by Friedel crafts acylation to furnish the synthesis of desired oxepin **(204)** in approx 50-65% yield. The oxepin **(204)** further undergoes a reduction with Pd/C to give the product **(205)** (Scheme **46**).



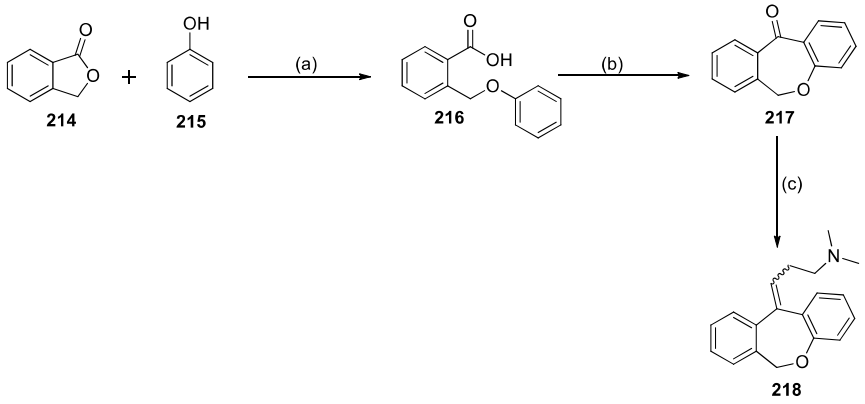
Scheme (46). Synthesis of oxepin derivative *via* Friedel crafts acylation. Reagents: **a)** K_2CO_3, KI, acetone; **b)** (i) LiOH, THF/H_2O (3:1); (ii) BnBr, K_2CO_3; (iii) LiOH, THF/H_2O; **c)** (i) cyanuric chloride, pyridine, DCM; (ii) $AlCl_3$; **d)** Pd/C; **e)** $NaBH_4$, EtOH.

Yeager and Schissel [26, 104] worked on the synthesis of fused oxepinone **(213)**. The 2-iodobenzaldehyde **(206)** undergoes a nucleophilic substitution reaction with phenol **(207)** to give 2-phenoxybenzaldehyde **(208)**, which further on reduction with sodium borohydride ($NaBH_4$) in methanol gives alcohol **(209)** as an intermediate. The **(210)** on reaction with $SOCl_2$ gives 1-(chloromethyl)-2-phenoxybenzene **(211)**, which was further converted into its cyanide followed by alkaline hydrolysis with KOH gives acid **(212)** followed by an intramolecular Friedel-Crafts acylation to give the cyclized product **(213)** in maximum yield (Scheme **47**).



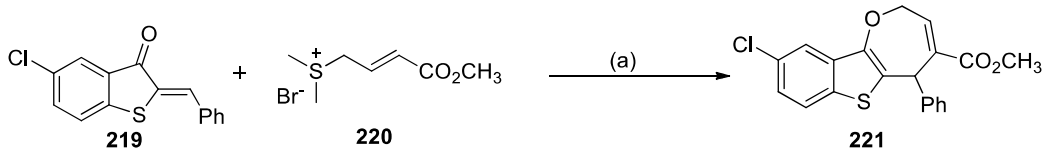
Scheme (47). Synthesis of dibenzo [b,f]oxepin-10(11H)-one *via* Friedel-Crafts acylation. Reagents: **a)** Cs_2CO_3, DMA, 150 °C, 2h; **b)** $NaBH_4$, methanol, 0 °C to rt; **c)** $SOCl_2$, pyridine, benzene, reflux, 24h; **d)** NaCN, DMSO, rt, 24h; **e)** KOH, EtOH, H_2O, reflux, 4h; **f)** (i) $(COCl)_2$, DMF, DCM, 30 min; (ii) $AlCl_3$, DCM, rt, 60 min.

Scoccia *et al.* [105] in 2017, reported the synthesis of compound **(218)** in moderate yield *via* a three-step reaction pathway (Scheme **48**) which possesses various biological properties. The first step involves the formation of benzoic acid derivative **(216)** in 71% yield by the reaction of a compound **(214)** and sodium phenoxide, which were derived by the reaction of phenol **(215)** with NaH using DMF as a solvent at reflux. The compound **(216)** undergoes intramolecular acylation using $FeCl_3$, DCME in the presence of DCM at r.t. to give the intermediate **(217)** which was further reacted with 3-dimethylamino propyl magnesium chloride to give the substituted product **(218)** in medium yield.



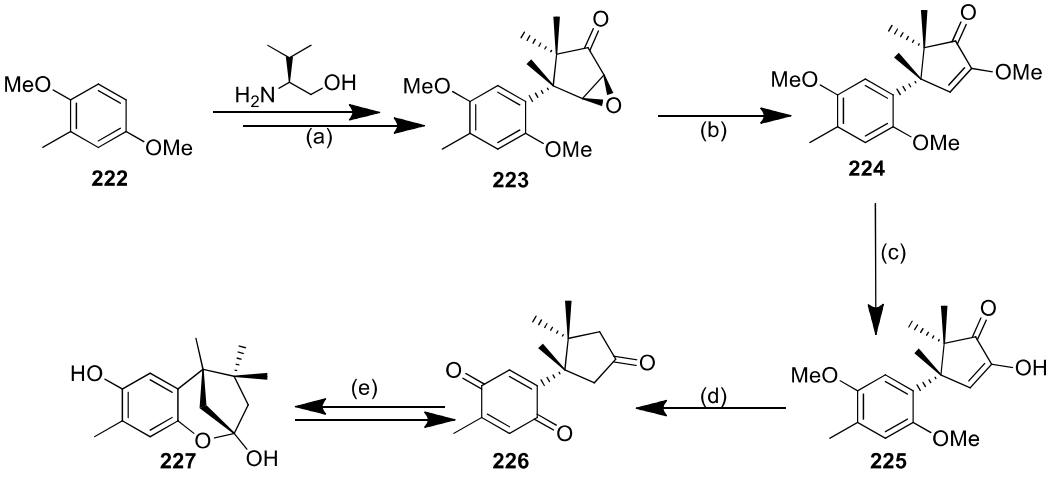
Scheme (48). Synthesis of dibenzoxepin derivative. Reagents: **a)** NaH (1.5 equiv), DMF, reflux, 24h, then conc. HCl; **b)** $FeCl_3$ (0.6 equiv), DCME (1 equiv), DCM (0.1M), rt, 3h; **c)** 3-(N,N-dimethylamino) propylmagnesium chloride, toluene, 65 °C, 2h, then conc, HCl, 1h, reflux.

Zhang *et al.* [106] in 2017 reported the synthesis of oxepine-4-carboxylate **(221)** *via* [4+3] cycloaddition reaction. The (Z)-2-benzylidene-5-chlorobenzo [b]thiophen-3(2H)-one **(219)** undergoes [4+3] cycloaddition reaction with sulfur ylides **(220)** using DCM as a solvent at r.t. to give the product **(221)** in 83% yield (Scheme **49**).



Scheme (49). Synthesis of oxepine-4-carboxylate *via* [4+3] pericyclic reaction Reagents: **a)** NaH, DCM, rt.

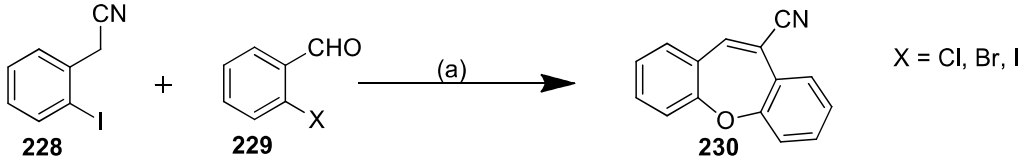
In 2018, Otaka *et al.* [107] reported the multi-step reaction pathway for the synthesis of benzo[b]oxepine derivative**(227)**. The epoxide **(223)** was synthesized *via* Kuwahara's protocol in 13 steps. The epoxide **(223)** was heated with sodium methoxide to afford the synthesis of 2-methoxycyclopentenone **(224)** followed by heating with hydrochloric acid to synthesize 2-hydroxycyclopentenone **(225)**. Compound **(225)** was further treated with hydriodic acid in AcOH to give compound **(226),** which was further cyclized to give the product in maximum yield, which possess anti-bacterial, anti-fungal, and anti-malarial parasite properties (Scheme **50**).



Scheme (50). Synthesis of benzo[b]oxepine-2,7-diol. Reagents: **a)** 13 steps; **b)** NaOMe, 60 °C, 10d; **c)** 1 M HCl, 80 °C, 3d; **d)** HI, AcOH, 110 °C, 5h; **e)** (i) $Na_2S_2O_4$, rt, 30 min; (ii) CAN, rt, 30 min.

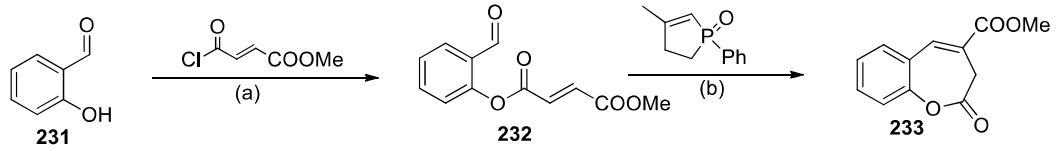
Villuri *et al.* [108] reported a novel route for the synthesis of seven-membered dibenzoxepine derivatives **(230)**. 2-iodo benzylcyanides **(228)** react with 2-halo

benzaldehydes **(229)** under the required reaction condition to give the intermediate product, which further undergoes intermolecular cyclization to give dibenzo[b,f]oxepine-10-carbonitrile **(230)** as a product in low to medium yield (Scheme **51**).



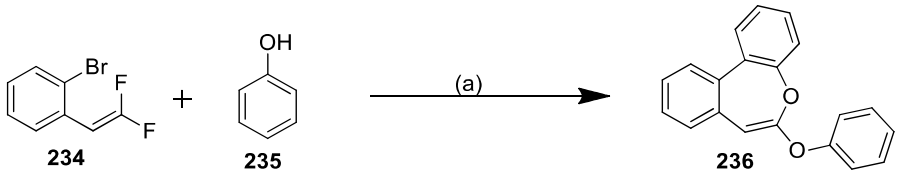
Scheme (51). Synthesis of dibenzoxepin derivative *via* intermolecular cycloaddition. Reagents: **a)** CuCl (20 mol5), Cs_2CO_3 (3.0 equiv), 100 °C.

In 2018, Grandane and co-workers [109] presented a Base-free Catalytic Wittig reaction for the synthesis of oxepine-4-carboxylate **(233)** in low to moderate yield. The first step involves the conversion of 2-hydroxybenzaldehyde **(231)** into 2-formylphenyl methyl fumarate **(232)** *via* the *o*-acylation of compound **(231)** with enoate under the optimized reaction conditions, which further reacts with 4-methyl-1-phenyl-2,3-dihydro-1H-phosphole 1-oxide to form the lactones **(233)** under the Wittig reaction conditions (Scheme **52**).



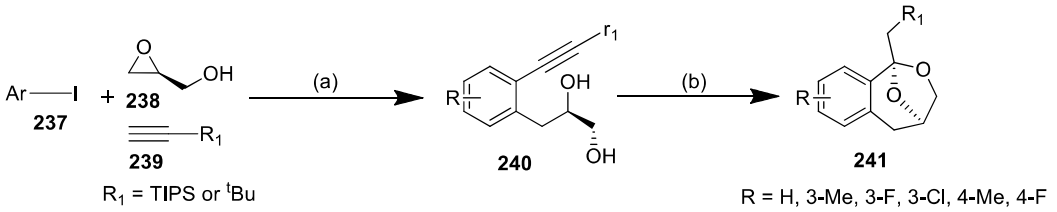
Scheme (52). Synthesis of methyl 2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate *via* Base-free Catalytic Wittig reaction. Reagents: **a)** NEt_3, DCM, rt, 16h; **b)** $PhCO_2H$, $(MeO)_3SiH$, toluene, 100 °C, 16h.

Ausekle and co-workers [110] described a one-pot cascade strategy for the synthesis of 6-phenoxydibenzo[b,d]oxepine **(236)**. The compound **(234)** undergoes nucleophilic vinylic substitution with phenol **(235)** to give ketene acetals as an intermediated followed by the Pd-catalyzed intramolecular C-H arylation to give the desired product **(236)** medium to excellent yield under the standard reaction condition (Scheme **53**).



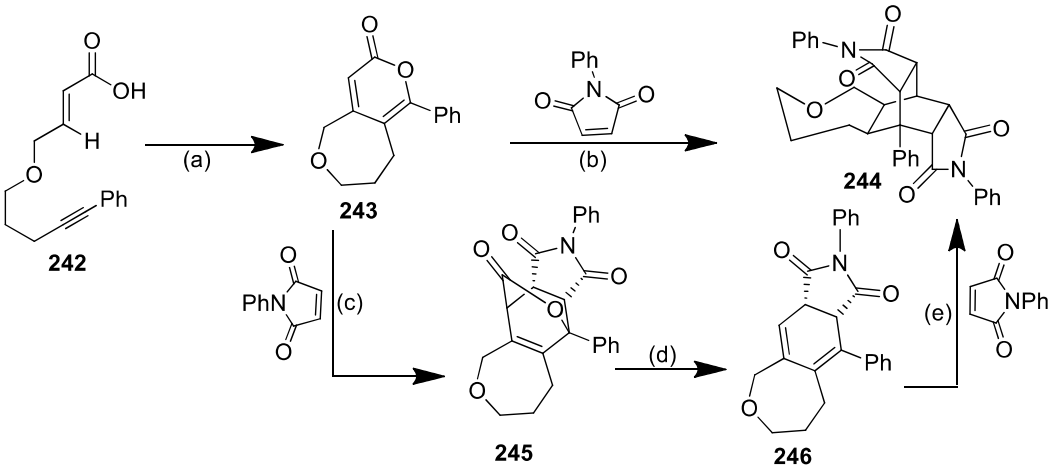
Scheme (53). Pd-catalyzed synthesis of 6-phenoxydibenzo[b,d]oxepine. Reagents: **a)** (i) K_2CO_3 (4 equiv), DMA, 100 °C, 6h; (ii) Pd(OA **c)**$_2$ (10 mol%), DavePhos (10 mol%), DMA, 140-145 °C, 15h.

Wu *et al.* [111] in 2019, represented their work on the synthesis of (1S,4R) 1-methyl-1,3,4,5-tetrahydro-1,4-epoxybenzo[c]oxepine **(241)**. The compound **(237)** is reacted with tert-butyl substituted alkyne **(239)** and (S)-oxiran-2-ylmethanol **(238)** under the standard reaction condition to give Catellani product **(240)** followed by ring-cyclization using $PdCl_2$ as a catalyst to afford the product **(241)** in a medium yield (Scheme **54**).



Scheme (54). Synthesis of (1S,4R)-1-methyl-1,3,4,5-tetrahydro-1,4-epoxybenzo[c]oxepine. Reagents: **a)** (i) standard condition; (ii) TABF (2.0 equiv), THF, 0 °C, 3h; **b)** $PdCl_2(PhCN)_2$, THF, rt, 12h.

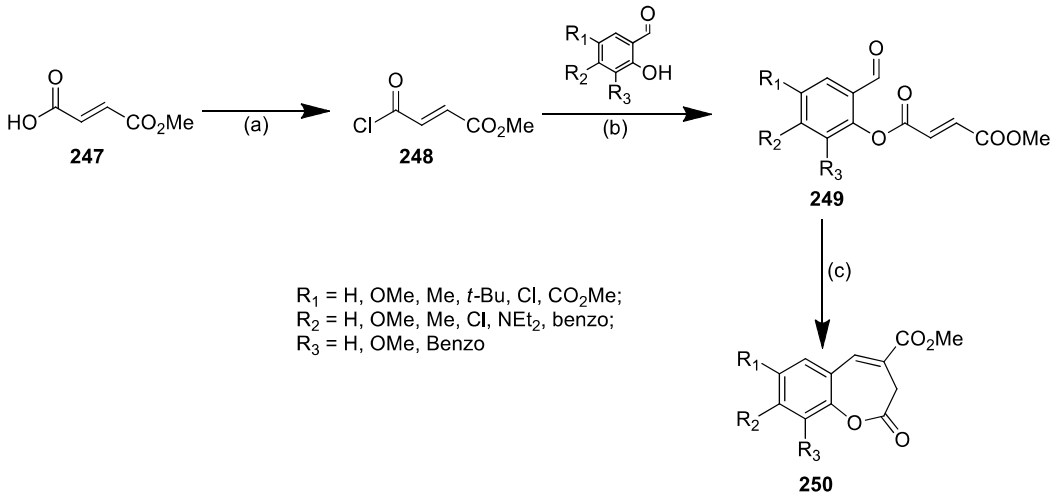
Fernandez and co-workers [112] in 2019, worked on a new reaction pathway for the synthesis of *bis*-oxepin derivative **(244)** *via* Diels-Alder reaction. The but--enoic acid **(242)** undergoes Rh-catalyzed intramolecular ring cyclization to form oxepin-3-one **(243),** which further undergoes Diels-alder cycloaddition reaction with *cis*-diene in pyrone adducts in dioxane at 140 °C to give the product **(244)** in acceptable yield (Scheme **55**).



Scheme (55). Synthesis of bis-oxepin derivative *via* Diels Alder reaction. Reagents: **a)** Ag_2CO_3 (1.5 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol), DMF (10.2 Ml, 0.2 M), 120 °C, 24h; **b)** dioxane, 140 °C, 36h.

Grandane *et al.* [113] demonstrated a three-step reaction pathway for the synthesis of anti-tumor agent *i.e.,* benzoxepinones derivatives (Scheme **56**). The first step

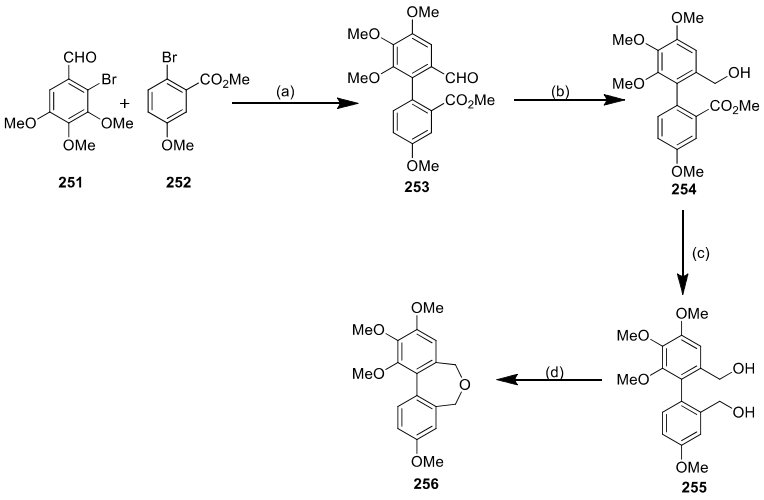
starts *via* the conversion of acid **(247)** into its acid chloride **(248)** using $SOCl_2$ in DCM and DMF as a catalyst. The compound **(248)** further undergoes acylation with 2-hydroxybenzaldehyde using DCM and triethylamine as a solvent to give 2-formylphenyl fumarates **(249)**. The fumarates **(249)** further undergo intramolecular base-free catalytic Wittig reaction to synthesize the target compound **(250)** in low to moderate yield.



Scheme (56). Synthesis of substituted benzoxepinones *via* the intramolecular base-free catalytic Wittig reaction. Reagents: **a)** $SOCl_2$, DMF(cat), DCM, reflux, 3h; **b)** NEt_3, DCM, rt, 16h; **c)** methyl-1-pheny--2-phospholen-1-oxide, benzoic acid, $(MeO)_3SiH$, toluene, 100 °C 16h.

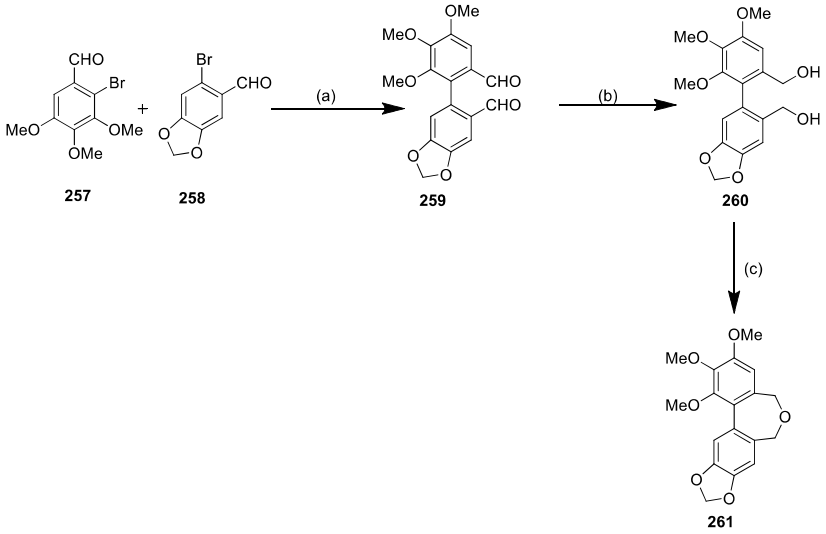
Coupling Reaction

Edwards, in 2011 [114], worked on the synthesis of substituted dibenzoxepin **(256)** *via* Ullmann Coupling. 2-bromo-3,4,5-trimethoxybenzaldehyde **(251)** undergoes Ullmann coupling reaction with methyl 2-bromo-5-methoxybenzoate **(252)** to give the biaryl product **(253)** which further undergoes reduction of aldehyde to give corresponding alcohol **(254)** followed by reduction of an ester to give diol **(255)**. The Diol **(255)** further undergoes ring cyclization to give the target product **(256)** under the labeled reaction product (Scheme **57**), which acts as an anti-tumor agent.



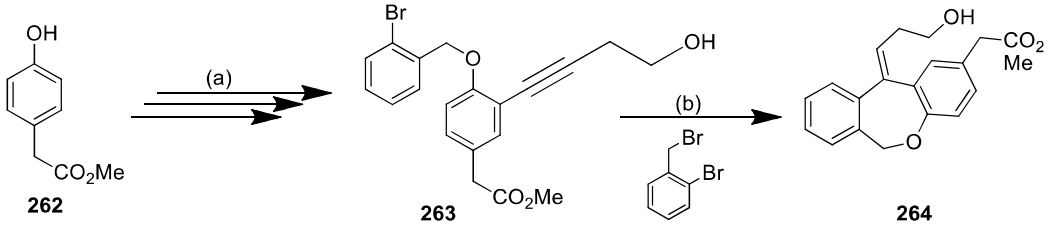
Scheme (57). Synthesis of oxepin derivative *via* Ullmann Coupling reaction. Reagents: **a)** Cu, DMF, 165 °C, 3h; **b)** $NaBH_4$, MeOH, 0 °C to rt, 1h; **c)** $LiBH_4$, Et_2O, reflux, 6h; **d)** $HCl.H_2O$, THF, heat.

Edwards, in 2011 [114], reported an Ullmann Coupling reaction for the synthesis of oxepine **(261)**. The substituted aldehyde **(257)** undergoes Ullmann cross-coupling reaction with 6-bromobenzo[d] [1, 3]dioxole-5-carbaldehyde **(258)** to give dialdehyde product **(259),** which further undergoes reduction with $NaBH_4$ to give corresponding alcohol **(260)**. The Diol **(260)** further undergoes ring cyclization to give the target product under the desired reaction product **(261)** (Scheme **58**).



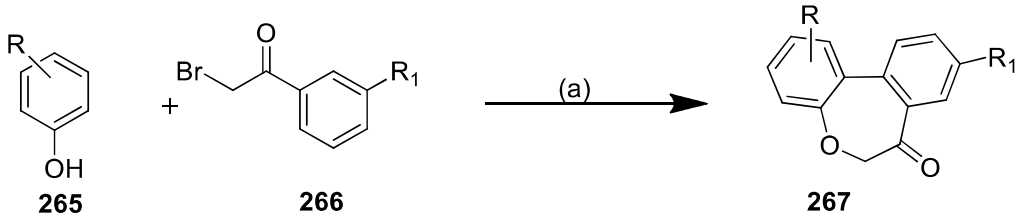
Scheme (58). Synthesis of Dibenzoxepin derivative *via* Ullmann Coupling reaction. Reagents: **a)** Cu, DMF, 165 °C, 3h; **b)** $NaBH_4$, MeOH, 0 °C to rt, 1h; **c)** $HCl.H_2O$, THF, heat.

Nishimura and Kinugawa [115] reported a reaction pathway for the synthesis of dibenzoxepine derivative. In the first step, methyl 2-(4-hydroxyphenyl)acetate **(262)** undergoes bromination followed by the protection of hydroxyl group with methoxymethyl to give the intermediate compound which further undergoes Sonogashira coupling under suitable reaction conditions followed by the deprotection under the mild acidic condition which was further coupled with 1-bromo-2-(bromomethyl)benzene to give the target product **(264)** (Scheme **59**).



Scheme (59). Synthesis of dibenzoxepine derivative *via* Sonogashira coupling. Reagents: **a)** (i) Br_2, AcOH; (ii) MOMCl, K_2CO_3, DMF; (iii) but-3-yn-1-ol, $PdCl_2(PPh_3)_2$, CuI, triethylamine, DMF; (iv) Cat. HCl, MeOH; (v) 1-bromo-2-(bromomethyl)benzene, K_2CO_3, DMF; **b)** Pd(OA **c)**$_2$, tri-o-tolylphosphine, HCO_2H, piperidine, MeCN.

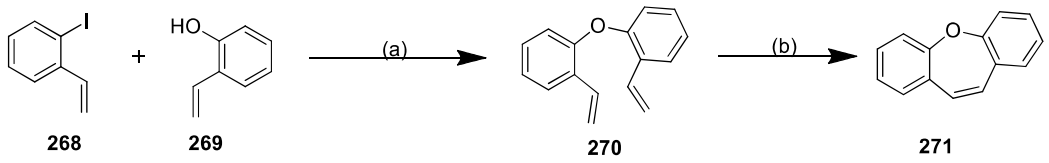
Fu *et al.* [116] in 2013 portrayed a new reaction pathway for the organic synthesis of dibenzo fused oxepin-7(6H)-ones **(267)** derivatives. The substituted phenol **(265)** undergoes C-C coupling cyclization or esterification reaction with substituted α-bromoacetophenones **(266)** *via* induced visible-light using Pd as a catalyst under the required reaction condition to give the cyclized product **(267)** in low to medium yield (Scheme **60**).



Scheme (60). Synthesis of dibenzoxepinone derivative *via* induced visible-light. Reagents: **a)** Pd(OA **c)**$_2$ (10 mol%), DDQ, blue LED, CH_3CN, Cs_2CO_3 (2.0 eq.), 80 °C.

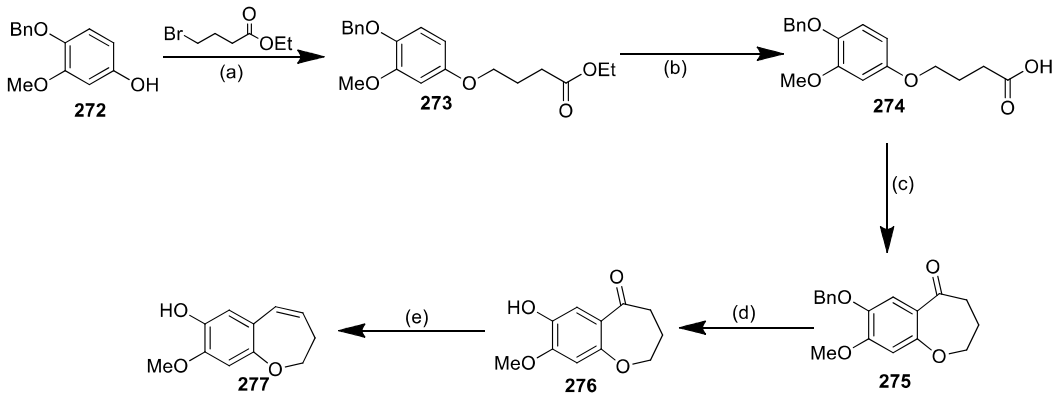
Bharath *et al.* [117] worked on the synthesis of Dibenzo[b,f]oxepins **(271)** *via* ring cyclization methodology. The 1-iodo-2-vinylbenzene **(268)** undergoes coupling reaction with 2-vinylphenol **(269)** under the Ullmann-type reaction conditions to give 2,2'-oxybis(vinylbenzene) **(270)** in a 40-50% yield. The compound **(270)** further undergoes ring-closing using Hoveyda–Grubbs catalyst

to give the tricyclic dibenzo[b,f]oxepin moieties **(271)** in 93% yield (Scheme **61),** which possesses a wide range of biological properties.



Scheme (61). Synthesis of Dibenzo[b,f]oxepins. Reagents: **a)** CuI (5 mol%), Salox (L_2) (2 mol%), Cs_2CO_3 (2.0 mol%), 4 MS (250 mg for 1.0 mmol), MeCN (4 ml for 1.0 mmol), 80 °C; **b)** Grubb's catalyst.

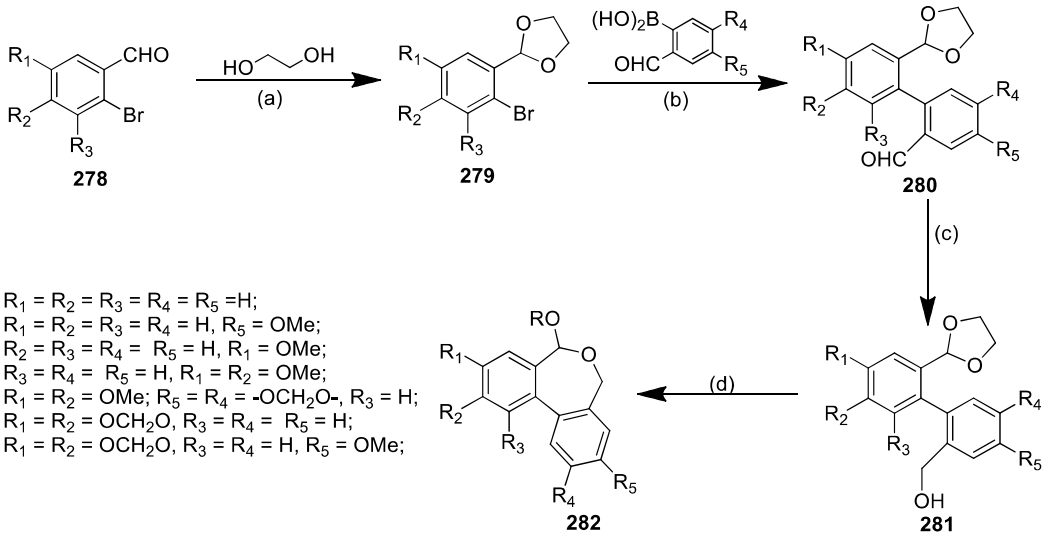
Herrmann and co-workers [47] in 2014 also worked on the synthesis of 8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **(277)**. The 4-(benzyloxy)-3-methoxy phenol **(272)** undergoes a coupling reaction with ethyl 4-bromobutanoate under the basic condition to give ethyl 4-(4-(benzyloxy)-3-methoxyphenoxy)butanoate **(273)** followed by saponification with LiOH in a mixture of THF/H_2O to give 4-(4-(benzyloxy)-3-methoxyphenoxy)butanoic acid **(274)**. The acid group of **(274)** was activated by using cyanuric chloride and pyridine with $AlCl_3$ followed by Friedel crafts acylation to furnish the synthesis of the cyclized product *i.e.* oxepin **(275)**. The **(275)** further undergoes deprotection of the alcohol group **(276)** followed by a reduction of the ketone to give the final target product **(277)** (Scheme **62**).



Scheme (62). Synthesis of 8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol. Reagents: **a)** K_2CO_3, acetone; **b)** LiOH, THF/H_2O (4:1); **c)** (i) cyanuric chloride, pyridine, DCM; (ii) $AlCl_3$; **d)** Pd/C; e) $NaBH_4$, EtOH.

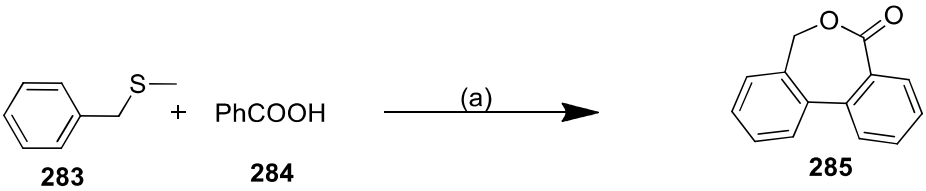
Yadav *et al.* [118] in 2015 demonstrated the multi-step synthesis of dibenzo[c,e]oxepine derivative **(282)**. The 2-bromobenzaldehydes **(278)** was reacted with ethylene glycol in diethoxymethoxyethane, THF, and using 4-methylbenzenesulfonic acid monohydrate as a catalyst to yield dioxolanes **(279)**

in high yield. dioxolanes **(279)** further undergoes Suzuki–Miyaura coupling with (2-formylphenyl)boronic acid under microwave condition to give the biarylaldehyde **(280)**, which further on reduction with sodium borohydride in MeOH at r.t. gives the corresponding alcohol **(281)** followed by ring-closing to give the target product **(282)** in acceptable yield (Scheme **63**).



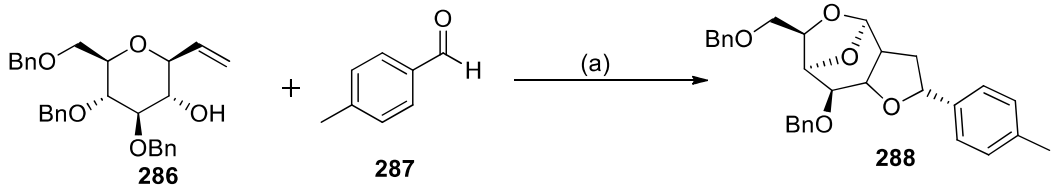
Scheme (63). Synthesis of dibenzo[c,e]oxepine derivative. Reagents: **a)** triethyl orthoformate, PTSA-H_2O, THF, 65-70 °C, 5h; **b)** $Pd(PPh_3)_4$, $NaHCO_3$, DMF/H_2O (1:1), 125 °C 125W, 25 min; **c)** $NaBH_4$, MeOH, rt, 1h; **d)** PTSA.H_2O (10-25 mol%), ROH, rt, 5-120 min.

Zhang *et al.* [73] in 2015 showed their interest in the synthesis of dibenzo oxepinone **(285)** *via* the oxidative coupling. The benzyl(methyl)sulfane **(283)** undergoes an oxidative coupling reaction with benzoic acid **(284)** using AgOAc as an oxidant and $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ as the catalyst to furnish dibenzo oxepinone as a final product with very low yield (Scheme **64**).



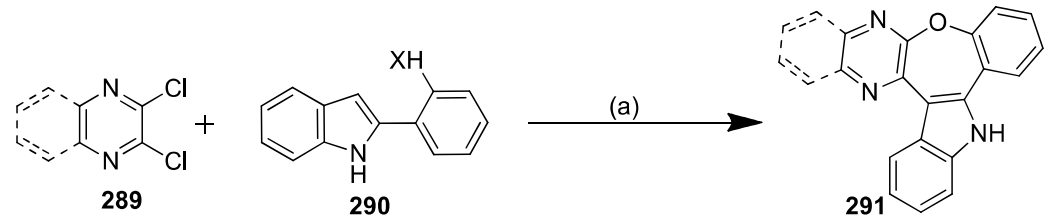
Scheme (64). Oxidative Coupling of benzyl(methyl)sulfane with benzoic acid. Reagents: **a)** $[Cp^*Rh(CH_3CN)_3][SbF_6]$ (5 mol%), 1-AmylOH (1 ml), air, 120 °C, AgOAc (2.0 equiv).

Rajasekaran *et al.* [119] in 2016 portrayed the scope of Prins pinacol-type rearrangement to give (2R,4R,6R,7R,8R)-8-(benzyloxy)-6-((benzyloxy)methyl)-2-(p-tolyl)octahydro-4,7-epoxyfuro[3,2-c]oxepine **(288)** as a product under the standard reaction condition. The compound **(286)** undergoes Prins pinacol-type rearrangement reaction with 4-methylbenzaldehyde **(287)** to give the compound **(288)** as a product (Scheme **65**).



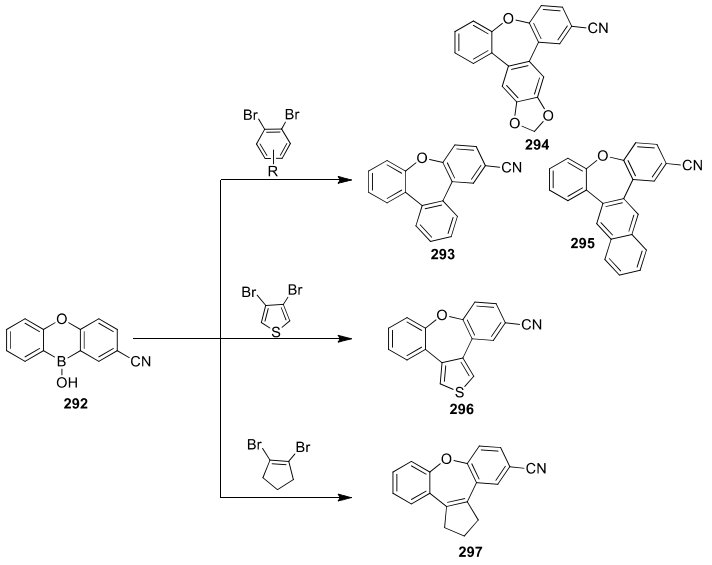
Scheme (65). Prins pinacol-type rearrangement reaction of substituted pyran-3-ol. Reagents: **a)** $BF_3.OEt_2$, DCM, 0 °C, 30 min.

Kumar *et al.* [120] in 2017, worked on the synthesis of indole-fused oxepines derivative **(291)** *via* the reaction of 2,3-dichloroquinoxaline **(289)** with 2-(1--indol-2-yl)phenol **(290)** using $FeCl_3$ as a catalyst in DCE (1,2-dichloroethane) at 80 °C to afford the product **(291)** in 87% yield (Scheme **66**). The product exhibit cervical and breast cancer cell lines inhibition properties.



Scheme (66). Synthesis of indole-fused oxepines. Reagents: **a)** $FeCl_3$, DCE, 80 °C, 3h.

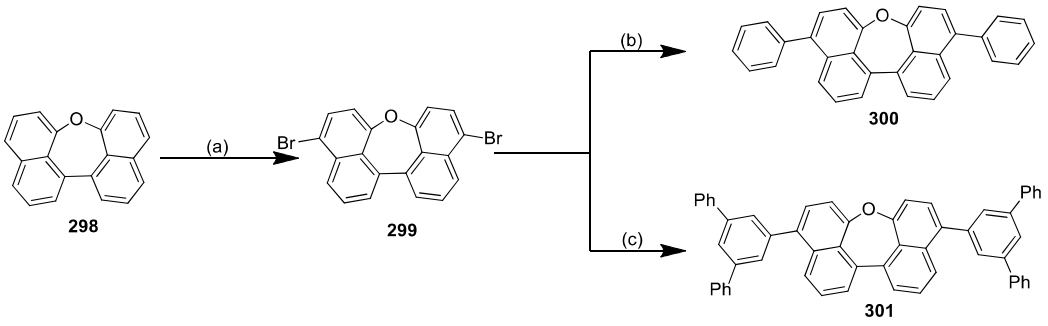
Igarashi *et al.* [121] in 2017 showed their interest in the synthesis of dibenzoxepin derivative **(293-297)** *via* Suzuki-Miyaura coupling. The carbonitrile **(292)** undergoes a cross-coupling reaction with 1,2-dibromo-(hetero)arenes to furnish the synthesis of dibenzoxepin derivatives **(293-297)** in medium yield under the optimized reaction condition (Scheme **67**). This tricyclic moiety is isolated from natural products [122] and used in anti-depressant drugs [69, 123].



Scheme (67). Synthesis of dibenzoxepin derivative *via* Suzuki-Miyaura coupling. Reagents: **a)** $Pd(dba)_3$, *t*-$Bu_3P.HBF_4$, Cs_2CO_3, H_2O in *t*AmOH at 100 °C for 24-48h.

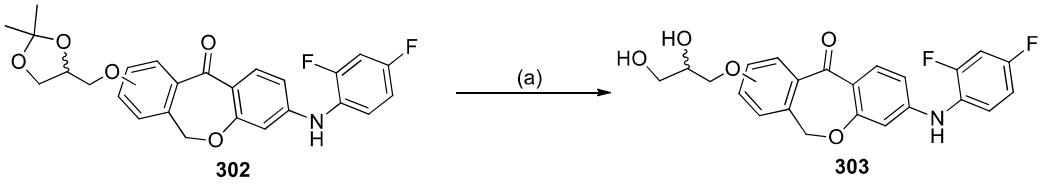
Reaction of Oxepines

Dobelmann *et al.* [69] also worked at the Palladium-catalyzed coupling reaction of tetra fused oxepine derivative **(298)**. The compound **(298)** undergoes a bromination reaction using NBS at 40 °C in DMF to give the dibromo product **(299),** which further undergoes a coupling reaction with phenyl- and *m*-terpheny--boronic acid to give compound **(300)** and **(301)** respectively in moderate yield (Scheme **68**).



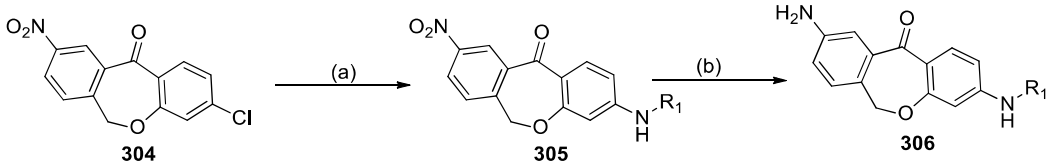
Scheme (68). Synthesis of dinaphtho[1,8-bc:1',8'-ef]oxepine derivatives *via* coupling reaction. Reagents: **a)** NBS, DMF, 40 °C; **b)** $PhBr(CH)_2$, K_3PO_4, Pd(OA **c)**$_2$, *p*(*o*-Tol), toluene/dioxane/water, 70 °C; **c)** *m*-*t*-$PhB(OH)_2$, K_3PO_4, Pd(OA **c)**$_2$, *P*(*o*-Tol), toluene/dioxane/water, 70 °C.

Goldstein and co-workers [26, 124] in 2013 worked on the one-pot reaction dioxolane **(302)** using *p*-TsOH as a catalyst and methanol and water as a solvent to give 3-methoxypropane-1,2-diol **(303)** derivative as a major product (Scheme **69**) which acts as an antiglaucoma agent.



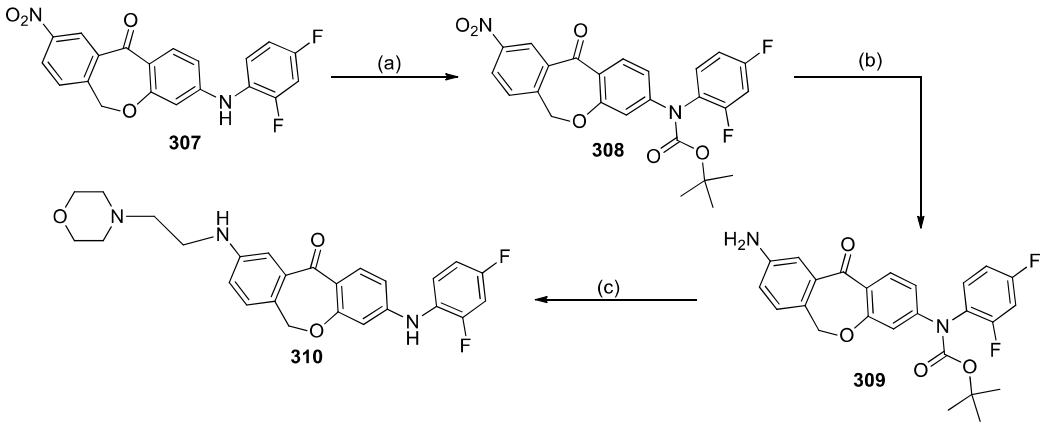
Scheme (69). The one-pot reaction of dibenzoxepinone derivative. Reagents: **a)** TsOH, $MeOH/H_2O$, reflux.

Karcher and co-workers [26, 125] in 2013 also portrayed the synthesis of compound **(306)** *via* a two-step reaction. The first step includes the reaction of chloro substituted oxepin-11(6H)-one **(304)** with different substituted aniline derivative *via* Buchwald−Hartwig coupling under the required reaction condition to form the intermediate product **(305),** which further undergoes the Pd-catalyzed reduction of the nitro group at room temperature to give amine derivative as a final product **(306)** (Scheme **70**).



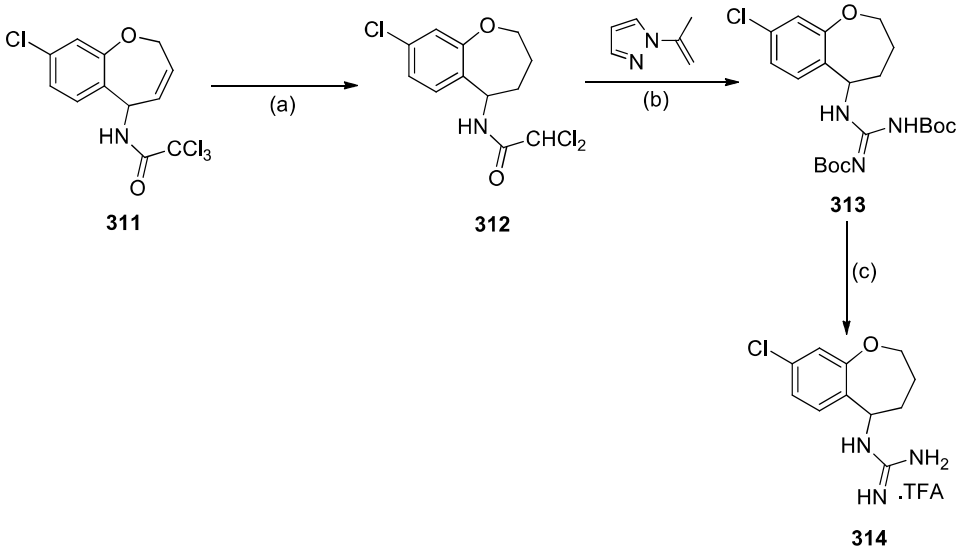
Scheme (70). Buchwald−Hartwig coupling reaction of substituted dibenzooxepine derivative. Reagents: **a)** substituted aniline derivative, Cs_2CO_3, X-Phos, Pd(OA **c)**$_2$, 1,4-dioxane, *t*-BuOH, reflux; **b)** Pd/C, H_2, ethyl acetate, rt.

The compound **(307)** undergoes protection of diaryl amine with the tert-butyloxycarbonyl group in DMAP and toluene to give the compound **(308),** which further undergoes reduction of the nitro group using Pd as a catalyst in ethyl acetate at room temperature to give compound **(309)** followed by the introduction of 2-morpholin-4-ylethyl and deprotection of the diaryl amine nitrogen simultaneously to give the compound **(310)** as a final product [26, 126] (Scheme **71**).



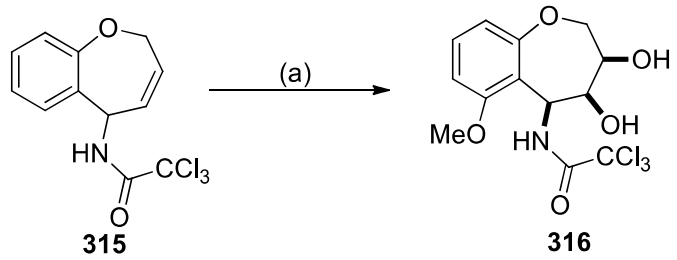
Scheme (71). Reaction of benzo-fused oxepin derivatices. Reagents: **a)** Boc_2O, DMAP, toluene, reflux; **b)** Pd/C, H_2, ethylacetate, rt; **c)** K_2CO_3, 4-(2-chloroethyl)morpholine hydrochloride, KI, microwave, 200W, 110 °C, MeCN.

Oxepin acetamide **(311)** was hydrogenated under optimized reaction conditions to give compound **(312)** as an intermediate product in 94% yield, which was further coupled with N,N'-bis (tertbutoxycarbonyl)-1H-pyrazole-1-carboxamidine under the optimized reaction condition to give Boc protected product **(313)**. Finally, the protected group **(313)** is removed with TFA to give compound **(314)** as a final product in a 40% yield [62] (Scheme **72**).



Scheme (72). Reaction of dihydrobenzo[b]oxepin derivative. Reagents: **a)** H_2, 10% Pd/C, EtOAc, rt, 1.5h; **b)** (i) 6 M HCl, MeOH, 100 °C, 144 h; (ii) $EtN(i\text{-}Pr)_2$, MeOH, rt, 48h; **c)** TFA, DCM, 45 °C, 48h.

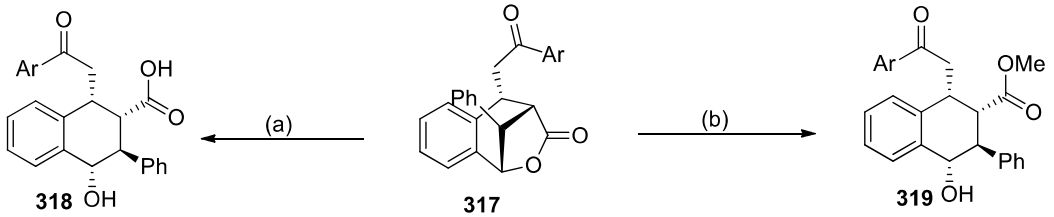
The compound **(315)** undergoes oxidation with osmium tetraoxide (OsO_4) and TMEDA under the optimized conditions to yield the corresponding diol **(316)** as a final product [62] (Scheme **73**).



315 **316**

Scheme (73). Oxidation of 5-amino-substituted 2,5-dihydro-1-benzoxepines. Reagents: **a)** OsO_4, TMEDA, DCM, -78 °C, 3h; **b)** *m*-CPBA, DCM, rt, 42h; **c)** 1.0 M H_2SO_4, 1,4-dioxane, rt, 48h.

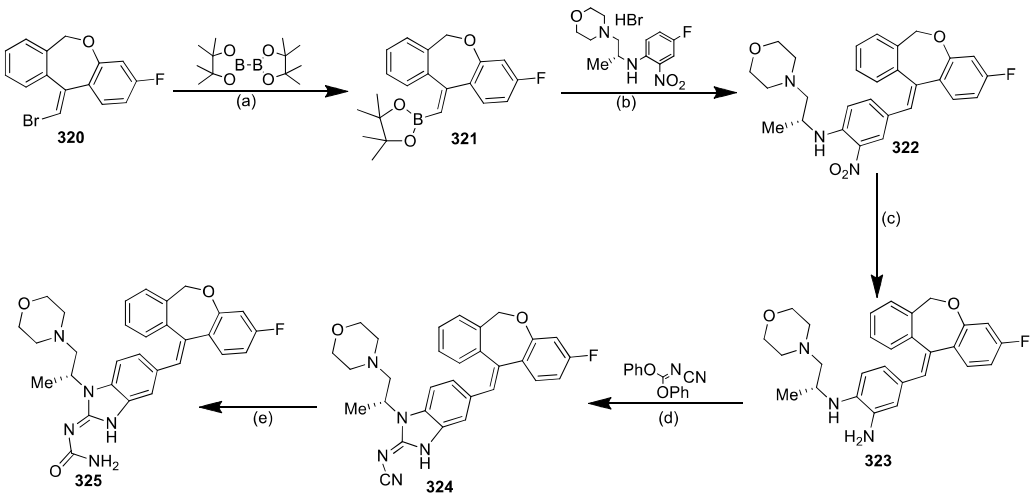
Wang *et al.* [127] demonstrated the reaction of oxepinone derivatives **(318 & 319)**. The compound **(317)** undergoes alcoholysis or hydrolysis with MeONa in methanol or 5% aqueous NaOH in THF at room temperature to give the carboxylates **(319)** or the carboxylic acids **(318)** as a product in 70-82% yield with high enantioselectivity *i.e.* 98-99% ee (Scheme **74**).



318 **317** **319**

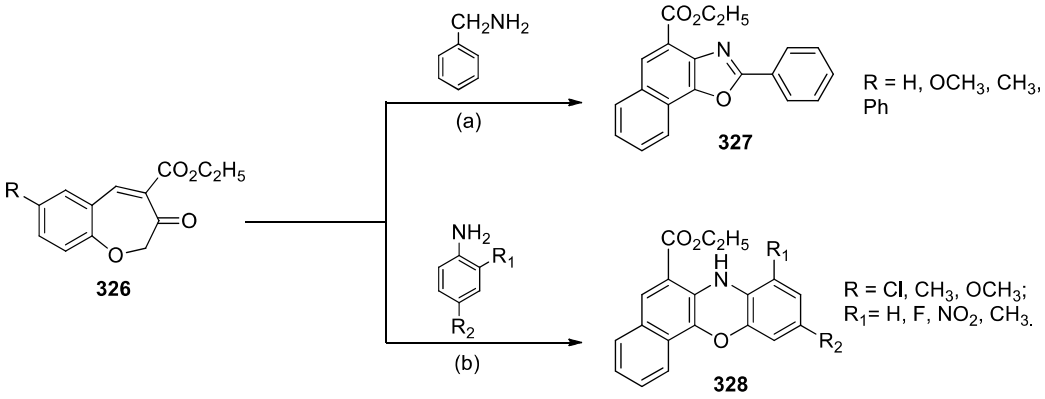
Scheme (74). Alcoholysis or hydrolysis of oxepinone derivative. Reagents: **a)** 5%NaOH/H_2O (10 equiv), THF, rt, 14h; **b)** MeONa (3 equiv), MeOH, rt, 12h.

Hansen *et al.* [27] in 2016 demonstrated the synthesis of dibenzoxepine derivative **(325)**. The first step proceeds with the Miyaura borylation [128] of compound **(320)** to dioxaborolane compound **(321)** which further undergoes Suzuki-Miyaura cross-coupling reaction [129] with aryl bromide to give compound **(322)** followed by the reduction of the nitro group to give corresponding aniline **(323)** which further reacts in solution with diphenyl cyanocarbonimidate to give corresponding cyanoguanidine **(324)** followed by the hydrolysis of cyanamide to give the resulting product **(325)** (Scheme **75**).



Scheme (75). Synthesis of dibenzoxepine derivative. Reagents: **a)** $Pd_2(dba)_3$ (1 mol%), Cy_3P (2 mol%), KOAc, dioxane, 85 °C, 6h; **b)** Pd(OA **c**)$_2$ (1 mol%), PPh_3 (3 mol%), K_2CO_3, dioxane, water, 80 °C, 6h; **c)** H_2, 5%Pt/C, Et_3N, THF, 25 °C; **d)** THF; **e)** (i) TFA/H_2O; (II) EtOAc.

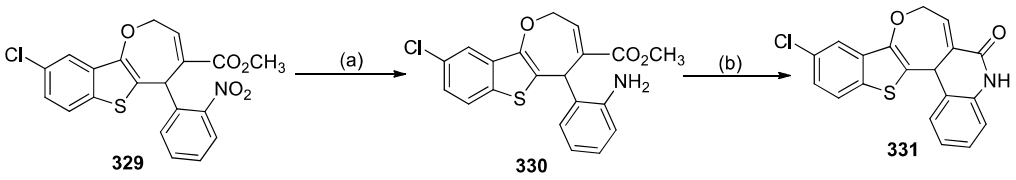
Prasad *et al.* [130] in 2016, demonstrated the catalyst-free reaction of substituted oxepine-4-carboxylate **(326)**. The compound **(326)** on reaction with phenylmethanamine and substituted aniline under the mild reaction condition give the substituted oxazole-4-carboxylate **(327)** and phenoxazine-6-carboxylate **(328)** respectively as a product (Scheme **76**).



Scheme (76). Reaction of oxepinone derivative. Reagents: **a)** 110 °C; **b)** Cu(OA **c**)$_2$ (30 mol%), 110 °C.

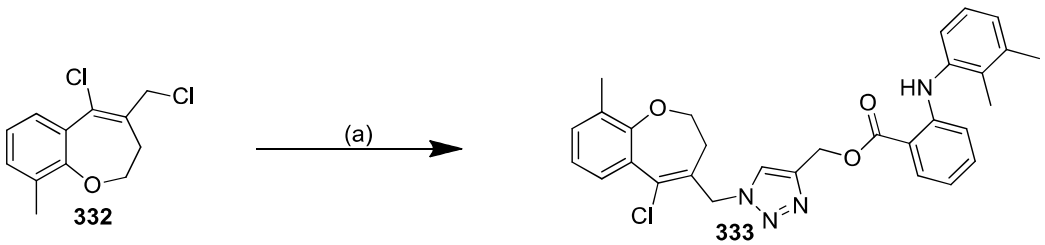
Zhang *et al.* [106] in 2017 carried out his further research for the synthesis of 11-chloro-8,14b-dihydrobenzo[4',5']thieno[2',3':6,7]oxepino[4,5-c]quinolin-6-5H)-one **(331)** *via* two-step reaction mechanism. In the first stage, ortho-NO_2

substituted compound **(329)** is easily reduced to an amine group **(330)** using the palladium catalyst in ethanol at room temperature, which further undergoes intramolecular cyclization in the presence of 4-Methylbenzenesulfonic acid and ethanol under reflux to give the target product **(331)** in very low yield (Scheme **77**).



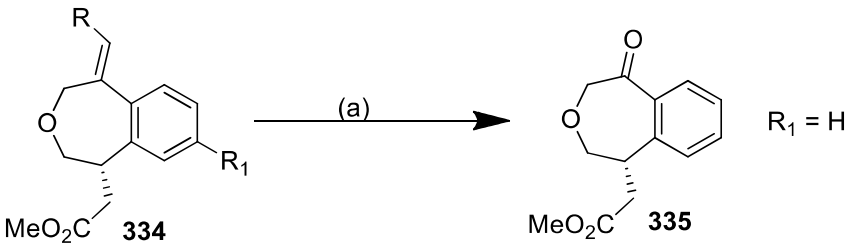
Scheme (77). Synthesis of oxepin derivative. Reagents: **a)** Pd/C, EtOH, rt, 9h; **b)** 4-Methylbenzenesulfonic acid, EtOH, reflux.

Dasari *et al.* [131] in 2019 worked on the synthesis of Benzo[b]oxepine derivative *via* the reaction of compound **(332)** with sodium azide in dry DMF to give the corresponding azide as an intermediate which is further reacted with prop-2-yn-1 yl-2-(2,3-dimethylphenyl)amino) benzoate in a solution of copper sulfate ($CuSO_4$) and sodium-ascorbate to give the target product **(333)** in excellent yield (Scheme **78**) which possesses anti-inflammatory properties.



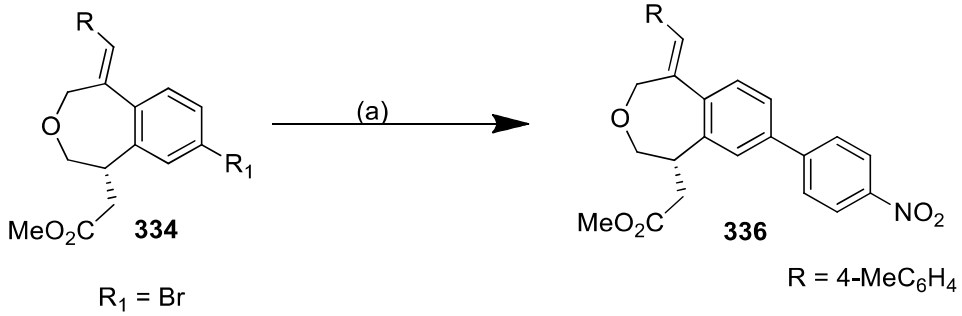
Scheme (78). Reaction of 5-chloro-4-(chloromethyl)-9-methyl-2,3-dihydrobenzo[b]oxepine. Reagents: **a)** NaN_3, DMF, rt, $CuSO_4.5H_2O$, Na-Ascorbate, rt, 5-10 min.

Selmani *et al.* [68] also worked on the Rh-catalyzed oxidative cleavage of the exocyclic double bond of tetrahydrobenzo[d]oxepines **(334)** derivative to give the corresponding product **(335)** as a product in excellent yield under the required reaction condition (Scheme **79**).



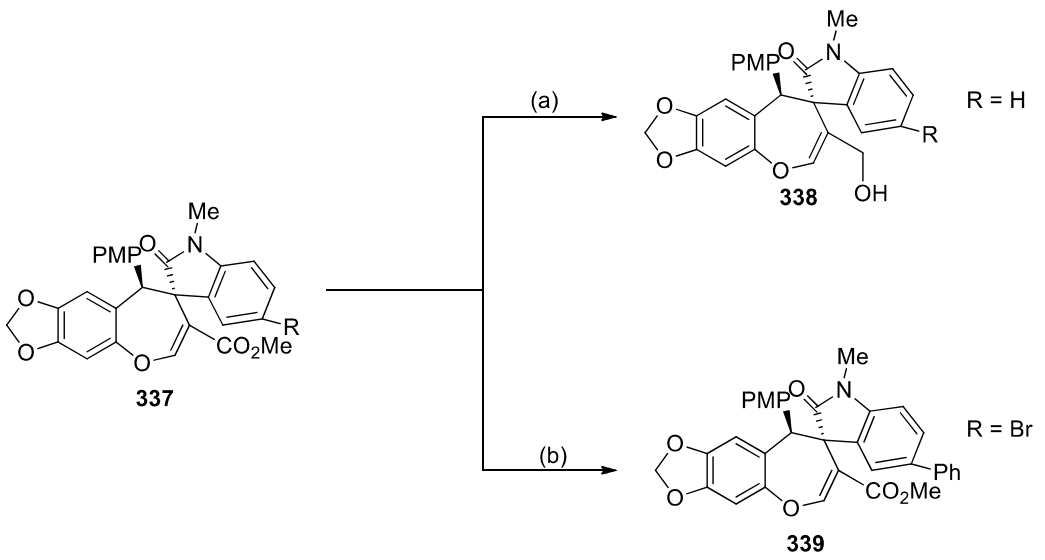
Scheme (79). Oxidative cleavage of the exocyclic double bond. Reagents: **a)** $RuCl_3.H_2O$ (20 mol%), $NaIO_4$ (4equiv), $ClCH_2CH_2Cl/H_2O$, rt.

Selmani *et al.* [68] demonstrated the Rh-catalyzed synthesis of compound **(336)** derivative *via* cross-coupling reaction to achieve a single crystal for X-ray analysis. The tetrahydrobenzo[d]oxepine **(334)** undergoes a cross-coupling reaction with 4-nitrophenylboronic acid to afford the synthesis of compound **(336)** under the desired reaction conditions (Scheme **80**).



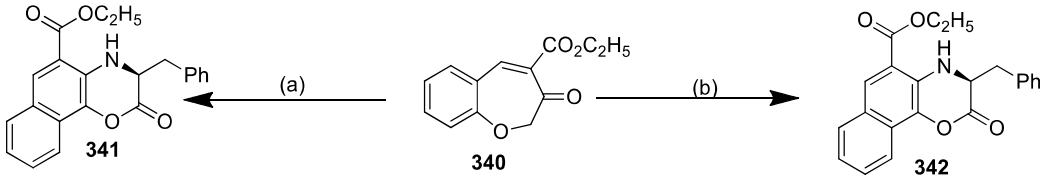
Scheme (80). The cross-coupling reaction of tetrahydrobenzo[d]oxepine with 4-nitrophenylboronic acid. Reagents: **a)** $Pd(OA\ \mathbf{c})_2$ (5 mol%), CataCXium A (10 mol%), $4\text{-}NO_2C_6H_4B(OH)_2$ (2equiv), K_2CO_3, DMF, 100 °C.

The benzo[b]oxepines **(337)** further undergo reduction with DIBAL-H at -40 °C to give the alcohol **(338)** as a product in medium yield. In addition to the reduction, the same compound **(337)** undergoes Suzuki coupling reaction using $Pd(PPh_3)_4$ as a catalyst, phenylboronic Acid, cesium carbonate, DMF, and water as a solvent to give the product **(339)** in 89% yield [93] (Scheme **81**).



Scheme (81). Reaction of benzo[b]oxepines. Reagents: **a)** DIBAL-H, THF, -40 °C; **b)** $Pd(PPh_3)_4$, $PhB(OH)_2$, THF/H_2O, 70 °C, 24h.

Kasagani *et al.* [132] in 2020 portrayed the reaction of benzoxepine-4-carboxylate **(340)** with (*S*)-2-amino-3-phenylpropanoic acid and ethyl (S)-2-amin--3-phenylpropanoate in the presence of *p*TsOH in ethanol under reflux to give the corresponding products **(341)** and **(342)** in low to moderate yield (Scheme **82**).



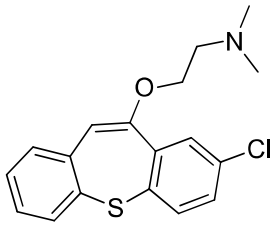
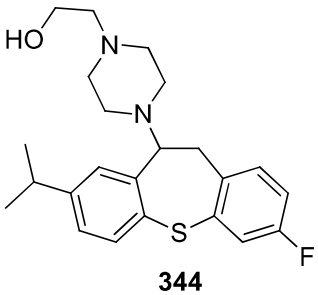
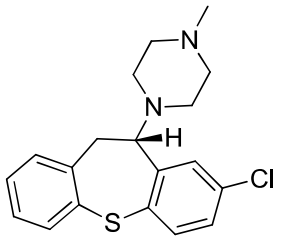
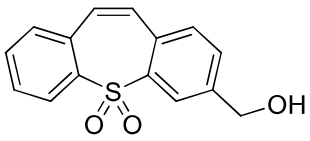
Scheme (82). Reaction of benzoxepine-4-carboxylate. Reagents: **a)** (S)-2-Amino-3-phenylpropanoic acid, *p*-TsOH, EtOH, reflux; **b)** Ethyl (S)-2-amino-3-phenylpropanoate, *p*-TsOH, EtOH, reflux.

S-CONTAINING SEVEN-MEMBERED HETEROCYCLES

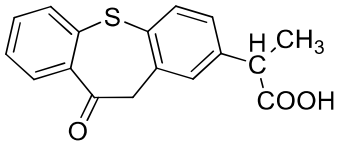
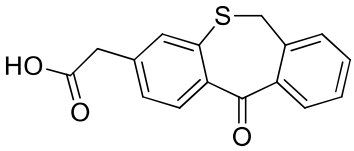
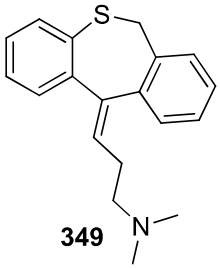
Thiepines are the seven-membered heterocycles with S as a heteroatom. Thiepine constitutes a remarkably valuable class of therapeutic agents, hence exploited extensively for chemical and biological activities. There is a long list of broad-spectrum biological properties that include prevention of inflammations by inhibiting tumor necrosis factor-α (TNF- α), treatment of a major depressive disorder, DNA helicase inhibitors, antidepressant, antihistaminic, antipsychotic, antimicrobial, insecticidal, acaricidal, and nematicidal [26 (**c**), 133-135]. Some of

the thiepine based well know commercially available drugs are listed as Dosulepine (antidepressant) [136], Dithiadene (antihistamini **c)** [137], and Tiopinac (antiinflammatory) [138] (Table **3**).

Table 3. Drugs containing Thiepine moiety.

S.No	Name	Structure	Biological Activity
1	Zetopine [139]	 **343**	Antipsychotic
2	Isofloxythiepine [140]	 **344**	Neuroleptic
3	Octoclothepin [141]	 **345**	Antischizophrenic activity
4	L-640,035 [142]	 **346**	Smooth muscle contraction

(Table 3) cont.....

S.No	Name	Structure	Biological Activity
5	CN-100 [143]	 **347**	Nonsteroidal anti-inflammatory agent
6	Tiopinac [138]	 **348**	Anti-inflammatory, analgesic, and anti-pyretic agent.
7	Dosulepine [136]	 **349**	Antidepressant

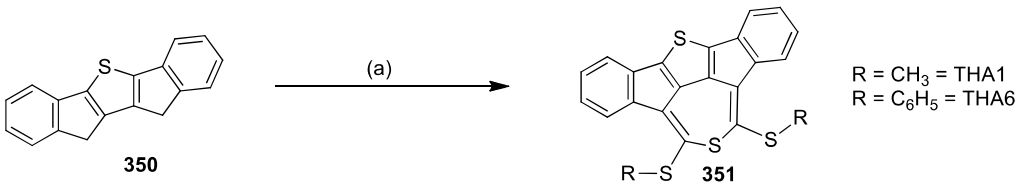
Synthesis of Thiepine and its Derivatives

In the last few years, various researchers found a topic of interest in the synthesis of Thiepine and its derivative, which has always been a tough task for the researchers. Their synthesis can be achieved either by intramolecular or intermolecular reactions.

Intramolecular Synthesis

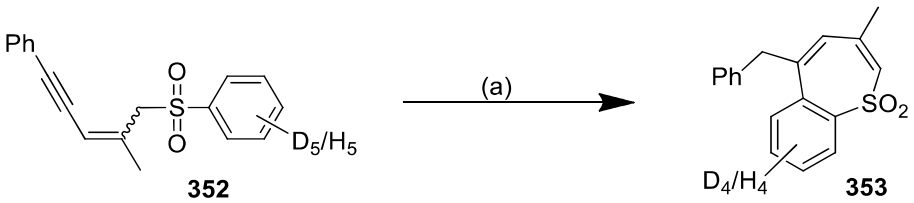
C-S Bond Formation

Cai *et al.* [144], in 2013, worked on the synthesis of THA1 and THA6. The substituted thiophene (**350**) was reacted with *t*-BuOK (tert-butoxide) and CS_2 (carbon disulphide); further, the reaction mixture was reacted with methyl iodide or with hexyl bromide to form corresponding THA1 or THA6 (**351**) in maximum yield (Scheme **83**) which act as a semiconductor.



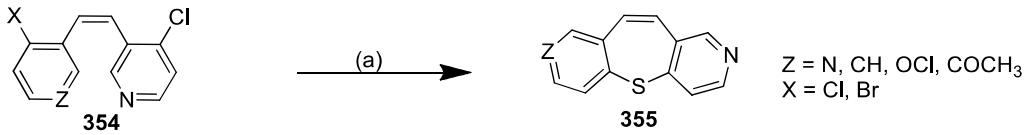
Scheme (83). Synthesis of THA1 and THA6. Reagents: **a)***t*-BuOK, CS_2, CH_3I, or $C_6H_{13}Br$.

Chen *et al.* [145] in 2015 worked on the synthesis of Rh(III)-catalyzed intramolecular cyclization of compound **(352)** in toluene to form benzothiepine sulfone **(353)** as a final product in very low yield under the mild reaction condition (Scheme **84**).



Scheme (84). Rh-catalyzed Synthesis of benzothiepine sulfone. Reagents: **a)** $[(Cp^*RhCl_2)_2]$, Et_3N, Cu(OA **c)**$_2$, DCE, 80 °C.

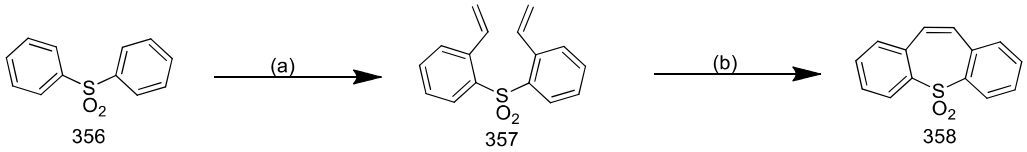
Bozinovic *et al.* [146] in 2016, working on the synthesis of Pd-catalyzed pyridines fused benzothiepines **(355)** *via* intramolecular C-S bond formation of compound **(354)** which possess anti-fungal property (Scheme **85**).



Scheme (85). Synthesis of pyridine fused benzothiepin. Reagents: **a)** Pd(OA **c)**$_2$, dppf, KSAc, NaO*t*-Bu, PhMe, 175 °C, μW.

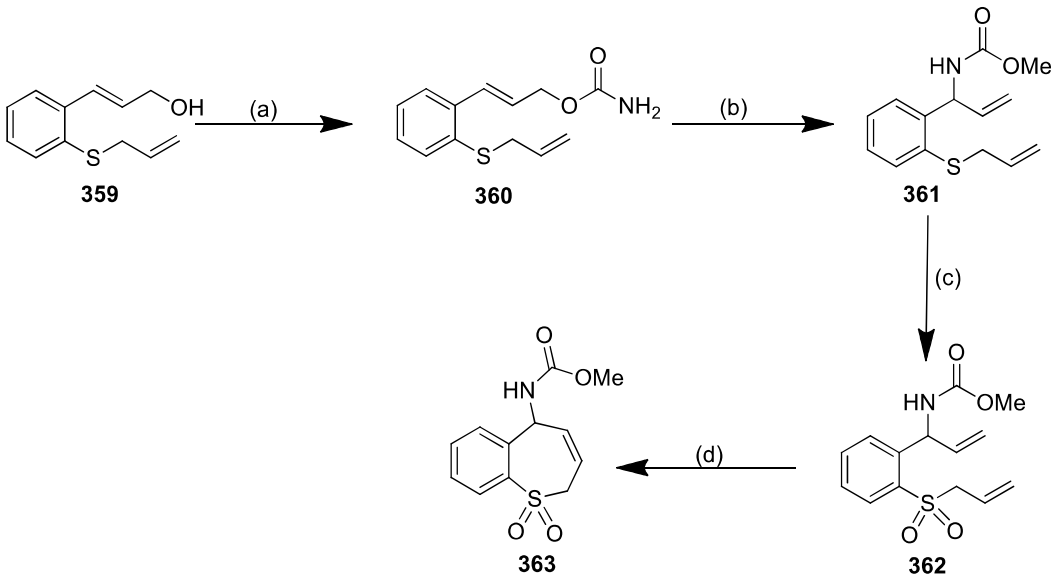
C-C Bond Formation

Matsuda and Sato [58] in 2013 demonstrated the synthesis of compound **(358)** *via* ortho-formylation and Wittig methylenation of compound **(356)**, to furnish Bis(2-vinylphenyl)sulfone **(357)** followed by Ru catalyzed subsequent ring cyclization metathesis to afford the synthesis of a product **(358)** in high yield (Scheme **86**).



Scheme (86). Synthesis of dibenzo[b,f]thiepine 5,5-dioxide. Reagents: **a)** (i) *n*-BuLi, DMF; (ii) $Ph_3P{=}CH_2$; **b)** [Ru].

Chwastek *et al.* [63] in 2016 reported the multi-step synthesis of thiepin carbamate **(363)**. The compound **(359)** was converted to allyl carbamate **(360)** followed by ring rearrangement to give compound **(361)**. The **(361)** further undergoes epoxidation followed by hydrolysis in DCM to give compound **(362)** followed by ring cyclization using Grubbs II catalyst in DCE to give the target compound **(363)** in excellent yield (Scheme **87**).



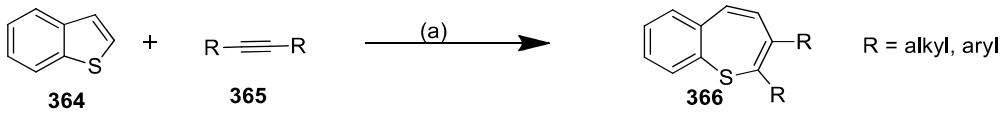
Scheme (87). Multi-step synthesis of thiepin carbamate. Reagents: **a)** (i) TCAI, DCM, rt; (ii) aq. K_2CO_3, MeOH, rt; **b)** (i) TFAA, Et_3N, THF; (ii) Bu_3SnOMe (10 mol%), MeOH; **c)** m-CPBA, DCM, rt; **d)** Grubbs II cat. (5 mol%), DCE, 50 °C.

Intermolecular Reaction

Cycloaddition

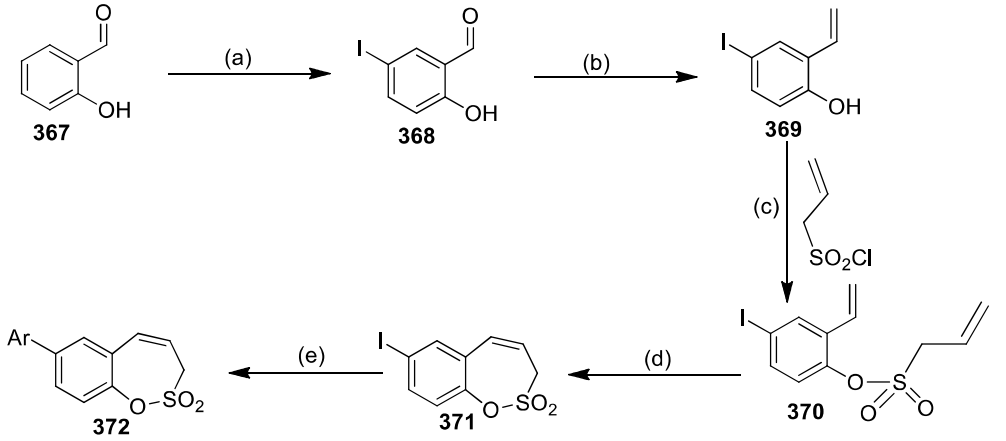
Inami *et al.* [147] in 2019, reported a new reaction pathway for the synthesis of benzo[b]thiepine **(366)** *via* [5+2] cycloaddition. The benzo[b]thiophene **(364)**

undergoes [5+2] cycloaddition reaction with substituted alkynes **(365)** in toluene using Ni(II) as a catalyst at 30 °C to give the target product, *i.e.* benzo[b]thiepine derivatives **(366)** in medium to high yield (Scheme **88**).



Scheme (88). Synthesis of benzo[b]Thiepine *via* [5+2] cycloaddition. Reagents: **a)** $Ni(cod)_2$ (10 mol%), PCy_3 (20 mol%), toluene, 30 °C.

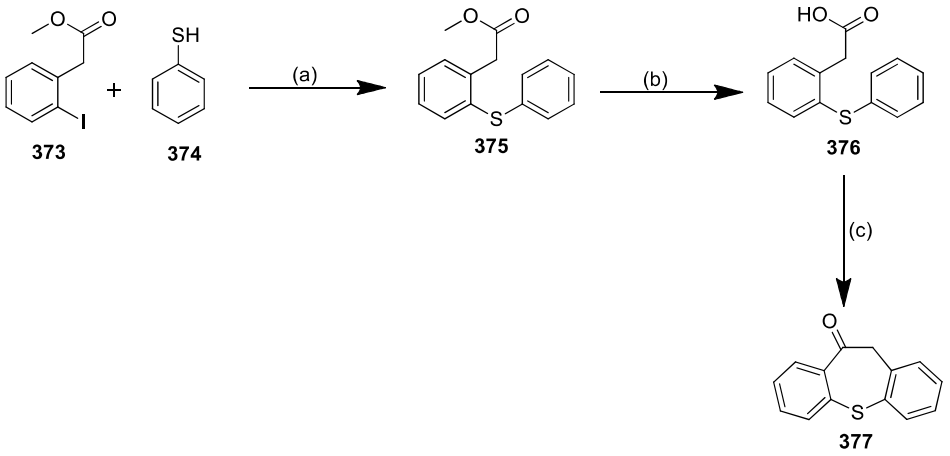
Pustenko *et al.* [148] in 2020 reported a new strategy for the synthesis of substituted benzoxathiepine 2,2-dioxides **(372)**. The 2-hydroxybenzaldehyde **(367)** undergoes iodination with iodine monochloride to give corresponding 2-hydroxy-5-iodobenzaldehyde **(368)**. Further, the iodine derivative **(368)** undergoes Wittig reaction to form olefin **(369)** followed by a reaction with sulphonyl chloride to give compound **(370)**. The compound **(370)** further undergoes Ru-catalyzed ring cyclization to give the 7-iodo-3H-benzo[f] [1, 2]oxathiepine 2,2-dioxide **(371)** as an intermediate. The compound **(371)** was further reacted with different aryl boronic acids (Ar-$B(OH)_2$) under the Suzuki coupling condition to give the target product **(372)** in medium yield (Scheme **89),** which possesses an anti-tumor agent.



Scheme (89). Multi-step synthesis of substituted benzoxathiepine 2,2-dioxides. Reagents: **a)** ICl, AcOH, 40 °C, 24h; **b)** KOtBu, $CH_3P(C_6H_5)_3Br$, THF, RT, 18h; **c)** NEt_3, DCM, 0 °C to RT, 4h; **d)** toluene, 70 °C, 4h; **e)** Ar-$B(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, toluene/H_2O, 100 °C, 16h.

Coupling Reaction

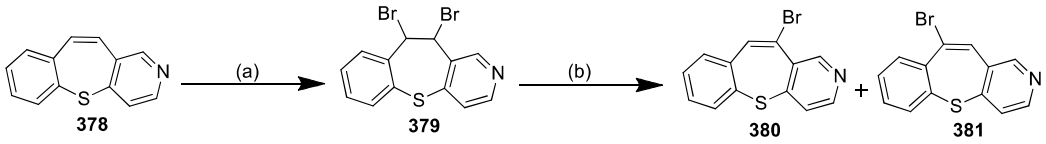
Ansari *et al.* [26], reported a three-step reaction pathway for the synthesis of thiepinone derivative **(377)** *via* Hetero-Ullmann coupling reaction [149, 150]. The thiophenol **(374)** undergoes Hetero-Ullmann coupling reaction with compound **(373)** gives methyl 2-(2-(phenylthio)phenyl)acetate **(375)**, which on basic hydrolysis gives 2-(2-(phenylthio)phenyl)acetic acid **(376)** followed by intramolecular cyclization to give the target product **(377)** in 75% yield (Scheme **90**).



Scheme (90). Synthesis of dibenzo[b,f]thiepinone. Reagents: **a)** CuI, Neocuproine, dry tpluene, 6h; **b)** KOH/EtOH (80% v/v), reflux, 4h; **c)** $(COCl)_2$, DMF, DCM, 30 min; **d)** $AlCl_3$, DCM, rt, 60 min.

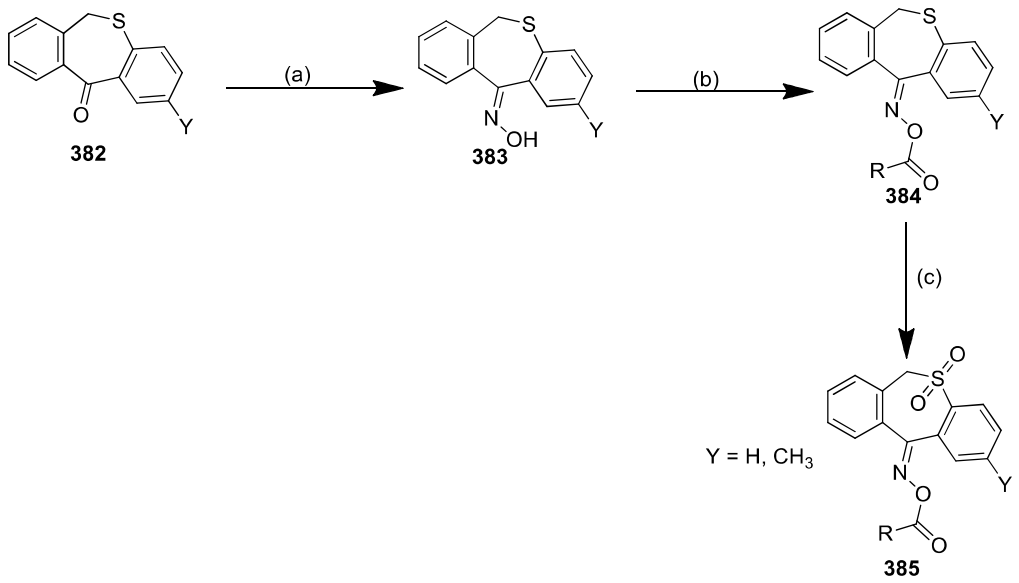
Reactions of Thiepine

Bozinovic in 2016 [146] portrayed a reaction pathway for the synthesis of bromo-substituted benzothiepino[3,2-*c*]pyridines **(380 & 381)**. The benzo [6, 7]thiepino [3,2-c]pyridine **(378)** undergoes bromination give vicinal dibromide **(379)** followed by the HBr elimination to give vinyl bromides **(380)** and **(381)** in low to medium yield with high regioselectivity under the optimized reaction condition (Scheme **91**).



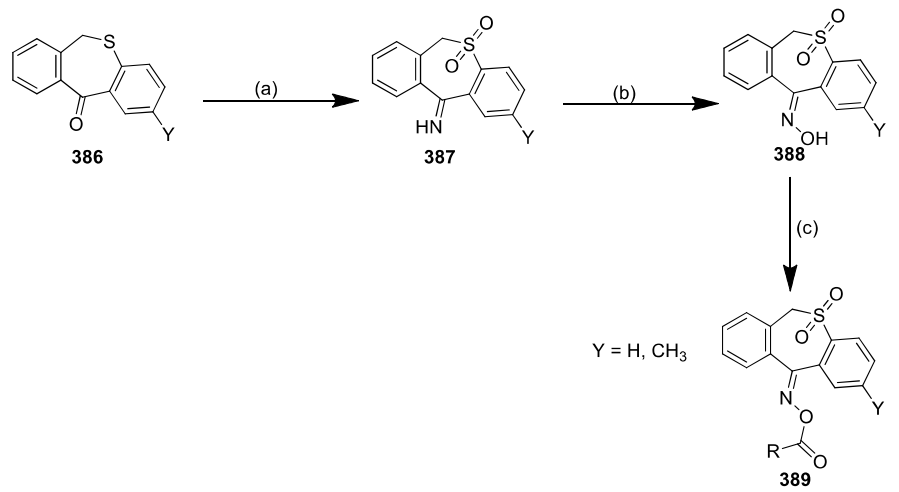
Scheme (91). The reaction of benzothiepino[3,2-*c*]pyridines. Reagents: **a)** Br_2, CCl_4, rt; **b)** KO*t*-Bu, *t*-BuOH, 85 °C.

Mihai *et al.* [151] in 2019 demonstrated the reaction of thiepin-11-ones derivatives **(385)**. The **(382)** was reacted with hydroxylamine hydrochloride under the standard conditions to form oxime derivatives **(383)**. The oxime derivatives **(383)** further undergo acylation by reaction with various acid chloride to form the corresponding intermediate **(384)** followed by the oxidation with hydrogen peroxide to form 5,5-dioxides **(385)** as a final product (Scheme **92**).



Scheme (92). The reaction of thiepin-11-ones derivatives. Reagents: **a)** $NH_2OH.HCl$, pyridine, reflux, 24h; **b)** RCOCl, benzene, pyridine, reflux, 2h; **c)** H_2O_2, CH_3COOH, reflux, 2h.

Mihai *et al.* [151] in 2019 demonstrated one more reaction pathway for the reaction of thiepin-11-ones derivatives **(386)** (Scheme **93**). The ketones **(386)** undergo oxidation with hydrogen peroxide to give 5,5-dioxides **(387)** followed by the reaction of hydroxylamine hydrochloride to form dioximes **(388)**. The oxime derivatives **(388)** further undergo acylation by the reaction with various acid chlorides to form the corresponding product **(389)**.

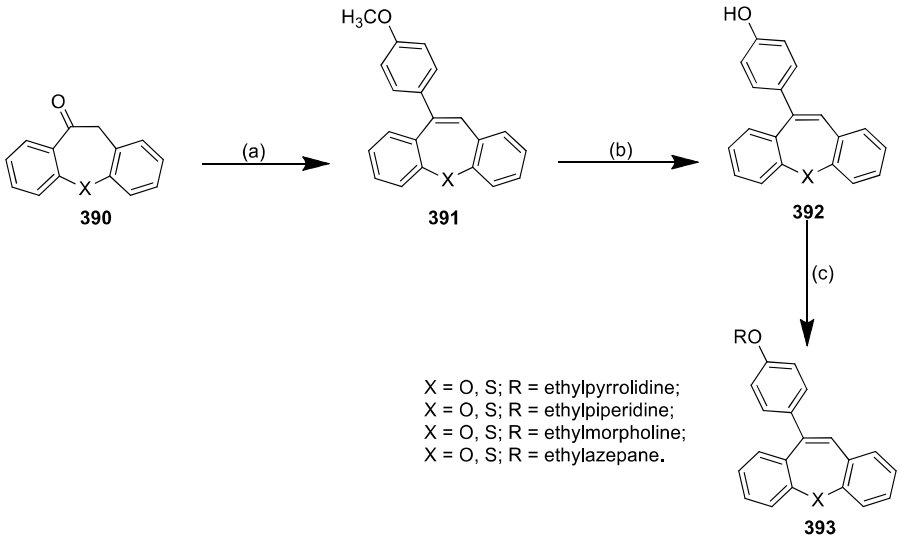


Scheme (93). Reaction of thiepin-11-ones derivatives. Reagents: **a)** H_2O_2, CH_3COOH, reflux, 2h; **b)** $NH_2OH.HCl$, pyridine, reflux, 24h; **c)** RCOCl, benzene, pyridine, reflux, 2h.

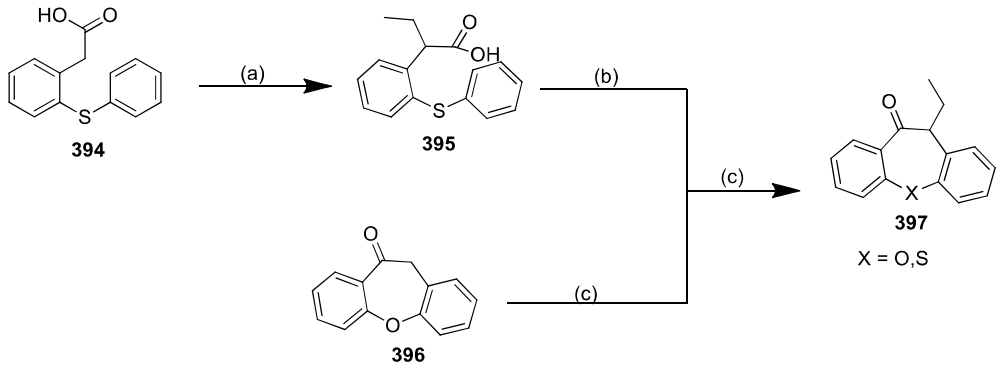
REACTION CONTAINING BOTH O, S-SEVEN MEMBERED HETEROCYCLIC

Adam *et al.* [26, 152] also worked on the reaction of dibenzo cyclic ketone **(390)** either with 4-methoxyphenylmagnesium bromide or with 4-bromoanisole and *n*-BuLi in THF to synthesize 7-arylated products in very low yield or carbinols, which on further acidic dehydration gives the target compound **(391)**. The compound **(391)** on demethylation with BBr_3 gives **(392)** followed by *O*-alkylated with *t*-aminoalkyl halides yielded thiepines or oxepinines derivatives **(393)** respectively (Scheme **94**).

Acton *et al.* [26, 153] also portrayed the synthesis of the seven-membered heterocyclic moiety **(397)** (Scheme **95**). The α-alkylation of 2-(2-(phe nylthio)phenyl)acetic acid **(394)** with C_2H_5I under anhydrous condition using LDA gives 2-(2-(phenylthio)phenyl)butanoic acid **(395)** respectively. The **(395)** undergoes intramolecular cyclization either on reaction with phenylpropano lamine, $AlCl_3$-$(COCl)_2$, or methanesulfonic acid to give the cyclized product in low yield or by using Eaton's reagent to give compound **(397)** in approx 60% yield. Similarly, α-alkylation of compound **(396)** with ethyl iodide under optimized reaction condition gives substituted dibenzo[b,f]oxepinone **(397)**.

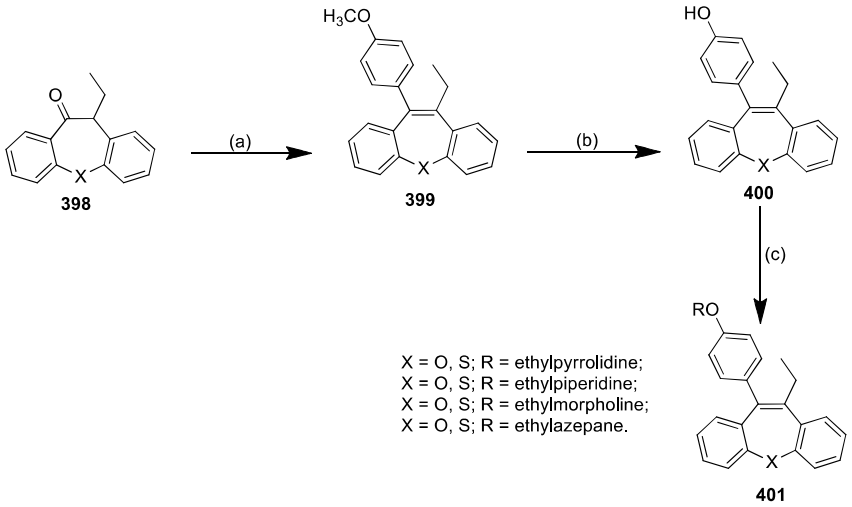


Scheme (94). The Reaction of dibenzo cyclic ketone either. Reagents: **a)** (i) 4-bromoanisole, *n*-BuLi, THF, 0 °C to rt; (ii) 2-3 drops H_2SO_4, MeOH, 60 °C, 30 min; **b)** BBr_3, DCM, -30 °C to rt, overnight; **c)** aminoalkyl monohydrochlorides, anhyd. K_2CO_3, acetone, reflux, overnight.



Scheme (95). Synthesis of the seven-membered heterocyclic moiety. Reagents: **a)** LDA, CH_3CH_2I, THF, -78 °C to rt; **b)** Eaton's reagent, 1h, rt; **c)** TBAHS, NaOH, CH_3CH_2I, rt, 60 min.

Adam *et al.* [26, 152] in 2015 worked on the arylation of the ketone (Scheme **96**). The dibenzoxepin **(398)** ketone was reacted with 1-Bromo-4-methoxybenzene and n-butyllithium in THF at -78 °C to rt gives the carbinols, followed by acidic dehydration to give the desired intermediate **(399)**, which further on demethylation with BBr_3 furnished the synthesis of alcohol **(400)** followed by *O*-alkylation with different tert-aminoalkyl halides group under the optimized reaction condition to give the target product **(401)**.



Scheme (96). Arylation of dibenzoxepin ketone. Reagents: **a)** (i) 1-Bromo-4-methoxybenzene, *n*-BuLi, tetrahydrofuran, -78 °C tort; (ii) sulfuric acid, methanol, 30 min; **b)** BBr_3, DCM, -20 °C to rt, overnight; **c)** tert-aminoalkyl monohydrochlorides, potassium carbonate, dry acetone, reflux, overnight.

CONSENT FOR PUBLICATION

Not Applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 4

Application of Nitriles on the Synthesis of 5-Membered Azaheterocycles: An Update from 2014 to 2020

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Abstract: Nitriles are organic compounds bearing the -C≡N functional group and thus derivatives of hydrocyanic acid. Besides their application in polymers, nitriles are also present in more than 30 pharmaceuticals, including antidepressants, antidiabetics, and anticancer drugs, since they can act as hydrogen acceptors, increase water solubility and shield the drug from oxidative metabolism. Moreover, nitrile derivatives are usually stable and inexpensive and can be converted into many functional groups and heterocycles, and, therefore, are very interesting precursors in the synthesis of robust molecular libraries in medicinal chemistry. It is also important to mention that 5-membered azaheterocycles are of the utmost importance in the medicinal chemistry field, being present in many marketed top-selling drugs. In this context, this chapter will provide an update on the synthesis of prominent 5-membered azaheterocycles from nitriles, focusing on the most interesting reactions and methodologies reported from 2014-2020.

Keywords: Azaheterocycles, Imidazoles, Indoles, Nitriles, Pyrazoles, Pyrroles, Synthesis, Tetrazoles, Triazoles.

INTRODUCTION

Nitriles are organic compounds bearing the -C≡N functional group and thus derivatives of the hydrocyanic acid. The prefix Cyano is also widely used in reference to this functional group [1]. In nitriles, both the carbon atom and the nitrogen atom show a sp hybridization, forming a triple bond ($\sigma_{sp\text{-}sp}$ + 2π bonds) with a bond length around 116pm in acetonitrile. Nitrile derivatives can be synthesized through various pathways such as ammoxidation, hydrocyanation, the formation of cyanohydrins, and the Sandmeyer reaction (Scheme **1**) [2 - 4].

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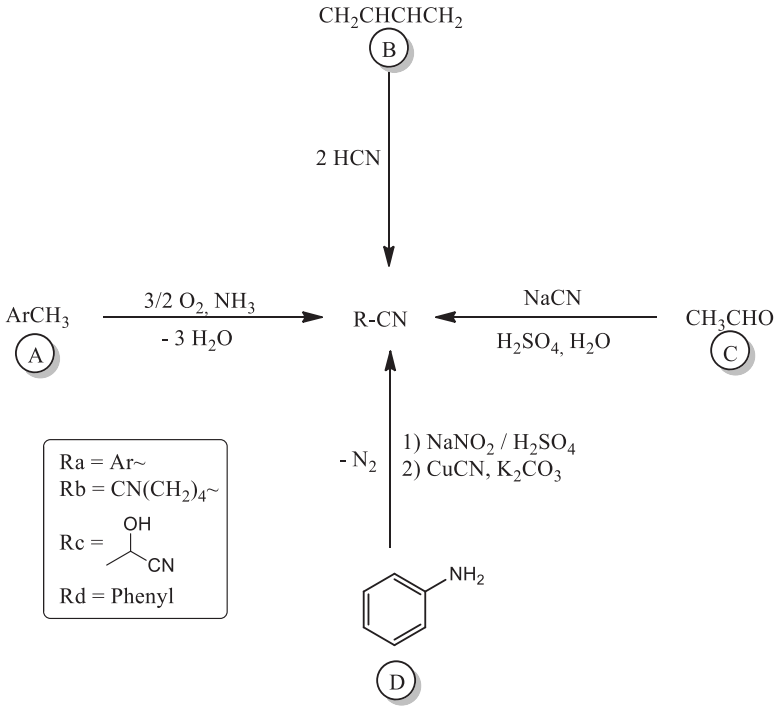
Atta-ur-Rahman, *FRS* (Ed.)



Scheme (1). Some methods for the preparation of nitriles: Ammoxidation **(A)**, hydrocyanation **(B)**, Cyanohydrin formation, **(C)**, and Sandmeyer Reaction **(D)**.

Besides their application in polymers, nitriles are also present in more than 30 pharmaceuticals, including antidepressants, antidiabetics, and anticancer drugs (Fig. **1**), since they can act as hydrogen acceptors, increase water solubility and shield the drug from oxidative metabolism [5 - 8].

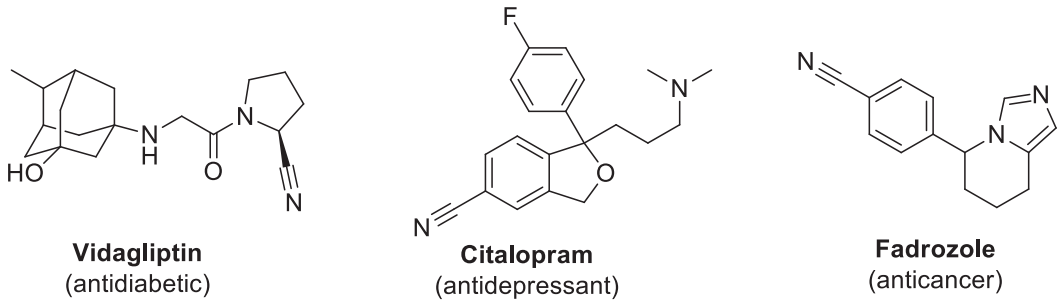
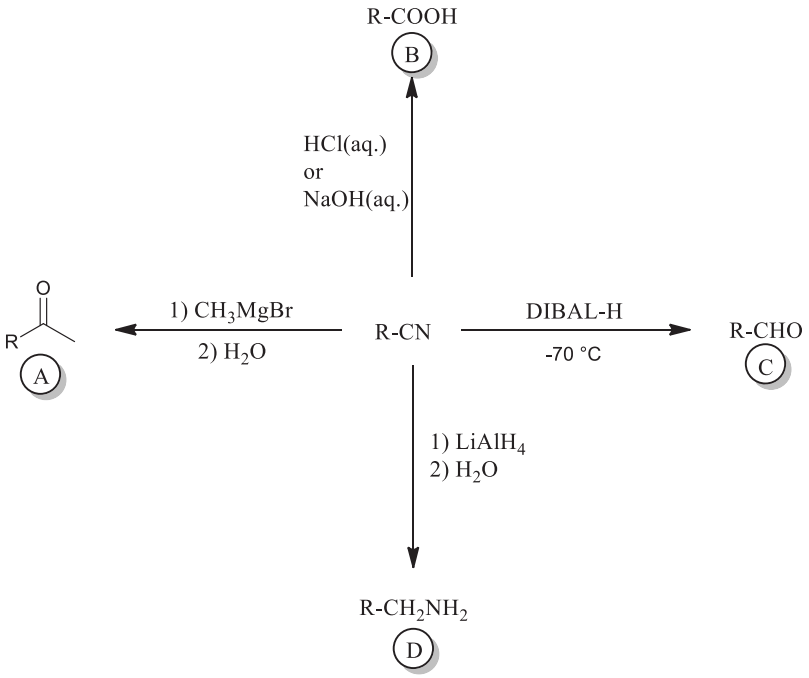


Fig. (1). Example of Nitrile-containing compounds in clinical use.

Moreover, the majority of nitriles are relatively stable and inexpensive compounds that support a high variation of substituents and can be converted into many functional groups (Scheme **2**) and heterocycles by various processes. Therefore, nitriles are interesting reagents in the synthesis of robust and diverse molecular libraries that may be used in high throughput screening assays on the search for novel drug candidates [9, 10].



Scheme (2). Example of the conversion of nitriles into some common functional groups: ketone **(A)**, carboxylic acid **(B)**, aldehyde **(C)**, and amine **(D)**.

Five membered-ring azaheterocycles have been extensively explored in medicinal chemistry and are present in many marketed drugs. Some of them, such as pyrrole, indole, triazole, and imidazole are found in top-selling drugs [11, 12] and many more are found in bioactive molecules [13, 14].

Therefore, considering the importance of the nitrile functional group as a precursor to many azaheterocycles, in this work we will review the new synthetic methodologies, reported from 2014 to 2020, for the synthesis of some prominent 5-membered azaheterocycles *via* nitrile intermediates.

PYRROLE AND INDOLE

Pyrroles and its derivatives are important 5-membered heterocycles, which are

present in many natural products and drugs [15]. Among them, indoles (2,3-benzopyrroles) are found in many bioactive molecules. Therefore, the search for new methods for the construction of these heterocycles is a hot topic in organic synthesis [16]. Fig. (**2**) shows a few natural products and drugs containing the pyrrole and indole moieties.

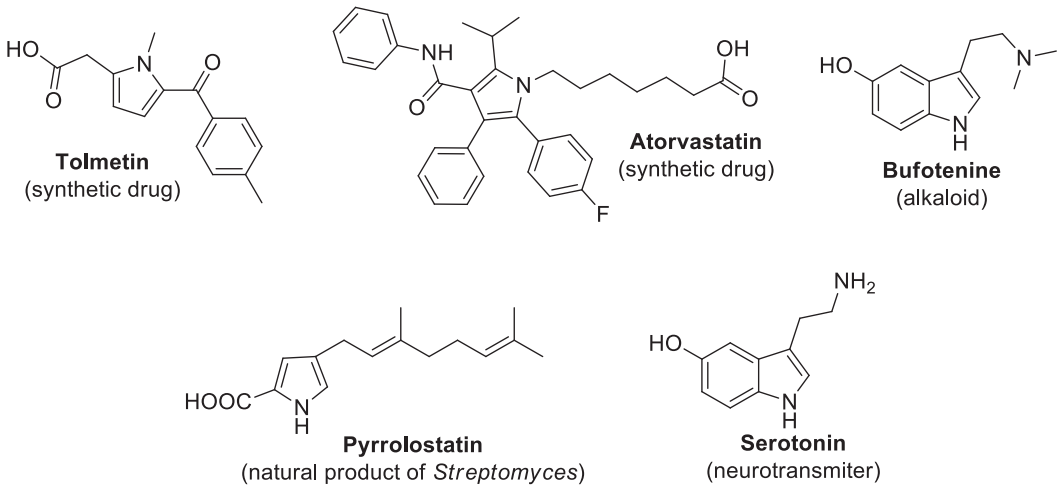
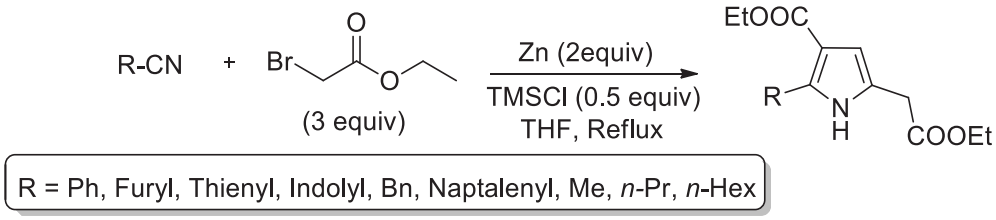


Fig. (2). Natural products and pharmaceuticals containing the pyrrole and indole moieties.

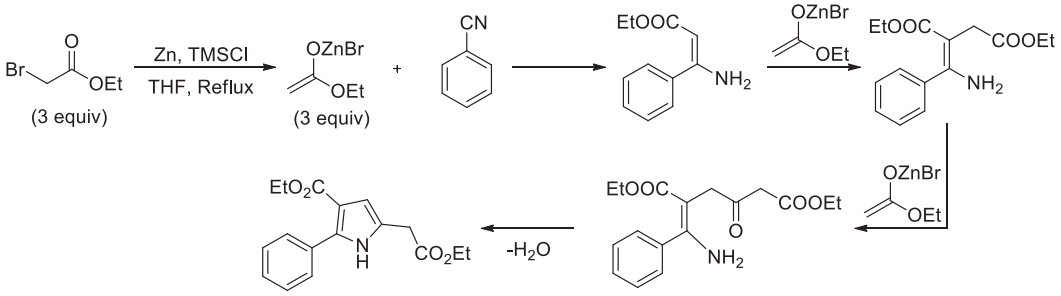
Synthetic Methods

Pyrroles are traditionally obtained through the Knorr, Paal–Knorr, Hantzsch, and Van Leusen reactions, but many other methodologies, such as 1,3-dipolar cycloadditions and metal-catalyzed condensation of electron-deficient nitriles have been reported in the past few years [15]. In 2014, Rao & Desai reported a straightforward, one-pot CN+3C procedure for the synthesis of regiodefined 2,3,5-trisubstituted pyrrole diesters. Their strategy consisted of modifying the classic Blaise reaction (Scheme **3**), used to synthesize *β*-keto esters or *β*-amino-*α,β*-unsaturated esters, to furnish pyrrole diesters. The authors synthesized fifteen examples with yields up to 91% as shown in Scheme **3** [17].



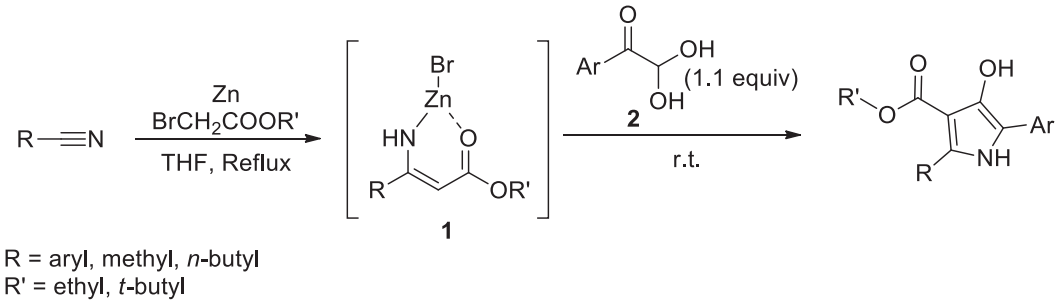
Scheme (3). One-pot synthesis of tri-substituted pyrroles [17].

The authors discussed the pathway for this transformation. The first step of the reaction is the formation of an enaminoester through the attack of the Zn enolate of ethylbromoacetate to the nitrile. The final product is then formed in three steps, a C-alkylation followed by Perkin ester condensation and dehydration. It was also possible to synthesize the product directly from the enaminoester, which helps to prove this mechanism (Scheme **4**) [17].



Scheme (4). Reaction pathway to tri-substituted pyrroles synthesized by Rao & Desai [17].

In 2017, Chen and co-workers expanded the scope of this reaction by using a similar strategy. The authors reacted the Blaise intermediate organozinc enaminoester (**1**) with arylglioxals (**2**) in a tandem reaction to form tetra-substituted pyrroles. The optimized reaction conditions and scope are shown in (Scheme **5**) [18].



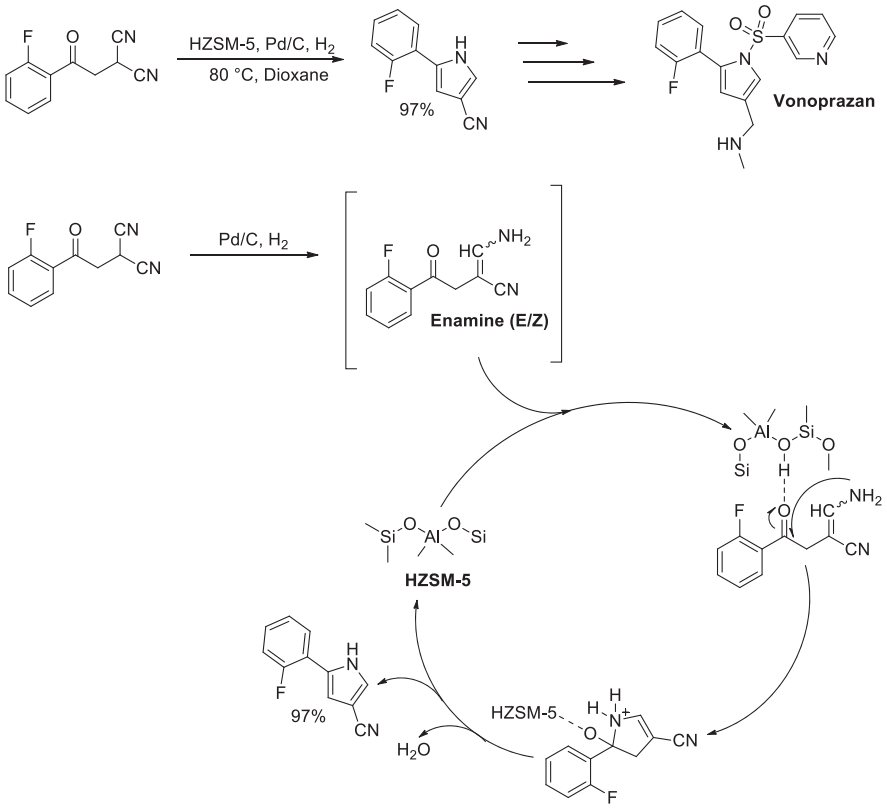
Scheme (5). Tetra-substituted pyrroles synthesized by Chen and co-workers [18].

β-enamino esters were also used as starting materials by Jang, *et al*. to furnish fully-substituted pyrrole. In 2019, the authors reported the divergent synthesis of pyrroles and pyrazoles by the copper-catalyzed oxidative annulation of these esters in the presence of nitriles. Their synthesis is controlled by the oxidant, with $Cu(OAC)_2$ leading to pyrazoles and di-*tert*-butyl peroxide leading to pyrroles. The best catalytic conditions were also evaluated and CuCl proved to be the best in

both cases (Scheme **6**) [19]. Even though nitriles are not used to form the desired pyrroles, in this case, it should be noted that the enaminoesters are formed from nitriles (Schemes **4** and **5**). The synthesis of pyrazoles will be further discussed in the next section.

R = Ph, Naph, *n*-Bu
R^1 = Et, *i*-Pr, Ph
R^2 = Et, *n*-Bu, *c*Hex, *t*-Bu
R^3 = Ph, Me, *n*-Pr

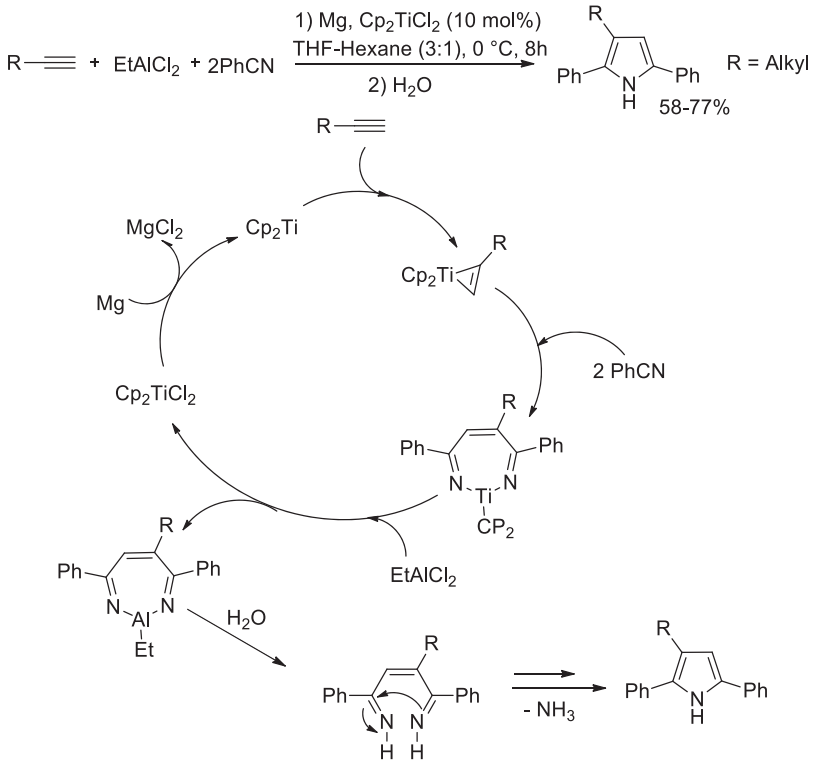
Scheme (6). Divergent synthesis of pyrroles and pyrazoles [19].



Scheme (7). Solid acid catalyzed synthesis of the vonoprazan building block and the proposed mechanism [20].

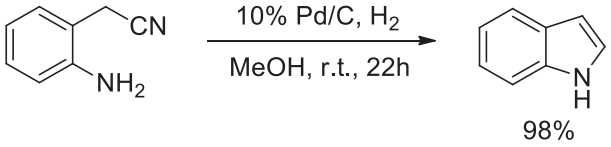
Chen *et al*., in 2019, published another interesting methodology for the synthesis of substituted pyrroles. The authors aimed to develop a greener and more efficient protocol for the synthesis of 1*H*-pyrroles-3-carbonitriles by using heterogeneous solid acid catalysts. After assessing a wide variety of solid acids and solvents, the zeolite HZSM-5(120) proved to be the best catalyst for this transformation, and 1,4-dioxane at 80°C was chosen as the best reaction condition. (Scheme **7**) shows an example product obtained by this methodology. This product is also an important building block for the synthesis of the drug vonoprazan, approved in 2015 for the treatment of gastroduodenal ulcers. The proposed mechanism involves the Pd/C catalyzed hydrogenation of the initial substrate followed by the intramolecular annulation of an enamine intermediate (Scheme **7**) [20].

Finally, 2,3,5-substituted 1*H*-pyrroles can be obtained *via* the multicomponent one-pot reaction of terminal acetylenes with organic nitriles in the presence of $EtAlCl_2$, metallic Mg, and Cp_2TiCl_2 as described by Khafizova and co-workers. The optimized reaction conditions and the proposed mechanism are shown in (Scheme **8**) [21].



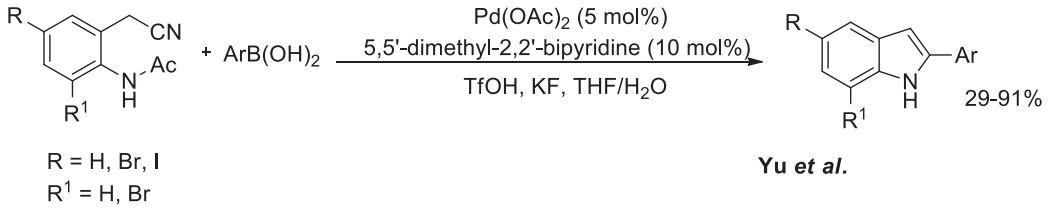
Scheme (8). Synthesis of 2,3,5-substituted 1*H*-pyrroles from terminal acetylenes and nitriles as described by Khafizova and co-workers [21].

Indoles, or 2,3-benzopyrroles, are classically synthesized from the reaction of anilines with ethylene glycol at high temperatures and by the very reliable Fischer indole synthesis, from phenylhydrazines and pyruvic acid. Many other strategies were developed through the years including the Bischer, Bartoli, Leimgruber-Batcho, Reissert, and Sundberg indole syntheses, among many others [22]. More recently, in 2004, the transformation of an *ortho*-amino nitrile into indole was reported (Scheme **9**) [23].



Scheme (9). Synthesis of indoles from *ortho*-amino nitriles [23].

In fact, nitriles can be interesting starting materials for the synthesis of a wide array of substituted indoles. In 2016 and 2017, Choi *et al.* [24] and Yu *et al.* [25], respectively, extended the scope of the reaction shown in Scheme (**9**). Their work is summarized in Scheme (**10**).

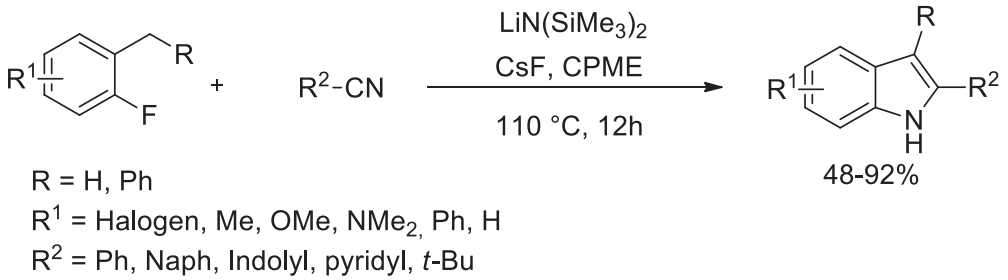


Scheme (10). Indole synthesis as reported by Choi *et al*. [24] and Yu *et al*. [25].

Choi *et al.* achieved the synthesis of 3-substituted indoles under mild conditions in a tandem procedure through the reductive cyclization of 2-(2-nitroaryl)aceto nitriles in the presence of Co_2Rh_2/C 5 mol%. It is important to mention that their procedure was effective not only for the synthesis indoles but also for azaindoles,

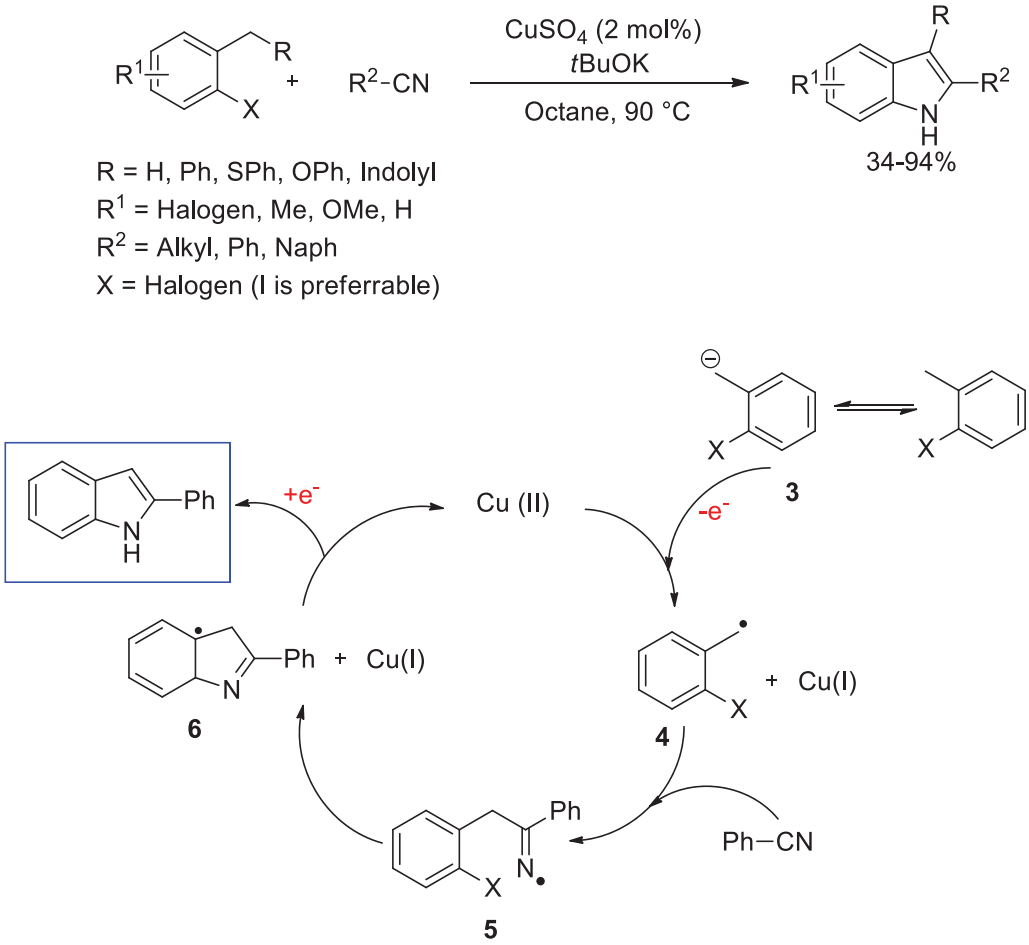
a very interesting nucleus for medicinal chemistry that is difficult to functionalize at the C3 position [24]. Yu *et al*., tandem reaction, involves the use of arylboronic acids to achieve the direct synthesis of 2-arylindoles. Their strategy is very interesting due to the chemoselectivity of the reaction and the tolerance to the presence of halogens in the indole ring [25].

Mao and co-workers reported another interesting indole synthesis from nitriles in 2019. The authors developed a one-pot convergent synthesis of indoles from 2-fluorotoluene and nitriles in the presence of $LiN(SiMe_3)_2$ (LiHMDS) and Cs salts. Various additives and solvents were tested and both CsF and CPME (Cyclopentyl methyl ether) were chosen as the best to carry out this domino reaction. The procedure has also shown interesting scope, with the authors being able to synthesize 38 examples, bearing substituents on each position of the indole backbone, in 48-92% yields (Scheme **11**) [26].



Scheme (11). Synthesis of indoles from nitriles by Mao and co-workers [26].

Shan *et al*. reported another outstanding route to indoles in 2019. The authors generate iminyl radicals *in situ* through a base-promoted C-H cleavage and catalyzed carbanion-radical redox relay. Their strategy uses the abundant $CuSO_4$ as the catalyst, avoiding radical initiators and the need for noble metals, to afford C2 and C3 substituted indoles from 2-halotoluenes and nitriles. The reaction proceeds through an initial base-promoted C-H cleavage to generate a benzyl anion **3**, which transforms into a benzyl radical **4** through a Cu(II)-mediated oxidation. The iminyl radical **5** is formed through the addition of the benzylic radical **4** to the nitrile and immediately form an indolyl radical **6** which is reduced by Cu(I) to form the desired indole. This proposed mechanism and the scope of the reaction are shown in (Scheme **12**) [27].



Scheme (12). Proposed mechanism and reaction scope for the synthesis of indoles in the presence of *t*BuOK and $CuSO_4$. [27].

PYRAZOLE AND IMIDAZOLE

Pyrazoles and imidazoles are planar five-membered heterocycles containing two nitrogen atoms and three carbon atoms. These moieties are extremely important for medicinal chemistry, being present in a variety of pharmaceuticals and natural products [28] (Fig. **3**).

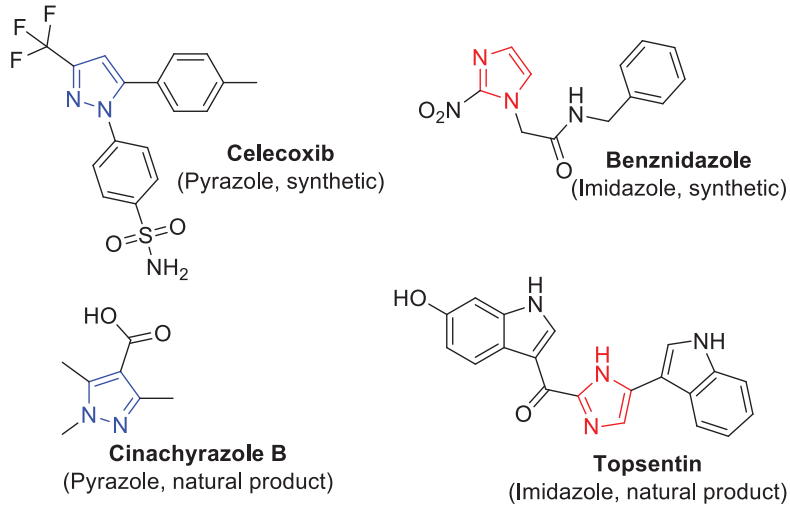
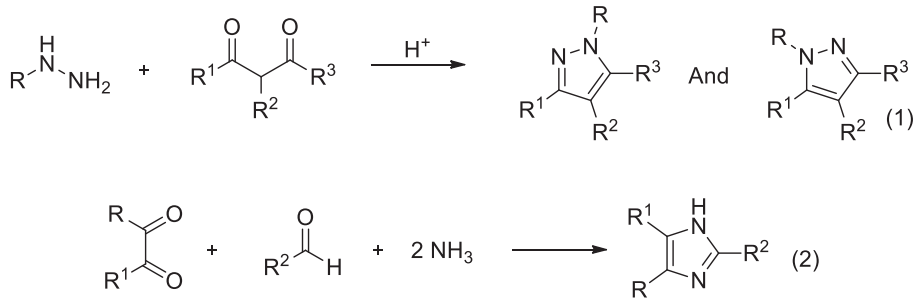


Fig. (3). Examples of drugs and natural products containing pyrazoles and imidazoles.

Synthetic Methods

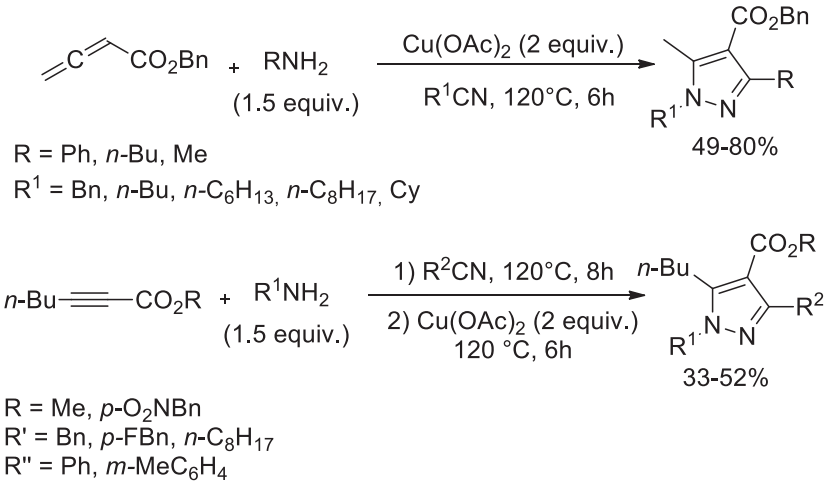
These nuclei are classically synthesized through the Knorr Pyrazole Synthesis and the Debus-Radziszewski imidazole synthesis. The Knorr process affords substituted pyrazoles from hydrazine and 1,3-dicarbonyl compounds using acid catalysts. Debus-Radziszewski synthesis produces substituted imidazoles from a 1,2-dicarbonyl compound, an aldehyde, and 2 equivalents of ammonia [52 - 54] (Scheme **13**).



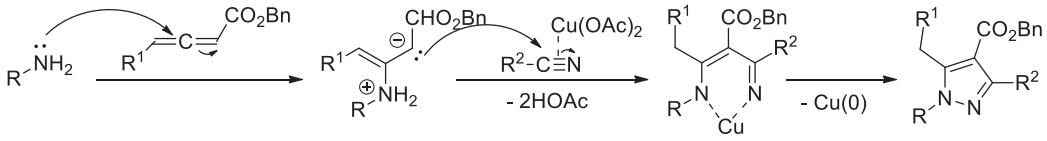
Scheme (13). General Knorr pyrazole synthesis **(1)** and Debus-Radziszewski multicomponent imidazole synthesis **(2)**.

Even though these reactions are still widely used nowadays, the search for novel methodologies for the synthesis of pyrazoles and imidazoles is still a hot topic in organic chemistry. In this context, some of the most recent strategies include the use of nitriles as starting materials. In 2014, a copper-mediated three-component

reaction of 2-alkynoates or 2,3-allenoates with amines and nitriles to pyrazoles was described. In their paper, Chen *et al.* studied the best proportion of amine, the best oxidizing agent, the effect of temperature on the reaction system, and the scope of the procedure. These data are summarized in (Scheme **14**). A possible mechanism to the reaction would start with the Michael addition of the amine to the alkynoate or allenoate followed by the formation of a bisimine product after the reaction with the corresponding activated nitrile. Finally, the desired product could be formed after a reductive elimination step [32] (Scheme **15**).

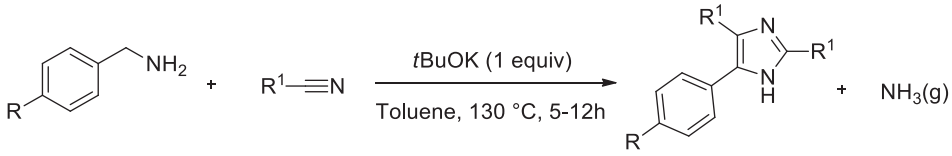


Scheme (14). Formation of pyrazoles by three-component reactions as reported by Chen *et al*. [32].



Scheme (15). Proposed Mechanism for the formation of pyrazoles from amines, nitriles, and allenoates [32].

Das *et al*. achieved the synthesis of imidazoles from the coupling of nitriles with benzylamines in 2017. This reaction happens in a transition metal-free environment in the presence of potassium *tert*-butoxide. Their process takes place through the initial formation of an *N*-benzylbenzimidamide intermediate from the reaction of benzylamine with benzonitrile, followed by cyclization with a second molecule of benzonitrile. It should be noted though that the benzylic CH_2 seems to be important for the mechanism, as aliphatic amines do not react. The optimal conditions and scope of the reaction are shown in Scheme **16** [33].

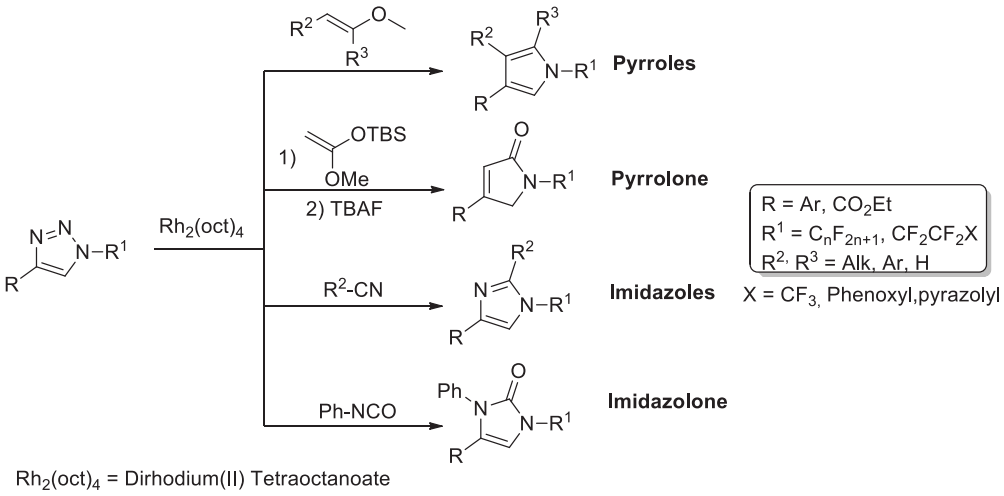


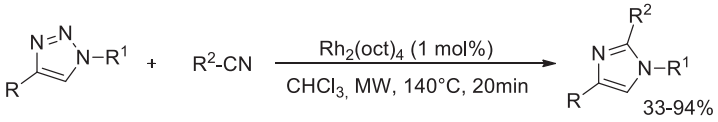
R = H, Me, OMe, Cl, F

R^1 = Ph, *i*Pr,Cyclohexyl, Naph

Scheme (16). Synthesis of imidazoles from benzylamines and nitriles in the presence of potassium *tert*-butoxide [33].

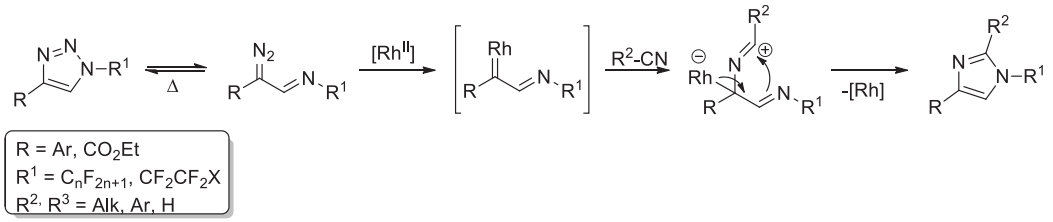
In an attempt to synthesize *N*-(per)fluoroalkyl-substituted five-membered heterocycles, Motornov *et al*. envisioned that the rhodium-catalyzed transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles could lead to various other five-membered nitrogen-containing heterocycles in a divergent synthesis approach. Their findings and the optimal conditions for the synthesis of imidazoles are summarized in Scheme **17** [34].





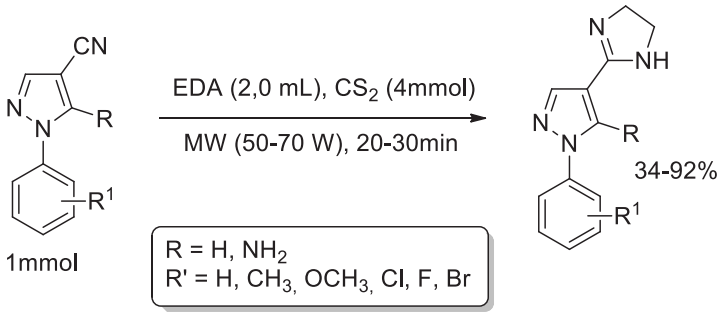
Scheme (17). Transannulation of *N* -(per)fluoroalkyl-1,2,3-triazoles and optimal conditions for the synthesis of imidazoles from nitriles [34].

The proposed mechanism for this transformation starts with the formation of an iminocarbene intermediate after the treatment of the triazole compound with Rh^{II} at high temperatures, followed by a [3+2] cycloaddition and elimination of the rhodium catalyst (Scheme **18**).



Scheme (18). A possible mechanism for the transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles to imidazoles as proposed by Motornov *et al.* [34].

Finally, dos Santos and his co-workers were able to synthesize some imidazoline derivatives from the reaction of nitriles with ethylenediamine (EDA) in the presence of carbon disulfide (CS_2) under microwave irradiation [35]. It is important to mention that the synthesis of some of these derivatives had been previously reported by the authors [36], however, the reactions were carried under reflux, resulting in long reaction times (14-15h). The use of microwave irradiation (50-70 W) greatly reduced reaction times to 20-30 min; the optimal conditions were found to be 2.0 mL of EDA and 4mmol of CS_2 (Scheme **19**).



Scheme (19). Synthesis of imidazolines from nitriles under microwave irradiation [35].

TRIAZOLE

Triazole consists of a doubly unsaturated 5-membered ring containing three nitrogen atoms and two carbon atoms. There are two isomeric forms of triazole, namely 1,2,3-triazole and 1,2,4-triazole (Fig. **4**) [37, 38].

Biological Applications

Triazole compounds are well known for having a variety of biological activities. Several derivatives of this class are used as drugs, possessing various activities such as antifungal, antiviral, antineoplastic, anxiolytic, antidepressant, antihypertensive, antiepileptic, and hypocholesterolemic. Among them, it is worth mentioning that fluconazole, a 1,2,4-triazole, is the first-choice drug for the

treatment of many fungous infections, and many others are frequently used in clinic (Fig. **5**) [37 - 40].

Fig. (4). The isomeric forms of triazoles.

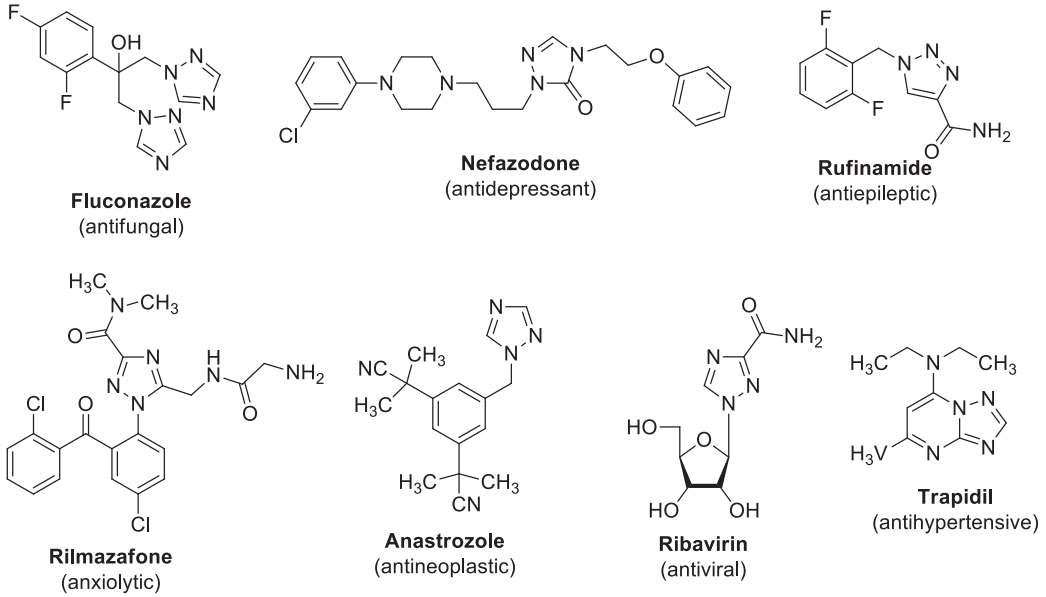
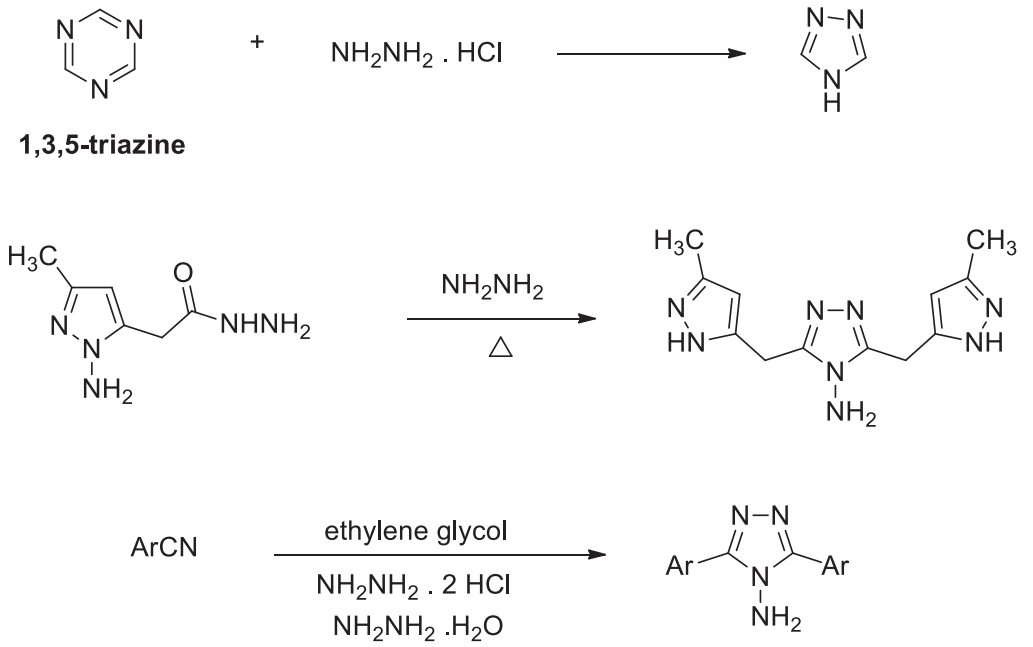


Fig. (5). Some triazole compounds with biological activities.

Synthetic Methods

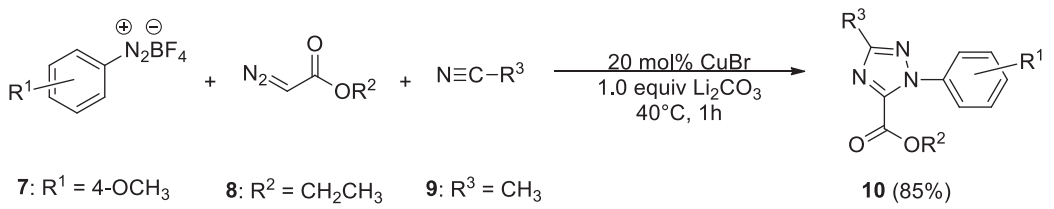
The most popular methodology for obtaining 1,2,3-tetrazoles consists of the reaction between organic azides and alkynes (Click Chemistry) [41]. Moreover, there are several methodologies for the synthesis of the 1,2,4-triazole ring. Among them, the reaction of hydrazine or substituted hydrazines with suitable electrophiles is the most common method (Scheme **20**) [39, 42, 43].



Scheme (20). Some examples of obtaining triazoles using hydrazine.

Owing to the great importance of the 1,2,4-triazole nucleus, many studies have been carried out to develop effective synthetic methods to form new derivatives. Some of them also use nitriles as starting materials.

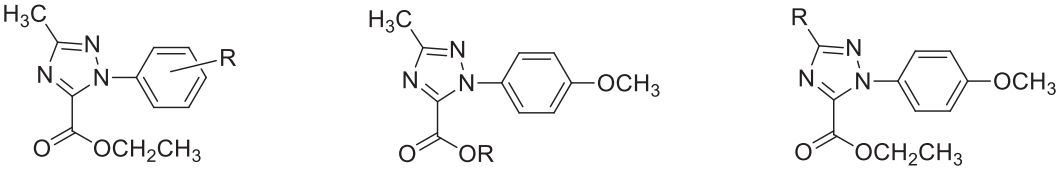
Wan and coworkers described the synthesis of 1,2,4-triazoles through the copper-catalyzed intermolecular [3+2] cycloaddition reaction between nitriles and diazonium salts. This reaction proceeds *via* the trapping of an intermediary nitrile ylide species by the diazonium salt. Aiming to optimize the reaction conditions, initially, the authors used *p*-methoxyphenyldiazonium tetrafluoroborate (**7**), ethyl 2-diazoacetate (**8**), and acetonitrile (**9**) as reaction substrates, tested some transition-metal catalysts and used various organic and inorganic compounds as bases. The best reaction condition was the use of 20 mol% of CuBr, 1 equivalent of Li_2CO_3, at 40°C for 1 hour (Scheme **21**). Employing this methodology, the 1,2,4-triazoles (**10**) were obtained, in moderate to high yields, in a one-step reaction under mild conditions, from readily available starting materials [44].



7: R^1 = 4-OCH_3 **8**: R^2 = CH_2CH_3 **9**: R^3 = CH_3 **10** (85%)

Scheme (21). Synthesis of 1,2,4-triazoles from nitriles and diazonium salts [44].

Concerning aryldiazonium tetrafluoroborate, the reaction proceeded well when halogen or electron-donating groups were present on the benzene ring of the diazonium salt, independent of the position of substituent on the ring. However, the reaction efficiency was relatively low when electron-withdrawing groups were present, and, for instance, the 4-nitrophenyl diazonium salt did not react under this condition. Multi-substituted phenyl diazoniums and naphthyl diazonium were used in this method, affording the 1,2,4-triazole in moderate yields. For the diazo compounds, a wide range of functional groups was well-tolerated in this transformation, but decreasing yields were detected when steric hindrance increased. Fig. (**3**) shows some examples of various functional groups present in the products. Primary, secondary, and tertiary nitriles were efficiently used in this methodology. It is worth mentioning that this reaction was also suitable for vinyl nitriles affording the desired products which were hardly achieved using previous methods described in the literature. Fig. (**6**) shows some examples of triazoles synthesized in this work [44].

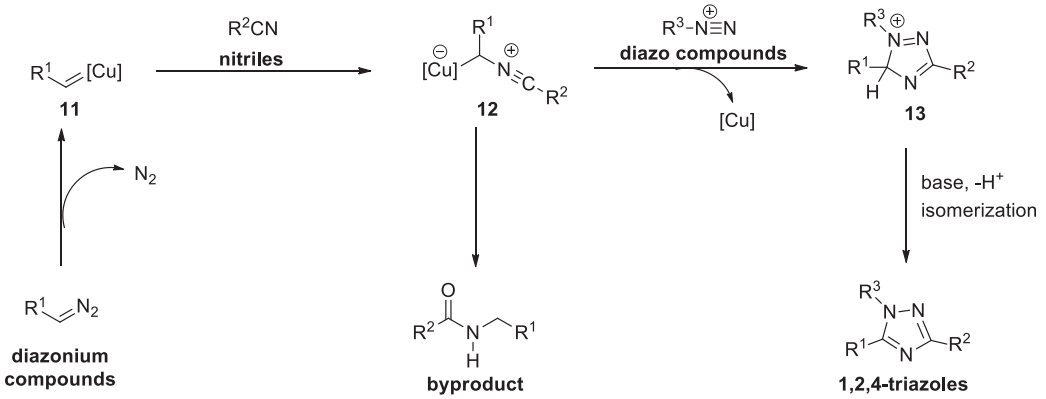


R = 4-CH_3	(71%)	R = *i*-Pr	(85%)	R = *i*-Pr	(76%)
= 3-CH_3	(69%)	= *t*-Bu	(46%)	= *t*-Bu	(68%)
= 4-Br	(53%)	= Ph	(86%)	= *n*-Bu	(59%)
= 3-Br	(40%)	= CH_2CF_3	(65%)	= $CH_2CH{=}CH_2$	(85%)
= 4-OCH_3	(85%)	= $CH_2CH_2CH{=}CH_2$	(72%)	= $CH_3CH{=}CH$	(66%)
= 2-OCH_3	(62%)	= $CH_2CH{=}CHCH_3$	(60%)	= PhCH=CH	(71%)
= 4-OCF_3	(46%)	= CH_2CH_2TMS	(53%)	= $ClCH_2CH_2CH_2$	(61%)
		= CH_2CF_3	(65%)	= $H_3COCH_2CH_2$	(52%)

Fig. (6). Some 1,2,4-triazoles synthesized from nitriles and diazonium salts [44].

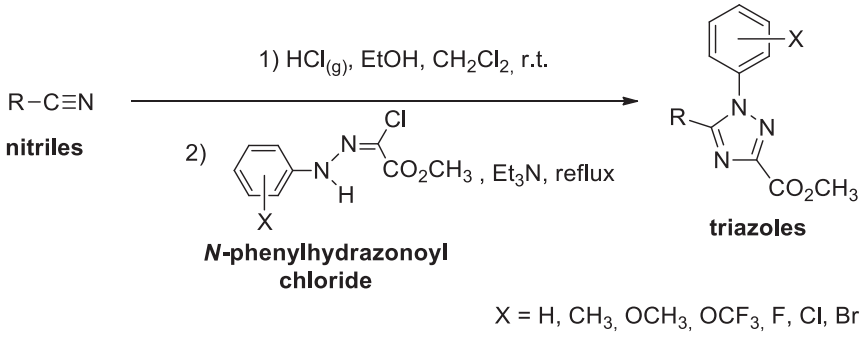
The authors proposed the reaction mechanism based on their experimental data, using the isotopic tracer technique and computational studies. Initially, carbenoids

11 are formed from the copper catalyst coordinated with diazo compounds. Then, intermediates **11** can suffer nucleophile attack by the nitriles, to afford intermediates **12**. Subsequently, **12** undergoes a [3+2] cycloaddition with the diazonium salts to furnish the five-membered ring intermediates **13**, which, in the presence of a base, lose a proton and isomerize to give the desired 1,2,4-triazole. Moreover, undesired amides were identified as byproducts from the reaction of nitrile ylides **12** with water (Scheme **22**) [44].



Scheme (22). Proposed mechanism for the synthesis of 1,2,4-triazoles from nitriles and diazonium salts [44].

Huang and coworkers developed a one-flask strategy for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and *N*-arylhydrazonoyl hydrochlorides under basic conditions (Scheme **23**). This reaction provided the desired products in moderate to excellent yields [45]. Fig. (**7**) shows examples of the structures synthesized in this work.



Scheme (23). Synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and *N*-arylhydrazonoyl hydrochlorides [45].

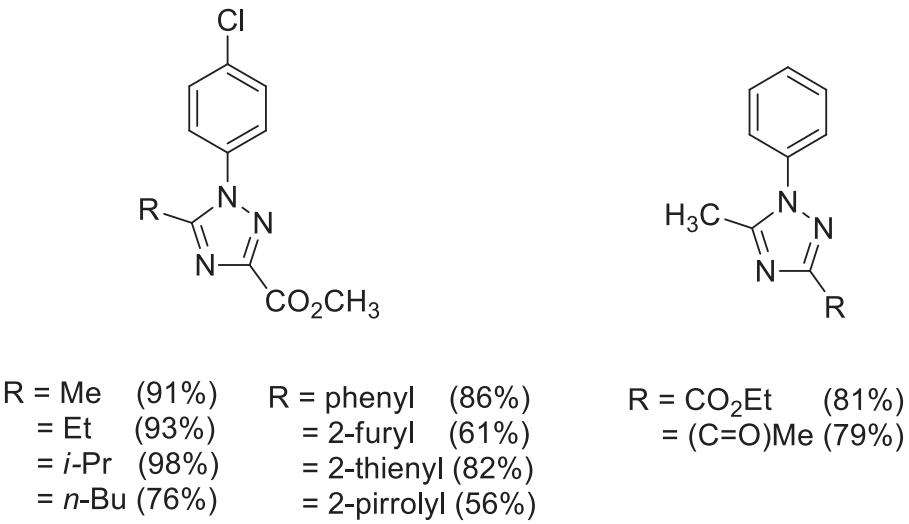


Fig. (7). Shows examples of the structures synthesized in this work [45].

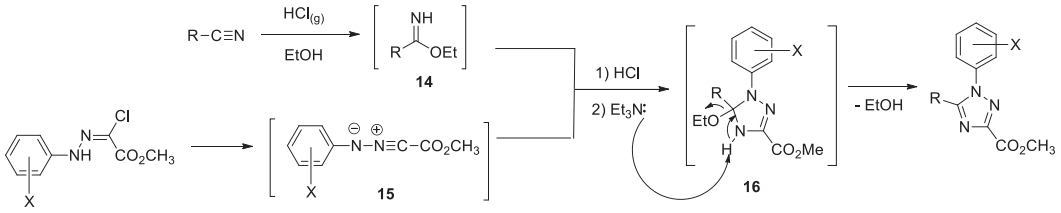
Initially, the authors studied the reaction between acetonitrile with $HCl_{(g),}$ and then with *N*-phenylhydrazonoyl chloride. They observed that this reaction did not occur without the presence of a base. Among the bases tested, only triethylamine displayed a satisfactory result.

Many *N*-phenylhydrazonoyl chlorides bearing different substituents on the phenyl ring were tested, and, in all cases, the reaction was efficient, affording the triazoles in moderate to excellent yields [45]. The best result was obtained when the substituent was 4-Cl, and a poor result was observed when 4-CH_3 was present on the phenyl ring. It was also observed that the reaction only occurs when *N*-phenylhydrazonoyl chlorides bearing ester or acetyl functionalities are used. The change of these functions for amido, ethyl, or phenyl groups did not give the corresponding 1,2,4-triazoles (see Fig. **7**).

With respect to nitriles, both aliphatic and aromatic nitriles gave the desired triazoles. In addition, heteroaromatic nitriles were also efficient in this methodology. However, aromatic and heteroaromatic nitriles demonstrate slightly poorer yields, probably due to the conjugation of the double bond of imidate with the π-system in the aryl group or due to the instability of π-excessive heteroaromatics, such as furyl, thienyl, and pyrrolyl (see Fig. (**7**)).

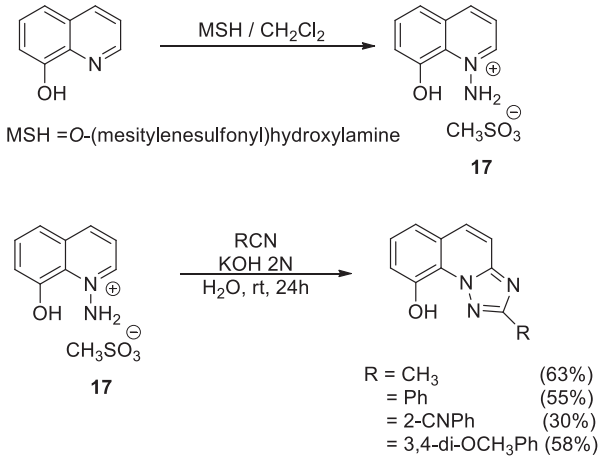
The proposed mechanism for the one-pot synthesis of 1,3,5-trisubstituted 1,2,4-triazoles begins with the formation of imidate **14** through the treatment of nitriles with HCl in EtOH. Parallelly, *N*-arylhydrazonoyl is converted to the corresponding nitrilimine **15** by Et_3N. Then, occurs the 1,3-dipolar cycloaddition

between imidate **14** and the nitrilimine **15** affording the cyclic intermediate **16**, which after aromatization gives the desired 1,2,4-triazole (Scheme **24**) [45].



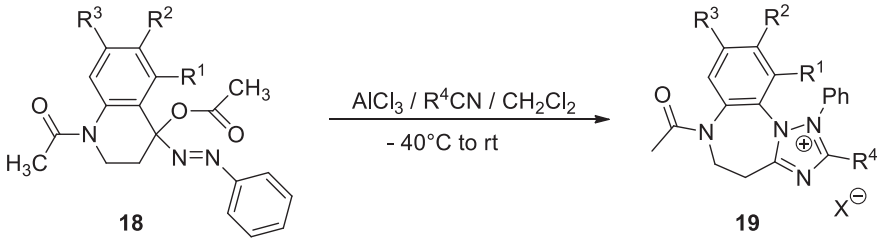
Scheme (24). Proposed mechanism for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and *N*-arylhydrazonoyl hydrochlorides [45].

Vorob'ev and coworkers described the synthesis of 1,2,4-triazolo[1,5-a]-quinolin-9-ol from 1-amino-8-hydroxyquinolinium mesitylene sulfonate **17** and nitriles. The 1-amino-8-hydroxyquinolinium salt was obtained by *N*-amination of 8-hydroxyquinoline, followed by the formation of the mesylate salt **17** (Scheme **25**). This reaction occurs in aqueous alkali solutions, with an excess of acetonitrile, affording the desired products in moderate yields. However, the use of other aliphatic nitriles such as propionitrile, butyronitrile, isobutyronitrile, and pivalonitrile was not efficient and the corresponding product was not formed. This methodology also worked well with benzonitrile, phthalodinitrile, and 3,4-dimethoxybenzonitrile giving the corresponding products in moderate yields. However, 4-hydroxy-3-methoxybenzonitrile did not participate in this reaction, probably due to the deprotonation of the OH group, which reduced the reactivity of the nitrile compound [46].

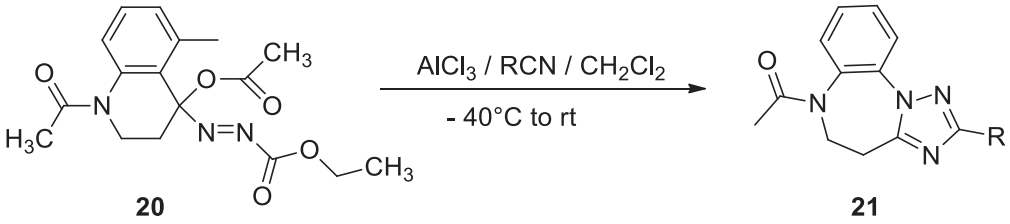


Scheme (25). Synthesis of 1,2,4-triazolo[1,5-a]-quinolin-9-ol [46].

Wang and coworkers developed the synthesis of 5,6-dihydro-4*H*-benzo[*b*] [1, 2, 4]triazolo[1,5-*d*] [1, 4]diazepinium salts **19** and the related, neutral, free base derivatives **21**. In the last step in their proposed synthesis, the triazole ring was formed through a cationic [3+2]-cycloaddition/rearrangement reaction (Scheme **26** and **27**). These reactions occur in the presence of $AlCl_3$ and in dry CH_2Cl_2, providing several advantages such as the readily available starting materials and good flexibility in terms of substitution [47].



Scheme (26). The syntheses of 5,6-dihydro-4*H*-benzo[*b*] [1, 2, 4]triazolo[1,5-*d*] [1, 4]diazepinium salts **19** [47].



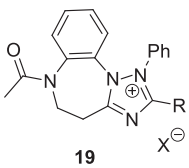
Scheme (27). Synthesis of *N*(1)-unsubstituted neutral tricyclic heterocycles **21** [47].

For the salts, the triazole ring is furnished from the key starting materials 4-acetoxy-4-azo-1,2,3,4-tetrahydroquinolines **18**, which was previously synthesized (**26**). It is noteworthy that changing the counter ion in the product from anion $AlCl_3(OAc)^-$ to a picrate anion proved to be beneficial for the formation of stable salts. In this method, it was observed that most of the aliphatic nitriles gave the desired products in moderate to good yields, moreover, this method works well with 2-phenylacetonitrile (Fig. **8**).

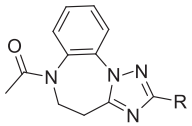
For benzonitriles, the desired products were obtained in good yields, independent of the substituents on the benzene rings, due to the nucleophilicity of the nitrogen atom of nitrile which is strong enough to override the electronic effect of the substituent. The authors also reported that there was no steric impact on the reaction with monosubstituted benzonitrile. However, for disubstituted benzonitriles, the final products were obtained in moderate yields only, due to the increased steric hindrance in nitrile moiety (Fig. **8**).

For the neutral tricyclic heterocycles, the synthesis starts from the ethoxycarbonylhydrazone compounds **20,** which suffers the loss of the ethoxycarbonyl group by hydrolysis. Then, intermediate **20** reacts with aliphatic and aromatic nitriles in the presence of $AlCl_3$ giving the desired product **21** (Scheme **27**, Fig. **8**).

The authors proposed a mechanism for the synthesis of compound **19** using the *α*-acetoxyphenylazo compound **18a** as a model substrate. At first, occurs the $AlCl_3$ coordination with the acetate moiety of **18a** to generate the azocarbenium ion **22.** Then, the nitrogen atom of the nitrile approaches to the central electron-deficient carbon atom in **23** to form a Ritter-type nitrilium salt **23.** Then, **23** undergoes a cyclization affording intermediate **24**, which, after ring expansion *via* [1, 2]-shift (the phenyl moiety moves from C(3) to N(2) furnishes the desired product (Scheme **28**) [47].



19

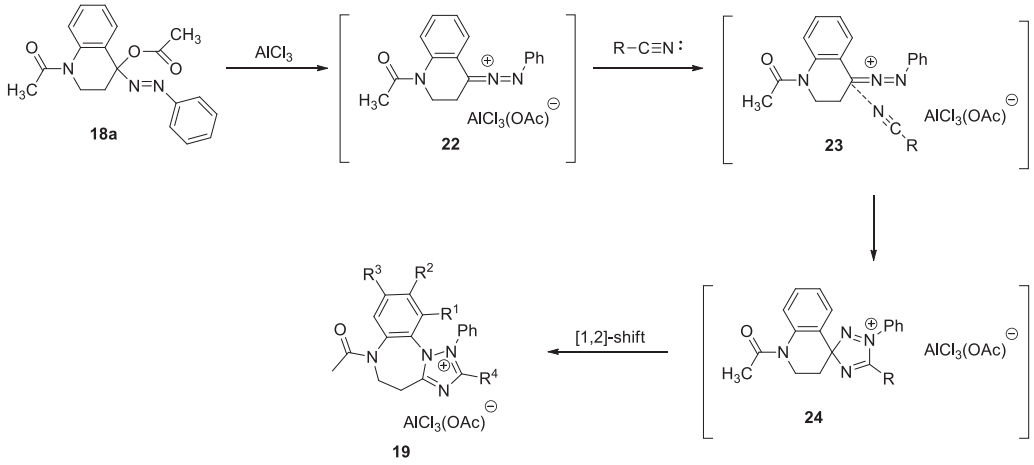


21

R = CH_3, X^- = picrate	(81%)
R = cyclopropyl, X^- = Cl	(83%)
R = Ph, X^- = picrate	(83%)
R = 4-OCH_3Ph, X^- = picrate	(91%)
R = 4-FPh, X^- = picrate	(82%)
R = 4-CH_3Ph, X^- = picrate	(81%)

R = CH_3	(23%)
R = $CH_2CH_2OCH_3$	(21%)
R = Ph	(24%)
R = 4-CH_3Ph	(27%)
R = 4-ClPh	(31%)

Fig. (8). Some molecules synthesized in this work [47].



Scheme (28). The proposed mechanism for the syntheses of 5,6-dihydro-4*H*-benzo[*b*] [1, 2, 4]triazolo[1,5-*d*] [1, 4]diazepinium salts **19** [47].

TETRAZOLE

Tetrazoles are 5-membered ring aromatic heterocycles, containing one carbon and four nitrogen atoms. They are unknown in nature. Based on the number of substituents, tetrazoles can be divided into parent tetrazoles (simplest tetrazoles), monosubstituted tetrazoles, and disubstituted tetrazoles (Fig. **9**) [48 - 50].

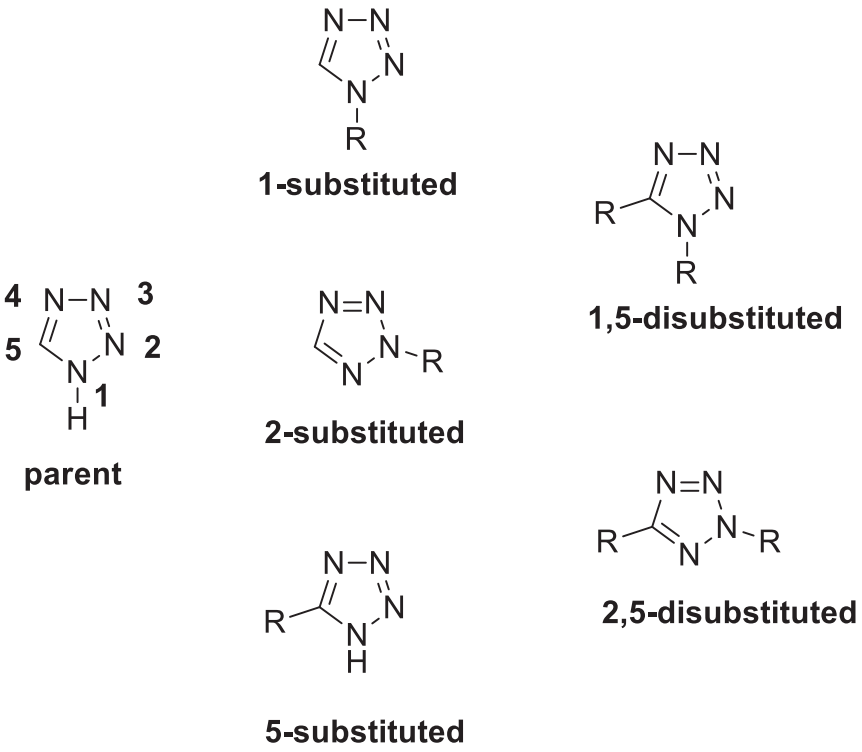


Fig. (9). Numbering and classification of tetrazole.

It is important to note that 5-Substituted tetrazoles may exist in two tautomeric forms (Fig. **10**) [50].

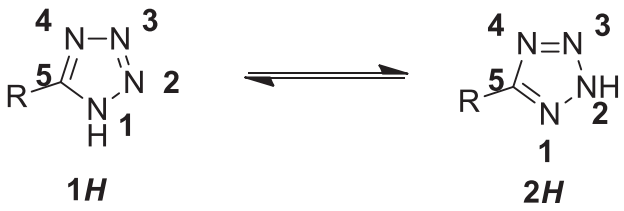


Fig. (10). The tautomeric forms of 5-substituted tetrazoles.

The tetrazole moiety exhibits a wide number of applications such as in material chemistry, coordination chemistry, organometallic and organocatalysis, and mainly in medicinal chemistry. Many compounds containing 1,5-disubstituted and 5-substituted tetrazoles have demonstrated biological activity [51, 52].

Biological Activity

It is known that 1,5-disubstituted tetrazoles serve as isosteres of the cis-amide bond of peptides while 5-substituted-1*H*-tetrazoles serve as nonclassical isosteres of the carboxylic group, due to their similar physicochemical properties, though structurally different [49, 52]. Besides that, those heterocycles have a more favorable pharmacokinetic profile and better metabolic stability than carboxylic acids and cis-amides moieties [51, 52].

Based on these important characteristics of the tetrazole rings, many review articles about their chemistry and biological activity have been published [49 - 60]. Many drugs containing a tetrazole ring have been marketed with different biological activities such as antihypertensive, antibiotic, anesthetic and analgesic, antiallergic, diuretic, thrombogenesis inhibitors, respiratory stimulant, among others (Fig. **11**).

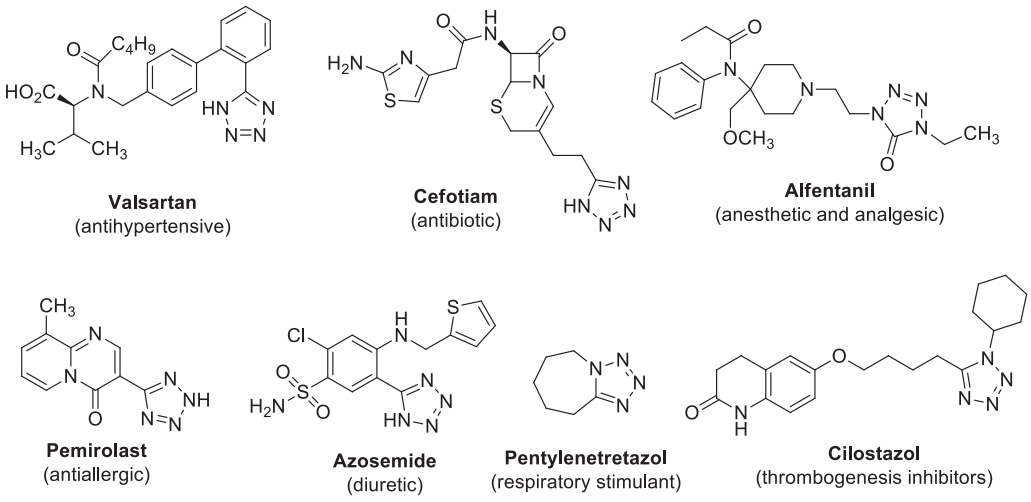
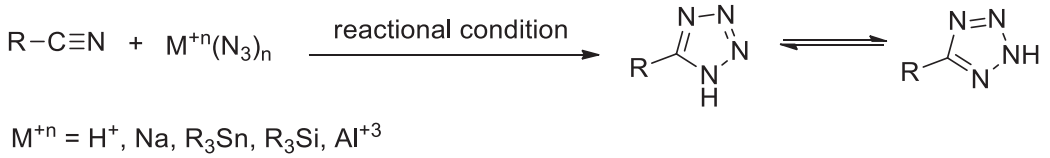


Fig. (11). Some tetrazole compounds with biological activity.

Synthetic Methods

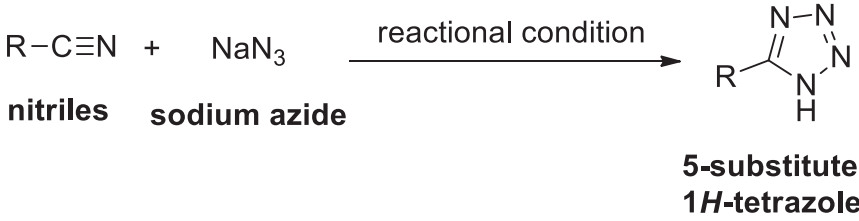
The chosen methodology for obtaining tetrazoles depends on the nature and substitution pattern of the desired tetrazole [61]. The most convenient protocol for the preparation of 5-substituted-1*H*-tetrazoles consists of a [3+2] cycloaddition between nitriles and azide compounds [61]. The reported methods use different

catalysts and, conventional or microwave heating (Scheme **29**). It should be mentioned, though, that many of the reported methods are still limited in their use due to harsh reaction conditions such as high temperatures and long reaction times. Moreover, some give the desired products in very low yields with the formation of side products. Other disadvantages described include the necessity of stoichiometric amount of catalysts, water sensitivity, difficulty in the separation and recovery of the catalyst, and the use of a large excess of sodium azide [62 - 64].



Scheme (29). General reaction for obtaining of tetrazoles from nitriles and azides.

Some methodologies have been developed to reduce the problems found in the syntheses previously described. The new methods use different catalysts, solvents, and different proportions between sodium azide and nitriles (Scheme **30**). For better visualization of the different methods recently described, they will be divided into three parts according to the type of catalyst: Lewis acids as catalysts; Transition metals as catalysts; and Others catalysts.



Scheme (30). Some new methods for obtaining of 5-substituted-1*H*-tetrazoles from nitriles.

Lewis Acids as Catalysts

In this section, the reactions between nitriles and excess sodium azide in the presence of zinc or boron compounds will be presented (Table **1**).

In entries **1** and **2**, Chamarthi and coworkers synthesized tetrazoles under heterogeneous catalysis ($ZnBr_2$-SiO_2). The great advantage of this method is the short reaction time and the use of a green solvent. It was observed that these reactions occurred much faster under microwave irradiation (10-20 minutes), with faintly improved yields (87-94%) when compared to conventional heating (1.5-

2.5h; 80-90%). Benzonitrile with electron-withdrawing substituted showed slightly lower yields than benzonitriles containing electron-withdrawing groups (87% from 4-amino-benzonitrile and 94% from 4-nitro-benzonitrile). However, in all cases, the tetrazoles were obtained in very high yields. The authors also synthesized some tetrazoles from the reaction between nitriles and AZT, leading to the desired products in excellent yields (Fig. **12**) [62].

Table 1. Some new methods for obtaining of 5-substituted-1*H*-tetrazoles from nitriles using Lewis acid.

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
1	$ZnBr_2$-SiO_2 / glycerol (0.2g) 1 mmol of nitrile 1.5 mmol of NaN_3 or AZT 90-100°C 3-4 h	80-90	aromatic nitriles; heteroaromatic nitriles; benzyl nitriles	Green solvent system; High yields; Short reaction time; Reusability of catalyst	[62]
2	$ZnBr_2$-SiO_2 / glycerol 1 mmol of nitrile 1.5 mmol of NaN_3 Microwave (465 Watt) 10-20 min.	87-94			
3	1 Zn(II)-complex with coumarin hydrazine ligand (0.05 mmol) 1 mmol of nitrile 2 mmol of NaN_3 H_2O, 90°C 2) HCl	Not reported	benzonitriles	Green solvent system; Reusability of catalyst	[63]
4	10 mL of Choline chloride-$ZnCl_2$ (1:2) 10 mmol of nitrile 15 mmol of NaN_3 140°C / 0.5-7h	70-94	Benzonitriles; Benzyl nitriles	Good to excellent yields; Short reaction time; Non-toxic and cheap catalyst; Mild reaction condition; Elimination of toxic hydrazoic acid formation	[64]
5	MCM-41@AMPD@Zn (100 mg) 1 mmol of nitrile 1.2 mmol of NaN_3 PEG 120°C / 7-540 min	90-99	aromatic nitriles; aliphatic nitriles	Excellent yields; Easy handling; Short reaction time; Eco-friendly and reusable catalyst	[65]

(Table 1) cont.....

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
6	$B(C_6F_5)_3$ (5mol%) 1 mmol of nitrile 1.5 mmol of NaN_3 DMF, 120°C 4-20 h	76-96	benzonitriles; heteroaromatic nitriles; aliphatic nitriles	Mild reaction condition; Easy work-up; High yields; Low catalyst loading; The catalyst is air-stable, water tolerant, and less toxic than others Lewis acid	[66]

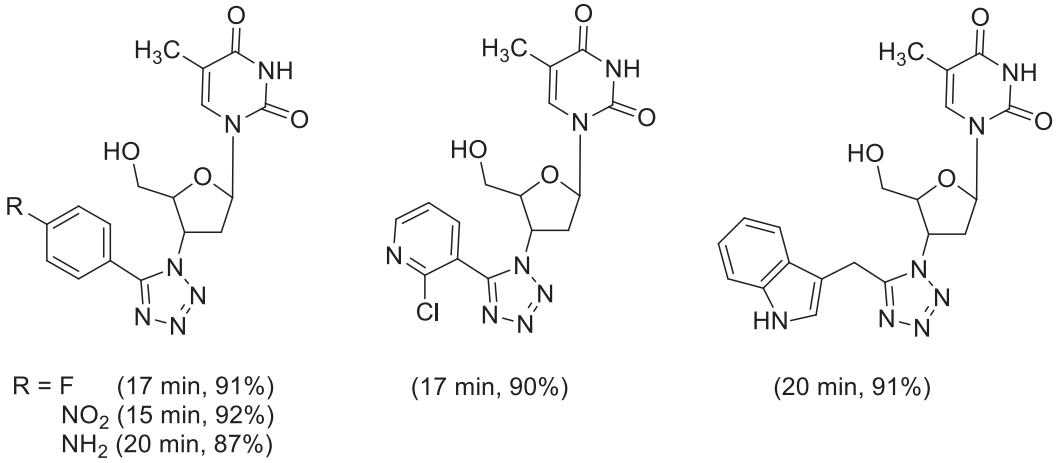
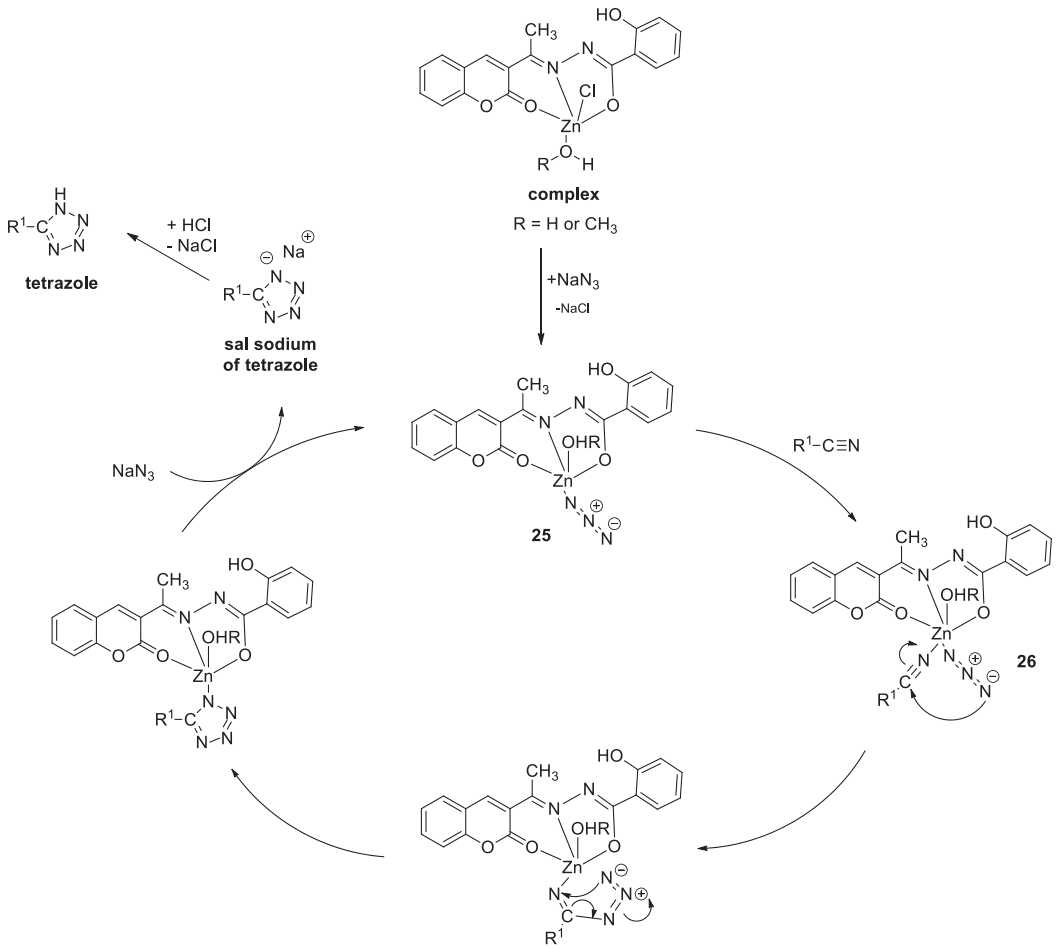


Fig. (12). Some examples of the tetrazoles synthesized by reaction between nitriles and AZT [62].

In entry **3**, Aslkhademi *et al.* used a Zn(II)-complex with a coumarin hydrazine ligand as the catalyst. The complex $[ZnCl(HL)(CH_3OH)_{0.76}(H_2O)_{0.24}](CH_3OH)$ was prepared from equimolar amounts of $ZnCl_2.4H_2O$ and *E*-2-hydroxy-*N'*-(1-(2--xo-2*H*-chromen-3-yl)ethylidene)benzohydrazine (H_2L) in methanol. This methodology for obtaining tetrazoles proved to be sensitive to the substituents present in the benzonitrile ring. Benzonitriles with electron-donating substituents gave the corresponding tetrazoles in shorter times (6.5 h for 4-methox--benzonitrile) when compared to benzonitriles with electron-withdrawing groups (9 h for 4-nitro-benzonitrile), probably due to the low coordination ability of electron-poor benzonitriles to the metal ion, which decreases the speed of the catalytic reaction.

A general mechanism for this catalytic reaction was proposed by the authors (Scheme **31**). Initially, the azide anion coordinates to the metal ion, affording

compound **25**. Then, the nitrogen atom of benzonitrile coordinates to Zn(II) giving compound **26** which, after cycloaddition between the coordinated azide and benzonitrile group, affords the tetrazole ring. The obtained tetrazole ring suffers the attack of another azide ligand, being released as the sodium salt (Scheme **31**) [63].



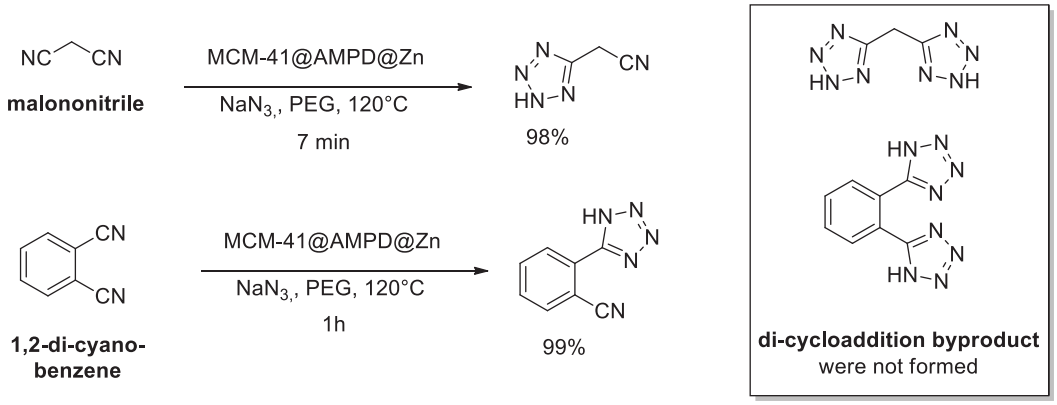
Scheme (31). Proposed mechanism for the synthesis of tetrazoles using a Zn(II)-complex with coumarin hydrazine ligand [63].

In entry **4**, Padvi and Dalal used choline chloride-$ZnCl_2$ as a Deep Eutectic Solvent (DES) to obtaining tetrazoles from nitriles and sodium azide.

DESs are a class of green reaction media. Their physical and chemical properties are similar to those of ionic liquids. They show low vapor pressure, non-volatility, high thermal stability, and recyclability. However, they have some advantages

such as being cheaply available, less toxic, and biodegradable. They act as both the catalyst and the reaction medium in organic synthesis. The reported methodology, in entry **4**, can be efficiently applied to benzonitriles, benzyl nitriles, and heteroaromatic nitriles. However, they do not work well with aliphatic nitriles. All tested benzonitriles, benzyl nitriles and heteroaromatic nitriles gave the corresponding tetrazoles in good to excellent yields, but the substituents present on the aromatic ring influence the reactivity of nitriles. It was noteworthy that nitriles bearing electron releasing substituents react much slower. For instance, 4-dimethylamino-benzonitrile and 4-chloro-benzonitrile required 5h and 50 minutes, respectively. The benzyl nitriles and heteroaromatic nitriles also required a longer reaction time than benzonitriles with electron-withdrawing groups. 4-chloro-benzyl nitrile and 1-*H*-indole-5-carbonitrile afforded the corresponding tetrazoles after 4.3h and 7h, respectively. It is important to say that this reaction's main advantage is not forming hydrazoic acid, besides leading to the desired products in short reaction time, under mild reaction conditions [64].

In entry **5**, Ghadermazi and co-workers udes zinc complex supported on 2-amin--2-methyl-1,3-propanediol-functionalized mesostructured MCM-41 (MCM-41@AMPD@Zn) as the catalyst. This methodology gave the desired tetrazoles in high yields (90-99%), irrespective of the substituents present on the ring. As an example, 2-hydroxy-benzonitrile and 4-nitrobenzonitrile afforded the corresponding tetrazoles in 91% and 98%, respectively. When malononitrile and 1,2-di-cyano-benzene were used, the tetrazoles were obtained in 98% and 99%, respectively, without the formation of a di-cycloaddition byproduct (Scheme **32**) [65].



Scheme (32). Synthesis of tetrazoles from malononitrile and 1,2-di-cyano-benzene [65].

In entry **6**, Babu and co-workers used tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] as the catalyst. The reported method demonstrated to be efficient for a wide range of

organic nitriles. In relation to benzonitriles, it was observed that benzonitriles with electron-withdrawing groups reacted faster, and afforded better yields when compared to benzonitriles with electron-donating groups (8h and 90% for 4-nitromethoxy-benzonitrile, and 14h and 84% for 4-methoxybenzonitrile). Heteroaromatic nitriles proved to be more reactive, giving the respective tetrazoles in a short time and good yields (4h and 90% for 6-chloronicotino nitrile). This methodology was also efficient to other nitriles such as phenylacetonitriles, heteroaromatic acetonitriles, and alkyl nitriles. However, in these cases, the desired product was obtained in lower yields when compared to benzonitriles and heteroaromatic nitriles (for example, 14 h and 78% for indole 3-acetonitrile) [66].

Transition Metals as Catalysts

In the period from 2014 to today, more methodologies have been reported for the synthesis of tetrazoles using transition metals as catalysts, than using lewis acids. Excess sodium azide is also used in these reactions (Table **2**).

Table 2. Some new methods for obtaining of 5-substituted-1*H*-tetrazoles from nitriles using transition metals as catalysts.

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
7	30%Cu-Cr-Al *N*-methyl-2-pyrrolidone 0.97 mmol of nitrile 1.45 mmol of NaN_3 Microwave 230°C	45-93	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	Easy work-up; Reusability of catalyst	[67]
8	Cu/AC/r-GO nanohybrid (8 mmol%) 10 mmol of nitrile 15 mmol of NaN_3 H_2O / *i*-PrOH 1:1, reflux 3-8h	75-94	Aliphatic nitriles bearing heterocyclic compounds such as cyclic amides, azoles, xanthine, purine, and pyrimidines nucleus	Chemically and thermally stable, cheap and environmentally friendly catalyst; Simple protocol; Good to excellent yields	[68]
9	Copper-doped silica cuprous sulfate (50 mmol%) 10 mmol of nitrile 15 mmol of NaN_3 H_2O / isopropanol (1:1, v/v), reflux 3-7h	82-92	Aliphatic nitriles bearing phenols and, heterocyclic compounds such as cyclic amides, azoles, xanthine, purine, and pyrimidines nucleus	Mild reaction condition; Excellent yields; Simple work-up; Use of cheap, stable catalyst; Catalyst easily recyclable The scaled-up procedure was also efficient	[69]

(Table 2) cont.....

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
10	CuCl (4 mol%) 1 mmol of nitrile 1.5 mmol of NaN_3 DMF / 120°C 4-24h	40-90	aromatic nitriles; heteroaromatic nitriles;	Good yields; Cheap, readily available and, environmentally friendly catalyst	[70]
11	CuO / aluminosilicate (35 mg) 1 mmol of nitrile 1.5 mmol of NaN_3 DMF, reflux 2-13h	80-93	aromatic nitriles; aliphatic nitriles	Good to excellent yields; Inexpensive and environmentally friendly catalyst; Simple and clean procedure	[71]
12	10mmol% of ceric ammonium nitrate (CAN) 1.5 mmol of NaN_3 DMF 110°C / 6h	82-99	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	Inexpensive and eco-friendly catalyst; excellent yields; Short reaction time; Easy work-up reaction; Elimination of hazardous and unsafe hydrazoic formation	[72]
13	30 mol% of ceric ammonium nitrate supported HY-zeolite (CAN) / DMF Nitrile (1 equiv) NaN_3 (3 equiv) 110°C / 2.5-9h	63-95	Benzonitriles; Benzyl nitriles	Green catalyst; Excellent yields; Short reaction time; Simple work-up reaction; Elimination of hazardous and unsafe hydrazoic formation	[73]
14	Ag-TiO_2 (20mg) 1 mmol of nitrile 1.5mmol of NaN_3 DMF / 120°C	92-98	aromatic nitriles	Simple work-up; Elimination of hazardous and unsafe hydrazoic acid formation; Easy preparation and handling of the catalyst	[74]
15	10 mmol% $AgNO_3$ NaN_3 (1.5 equiv) DMF / 120°C 5h	73-87	aromatic nitriles; heteroaromatic nitriles	Easy availability of catalyst; Elimination of toxic hydrazoic acid formation; Simple work-up procedure; Good yields	[75]

(Table 2) cont.....

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
16	SBA-15@creatinine@Y 1 mmol of nitrile 1.2 mmol of NaN_3 H_2O / 100°C / 7-500min	92-97	aromatic nitriles	High yields; Easy separation of catalyst; Short reaction time; Inexpensive and non-toxic catalyst	[76]
17	SBA-15@creatinine@Ce 1 mmol of nitrile 1.2 mmol of NaN_3 H_2O / 100°C / 4-485min	93-99			
18	Nano TiO_2 / SO_4^{2-} 1 mmol of nitrile 3 mmol of NaN_3 DMF / 100°C	60-97	aromatic nitriles; heteroaromatic nitriles	Simple and easy work-up; Easy preparation and handling of the catalyst	[77]
19	1) WAlPO-5 (0.1g) / DMF 2.5 mmol of nitrile 5.3 mmol of NaN_3 120°C / 24h 2) HCl	74-95	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	Simple procedure; Mild reaction condition; Good to excellent yields	[78]
20	Ni-SMTU@boehmite (25 mg); PEG-400, 120°C 1 mmol of nitrile; 1.4 mmol of NaN_3	69-97	aromatic nitriles; aliphatic nitriles; allylic nitriles	Good to high yields; Stable, reusable, and commercially available catalyst	[79]
21	$Yb(OTf)_3.H_2O$ (0.1 equiv) 2 mmol of nitrile 4 mmol of NaN_3 DMF / 110°C / 16h	23-98	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	Moderate to good yields; Mild reaction condition	[80]
22	Nanonickel ferrite nanoparticles (5mol%) 2 mmol of nitrile 4 mmol of NaN_3 1 mmol of NH_4OAc DMF / 100°C / 1-3h	90-98	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	High yields; Simple methodology; Easy work-up;	[81]
23	Pd-SBT@MCM-41 (30mg) 1mmol of nitrile 1.4 mmol of NaN_3 PEG-400 / 120°C		aromatic nitriles; aliphatic nitriles	Easy availability and handling of the catalyst; High stability and reusability of the catalyst; Short reaction time; Simple experimental and work-up procedure	[82]

In entry **7**, Joshi *et al*. synthesized some 5-substituted 1*H*-tetrazoles using copper-based nanostructured catalysts and *N*-methyl-2-pyrrolidone (NMP) as the solvent. The best catalyst tested was the 30%Cu–Cr–Al that has a molar composition of 30%Cu, 39%Al, and 31%Cr.

Among the explored nitrile compounds, benzonitriles having electron-withdrawing groups or weak donors at the 4-position gave better results (excellent yields and shorter reaction times). Benzonitriles containing electron-donating groups on the same position require more reaction time, however, they also afforded the tetrazoles in excellent yields.

For example, 4-trifluoro-benzonitrile, 4-methyl-benzonitrile, and 4-hydroxy benzonitrile gave the corresponding tetrazoles in 82% (3 min), 85% (6 min), and 50% (30 min) yields, respectively. Surprisingly, 3-nitro-benzonitrile gave the correspondent tetrazole in poor yield (45%) after 30 minutes of reaction. However, doubling the amount of catalyst results in a 91% yield in a 10 minutes reaction. For *t*-butyl nitrile, a long reaction time was needed, and even so, the correspondent tetrazole was obtained only in moderate yields (58% yield for 30 min), probably due to steric hindrance. In this case, doubling the amount of the catalyst did not improve the reactivity of nitrile [67].

In entry **8**, Rad and co-workers used diverse aliphatic nitriles bearing heterocyclic compounds such as cyclic amides, azoles, xanthine, purine, and pyrimidines nucleus, among others, to obtain the corresponding tetrazoles, in good to excellent yields, through the reaction between nitriles and sodium azide, using Cu/aminoclay/reduced graphene oxide nano-hybrid (Cu/AC/r-GO nanohybrid) as a nanocatalyst. Fig. (**13**) shows some examples of the tetrazoles synthesized in this work [68].

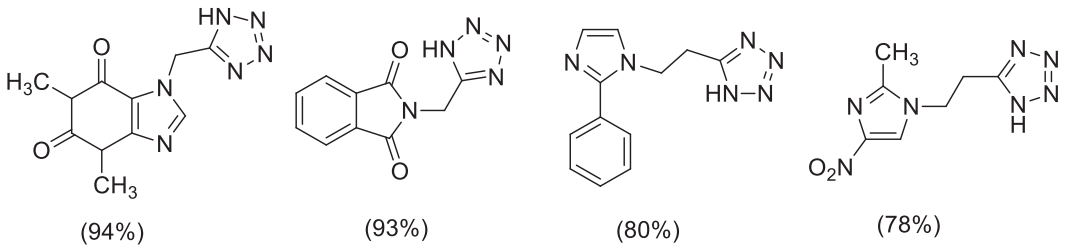


Fig. (13). Some examples of the tetrazoles synthesized using Cu/aminoclay/reduced graphene oxide nano-hybrid (Cu/AC/r-GO nanohybrid) [68].

In entry **9**, Rad employed diverse aliphatic nitriles, previously synthesized, to synthesize the corresponding tetrazoles in excellent yields, using Copper-doped silica cuprous sulfate as a catalyst. Fig. (**14**) shows some examples of the tetrazoles synthesized in this work [69].

In entry **10**, Kaya and co-workers used CuCl as the catalyst. The best results were obtained for benzonitriles containing electron-withdrawing groups. For example,

4-nitro-benzonitrile and 4-methyl-benzonitrile afforded the corresponding tetrazoles in 90% at 8h and 80% after 20h, respectively, while 4-amino benzonitrile did not react even after 24 h. When 4-cyano-pyridine was used as the starting material, the desired tetrazole was obtained in 88% after 4h, proving that this methodology is also efficient for heteroaryl nitriles [70].

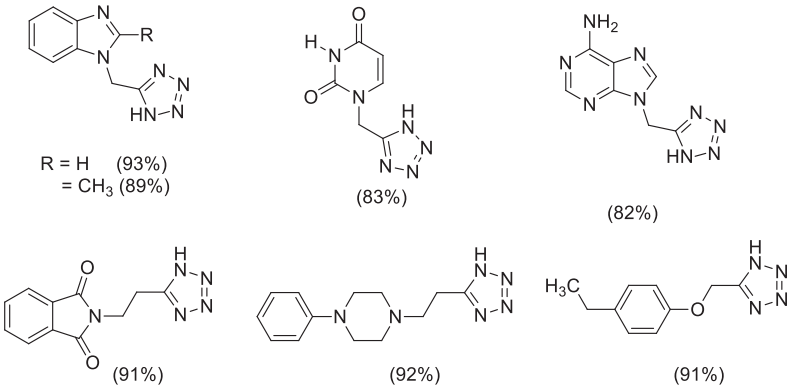


Fig. (14). Some examples of the tetrazoles synthesized using copper-doped silica cuprous sulfate [69].

In entry **11**, Movaheditabar and co-workers used CuO/aluminosilicate as the catalyst affording the corresponding tetrazoles in good to excellent yields for all tested nitrile compounds [71]. Fig. (**15**) shows some examples of the tetrazoles synthesized in this work. In both entries **10** and **11**, the methodologies use an inexpensive and environmental friendly catalyst.

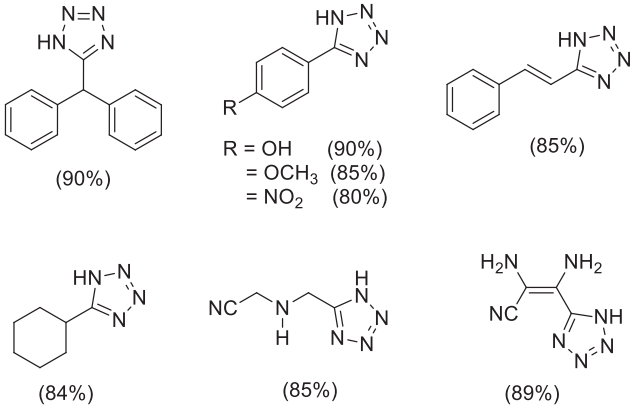


Fig. (15). Somes tetrazoles synthesized by Movaheditabar and co-workers [71].

In entry **12**, Awasthi and co-workers synthesized some tetrazoles in a simple and eco-friendly procedure using ceric ammonium nitrate (CAN) as the catalyst. This

methodology proved to be efficient, giving the desired products in good to excellent yields irrespective of the nature of the nitrile (aromatic/aliphatic) and the substituents present on the ring, in the case of aromatic nitriles. This protocol was also tolerant with a wide range of substituents, for example, alcohol, ether, thioether, ester, and alkyl groups remain intact under the optimized reaction condition. When 2-chloro-3-cyanopyridine was used, the corresponding tetrazole was obtained in a 98% yield, demonstrating that this protocol is also suitable for heteroaryl nitriles The di-cyano derivatives gave the corresponding di-tetrazoles in good yields, however, in this case, it was necessary to double the amount of sodium azide and catalyst. Fig. (**16**) shows some examples of the tetrazoles synthesized in this work [72].

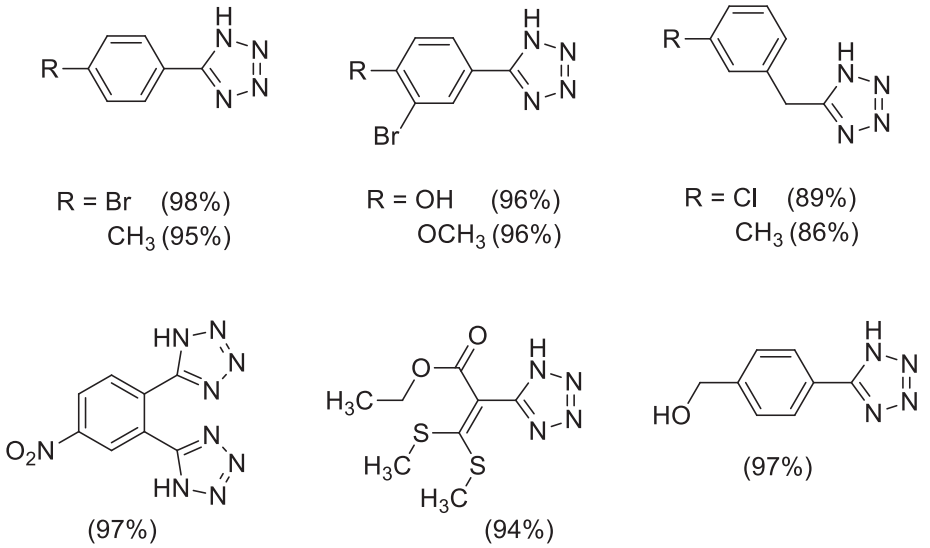


Fig. (16). Some tetrazoles synthesized by Awasthi and co-workers [72].

The methodology reported in entry **13** by Lalitha and co-workers was efficient for obtaining tetrazoles from aryl nitriles having both electron-donating and electron-withdrawing groups on the ring (69-95% yields). Benzyl nitriles also afforded the desired products in good yields (83-88%). However, disubstituted aromatic nitriles gave the corresponding tetrazoles in relatively lower yields (63-67%) Fig. (**17**) shows some examples of the tetrazoles synthesized in this work [73].

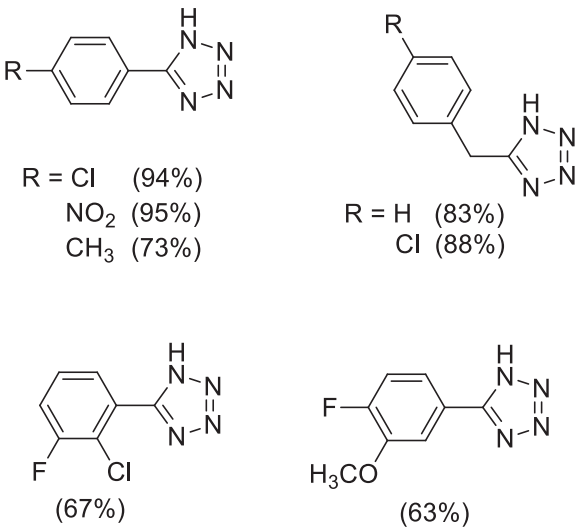


Fig. (17). Some tetrazoles synthesized by Lalitha and co-workers [73].

In entry **14**, Wani *et al*. synthesized some 5-substituted-1*H*-tetrazoles through the reaction of benzonitriles and sodium azide using nano-Ag-TiO_2 as a heterogeneous catalyst. This methodology gave the desired tetrazoles in high yields (92-98%), irrespective of the substituents present on the ring. The reaction using 4-cyano-pyridine as starting material afforded the corresponded bis-tetrazole in 98%. Fig. (**18**) shows some examples of the tetrazoles synthesized in this work [74].

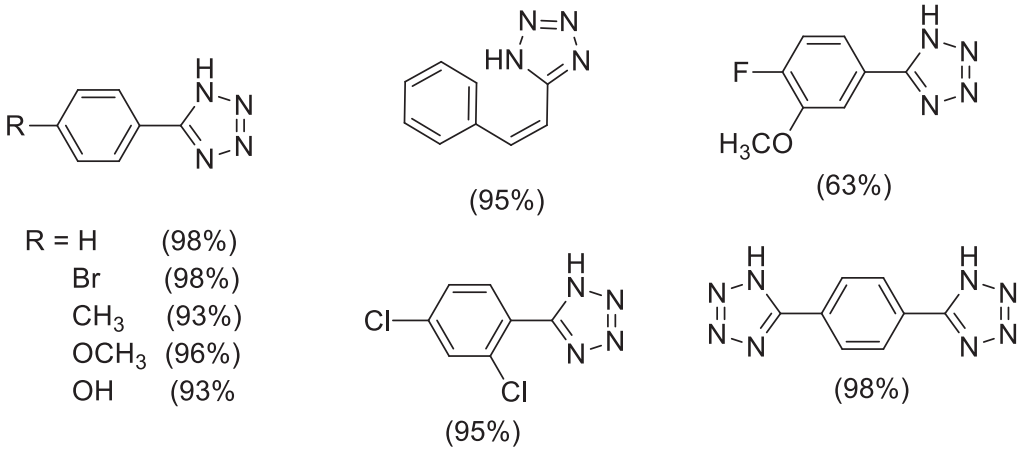


Fig. (18). Some tetrazoles synthesized by *Wani et al*. [74].

In entry **15**, Awasthi and co-workers used $AgNO_3$ as the catalyst in the reaction between nitriles and sodium azide. This protocol is simple, safe, and afforded the desired tetrazoles in good yields, both from aryl- and heteroaryl-nitriles, irrespective of the substituents present on the ring. Fig. (**19**) shows some examples of the tetrazoles synthesized in this work [75].

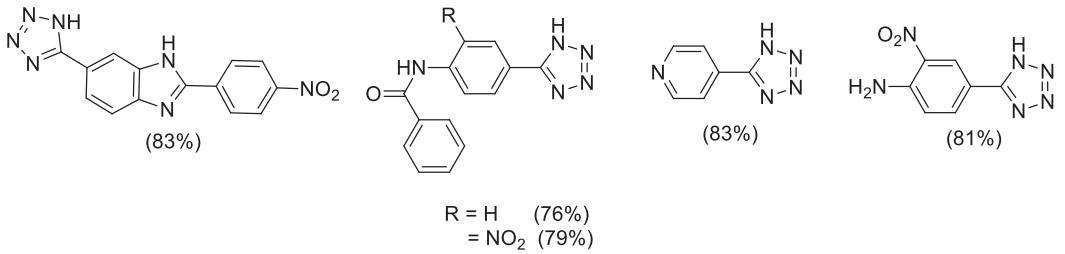
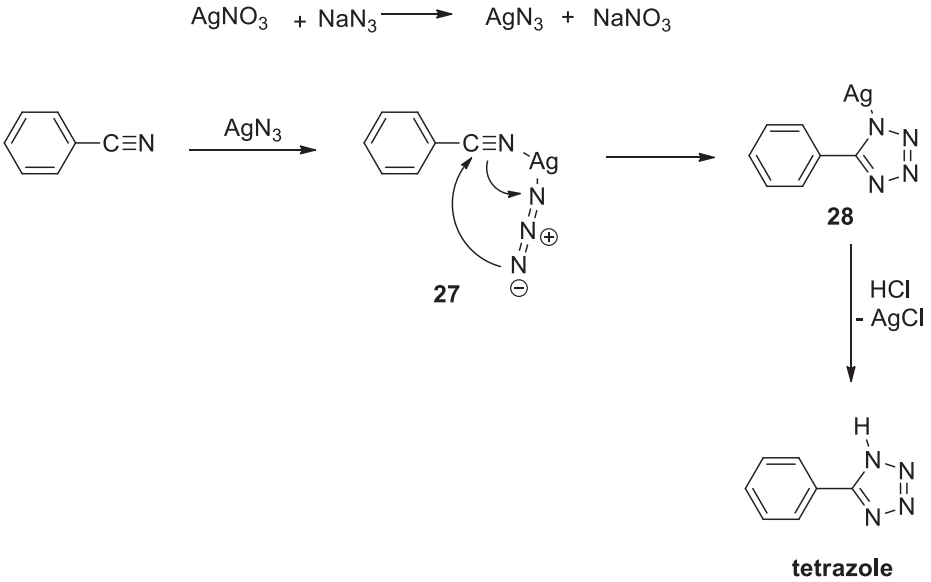


Fig. (19). Some tetrazoles synthesized by Awasthi and co-workers [75].

Based on their experimental data, the authors proposed a mechanism for this reaction. Initially, $AgNO_3$ reacts with NaN_3 producing AgN_3. Then occurs the [3+2] cycloaddition between the C–N bond of the nitrile and AgN_3, giving intermediate **27**. The pre-coordination of the nitrogen atom of nitrile with silver azide gives complex **28**, which, after protonolysis by HCl affords the 5-substituted 1*H*-tetrazole **2a** and AgCl (Scheme **33**) [75].



Scheme (33). The proposed mechanism for the obtaining of tetrazoles using $AgNO_3$ as a catalyst [75].

In entry **16** and **17**, Molae *et al*. used ordered mesoporous SBA-15 functionalized with yttrium(III) and cerium(III) complexes as the catalyst in the reaction between nitriles and sodium azide. The catalytic activity of the yttrium and cerium complexes are similar. Benzonitriles containing both electron-withdrawing and electron-donating groups gave the desired products in good yields (90-97%). This protocol was also efficient for benzyl nitrile (98%). It is worth mentioning that, even in the presence of twice the amount of sodium azide and catalyst, when malononitrile and 1,2-dicyano-benzene were used, the formation of the di-addition product was not observed. The mono tetrazoles were obtained in excellent yields (98 and 99%, respectively) [76].

The methodology reported in entry **18** by Hosseini-Sarvari and Najafvand-Derikvandi used nano TiO_2/SO_4^- as a heterogeneous solid acid catalyst, and can be applied to aryl- and heteroaryl-nitriles. One of the advantages of this methodology is that it is not necessary to use an excess of sodium azide. The heteroaryl-nitriles gave the corresponding tetrazoles in excellent yields (90-95%). Concerning benzonitriles, the unsubstituted one and those containing an electron-withdrawing group on the ring, also gave the desired products in excellent yields (90-97%). However, those containing an electron-donating group gave the corresponding tetrazoles only in moderate yields (60-80%). The di-cyano-benzenes afforded the mono-addition product in excellent yields (90-95%) Fig. (**20**) shows some examples of the tetrazoles synthesized in this work [77].

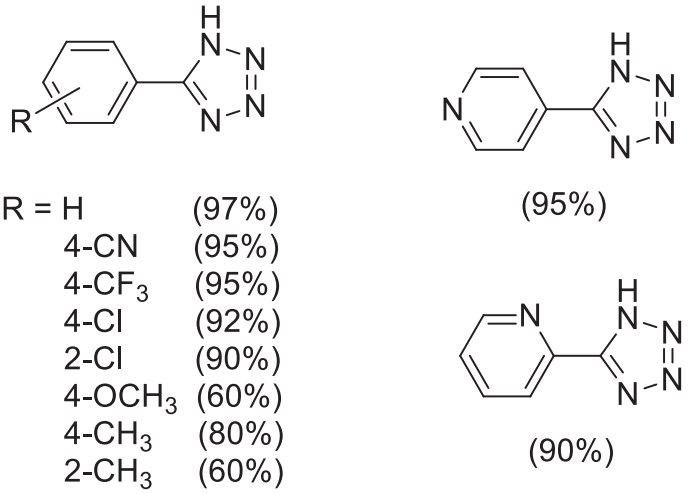


Fig. (20). Some tetrazoles synthesized by Hosseini-Sarvari and Najafvand-Derikvandi [77].

In entry **19**, Kong *et al*. used a tungsten atom-containing AlPO-5 microporous molecular sieve (termed as WAlPO-5) as the catalyst. In this methodology, the

electronic effect and the position of the substituent on the aryl nitrile ring had little influence on the reactivity of the nitrile. For instance, 4-methyl-, 4-nitro- and 2-methyl-benzonitrile gave the corresponding tetrazoles in 74%, 88% and 75%, respectively [78].

In entry **20**, Ghorbani-Choghamarani and co-workers used nickel-S-methy lisothiourea complex immobilized on boehmite nanoparticles (Ni-SMTU@ boehmite) as the catalyst. All tested nitrile compounds gave the corresponding tetrazoles in good to high yields (69-97%). Fig. (**21**) shows some examples of the tetrazoles synthesized in this work [79].

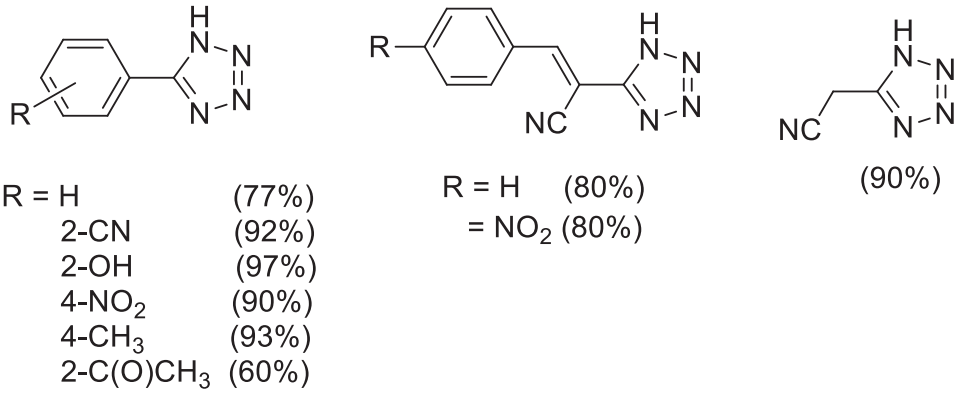


Fig. (21). Some tetrazoles synthesized by Ghorbani-Choghamarani and co-workers [79].

In entry **21**, Coca and Turek synthesized many tetrazoles using ytterbium triflate as the catalyst. The optimized reaction condition consists of 0.1 equivalent of the catalyst, in DMF at 110°C for 16h. In relation to aryl nitriles, this methodology is sensitive to the electronic effect of substituents on the ring, as benzonitriles with electron-withdrawing groups gave the best results. For example, 4-nitro benzonitrile afforded the corresponding tetrazole in a 95% yield after 16h at 110°C while 4-methoxy-benzonitrile gave the desired product in only a 69% yield after 24h at 120°C. This procedure was also sensitive to steric hindrance; the 2-substituted benzonitriles gave the tetrazoles only in poor yields (23-43%). For di-cyano-benzene, the di-tetrazoles were obtained in good yields (75-97%), however, in this case, the amount of NaN_3 was doubled. Aliphatic nitriles were also reacted under this condition; however, they were less reactive than the aryl nitriles, giving the desired products in moderate yields (31-50%) Fig. (**22**) shows some examples of the tetrazoles synthesized in this work [80].

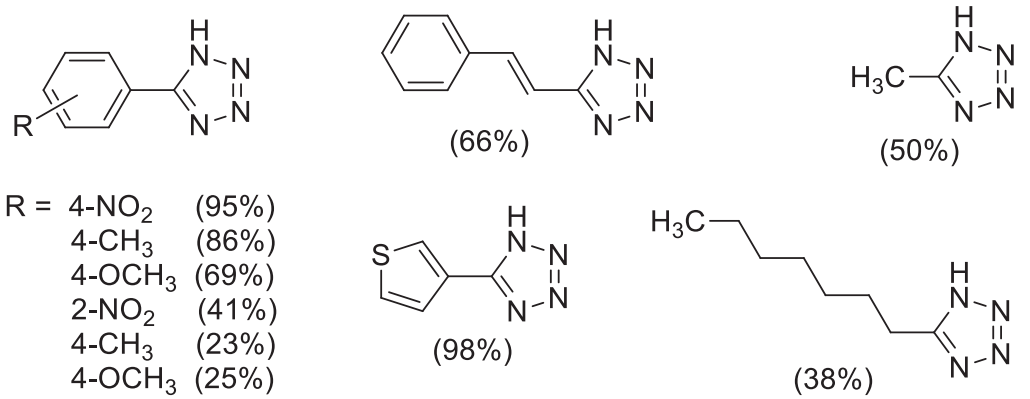


Fig. (22). Some tetrazoles synthesized by Coca and Turek [80].

In entry **22**, Abrishami and co-workers sinthezised some tetrazoles in good to excellent yields, after a short time, both from benzonitriles with electron-withdrawing and electron-donating groups, using nanonickel ferrite as the catalyst. For example, 4-methyl-benzonitrile and 4-nitro-benzonitrile gave the corresponding tetrazoles in 90% after 3h and 95% after 1h, respectively. This methodology was also efficient using heteroaryl nitriles. (For example, 3-cyanopyridine and 4-cyanopyridene gave the corresponding tetrazoles in 95 and 96%, respectively). When di-cyanobenzene and malononitrile were employed, only the mono-addition product was observed even in the presence of two equivalents of NaN_3 and a double amount of the catalyst [81].

In entry **23**, Nikoorazam *et al*. used a palladium *S*-benzyllisothiourea complex anchored on functionalized MCM-41 as the catalyst in the reaction between nitriles and sodium azide. This methodology was not very sensitive to the substituents present in the benzonitrile ring, both electron-withdrawing and electron-donating groups gave the corresponding tetrazoles in similar yields. The 4-nitro-benzonitrile and 4-hydroxy-benzonitrile gave the corresponding tetrazoles in 96% (8h) and 93% (5h) yield, respectively. This methodology was also not very sensitive to the position of the substituent on the ring; As an example, 2-hydroxy-benzonitrile afforded the desired product in a 90% yield (6h). When 1,4-dicyano-benzene and malononitrile were used, only the mono-cycloaddition products were formed. However, both reactions gave the tetrazoles in lower yields, 80% and 76%, respectively. In the case of malononitrile, the reaction was carried out at 130°C [82].

Other Catalysts

In this section, methods for obtaining tetrazoles using other catalysts will be presented (Table **3**).

Table 3. Some new methods for the obtaining of 5-substituted-1*H*-tetrazoles from nitriles using other catalysts.

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
24	$BnNH_2$.HCl (1.5 equiv) $BnNH_2$ (0.5 equiv) Nitrile (1 equiv) NaN_3 (1.1 equiv) 1.5M in 5:1 THF-water 60°C, 8-48 h	5-99	aromatic nitriles; heteroaromatic nitriles	High yields; Safer procedure The scaled-up procedure was also efficient and safer	[83]
25	$BnNH_2$.HCl (1.5 equiv) $BnNH_2$ (0.5 equiv) Nitrile (1 equiv) NaN_3 (1.1 equiv) 1.5M in 5:1 N-methyl-2-pyrrolidone-water 90°C, 1.5-48 h	18-98			
26	NaN_3 (1.25 equiv) Urea (1.25 equiv) H_2O/DMF/AcOH 110°C	65-95	aromatic nitriles; heteroaromatic nitriles	Good to high yields; Safer procedure; Use of cheap and non-toxic catalyst	[84]
27	Activated Fuller's earth (10 wt%) Nitrile (1 equiv) NaN_3 (1.5 equiv) DMSO, 120°C	60-91	aromatic nitriles; heteroaromatic nitriles	Good to high yields; Simple and safer procedure; Use of cheap, stable, and non-toxic catalyst Easy recovery of the catalyst	[85]
28	Cyanuric chloride (20 mol%) Nitrile (1 equiv) NaN_3 (1 equiv) DMF, 120°C	41-93	aromatic nitriles;	Simple procedure; Mild reaction condition; Short reaction time; The catalyst is stable, non-volatile, inexpensive and easy-to-handle	[86]

(Table 3) cont.....

Entry	Reactional Condition	Yield (%)	Substrate Scope	Advantages	References
29	4-(*N,N*-dimethylamino)pyridinium acetate (15 mol%) 1 mmol of nitrile 1 mmol of NaN_3 100°C	42-96	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	Moderate to excellent yields; Catalyst easily recyclable; Easy work-up; Solvent-free conditions	[87]
30	0.2 equiv $BiCl_3$ Isopropanol / H_2O 3:1 MW 2 mmol of nitrile 4 mmol of NaN_3 120-160°C / 0.5-4h	61-98	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles vinyl nitriles	Good yields; Short reaction time; This method was also efficient for nitriles less reactive such as vinyl nitriles	[88]
31	1) Graphene (0.03g) 2.5 mmol of nitrile 2.75 mmol of NaN_3 DMF 120°C / 36h 2) HCl	58-73	benzonitriles; benzyl nitriles; heteroaromatic nitriles;	Moderate to good yields; Easy preparation and separation of catalyst; Non-toxic and environmentally friendly catalyst	[89]
32	SiO_2-melamine tri sulphonic acid (0.2g) 1 mmol of nitrile 3 mmol of NaN_3 / DMF 120°C / 5-8h	73-83	aromatic nitriles; heteroaromatic nitriles; aliphatic nitriles	Simple work-up; Mild reaction condition; Easy separation of the catalyst; Good to excellent yields; Short reaction times	[90]
33	KIT-6-Pr-SO_3H (20mg) 1 mmol of nitrile 3 mmol of NaN_3 DMF 120°C / 16h	71-89	aromatic nitriles; heteroaromatic nitriles;	Moderate to good yields; Simple and environmentally friendly protocol	[91]

In entries **24** and **25**, Treitler and co-workers developed a safe procedure for the acid-mediated tetrazole synthesis from aryl nitriles and sodium azide in presence of $BnNH_2$/$BnNH_2$.HCl . This method was demonstrated to be sensitive to the steric and electronic properties of the substrate. On the one hand, electron-deficient benzonitriles reacted fast, giving the correspondent tetrazoles in excellent yields (89-99%); on the other hand, electron-rich benzonitriles afforded the desired products in poor to moderate yields (5-75%). Among benzonitriles with the same substituent, it was observed that 4-substituted benzonitriles gave better yields than the 2-substituted benzonitriles, due to their steric hindrance. For example, when comparing the reaction with 4-methoxy- and 2-meyhoxybenzo

nitrile the yields were 75% and 18%, respectively, under the reaction condition described in entry **25**. The 2-hydroxy-benzonitrile (99%, 1.5h) was an exception, exhibiting significantly higher reactivity than both benzonitrile (89%, 24h), which is less electron-rich, and 4-hydroxybenzonitrile (61%, 48h). The authors suggested that it could be attributable either to an entropy-reducing directing effect, perhaps *via* a hydrogen bonding interaction with the azide moiety, or due to the hydrogen bond stabilization of a partial negative charge that builds upon the nitrile nitrogen during the transition state [83].

This methodology also proved to be efficient for heteroaryl nitriles, giving the correspondent tetrazoles in good to excellent yields. Fig. (**23**) shows some examples of the tetrazoles synthesized in this work [83].

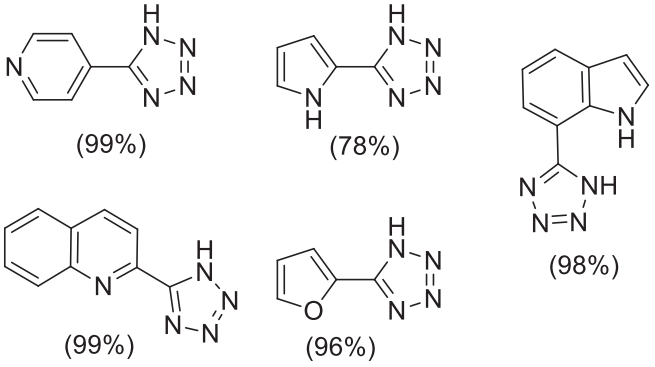


Fig. (23). Some tetrazoles synthesized by Treitler and co-workers [83].

In entry **26**, Bandichhor and co-workers synthezides some tetrazoles *via* a urea-azide-mediated cycloaddition in a mixture of water and *N,N'*-dimethylformamide with acetic acid. This method was efficient for benzonitriles as both electron-deficient and electron-rich benzonitriles gave the corresponding tetrazoles in good to excellent yields yields. However, this procedure was sensitivity to steric hindrance, as 4'-methyl-[1,1'-biphenyl]-2-carbonitrile gave the corresponding tetrazole in only a moderate yield (60%). This methodology was also efficient with heteroaryl nitriles giving the desired products in moderate to high yields. However, it was not adequate to aliphatic nitriles, probably due to the electron-donating capacity of alkyl groups making these nitriles less reactive when compared to aryl nitriles. Fig. (**24**) shows some examples of the tetrazoles synthesized in this work [84].

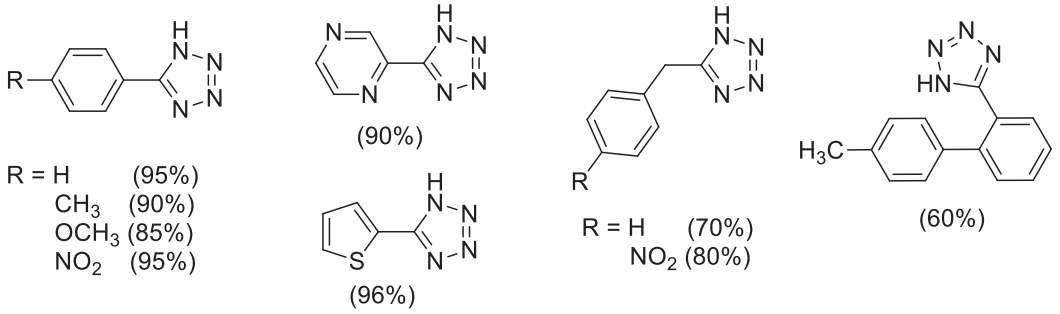
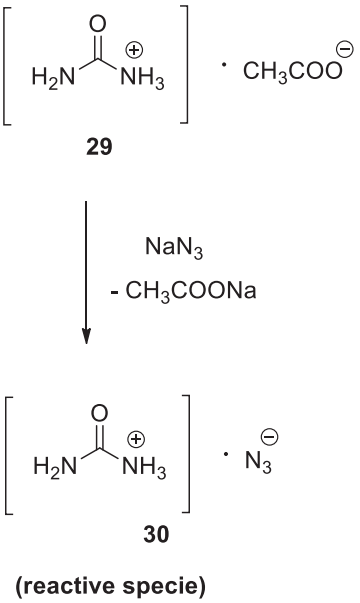
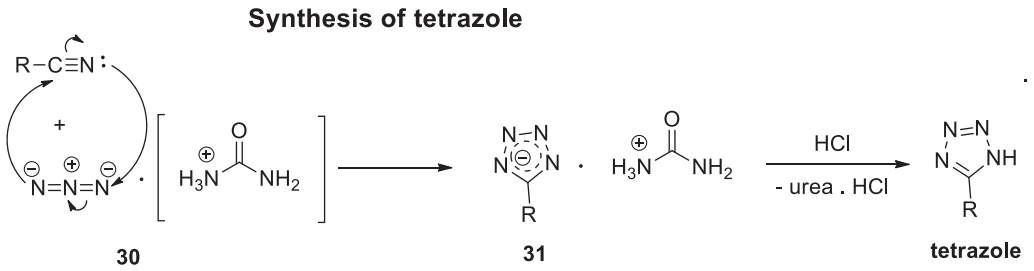


Fig. (24). Some tetrazoles synthesized by Bandichhor and co-workers [84].

Based on the experimental results, the authors proposed a plausible mechanism for this reaction. Initially, urea reacts with acetic acid affording the acetate salt of urea **29** which, in presence of sodium azide, gave the reactive species urea azide **30**. Then, compound **30** underwent a cycloaddition reaction with nitrile derivatives to afford intermediate **31**. The desired tetrazoles were obtained after the protonolysis of intermediate **31** by aqueous HCl (Scheme **34**) [84].



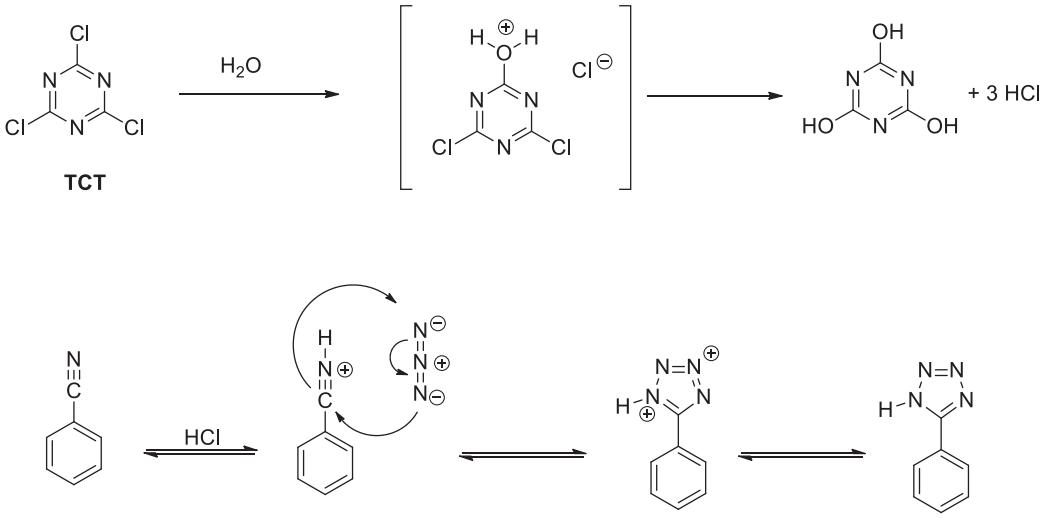


Scheme (34). Proposed mechanism for the synthesis of tetrazoles *via* urea azide mediated cycloaddition [84].

In entry **27**, Chaturbhuj and co-workers synthesized some tetrazoles in good to high yields through a simple protocol using activated Fuller's earth as a catalyst. Many aryl and heteroaryl nitriles were synthesized employing this methodology. The best results were observed for unsubstituted benzonitrile and benzonitriles bearing electron-withdrawing substituents at the *orto*- and *para*-positions on the ring (1.5-3h, 85-91%). When electron-donating groups were present on the ring, the reaction took more time (6-8h) and the desired products were obtained in 77-80% yields. however, the reaction of aliphatic nitriles under the optimized reaction conditions was not efficient, giving the corresponding tetrazole in poor yields [85].

In entry **28**, Lalitha and co-workers synthesized some 5-substituted-1*H*-tetrazoles using cyanuric chloride (TCT) as the catalyst, acting as a source of hydrochloric acid. In this protocol, it was observed that aryl nitriles bearing functional groups such as $-CH_3$, $-OCH_3$, -Cl, -Br, $-NO_2$ and $-CH(CH_3)_2$ gave the corresponding tetrazoles in good to excellent yields irrespective of the substituent position on the ring (67-93%). However, when substituents such as -F, $-CF_3$ were present, the yields were relatively poor (41-68%). This methodology was also efficient to benzylic nitriles, affording the corresponding products in good to moderate yields (58-75%) [86].

The authors proposed a plausible mechanism for this reaction. Initially, the reaction of cyanuric chloride with atmospheric moisture produces 3 molecules of HCl and cyanuric acid as a byproduct. Then, the HCl protonates the phenyl nitrile leading to the formation of highly activated nitrilium cation which suffers an attack by the azide compound forming the tetrazole (Scheme **35**) [86].



Scheme (35). Proposed mechanism for the synthesis of tetrazoles using cyanuric chloride (TCT) as a catalyst [86].

In entry **29**, Nowrouzin and co-workers synthesized some e 5-substituted-1*H*-tetrazoles were synthesized using 4-(*N,N*-dimethylamino)pyridinium acetate as a recyclable catalyst with an ionic liquid character. The best results observed in this methodology were obtained for benzonitriles with electron-withdrawing groups. For example, 4-trifluoromethylbenzonitrile afforded the correspondent tetrazole in 98% yields after 30 minutes, while 3-aminobenzonitrile provided the tetrazole in a poor 20% yield after 3 hours. This method was also efficient for obtaining tetrazoles from heteroaromatic- and aliphatic nitriles, giving the desired products in excellent yields. For example, 3-cyano-pyridine, 4-cyano-pyridine and phenylacetonitrile gave the corresponding tetrazoles in 94%, 96% and 90, respectively. Moreover, mono addition products were afforded from the reaction of 1,2-dicyanobenzene and malononitrile even when the number of equivalents of sodium azide was doubled. However, in these cases, the desired tetrazoles were obtained only in moderate yields (42-65%) [87].

In entry **30**, Coca *et al*. synthesized some 5-substituted-1*H*-tetrazoles using $BiCl_3$ as the catalyst under microwave heating. The desired products were obtained in good to excellent yields (75-98%) and in a short time (0.5-1h), from benzonitriles having electron-withdrawing groups. However, for benzonitriles with electron-donating groups, the yields were poor, and more reaction time was necessary to improve the yields. For example, 4-methoxybenzonitrile gave the corresponding tetrazoles in 20% and 61% after 1h and 4h, respectively. For di-cyano-ben zonitriles, the tetrazoles were obtained in good yields (77-82%), without the formation of the product of di-cycloaddition. In this case, it was necessary to

double the amount of $NaN_3/BiCl_3$ and increase the reaction time (4h). This methodology was also efficient for heteroaryl nitriles (55-99%) and vinyl nitriles (49-89%). Fig. (**25**) shows some examples of the tetrazoles synthesized in this work [88].

In entry **31**, Qi *et al*. used graphene as the catalyst, and the tetrazoles were obtained in moderate to good yields (58-73%). Among the tested nitriles, benzyl cyanide gave the lowest results, affording the corresponding tetrazole in only a 58% yield. For benzonitriles, it was observed that this method is sensitive to the position of the substituents on the ring. For instance, 2-chloro- and 4-chloro-ben zonitrile gave the desired products in 63% and 73%, respectively. It is interesting to note that in these reactions, benzonitriles containing electron-donating groups, showed better results when compared to benzonitriles with electron-withdrawing groups. As an example, 4-methyl- and 4-nitro-benzonitrile gave the corresponding tetrazoles in 71% and 64%, respectively [89].

In entry **32**, Mahajan and co-workers used silica-supported melamine trisulphonic acid catalyst (SMTSA) to obtain tetrazoles from nitriles and sodium azide. This methodology can be efficiently applied with aliphatic, aromatic, and heteroaromatic nitriles, affording the corresponding tetrazoles in an excellent yield without any contamination. Fig. (**26**) shows some examples of the tetrazoles synthesized in this work [90].

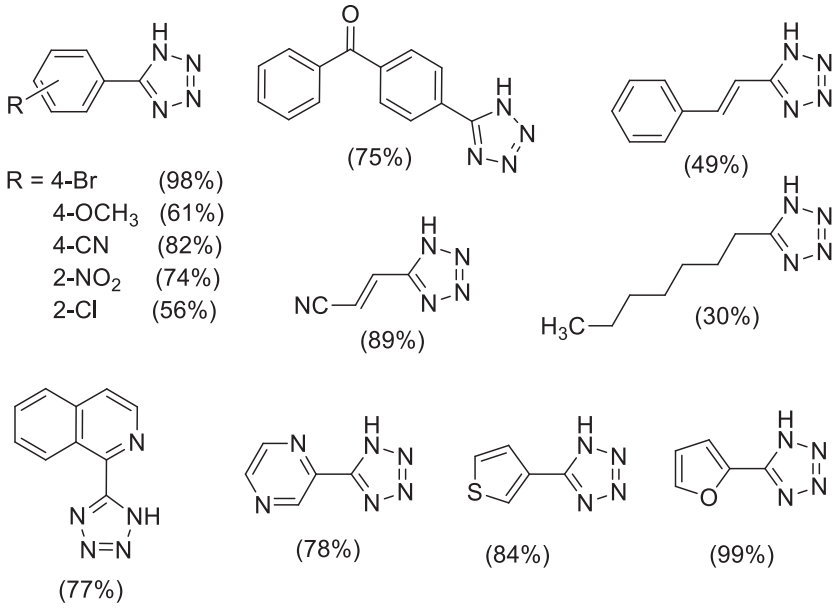


Fig. (25). Some tetrazoles synthesized by Coca *et al*. [88].

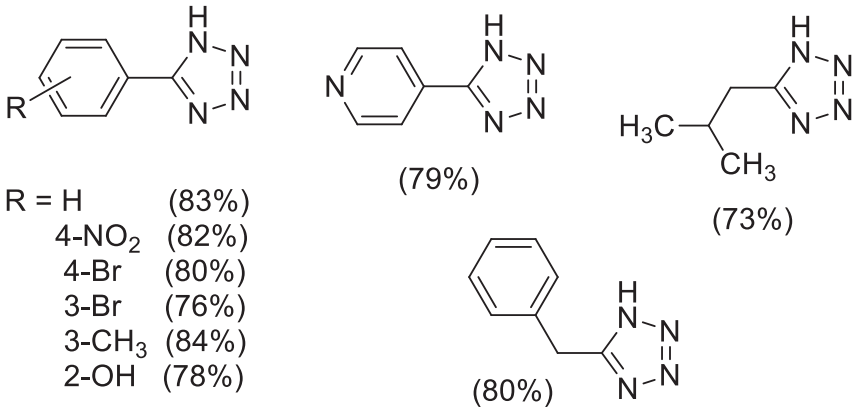


Fig. (26). Some tetrazoles synthesized by Mahajan and co-workers [90].

In entry **33**, Chermahini *et al.* used KIT-6 material functionalized with propyl sulfonic acid moiety as a hybrid inorganic/organic catalyst for the synthesis of tetrazoles from the reaction between nitriles and sodium azide. All aryl- and heteroaryl nitriles tested gave the desired products in moderate to good yields. For example, 4-nitro-, 4-methyl-benzonitrile, and 4-cyano-pyridine afforded the corresponding tetrazoles in 77%, 75%, and 75%, respectively [90].

CONCLUDING REMARKS

Nitriles are very versatile starting materials for the synthesis of nitrogen-containing heterocycles. In this chapter, we have shown many possible methods for the synthesis of pyrroles, indoles, pyrazoles, imidazoles, triazoles, and tetrazoles, covering some of the most important 5-membered nitrogenated cores. It is important to mention, though, that other compounds, such as oxazoles, thiazoles, oxadiazoles, and many essential 6-membered heterocycles are also accessible through nitrile chemistry, making this a hot topic in organic chemistry.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 5

The Role of Carbon-based Solid Acid Catalysts in Organic Synthesis

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Abstract: In synthetic organic chemistry, heterogeneous catalysis has opened a new era for progressive green and eco-benign synthesis. Fundamentally, it is interminably interesting and perennially novel. Carbon materials are widely used for renewable energy and environmental studies. Significant advancements have been achieved in modern organic chemistry by replacing conventional acid catalysts with pollution-free, recyclable, and eco-benign solid acid catalysts to reduce toxicity and increase efficiency. Solid acid catalysts play a profound role in organic synthesis as they are heterogeneous, recyclable, ease of workup, corrosion-free, immiscible in routine organic solvents, easy recovery from the products, selective synthesis, *etc.* Furthermore, carbon-based solid acid catalysts have attracted scientists because of its simple preparation method, increased acidity, selectivity, high stability, easy separation of products, no corrosion of equipment, easy recovery and recyclability, *etc.* They exhibit remarkable catalytic activity for various acid-catalyzed reactions, such as biofuel production, hydration, hydrolysis, and esterification of higher fatty acids. This article profoundly discusses the synthesis, properties, and applications of carbon-based solid acid catalysts in organic synthesis.

Keywords: Biginelli reactions, Bio-diesel, Carbon-based solid catalyst, Catalysis, Condensation reactions, Esterification, Green synthesis, Heterocycles, Organic reactions, Synthetic organic chemistry.

INTRODUCTION

Currently, scientists are paying significant attention to design eco-friendly pathways for organic transformations. There has been a spike in the interest of researchers for more environmentally acceptable processes in the chemical industries. This tendency is known as “Green Chemistry” or Sustainable Technology [1, 2]. The basic concept of Green Chemistry is the use of chemical

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skills and knowledge to reduce or eliminate the use or production of toxic substances during the planning, manufacturing, and application of chemicals to minimize threats to the health of operators and the environment [2]. In brief, the principles of Green Chemistry are based on the minimization or non-use of toxic solvents in chemical processes and analyses and the non-generation of waste. One of the best ways of implementing the principles is to use recoverable and reusable catalysts. The catalysts play an imperative role in the reduction of pollution in our environment. It is one of the most elementary pillars of "Green Chemistry". With the use of catalysts, the reaction becomes more effective, selective and productive, thereby eliminating huge amounts of toxic waste and by-products and also saves resources [3]. They are usually applied for the synthesis of chemical products of industrial and laboratory importance [4]. Thus, catalysts act as a master key in reducing both the investment and operation cost of a chemical process. Acid catalysts are the most important area of catalysts that are studied and developed in recent decades. A variety of industrial reactions are catalyzed by mineral acids or organic acids. Various reactions, such as Friedel–Crafts alkylation and acylation, sulfonylation, aromatic halogenation, nitration, isomerization, and oligomerization occur in the presence of the acid catalysts. The acid catalysts can be categorized into homogenous and heterogeneous acid catalysts according to their states in the reaction. Several mineral acids, such as H_2SO_4, HCl, HF, H_3PO_4, *etc.* are used on a large scale as liquid homogenous acid catalysts, which give the desired products at low temperatures because they mostly involve the reactions in their original molecular state. However, there are few disadvantages of using liquid acid catalysts, *e.g.*, production of a huge amount of waste liquors, tedious separation and filtration of liquid catalysts, the uneasiness of successive reaction operations, *etc.* These reagents are perilous in handling, detriment the plant through their corrosiveness, and involve process complexities by employing quenching and separation stages. Therefore, the use of mineral acids is undesirable due to the following issues [4]:

- The amount of waste generation is larger than the amount of product formed.
- The waste disposal cost increases the cost of the operation.
- It causes environmental pollution.
- Leads to a separation problem.

In continuation to resolve the problems brought by liquid acid catalysts into the reaction, a survey of environmental-benign and simple recyclable heterogeneous solid acid catalysts becomes meaningful. The great potential of solid acid catalysts has been experienced in synthesizing organic compounds [5 - 8]. Solid acid catalysts are used at a large scale for the acid-promoted processes in organic synthesis [9, 10]. Moreover, they are heterogenized on different solid supports to

reduce the toxicity or increase efficiency [11 - 13]. They are grouped into various parts, such as silica-based solid acid [14, 15], zeolite-based solid acid [16], polymer-based solid acid [17, 18], and carbon-based solid acid [19 - 21], and so on, as shown in Fig. (**1**).

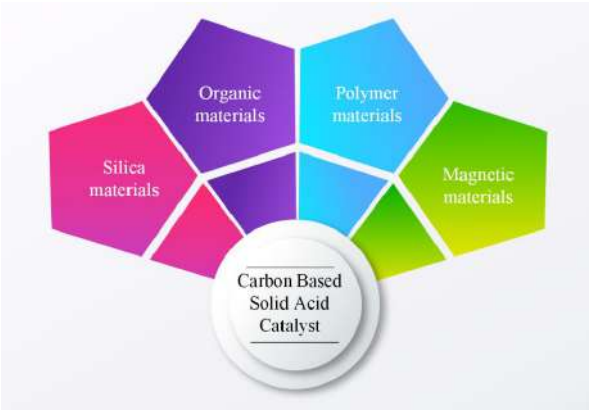


Fig. (1). Different types of solid acid catalysts.

CARBON-BASED SOLID ACID CATALYST

From the last few years, carbon materials have become a prominent topic in the research area as they are used to catalyze several reactions [22]; in lieu of this, carbon-based solid acid catalysts are developing rapidly. They have served as precious materials for industrial process and organic reactions because of its several advantages that are appended below and also shown in Fig. (**2**).

Fig. (2). Various catalytic properties of a carbon-based solid acid catalyst.

- The separation of the catalyst from the reaction mixture is easy for solid acid catalyst system *i.e.* the catalysts are automatically separated from phase reaction or can be separated by simple filtration for liquid phase reaction. Thus, recycling catalyst is easy.
- These are not corrosive and can be used in the reactor system made of usual materials.
- The production of by-products can be minimized.
- Multifunctional catalysts can be designed based on the solid acid catalyst. Catalytically active components other than acid sites can be located on the solid acid catalyst surfaces to promote reactions other than acid-catalyzed ones.
- Easily recyclable and recoverable and can be reused several times without loss in catalytic activity.
- Reactions are usually clean and products are acquired in high purity.
- Reactions being selective in nature.
- Thermal and chemical stability of the solid acid catalyst throughout the reaction process and for batch reactions during the separation stage.

All these listed advantages pave smooth and easy designing protocols for environmentally benign catalytic processes [23]. A huge range of various carbon-based solid acid catalysts have been synthesized and used [24 - 30]. Due to these rewards, solid acids are used as catalysts in organic chemistry [[31 - 37]]. These catalysts are also used in cellulose hydrolysis [38, 39], cellobiose hydrolysis [40], production of fatty acid methyl ester, which can be used in diesel compression engines without modification [41 - 45], dehydration, acetalization [46], the formation of ethyl acetate from ethanol and acetic acid, esterification [47, 48], trans-esterification [49 - 51] and trans-esterification of various oils with methanol into biodiesel [52], hydrogen production by water electrolysis [53], *etc.* They are also used to catalyze xylose to furfural [54], fructose to 5-hydroxymethylfurfural [55], and careful transformation of starch to glucose [56].

Numerous synthetic strategies have been employed for the synthesis of carbon-based solid acid catalysts that involve the use of non-toxic, low-cost, reusable, and different eco-friendly methodologies to improve catalytic efficiency and yield, *etc.* However, several review articles have been published so far that emphasize the various methods of synthesis and applications of solid acid catalysts in reactions as well as their use in biodiesel production. Earlier, applications of CBSA catalysts have been partially reviewed, but up to now, no literature has been scientifically reported on the recent advancements of carbon-based solid acids in organic reactions. In 2009, Jothiramalingam and Wang discussed the recent developments in solid acid catalysis for biodiesel production *via* trans-esterification [57]. Adam and co-workers synthesized rice husk derived silica, which was used to generate heterogeneous catalyst and these catalysts were used

to catalyze several organic reactions [58]. Kang *et al.* [59] in 2013 represented the study of carbon-based sulfonated catalyst and their preparation and applications. After that, Su and Guo summarized solid acid catalysts for biodiesel production [60]. Pan and Jhuma [61] reviewed the chitosan-based catalyst and its role in organic synthesis. Vekariya and Patel represented the advantages of cellulose sulfuric acid (CSA) and starch sulfuric acid (SSA) in organic synthesis [62]. Mansir *et al.* [63] explicit the use of solid acid catalysts for biodiesel production. In 2018, Sharghi *et al*. [64] provided an outline of the synthesis of CBSA and its catalytic applications in chemical processes. We believe that a complete and systematic study of the established methodologies for synthesizing heterogeneous carbon-based solid acid catalysts and their applications in organic transformations would be useful to a vast community of researchers working in chemistry laboratories and industries. The detailed study of synthetic approaches using carbon-based solid acid catalysts is still untouched and needs to be focussed. This chapter spotlights recent organic transformations in different environmental conditions to synthesize five-membered, six-membered and other membered heterocycles and esterification along with their role in miscellaneous reactions. The chapter is a piloted study of literature from 2005 to 2020 and will be helpful to the researchers working on designing more promising clinical lead compounds through eco-benign pathways. The major perspective of the chapter is to summarize the recent advancements done so far in the synthetic applications of carbon-based catalysts.

Role of Carbon-based Solid Acid Catalysts in Organic Transformations

Carbon-based solid acid catalysts have been prepared using different precursors such as starch, cellulose, rice husk, camphor, glycerol, almond peels, and carbon-based raw materials *viz.* aromatic compounds, biomass, activated carbon, carbon nanotubes in the presence of sulphonating agents like hydroxylethylsulfonic acid, fuming H_2SO_4, conc. H_2SO_4, *etc.* They have been applied for several organic transformations like coupling reactions, condensation reactions, nucleophilic addition reactions, esterification, trans-esterification reaction, and their utility in bio-diesel production. Moreover, they have been used in the synthesis of five and six-membered heterocycles along with their role in miscellaneous organic reactions. Their applications to catalyze various organic reactions are shown in Fig. (**3**).

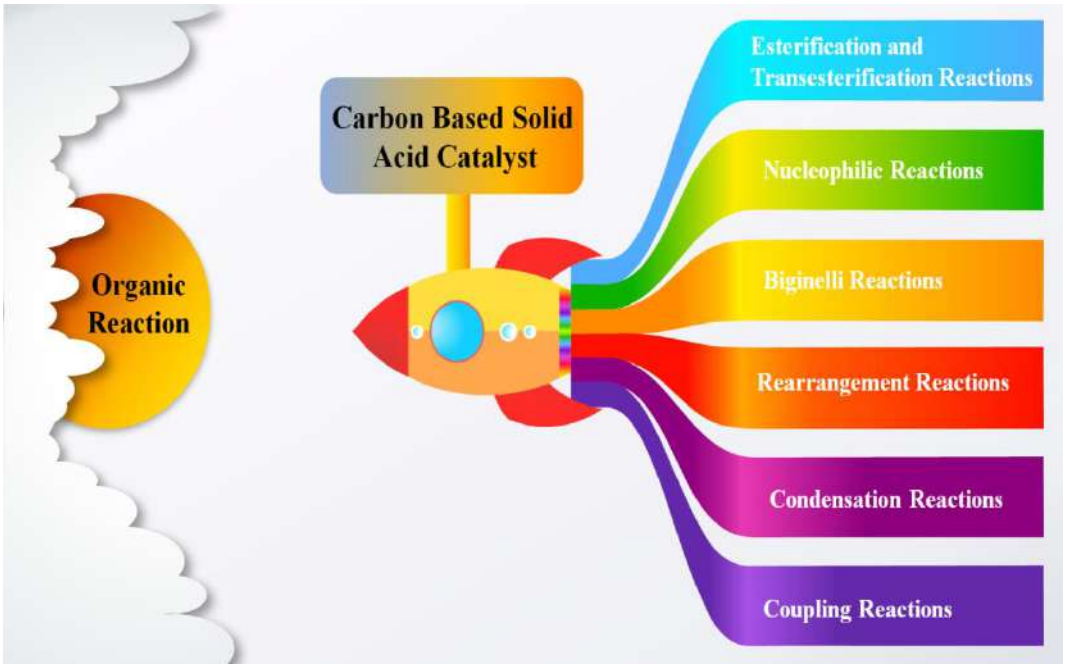


Fig. (3). Applications of carbon based catalyst in organic synthesis.

Esterification and Biodiesel Generation

Several carbon-based solid acid catalysts were used in esterification and biodiesel generation. Naphthalene, as a precursor was reacted with sulphuric acid to furnish the solid acid catalyst and was used in esterification [65]. Sugars are the key source of carbon and their sulphonation and carbonization gave the catalyst. In continuation of this, Takagaki *et al.* synthesized an amorphous carbon-based solid acid catalyst from D-glucose and used it for the esterification of higher fatty acids [66]. Wood powder is also used as a precursor to synthesize the catalyst that possessed good catalytic activity for esterification of acetic acid as well as for the benzylation of toluene [67]. Later on, cellulose-based carbon sulphonic acid was synthesized and used for biodiesel production using oleic acid and methanol [68]. The catalyst is easily recyclable and can be used for the production of biodiesel from crude vegetable oils. A sulfonated graphitic carbon nitride (Sg CN) as a metal-free nanomaterial was manufactured and used it for room temperature synthesis of biodiesel [69]. Many scientists have worked to fabricate green methods for esterification or trans-esterification, as shown in Fig. (**4**).

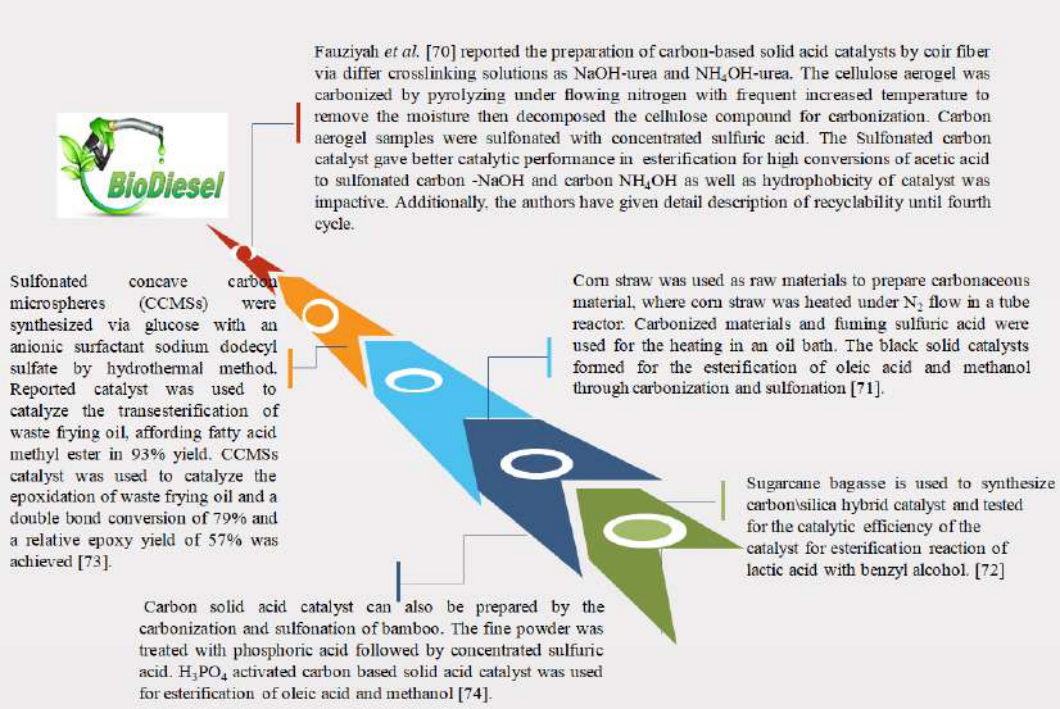
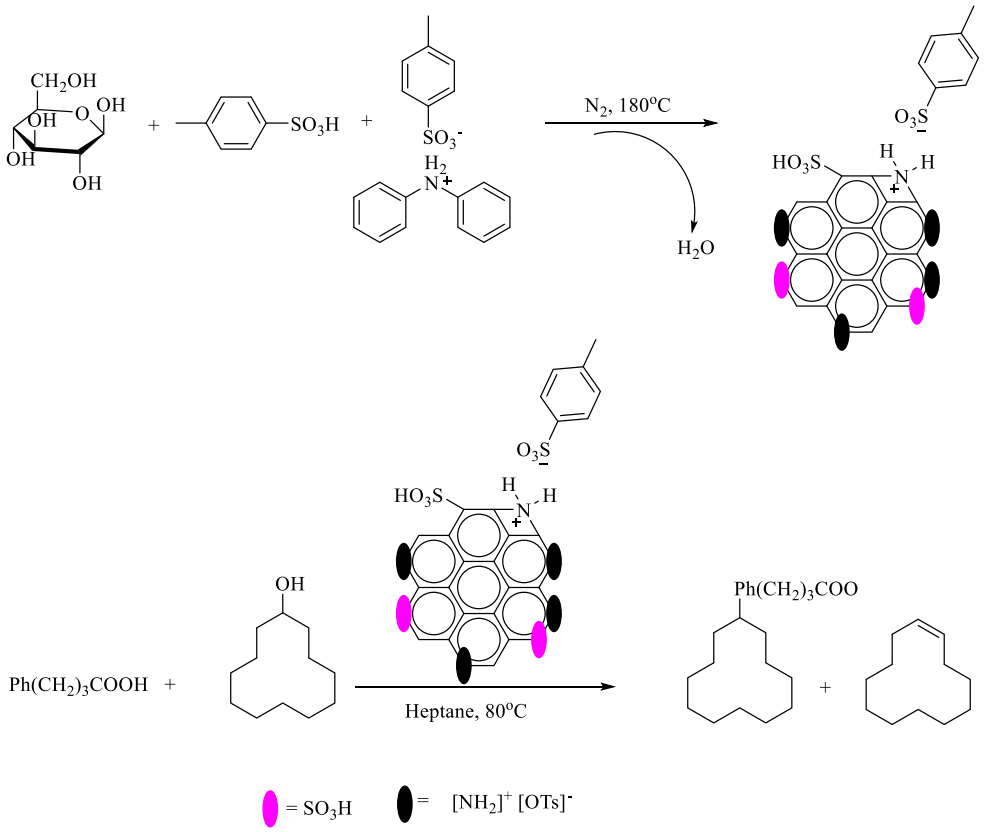


Fig. (4). Biodiesel production using different carbon- based solid acid catalysts.

Sulphonated catalyst from seed cake of *Calaphyllum Inophyllum* (polanga), an inedible tropical seed, was incompletely carbonized at 400°C and the synthesized black fine powder was sulphonated with conc. H_2SO_4. The obtained carbon was examined to be amorphously composed of thin aromatic sheets irregularly. It was used for esterification and trans-esterification and to examine the catalytic potential of the sulphonated seed cake catalyst. The catalyst synthesized from the seed cake recorded a biodiesel yield of 99% [75].

KOH/Corncobs derived carbon solid acid catalysts were also used to form bio-diesel in a single step. The catalyst was active in both the cases *i.e.*, in trans-esterification and esterification. To manufacture the catalyst, a 5:1 ratio of sulphuric acid to corncobs was used and heated at 600°C for 1h. For the generation of bio-diesel formation, the most favorable reaction conditions were 45°C temperature and heating the waste oil for 1 h in (18:1) methanol: oil molar ratio with catalyst loading (1%) and 97.8% yield was obtained. The obtained biodiesel was as per the ASTM standards. The catalyst was stable and recyclable for up to five consecutive runs to catalyze esterification, but in the case of trans esterification, the catalyst became inactive due to the leaching of KOH [76].

A novel carbon-based solid acid catalyst was synthesized from a mixture of D-glucose, diphenylammonium tosylate, and p-toluenesulfonic acid (Scheme **1**). The $-NH_2^+$ and $-SO_3^-$ groups were functionalized with carbon material and had a strong hydrophobic effect. The catalytic efficiency of the catalyst was evaluated for the esterification reaction of carboxylic acids with acid-sensitive alcohols [77].



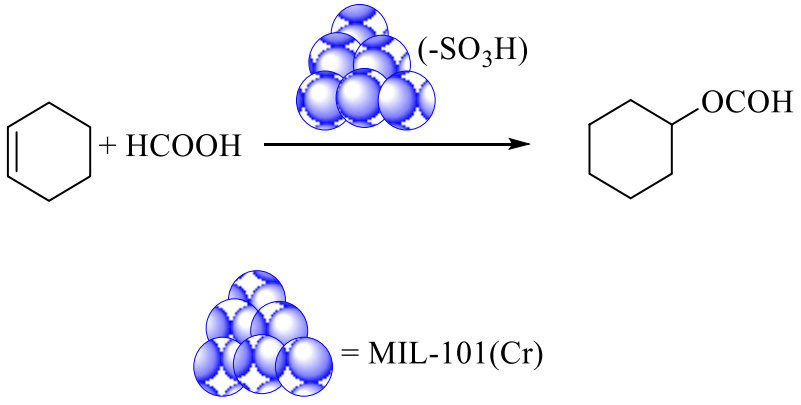
Scheme (1). Preparation of glucose diphenylamine tosylate-derived carbon solid acid and its use for esterification.

Environmental friendly and the reconstructive carbon-based solid acid catalyst was derived from glycerol *via in situ* carbonization and sulfonation [78]. Glycerol was sulfonated in the presence of H_2SO_4 to produce biodiesel. The synthesized catalyst was used for the esterification of palm fatty acid distillate (PFAD). The synthesized catalyst has a large surface area and acid sites that are helpful for esterification. The results confirmed that the synthesized catalyst exhibited excellent catalytic activity of being reused with better yields, >96%, along with regeneration property. It has also been observed that there was a difference in the

percentage of yield and the catalytic activity after 4 cycles of catalyst. With the reuse of the catalyst, there was leaching of the sulfonic group that decreased its catalytic efficiency.

D-glucose was used to synthesize carbon-based solid acid by incomplete carbonization at 400°C for 15 h under N_2 flow. It was scrutinized to catalyze the esterification of oleic acid and subsequently waste cooking oil. The catalytic ability of this sulphonated sugar catalyst was compared to three typical solid acid catalysts, namely sulphonated zirconia, niobic acid, and Amberlyst 15 resins. The reaction was carried out at 80°C, with an alcohol to oil molar ratio of 10:1. The sugar catalyst demonstrated a higher catalytic activity than sulphated zirconia and Amberlyst 15. It was reflected in the yields of methyl oleate from (87- 93.5%) achieved by the various catalysts [79].

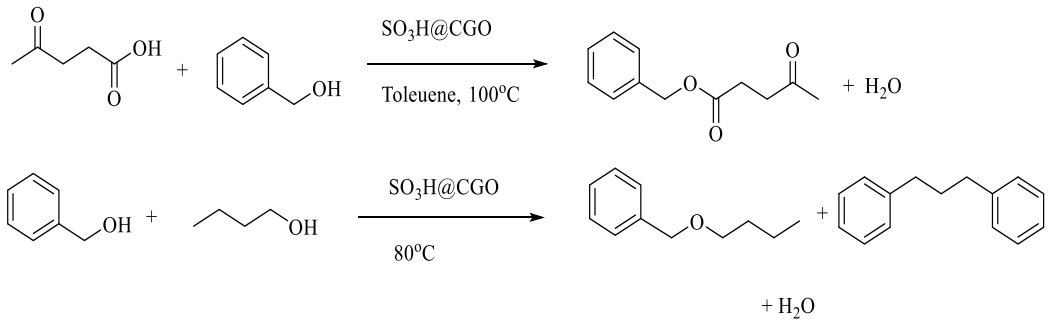
MIL-101-SO_3H catalyst was prepared *via* three different acids and their catalytic efficiency was compared. The catalyst was prepared from a one-pot multi-component reaction of monosodium salt of 2-sulfoterephthalic acid and CrO_3 in the presence of water with three different acids as HCl, HF, and NaAC to give MIL-101-SO_3H_{HCl} MIL-101-SO_3H_{HF}, MIL-101-SO_3H_{NaAC} respectively. These catalysts were used for the esterification of cyclohexane with formic acid. The catalytic performance of reported catalysts was good and it was found that MIL-101-SO_3H_{HCl} showed better catalytic activity than MIL-101-$SO_3H_{NaAC,}$ but MIL-101-SO_3H_{HF} was excellent than MIL-101-SO_3H_{NaAC}. The -SO_3H was the primary active group in MIL-101-SO_3H and MIL-101-SO_3H_{HCl} performed best in the esterification. The authors revealed that MIL-101-SO_3H showed reusability up to three runs [80] (Scheme **2**).



Scheme (2). Esterification of cyclohexene with formic acid by using MIL-101(Cr)-SO_3H.

Sulphonated mesoporous carbons (S-OMCs) were synthesized from the self-assembly of phenolic resol and triblock copolymer F127 in ethanol, pursued by sulfonation with isoamyl nitrite and 4-aminobenzenesulfonic acid [81 - 83]. The sulfonated mesoporous carbon was used as a catalyst for the esterification of oleic acid and methanol. The high acid density and hydrophobic surface property of sulfonated mesoporous carbon made it a highly efficient catalyst. The catalyst displayed a high catalytic activity with the oleic acid conversion of 96.25% and a long lifetime for at least nine times reuse.

The surge of investigation of highly active carbon-based solid acid catalysts led to the synthesis of an active catalyst by sulfonating carbon nanostructures, embedded in an amorphous matrix fabricated from bio-oil. It was used as a catalyst for the esterification of oleic acid with methanol. The reported catalyst was based on carbon nanostructures implanted in amorphous carbon [84]. Nakhate *et al.* [85] synthesized carbon solid acid *via* glucose in the presence of graphene oxide as a structure directing agent. The important use of the reported catalyst was esterification of levulinic acid with benzyl alcohol (Scheme **2**).



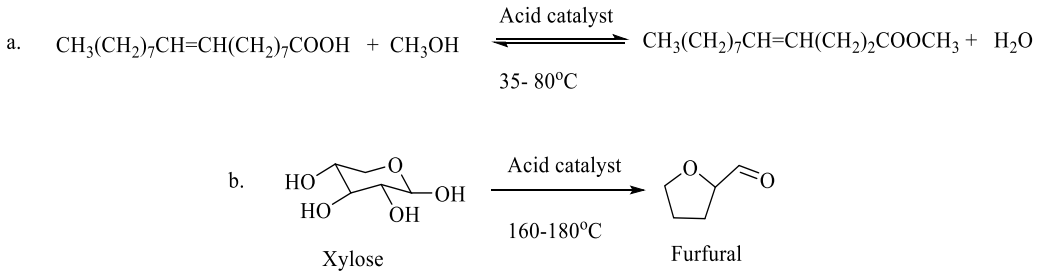
Scheme (3). Esterification of levulinic acid and benzyl alcohol using sulfonic acid-functionalized graphene oxide monolith.

Similarly, a carbon-based solid acid catalyst was prepared by the sulfonation of mesoporous carbon substrates with thin pore walls for the esterification of oleic acid with methanol. Besides, the catalyst was reported to be recoverable and reusable up to five runs. Thus, the high catalytic activity may be attributed to the good dispersion of the catalyst in methanol [86].

Carbonaceous material was prepared *via* one-step hydrothermal carbonization of water hyacinth (WH) with p-toluenesulfonic acid (PTSA) [87]. Carbonaceous material for sulfonated carbon solid acid catalyst was already prepared from hydrothermal carbonization (HTC) of aqueous furfural (2-furanaldehyde) with hydroxyethylsulfonic acid [88] or p-toluenesulfonic acid (PTSA) [89]. The carbon

-based solid acid with the highest acid density exhibited maximum catalytic activity, although the material was prepared at higher temperature. It can be recovered and reused. Additionally, it was reported that SO_3H-functionalized carbonaceous material was used as a catalyst for esterification of oleic acid, and dehydration of xylose to furfural. The catalyst acted as highly efficient and reusable due to enhanced graphitization and hydrophobicity (Scheme **4**).

Different carbon-based catalysts and their catalytic role are illustrated in Table **1**.



Scheme (4). Acid-catalyzed reactions used to the catalytic efficiencies of the prepared carbon-based solid acids. **a)** Esterification of oleic acid **b)** Dehydration of xylose into furfural.

Table 1. Various carbon-based catalysts and their catalytic applications.

S.No.	Catalyst	Preparation	Applications	References
1.	Biochar-derived catalyst	Waste peanut shells were used as a biomass feedstock for a biochar catalyst. The waste peanut shells were carbonized and sulphonated with concentrated H_2SO_4. The catalyst showed better stability. A steady loss in catalytic activity was examined and it was observed that till 5 runs the catalyst maintained at 50% of its activity with acid site density 6.9 mmol/g. After that, acid site density decreased to 3.4 mmol/g and the maximum catalytic activity could be recovered by regeneration process.	The catalyst formed from waste peanut shells was very attractive and found viable for bio-diesel production. The reported catalyst was inexpensive, environmentally benign, and easily available, the resulting catalyst showed high conversion and stability.	[90]

(Table 1) cont.....

S.No.	Catalyst	Preparation	Applications	References
2.	Rice husk derived **SO_3H-RH,** Moringa oleifera seeds derived **SO_3H-MOR** and algae biomass based **SO_3H-BM.**	Carbon solid acid was obtained by the carbonization and sulfonation of rice husk, *Moringa oleifera* seeds and algae biomass, and was depicted as SO_3H-RH, SO_3H-MOR and SO_3H-BM.	Rice husk derived SO_3H-RH catalyst possessed higher acid density as compared to SO_3H-MOR, and SO_3H-BM. Furthermore, the carbon-based solid acid catalyst exhibited excellent recyclability, and high yield (100%) was obtained.	[91]
3.	MPTMS derived carbon solid catalyst	Trejda *et al.* used a solvo-thermal technique for the modification of SBA-15 materials with (3-mercaptopropyl)trimethoxysilane (MPTMS).	The materials obtained showed high activity and stability in the esterification of acetic and propionic acids with n-butanol and n-hexanol.	[92]
4.	Graphene oxide -based catalyst	Masteri-Farahani *et al.* represented the synthesis of solid acid catalyst for biodiesel from surface silylation of GO. Graphene oxide was prepared from the modified hummer's method [94]. Surface silylation of GO was done by (3-mercaptopropyl) trimethoxysilane and GO in dry toluene was refluxed under N_2 atmosphere. The SH group was converted to SO_3H acidic sites, and GO-$PrSO_3H$ was obtained.	GO-$PrSO_3H$ catalyst was examined for the esterification of acetic acid and butanol as well as oleic acid and methanol. The catalyst was recyclable and reusable up to 5 runs.	[93]
5.	Carbon -based catalyst	A carbon-based biocatalyst was synthesized from non-edible agro-industrial waste de-oiled *Pongamia pinnata* seed cake. The process involved partial carbonization of waste followed by sulfonation. The comparison of the efficiency of a lignocellulosic waste catalyst with some commercial catalysts such as sulfuric acid, methane sulfonic acid, and Amberlyst-15 was done.	The esterification of lactic acid and n-butanol was performed by using the prepared sulfonated catalyst.	[95]

(Table 1) cont.....

S.No.	Catalyst	Preparation	Applications	References
6.	MKSB-SO_3H.	Agro-industrial (marumur kernel shell) wastes were used to synthesize biocatalyst *via* partial carbonization and sulfonation and were named as MKSB-SO_3H.	A synthesized catalyst was optimized for the esterification and trans-esterification reaction of low-cost lipid matrices. The reusability of catalyst was also studied and the catalyst could be used until 5 cycles with a small loss in catalytic efficiency.	[96]
7.	Cacao shell-based carbon solid acid catalyst	Cacao shells were used to synthesize CBSA catalyst from carbonization followed by sulfonation. Volatile matter and other components of the cacao shells were released during carbonization. After that, the carbonized biomass was functionalized by sulfonation where sulfonic groups were attached to aromatic hydrocarbon sheets.	The synthesized catalyst was used in the esterification of oleic acid with methanol. The reusability of catalyst up to 5 runs with a small loss in catalytic capability was also investigated.	[97]
8.	Cacao shell - based carbon solid acid catalyst	Cacao shells underwent direct sulphonation under different range of temperature (80, 100, 120 °C for an adequate time 4, 6, 8 hour) to furnish carbon-based solid acid catalysts. The fixed carbon content for cacao shells is close to the coconut shells (24.4%W/W).	The maximum catalyst yield was obtained for the catalyst, prepared after direct sulfonation at 80°C for 4 h, whereas the lowest yield was found for the catalyst, prepared at 120 °C for 8h. This suggested that with an increase in sulphonation temperature, the yield decreased. The carbon solid acid catalyst synthesized at 120°C for 6 h exhibited the highest sulfonic acid density. The catalyst was used for the esterification reaction of oleic acid with methanol. Among all the three- carbon solid acid catalysts, the catalyst prepared at 120°C for 6h showed the highest catalytic activity.	[98]

(Table 1) cont.....

S.No.	Catalyst	Preparation	Applications	References
9.	Sugar cane bagasse derived CBSA catalyst	Carbon solid acid catalyst was synthesized using sugar cane bagasse as a raw material through carbonization and sulfonation.	The prepared catalyst was used for the conversation of PFDA (purchased from IOI Oleochemical Industries Berhad, Penang, Malaysia) into methyl esters *via* esterification. Further, the work also revealed that the catalyst could be recycled up to several times.	[99]
10.	Glu-SO_3H	The novel carbon-based solid acid catalyst was fabricated by mixing of glucose and p-toluenesulfonic acid (TsOH). Initially, glucose was dehydrated into small organic molecules that were hydrothermally carbonized into a carbon-rich resin, then reacted with TsOH and sulfonic acid groups, denoted as Glu-SO_3H.	The synthesized catalyst was used for the esterification reaction of succinic acid and ethanol. The easy and fast workup procedure with high yields, mild reaction conditions, non-toxic, and low cost are the main benefits of using the readily recoverable and reusable sulfonated glucose catalyst.	[100]
11.	Coir -fiber based CBSA catalyst	Carbon-based solid acid was manufactured from an eco-benign and easily available waste material, coir fiber. Carbonization and sulfonation protocols were used to prepare the catalyst.	The obtained sulfonated carbon catalysts gave an excellent catalytic performance in the esterification reaction.	[101]
12.	Magentic CBSA catalyst	The magnetic carbon-based solid acid catalyst was synthesized by chemical activation method for empty fruit brunch with magnetic cores followed by sulfonation of carbonaceous intermediate with sulfonic acid.	The catalyst was used for the production of biodiesel from high PFAD *via* esterification. The biomass supported Fe_3O_4 magnetic catalyst revealed amazing properties such as ferromagnetic, high surface area, high reusability and high thermal stability.	[102]

(Table 1) cont.....

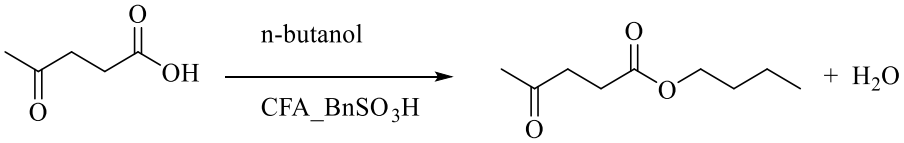
S.No.	Catalyst	Preparation	Applications	References
13.	Rice-husk derived catalyst	Rice husk char was used to generate carbon based catalyst by carbonization and sulfonation process with concentrated sulfuric acid.	The catalytic capability of the catalyst was tested by esterification of oleic acid and methanol. Further, the active and highly efficient catalyst exhibited excellent recyclability up to seven cycles.	[103]

Abdu *et al.* [104] represented a facile and versatile method for the synthesis of scalable carboxylate carbon-based catalysts *via* a one-pot multistep reaction of eucalyptus biomass (ECS). The process involved ball milling of eucalyptus as a source of carbon with dry ice as an oxidant followed by acidification. The catalyst hydrolyzed eucalyptus biomass to xylose and glucose in excellent yields.

Coal fly ash from different sources with different size fractions was used as a raw material to form carbon-based catalyst. Sulfonation was done by two methods that include one-pot organosilylation and two-step benzyl alcohol condensation. The catalytic efficiency of the catalyst was tested for biodiesel production by the esterification reaction of levulinic acid with butanol [105]. Additionally, the CFA_$BnSO_3H$ catalyst could be effortlessly recovered by filtration and reused up to 5 times without any treatment. The other advantages of the catalyst include excellent yield production, inexpensive nature, and stability (Scheme **5**).

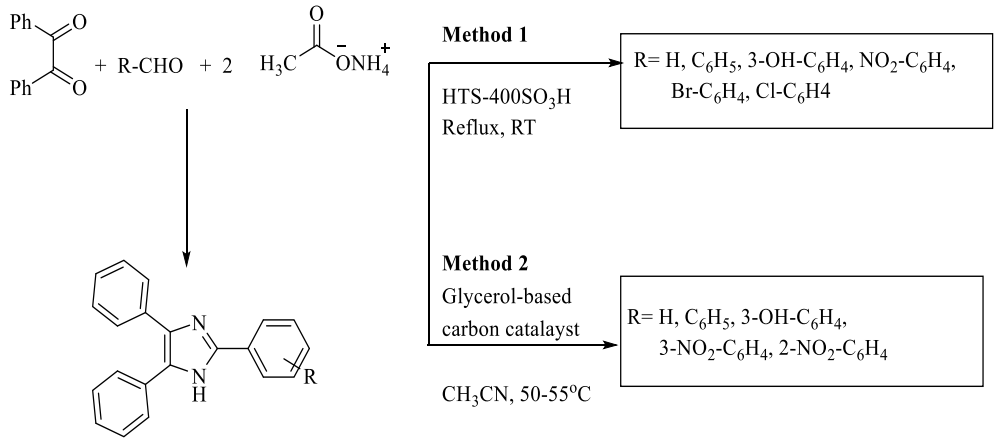
Synthesis of Five-Membered Heterocycles

The heterocyclic scaffolds are imperative moieties that have wide applications in medicinal and chemical industries. As a result, the synthesis of heterocyclic based compounds is the basic requirement for the pharmaceutically active molecules. Several methods have been developed to generate biologically active structures, but they include use of expensive catalysts, solvents, high temperature, and multistep reactions. To overcome these problems, the researchers are focusing on designing new green protocols. Amongst one such method is the use of carbon-based catalysts.



Scheme (5). Esterification reaction of levulinic acid with n-butanol.

Imidazoles are valuable heterocycles that exhibit anti-bacterial, anti-cancer, and inhibitor properties, *etc*. [106]. A simple method for the synthesis of 2,4,5-triphenylimidazole by one-pot, multi-component condensation reaction of benzil, benzaldehyde, and NH_4OAc was developed using HTS-400SO_3H [107]. The reported protocol has numerous benefits such as effortless procedure, excellent yields, facile work-up, short reaction times, and greener conditions (Scheme **6**, **Method: 1**). Various catalysts such as chitosan-SO_3H, AS-MNPs, and HTS-40--SO_3H were used by the authors in the synthesis of imidazole derivatives for the comparative study. However, HTS-400-SO_3H showed the best activity as compared to others. It was also revealed that the catalytic activity decreased slightly, preserving 92% and 76% at five and ten recycling due to the leaching of SO_3H during reusing.



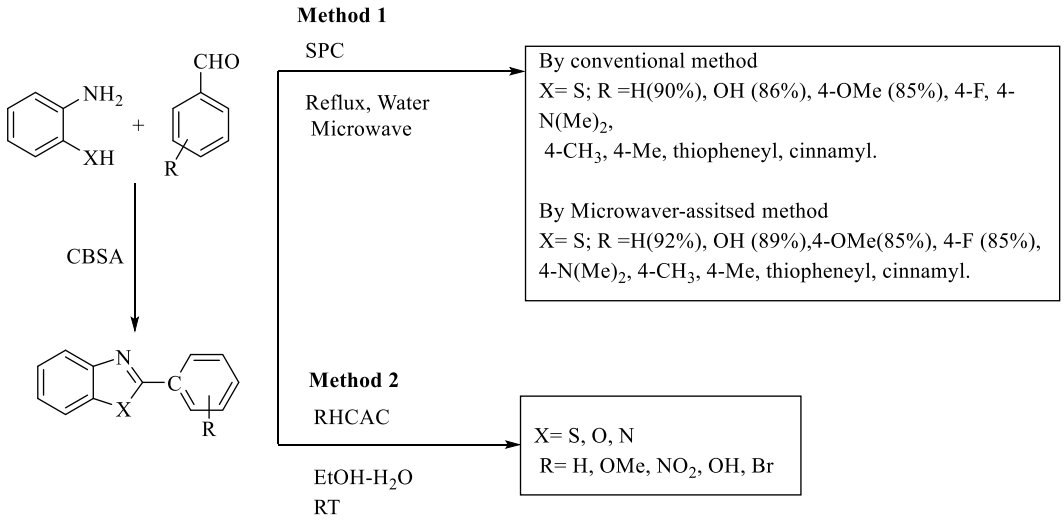
Scheme (6). Synthesis of 2,4,5-triphenyl-imidazole by using a different type of carbon-based solid acid catalyst.

Bioglycerol based carbon solid acid catalyst was used for the efficient and green synthesis of 2,4,5-trisubstituted imidazoles [108]. The synthetic protocol involved aromatic aldehydes, 1,2-diketones, and ammonium acetate/amine as reactants in acetonitrile to afford the targeted compounds, 2,4,5-trisubstituted imidazoles in (80-85%) yields (Scheme **6, Method 2**).

Sethiya *et al.* reviewed the synthesis of 2-arylbenzothiazole and it was observed that different carbon-based solid acid catalysts like succinimide sulphonic acid, graphene oxide, *etc.* were employed for its synthesis [109].

Sulphonated porous carbon was used as a catalyst for the synthesis of benzothiazole derivatives. The catalyst was prepared from pinewood powder using HCl and $ZnCl_2$. They envisioned two techniques for the protocol (Scheme **7,**

Method 1). The catalyst has good compatibility with diversely substituted aldehydes and it could be reused for 3 cycles [110].

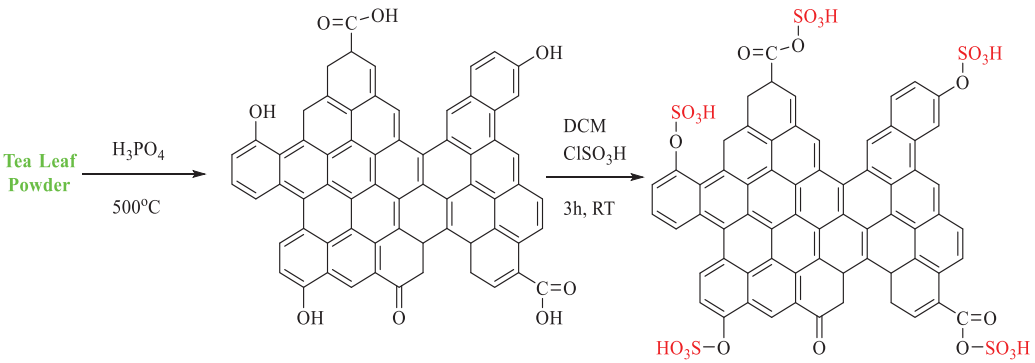


Scheme (7). Synthesis of benzothiazole by various methods and different catalysts.

a. Conventional heating (77-90% yield in 70-250 min).
b. Microwave heating (81-92% yield in 6-15 min).

Asatkar *et al.* [111] envisioned a rice husk derived carbon catalyst and investigated its efficiency in the synthesis of 2-substituted benzothiazole, benzoxazole, and benzimidazole at room temperature using H_2O: EtOH (2:1) as a solvent. (Scheme **7, Method 2**) The desired products were obtained in excellent yields (95-98%) in a short reaction time of 10 min. The catalyst has reusability up to eight runs.

Carbon-based solid acid catalyst was manufactured by using matured tea leaf (MTL) as a raw material for the preparation of activated carbon. MTL powder was soaked in H_3PO_4 to form (MTL: H_3PO_4). The catalyst was synthesized by the previously reported method [112] (Scheme **8a**). A green, direct, and easy method was developed for the synthesis of benzimidazole and benzothiazole derivatives by using synthesized sulfonic acid modified activated carbon MTLAC-SA [113]. The authors compared the catalytic efficiency of MTLAC-SA with diverse catalysts and have been appended below in Table **2**.

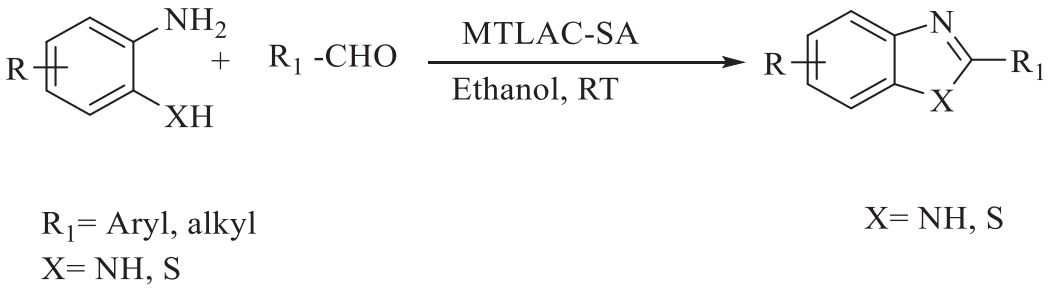


Scheme (8a). Representation of the process of synthesis of carbon-based solid acid.

Table 2. Synthesis of Benzothiazole and Benzimidazole derivatives in the presence of different catalysts.

Catalyst	Reaction Time	Temperature	Yield%
Montmorillonite K10	2400 min	RT	47.1
Nano-ZnO	80 min	Reflux	70
$MnFe_2O_4$	300 min	RT	82
Copper triflate	270 min	Reflux	88
MTLAC-SA	45 min	RT	94
K10-SA	90 min	RT	87

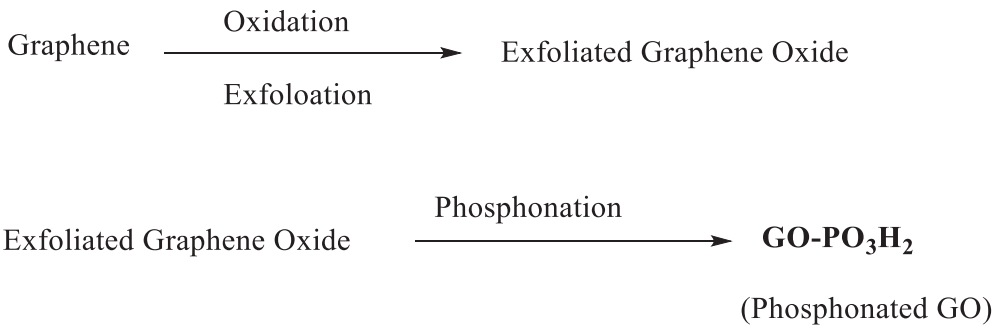
MTLAC-SA showed better catalytic activity as compared to K10-SA. The surface area as well as the acid capacity of MTLAC-SA, was higher than K10-SA. MTLAC-SA has a large number of active sites. The catalytic efficiency of both the catalysts was compared by employing them in the synthesis of benzimidazole and benzothiazole using 4-methylbenzaldehyde and ortho-phenylenediamine or orthoaminothiophenol. Consequently, benzimidazole and benzothiazole were synthesized by the green protocol using the MTLAC-SA in 75–94% yields. The recovered catalyst was used in seven consecutive runs without much loss of activity (Scheme **8b**).



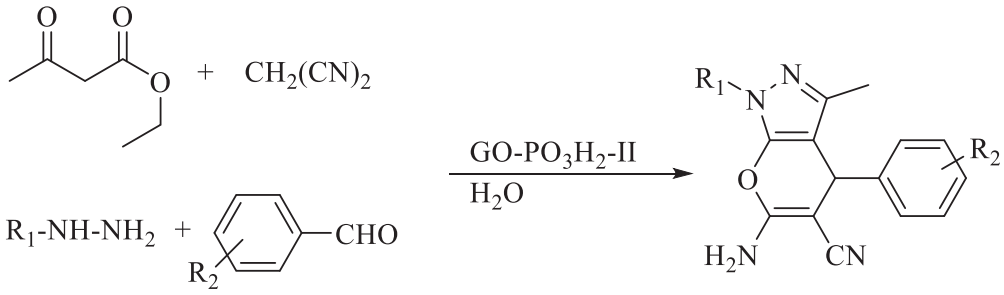
Scheme (8b). Synthesis of benzimidazole and benzothiazole derivatives.

A novel highly dispersible phosphoric acid functionalized carbon-based catalyst through GO and phosphoric acid was developed. After that, a mixture of polyphosphoric acid and phosphoric acid (1/5, wt%/wt %) was homogenized by sonication (Scheme **9a**). The pH was maintained at 5 value by adding 0.4 M NaOH and then it was washed with deionized water. The phosphonated GO nanocatalyst was used as a highly effective catalyst to synthesize dihydropyrano [2,3-c] pyrazole derivatives *via* several aromatic aldehydes, ethyl acetoacetate, malononitrile, and hydrazine hydrate by refluxing in water for 15 min. Further, the work also showed that the catalyst could be recycled up to 6 runs withhigh yield production (80-90%) (Scheme **9b**) [114].

Direct and green synthesis of diverse 1-*H* spiro[isoindoline-1,2-quinazoline]-3, 4-(3*H*)-diones was developed from the one-pot multi-component reaction of aliphatic or aromatic primary amines, isatin, and isatoic anhydride in the presence of acidic magnetic graphene oxide nanosheets, Fe_3O_4–GO–SO_3H catalyst (Scheme **10**) [115]. The effect of the amount of Fe_3O_4–GO–SO_3H loading and solvent on the reaction rate and yield of product was also studied. The catalytic role of Fe_3O_4–GO–SO_3H was assessed and it was shown that the carbonyl group of isatoic anhydride was activated by the acidic site of the catalyst and was then attacked by amine to form an intermediate. Later, isatin was attacked by the amine group of this intermediate. This was followed by water elimination and cyclization to afford the final product. Thus, the high surface area and acidic nature of the catalyst, due to the sulphonic and carboxylic groups, resulted in good yields (61-90%) in 2-10 hours. Moreover, the catalyst was separated easily using an external magnet and recycled up to four times without significant loss of activity. The use of Fe_3O_4–GO–SO_3H catalyst was found better to conventional catalysts such as $KAl(SO_4)_2 \cdot 12H_2O$ [116] and sulphamic acid [117] because traditional catalysts suffer from drawbacks such as production of lower yields, use of solvents, and non-recoverability of catalysts.

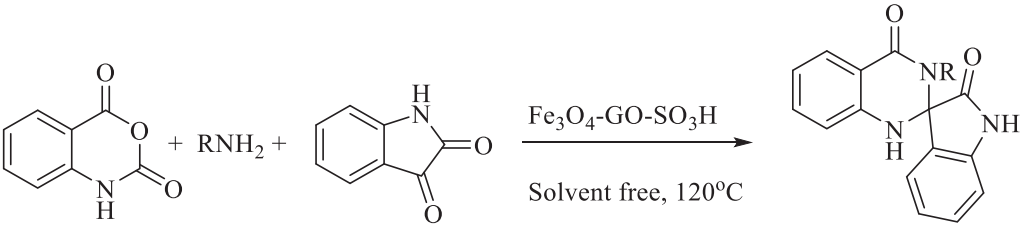


Scheme (9a). Formation of phosphonated GO.



R_1 = H, Ph R_2= *p*-H, *p*-F, *p*-Cl, *p*-OMe, *p*-NO_2, *m*-Br, *p*-OH-*m*-OMe

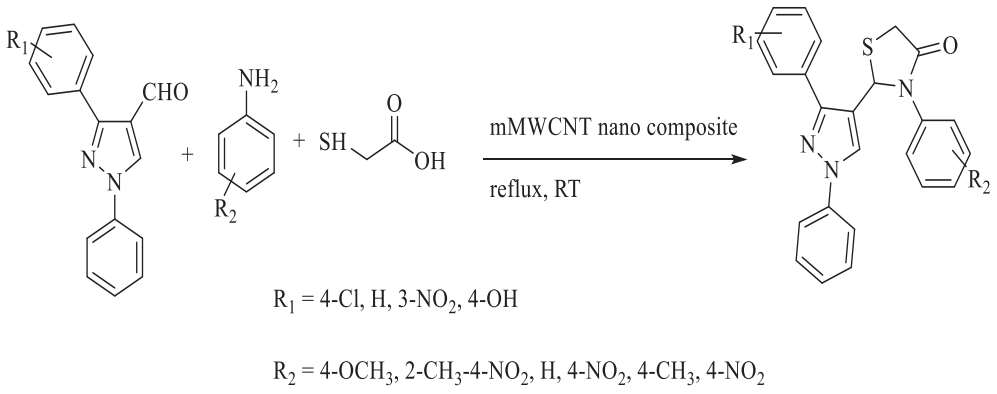
Scheme (9b). Synthesis of pyrano[2,3-c] pyrazoles using phosphonated GO as a nanocatalyst.



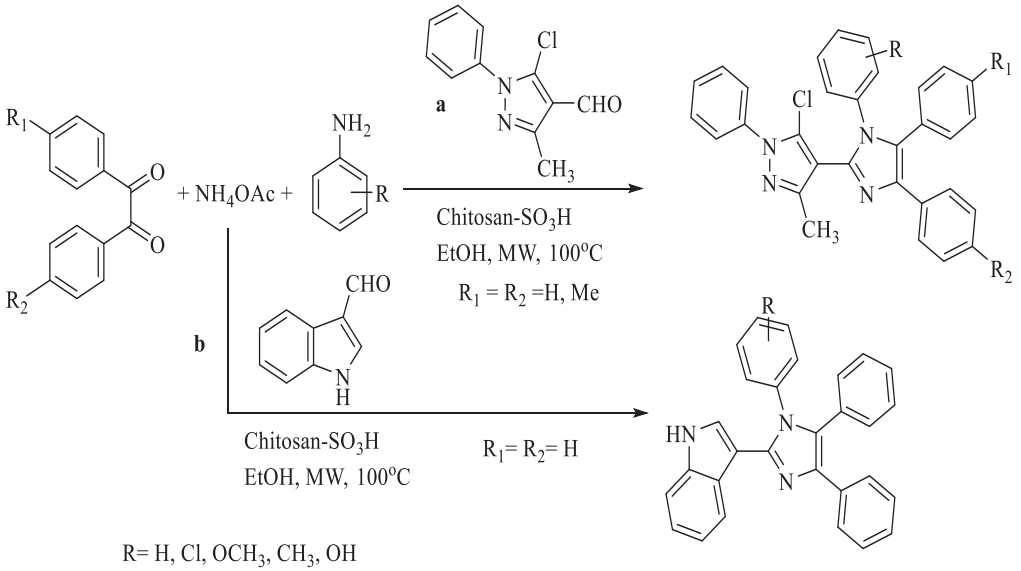
R = H, cyclohexyl, Ph, n-Bu, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 3-CH_3O-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 4-NO_2-C_6H_4

Scheme (10). Synthesis of 1'H-spiro[isoindoline-1,2'-quinazoline]-3,4'(3'H)-dione Derivatives in the Presence of Fe_3O_4–GO–SO_3H.

A novel and highly effective magnetic nanocomposite of multiwalled carbon nanotube (mMWCNT) was designed and used to synthesize pyrazolo-thiazolidine-4-one derivatives *via* one-pot multi-component reaction of pyrazolcarbaldehydes, various anilines, and thioglycolic acid in the presence of mMWCNT as a catalyst at room temperature. The study revealed that the reaction was simple, high yielding (82-92%), eco-friendly, inexpensive, and reusability of nanocatalyst up to 7 runs (Scheme **11**) [118].



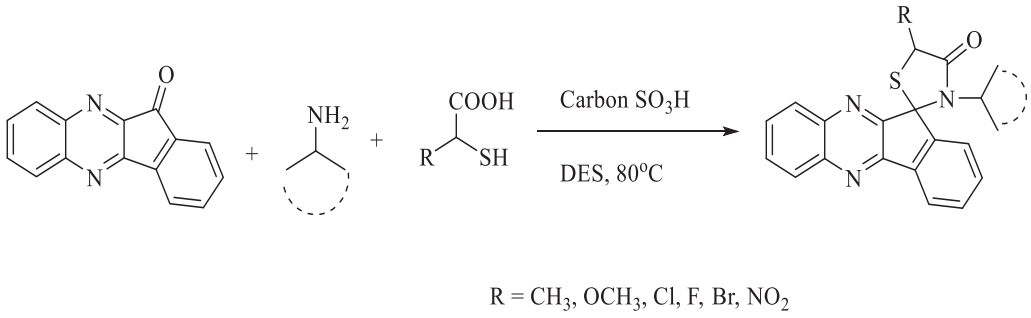
Scheme (11). Synthesis of 1,3-thiazolidine-4-ones in presence of mMWCNT nanocomposite.



Scheme (12). Synthesis of tetrasubstituted imidazole in the presence of Chitosan-SO_3H as carbon-based solid acid catalyst.

Imidazole derivatives were synthesized *via* one-pot four component reaction of 1-phenyl-3-methyl-5-pyrazole-3-carbaldehyde (**a**)/3-formylindole (**b**), benzil, various aldehydes, substituted amines, and ammonium acetate in the presence of chitosan-SO_3H under microwave irradiation (Scheme **12**) [119]. Different solvents have also been compared for the synthesis of imidazole. The reaction offered several advantages such as low catalyst loading, without using toxic transition metals, short reaction times, high yields (87-91%), easy separation by filtration, and reusability of the catalyst.

A one-pot, multicomponent, facile and eco-friendly route was used for the fabrication of hybrid spiro[indeno[1,2-b]quinoxaline-[11,2']-thiazolidine]-4'-ones using indeno [1,2-b] quinoxalinone, thiogylcolic acid, and different types of amines, carbon-SO_3H as a solid acid catalyst, and urea-choline chloride as a green deep eutectic solvent. This methodology generated a thiazolidine ring fused to indeno[1,2-b]quinoxaline through spiro carbon in good to excellent yields (88-92%) (Scheme **13**) [120].



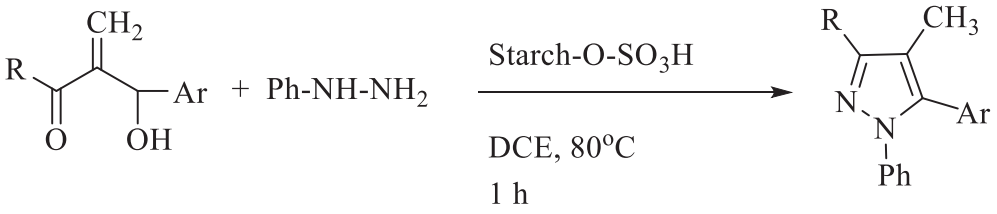
Scheme (13). Synthesis of spiro[indeno[1,2-b]quinoxaline-[11,2']-thiazolidine]-4'-ones using carbon SO_3H.

An efficient and eco-friendly method was reported for the synthesis of pyrazole derivatives using silica-sulfuric acid as a catalyst [121]. The reaction was regioselective, and the desired compounds were obtained by the condensation of Baylis—Hillman adducts (I) with phenylhydrazine (Scheme **14**).

Six Membered Heterocycles

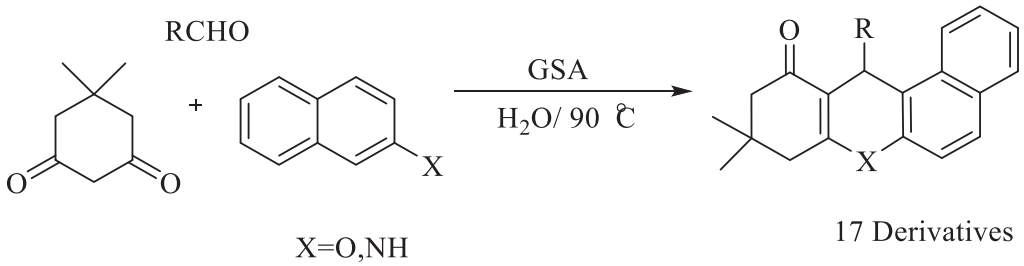
A novel, greener, and highly efficient glucose-containing Brønsted acid catalyst was synthesized and employed for the synthesis of tetrahydrobenzo[a]xanthenes and tetrahydrobenzo[a]acridine derivatives [122]. Condensation of dimedone, different aldehydes, and 2-naphthol/β-naphthylamine in water media and glucose sulfonic acid (GSA) catalyst was performed to acquire xanthene and acridine derivatives in high yields. A simple and one-pot method, low-priced catalyst, high

acidity, and activity of the catalyst and avoid by-product generation are the plus points of this process (Scheme **15**).



Ar - C_6H_5, 3-NO_2-C_6H_4, 2-NO_2-C_6H_4, 4-ClC_6H_4
R= Me, Et

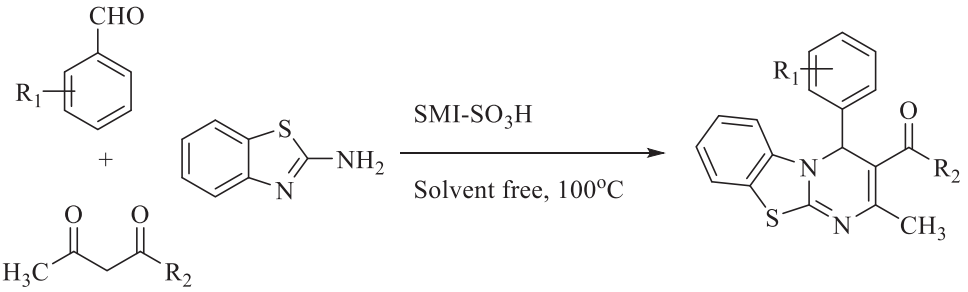
Scheme (14). Synthesis of pyrazole derivatives using starch-sulfuric acid.



Scheme (15). The synthesis and catalysis of GSA in the preparation of tetrahydrobenzo[a] xanthens (acridines).

Synthesis of pyrimidobenzothiazole derivatives was developed *via* ethyl acetoacetate, benzaldehyde, and 2-aminobenzothiazole using SMI-SO_3H as a highly efficient catalyst by stirring at 100°C in an oil bath (Scheme **16**). It is worth mentioning that no product was formed in the absence of a catalyst. Further, the active and green catalyst exhibited excellent recyclability [123].

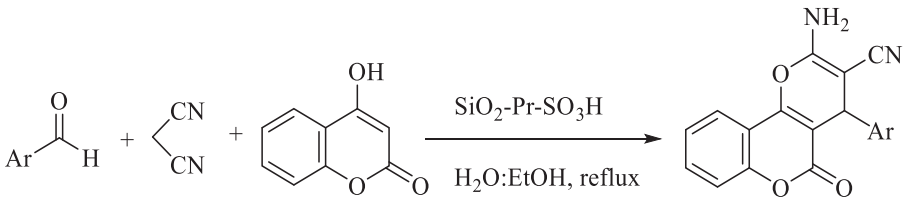
A fine powdered carbon-based solid acid (SiO_2-Pr-SO_3H)_ was synthesized from 3-mercaptopropylsilica, acetone and H_2O_2 [124]. The synthesized catalyst was used to prepare 3,4-dihydropyrano[c]chromene derivatives *via* aryl aldehyde, malononitrile, and 4-hydroxycoumarin in H_2O and ethanol at reflux. Additionally, the catalyst could be effortlessly recovered by filtration and reused several times without any treatment. In the investigation, different solvents were screened such as water, ethanol, and H_2O: EtOH. The best results were observed with H_2O: EtOH (100% yield of product) (Scheme **17**).



R_1- H, 4-Cl, $3NO_2$, 4-OH, 4-OMe, $4\text{-}NO_2$

R_2 - OMe, OEt

Scheme (16). Synthesis of benzothiazole derivatives by using SMI-SO_3H as a catalyst.

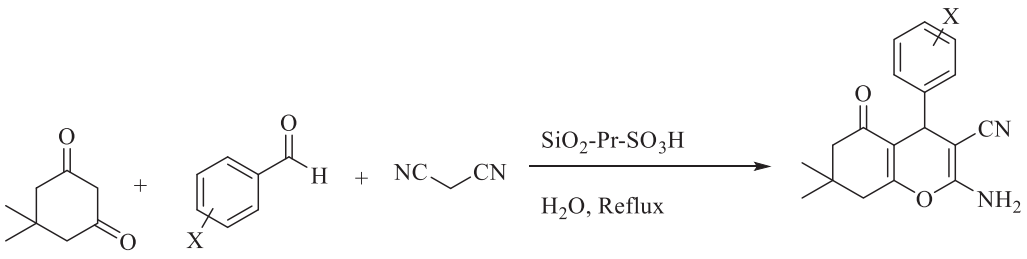


Ar= Ph, $4\text{-}NO_2C_6H_4$, $4ClC_6H_4$, $2,6\text{-}Cl_2C_6H_4$, $4\text{-}FC_6H_4$, $4\text{-}OCH_3C_6H_4$, $2,4\text{-}(OCH_3)_2C_6H_4$, $4\text{-}OHC_6H_4$

Scheme (17). Preparation of 3,4-dihydropyrano [c] chromene derivatives.

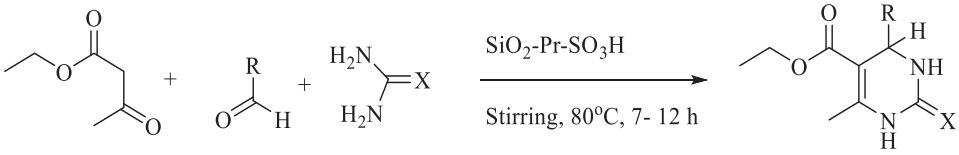
Furthermore, the synthesis of tetrahydrobenzo[b]pyran derivatives was performed from one-pot, multicomponent condensation reaction of dimedone, aromatic aldehydes, malononitrile in the presence of SiO_2-Pr-SO_3H as a catalyst and water/ethanol [4:1] as a solvent at reflux conditions. In the investigation, different solvents were scrutinized such as water, ethanol and, ethanol:water. The best results were observed with H_2O/EtOH (100% yield of product). Very short reaction time and high yield of products are the key advantages of reaction. The catalyst was recyclable up to several runs without any loss in catalytic activity (Scheme **18**) [125].

An efficient synthesis of 3,4-dihydropyrimidinone derivatives through a one-pot, three-component reaction of various aldehydes, ethyl acetoacetate and urea/ thiourea in the presence of SiO_2-Pr-SO_3H at 80°C in an oil-bath for an appropriate time. 0.2g, 2.4 mol% of the catalyst was selected as an optimum catalyst loading for the reaction. Direct, easy workup, eco-benign, and high yields (62-95%) are the advantages of the catalyst (Scheme **19**) [126].



X= Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-OHC_6H_4, 2,4-$Cl2C_6H_4$

Scheme (18). Synthesis of tetrahydrobenzo[b] pyran derivatives using SiO_2-Pr-SO_3H.



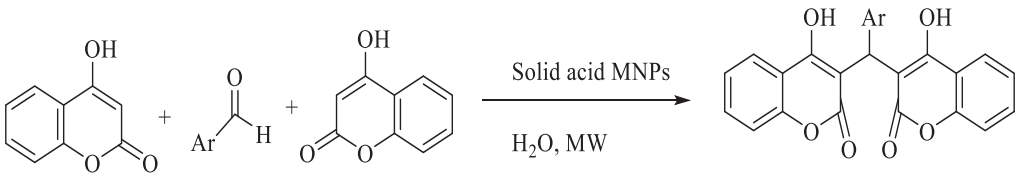
X= O, S

R= C_6H_5(90%), 4-$MeOC_6H_4$(92%), 2-furfurl (89%). 4-ClC_6H_4(93%), Ph-CH=CH (87%), 4-HO-3-$MeOC_6H_3$ (90%)

Scheme (19). Synthesis of 3,4-dihydropyrimidinones derivatives by using SiO-Pr-SO_3H.

The synthesis of bis-coumarins was performed *via* a one-pot two-component reaction of aromatic aldehydes and 4-hydroxycoumarin by using Fe_3O_4@ sulfosalicylic acid as a catalyst under microwave irradiation at 180W (Scheme **20**) [127]. The optimization of an amount of catalyst was studied and it was found that as the amount of catalyst was increased from 0.03 to 0.05 g with microwave power and time, the yield increased from 89 to 96%. No reaction was observed without the catalyst. The Fe_3O_4@sulfosalicylic acid catalyst could be effortlessly recovered and reused up to several times without any treatment. The study also revealed that few of the bis-coumarin derivatives were reported earlier from different catalysts [128]. The catalyst offered few advantages such as short reaction time, low catalyst loading, and reduction of the use of toxic transition metals, high yields (89-96%), reusability, and easy separation by filtration of this catalyst.

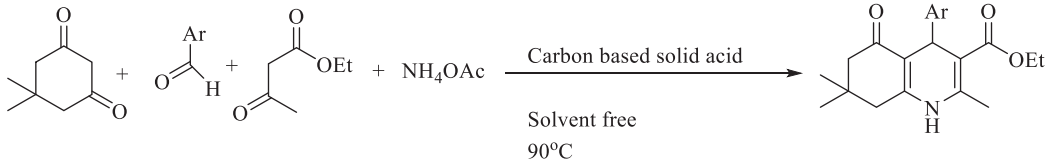
Biscoumarins were synthesized from various catalysts and methods [129]. Various types of carbon-based solid acid catalysts were used in the synthesis of biscoumarins, illustrated below in Table **3**.



Ar = Ph, 4-$NO_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4,5-$CH_3OC_6H_3$

Scheme (20). Synthesis of bis-coumarin using carbon-based solid acid catalyst.

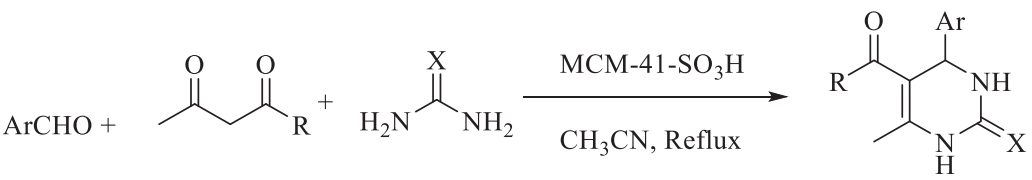
An efficient, simple, and fast synthesis of polyhydroquinoline derivatives was developed through one-pot four-component Hantzsch condensation reaction of dimedone, aryl aldehyde, ethyl acetoacetate, and ammonium acetate using earlier reported CBSA catalyst [137]. The reaction was done *via* heating in the oil bath at 90°C for 18-35 min. No reaction was observed without catalyst. Different amounts of the catalyst (0.01 g, 0.015 g, 0.02, 0.03, and 0.05 g) were checked and 0.02 g of the catalyst was selected as the optimum catalyst loading for the reaction. It was also noted that the catalyst was recovered and reused up to 3 times without any loss in catalytic activity. The use of CBSA catalyst offered numerous advantages such as high yield, simple, fast, reusability, and recyclability of catalyst (Scheme **21**).



Ar = 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 3-HOC_6H_4, 4-HOC_6H_4,C_6H_5

Scheme (21). Carbon-based solid acid catalyzed synthesis of polyhyroquinoline derivatives.

Efficient and mild preparation of MCM041-ER-SO_3H was reported [138] (Scheme **22**). Additionally, 3,4-dihydropyrimidinones were synthesized *via* condensation reaction of *p*-anisaldehyde, ethyl acetoacetate, and urea using highly effective catalyst MCM041-ER-SO_3H at reflux conditions for 6h with acetonitrile as a solvent system and produced 82-94% yields. This reusable synthesized catalyst added several advantages to this protocol such as facile procedure, easy work-up, low energy requirement, low catalyst loading, and good product yield.

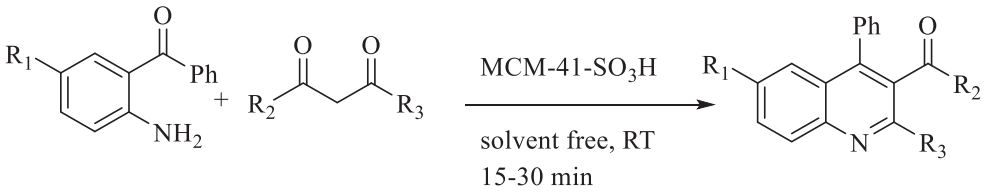


Ar = C_6H_5, 4-MeC_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 4-Cl-C_6H_4
R= OEt, CH_3, OMe
X= O, S

Scheme (22). 3,4-dihydropyrimidinones was synthesized in the presence of MCM-41-SO_3H.

Synthesis of highly effective carbon-based solid acid *via* sulfonation of MCM-41 was done for tert-butylation of hydroquinone in the presence of microwave irradiation. Reusability of catalyst up to several times was the advantage of the catalyst [139].

Substituted quinoline derivatives were synthesized *via* a one-pot two-component condensation reaction of 2-aminoaryl ketones and active methylene carbonyl compounds in the presence of MCM-41-SO_3H as a catalyst under solvent-free conditions at room temperature. Furthermore, it was found that the effect of catalyst was more pronounced in the absence of polar-protic solvent. The optimum catalyst loading was evaluated and found to be 15mg producing 93% product yield. The procedure offered several advantages such as low catalyst loading, short reaction time, high yield (93%), and reusability of the catalyst up to 6 runs without any loss in catalytic activity (Scheme **23**) [140].

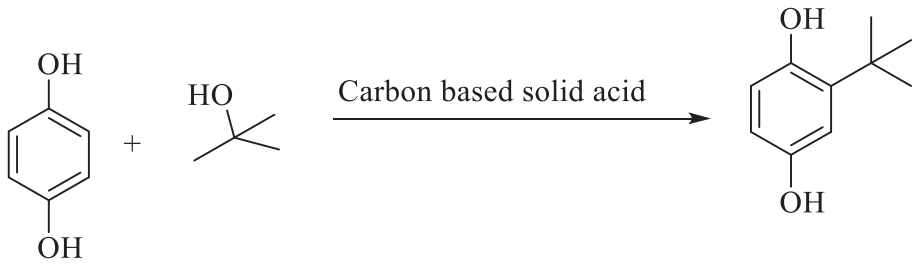


R_1= H, Cl
R_2, R_3 = alkyl and aryl

Scheme (23). Synthesis of substituted quinolines derivatives in the presence of MCM-41-SO_3H.

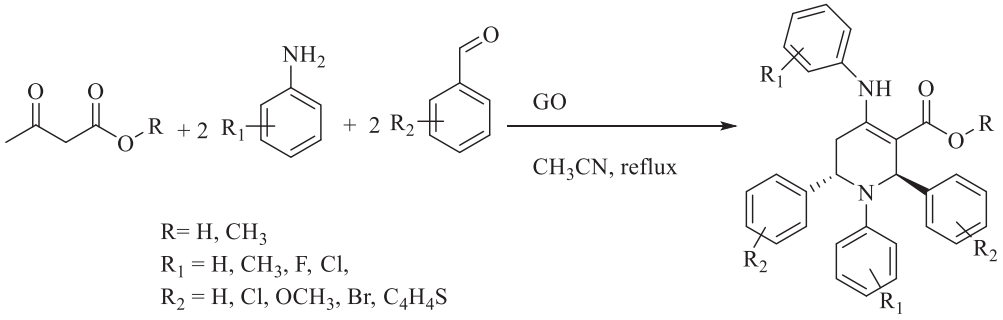
2-tert-butylhydroquinone (2-TBHQ) was widely used as an anti-oxidant. It was prepared by the alkylation of hydroquinone with tert-butanol. Sulfonated carbon nanotube was used as a solid acid catalyst in the alkylation of hydroquinone with

tert-butanol for 2-tert-butylhydroquinone formation (Scheme **24**) [141]. Additionally, the conversion ratio was 73.3% and 53.7% of 2-TBHQ yield.



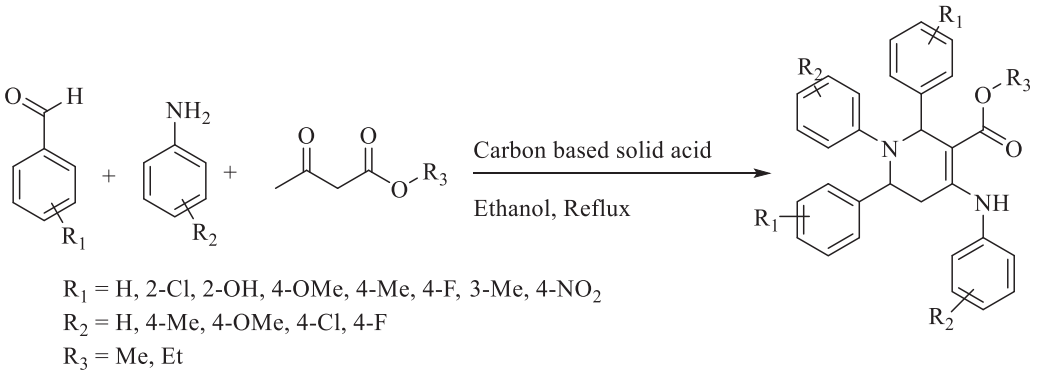
Scheme (24). Catalytic alkylation of hydroquinone with tert-butanol.

Easy and fast synthesis of tetrahydropyridine derivatives was designed *via* condensation reaction of methylacetoacetate, 4-chlorobenzaldehyde, and aniline using recyclable graphene oxide as a highly effective catalyst andCH_3CN as a solvent system (Scheme **25**) [142]. Additionally, the GO catalyst could be effortlessly recovered by filtration and reused up to five times without any treatment. The other advantages of the catalyst include inexpensive nature and stability.



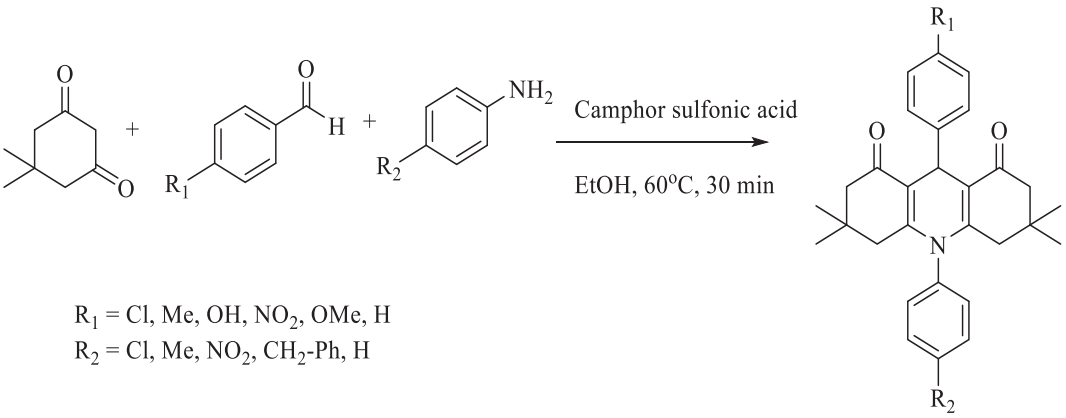
Scheme (25). Synthesis of substituted tetrahydropyridines using graphene oxide.

In context to this, an efficient protocol for the synthesis of piperidine derivatives using camphor sulphonic acid as a catalyst was developed. It was a multi-component synthesis of two equivalents of substituted aromatic aldehydes, two equivalents of substituted anilines, and β-keto esters in the presence of ethanol as a solvent using 10 mol% of camphor sulfonic acid at reflux. The important benefits of the present protocol include shorter reaction time, wide substrate scope, easy workup procedure, excellent yield (82-93%), and high atom economy [143] (Scheme **26**).



Scheme (26). Synthesis of substituted piperidines by using carbon- based solid acid catalyst.

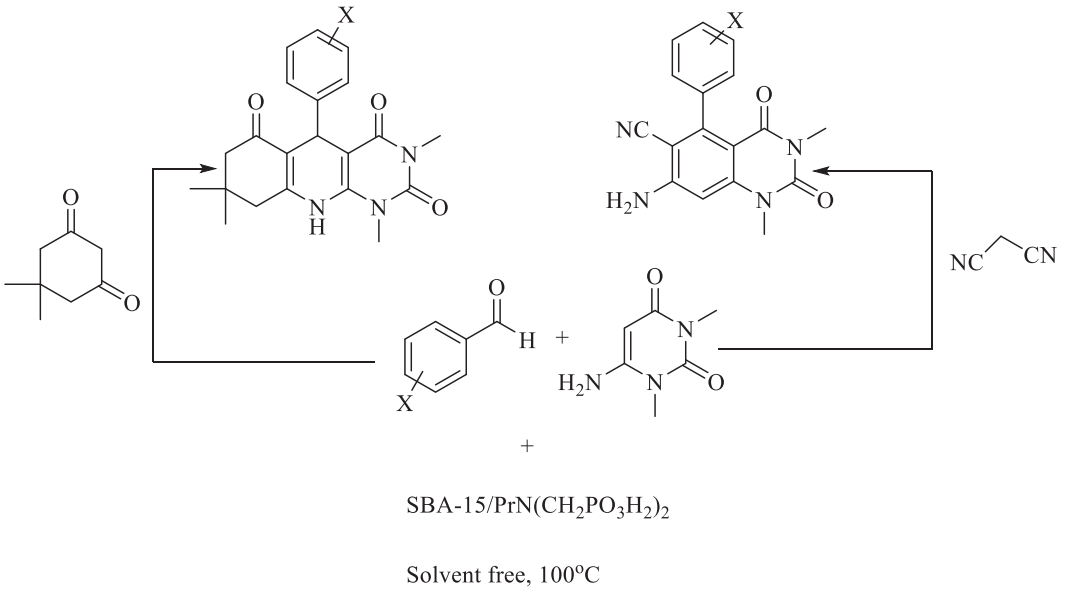
Synthesis of acridine derivatives was performed using camphor sulfonic acid as a catalyst in ethanol at 60°C from one-pot 3 component reaction of cyclo-hexanedione, various aldehydes, and aniline. An investigation of suitable solvents revealed that ethanol (product yield 90%) was the best solvent amongst DMF (yield 75%), methanol (yield 80%), and toluene (yield 60%). The optimum amount of catalyst for this reaction was also evaluated. The best results were observed with 10 mol% of the catalyst that afforded 90-94% yield [144] (Scheme **27)**.



Scheme (27). Synthesis of acridine derivatives by using camphor sulfonic acid.

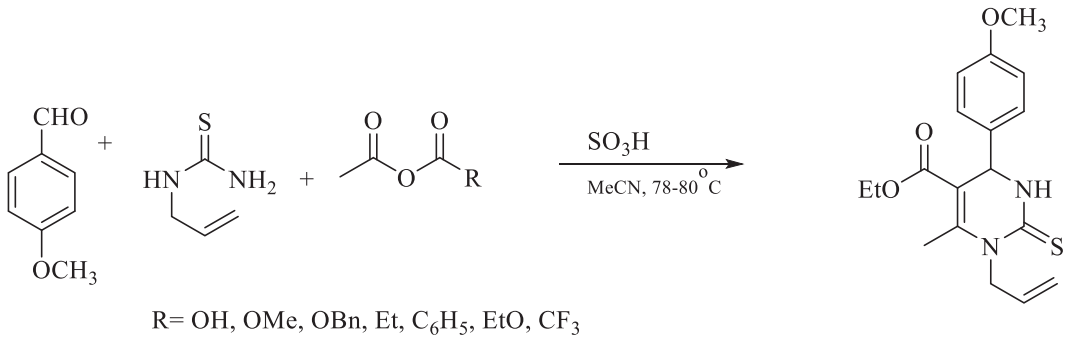
Pyrido[2,3-d]pyrimidine and pyrimido [4,5b]quinoline derivatives were synthesized using various aldehydes, 6-amino-1,3-dimethylpyrimidine-2,4(1*H*, 3*H*)-dione, malononitrile or dimedone in the presence of SBA-15/PrN $(CH_2PO_3H_2)_2$ under solvent-free conditions [145]. Various solvents and catalysts

were screened and the best results were observed with solvent free conditions. Further, the work also presents that the catalyst could be recycled up to five runs. The easy procedure with high yields, short reaction time, and eco-benign are the main benefits of the catalyst (Scheme **28**).



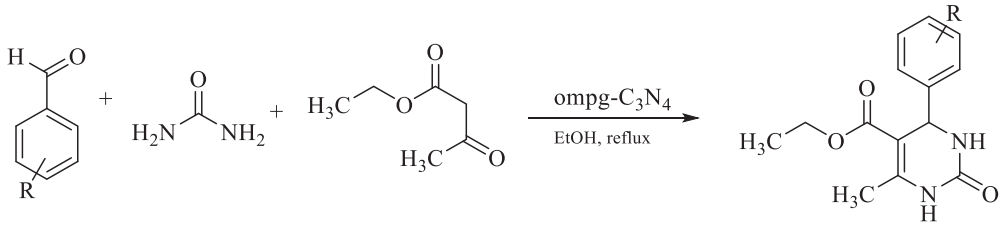
Scheme (28). Synthesis of pyrido[2,3-d]pyrimidines and pyrimido[4,5-b] quinolone.

3,4-dihydropyrimidin-2-(1H)-one derivatives were synthesized by the reaction of urea, aldehydes, and 1,3 dicarbonyl compounds. The prominent characteristics of the present protocol are easy work-up, recyclability of the bioglycerol-based carbon catalyst, and good yields. It also offers a simple, inexpensive, recoverable, and reusable catalyst up to four runs [146] (Scheme **29**).



Scheme (29). The Biginelli reaction catalyzed by SO_3H to prepare 3,4-dihydropyrimidin-2-(1H)- ones.

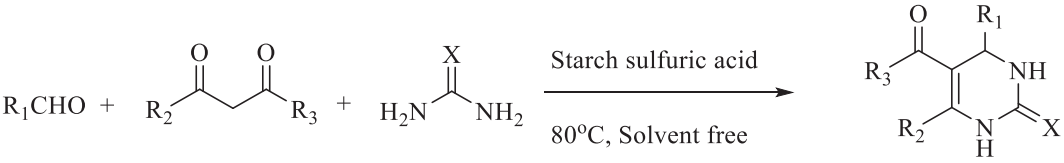
The synthesis and use of ordered mesoporous graphitic carbon nitride (ompg-C_3N_4) as a catalyst was developed for the preparation of 3,4-dihydroprimidin-2-(1*H*)-one derivatives *via* various aldehydes, ethyl acetoacetate, and urea in the presence of ompg-C_3N_4 under reflux conditions (Scheme **30**). Moreover, the catalyst was easy to prepare, inexpensive, and recyclable. Different amounts of catalyst were tested to select the optimum amount of catalyst. The recyclability of the catalyst was also investigated, and it was found that the catalyst could be reused until four cycles [147].



R= H, Cl, OCH_3' CH_3' F, OH, NO_2' CN, OH, MeO_2C

Scheme (30). The Biginelli reaction catalyzed by ompg-C_3N_4/SO_3H to prepare 3,4-dihydropyrimidin-2-(1H)-ones.

One-pot MCR strategy for the synthesis of 3,4-dihydropyrimidinone derivatives using starch sulfuric acid was designed using aromatic aldehydes, β-keto esters, and thiourea/ urea under solvent-free conditions [148]. The desired compounds were obtained in 77-92% yields in a short reaction time of 35-70 min. The catalyst can be easily recovered and reused up to 3 times (Scheme **31**).

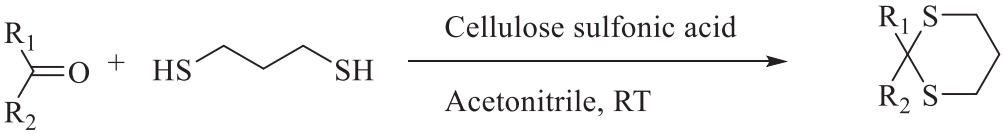


X= O, S
R_1= C_6H_5, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, PhCH=CH, 2-Furyl,
R_2= CH_3
R_3 = OC_2H_5, CH_3

Scheme (31). Synthesis of 3,4-dihydropyrimidinone derivatives by using starch sulfuric acid.

Cellulose sulphonic acid was used in the protection of carbonyl compounds. It also catalyzed the carbon–sulfur bond formation thereby facilitating dithioacetal formation of carbonyl compounds. It was revealed that carbon sulphonic acid is an efficient, eco-friendly, and recoverable catalyst for the synthesis of 1,1-

dithioacetals or 1,1-dithioketals. Several aldehydes or ketones easily underwent thioacetalization with any of the 1,2-dithiol, or 1, 3-dithiol. It was observed that 1,3-dithiol protection was superior to 1,2-dithiol in correspondence to yields and reaction times (Scheme **32**) [149].

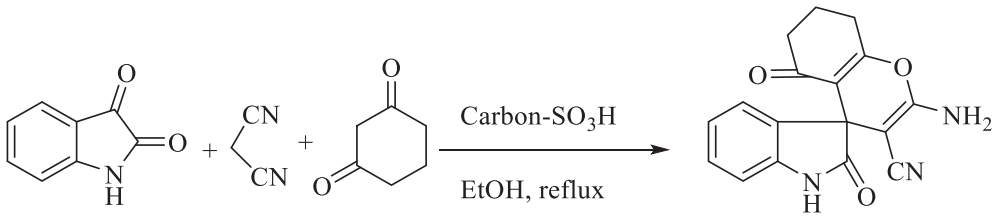


R_1=H

R_2= C_6H_5, Br-C_6H_4, Me-C_6H_4, OMe-C_6H_4, Cl-C_6H_4, NO_2-C_6H_4

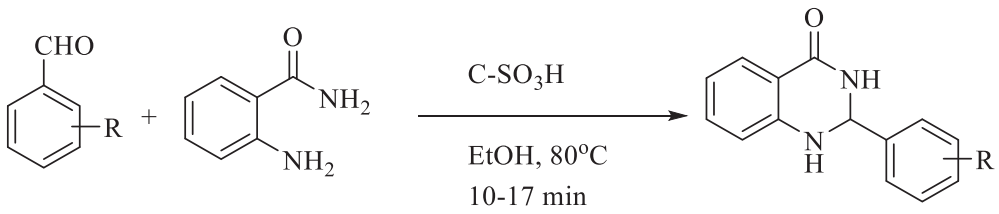
Scheme (32). Synthesis of 1, 1-dithioacetals by using cellulose sulfuric acid.

A facile, productive, and glycerol-based carbon catalyzed synthetic pathway for the synthesis of spiro [4H-pyran-3,3'-oxindoles] using malononitrile, 1,3-dica--bonyls, and isatin as the precursors was developed [150]. The catalyst was reusable up to 5 cycles with a slight decrease in their activity. The excellent yields (82-95%), wide substrate scope, and cost-efficiency are the advantages of the reported method (Scheme **33**).



Scheme (33). Synthesis of spiropyrans using carbon-SO_3H.

A green, compatible synthetic protocol for the synthesis of 2,3-dihydroquinazoli--4(1H)-ones was developed by the condensation reaction of 2-aminobenzamide with different substituted aromatic aldehydes or cyclic ketones under mild reaction conditions (stirring in ethanol at 80°C) in the presence of carbon-SO_3H as a catalyst, manufactured from glycerol. This pathway gave an imperative way for the access of products with excellent yields (90-97%) with a wide substrate scope. The recovered catalyst was used for four subsequent runs with substantial activity [151] (Scheme **34**).



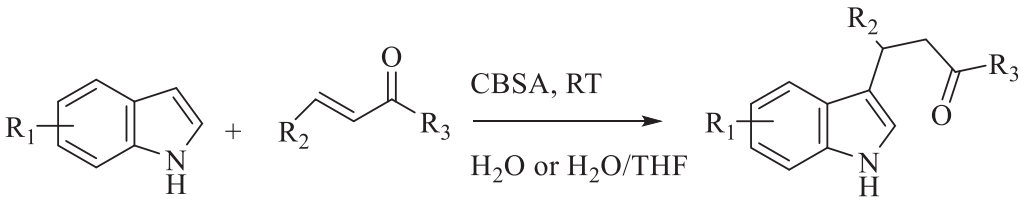
R= Br, Cl, NO_2, OH, CN, F, C_6H_5

Scheme (34). Synthesis of 2,3-dihydroquinazolin-4(1H)-ones using C–SO_3H as a catalyst.

Miscellaneous usage of CBSA in Organic Reactions

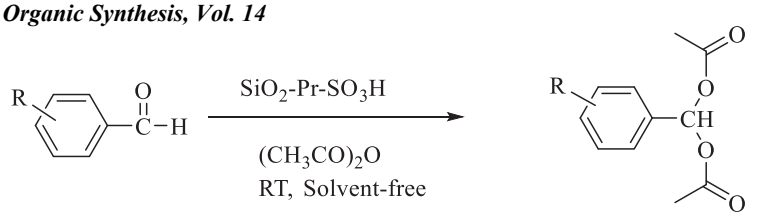
Carbon-based solid acid is used as a highly effective catalyst in Friedel-Craft reaction using indole and α,β-unsaturated carbonyl compounds in the presence of water as a solvent (Scheme **35**). The authors also reported the reaction of indole derivatives with methyl vinyl ketones at room temperature in the presence of 5 mol% of catalyst, giving good yields (85-96%) of isolated products without any side reaction [152].

An efficient and mild protocol used for the conversion of aldehydes to 1,1-diacetates *via* acetalization of aldehydes and acetic anhydride using SiO_2-Pr-SO_3H as a catalyst was reported [153]. The authors did a comparative study of SiO_2-P--SO_3H with other reported catalysts. However, it showed the best activity compared to others. Thus, the SiO_2-Pr-SO_3H catalyst exhibited remarkable properties such as ease of preparation, reusability, low cost, and high efficiency, yielding large quantities of products in a short time (Scheme **36**).



R_1 = H, Br ; R_2 = H, C_6H_5 ; R_3 = H, CH_3, C_6H_5

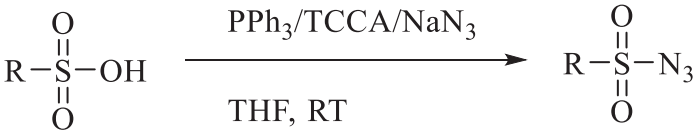
Scheme (35). Michael-type Friedel-Crafts of indoles with α, β-unsaturated carbonyl compounds.



Benzaldehyde, 2-OH-benzaldehyde, Cinnamaldehyde, 3,4-$(OCH_3)_3$-benzealdehyde
4-Cl-benzealdehyde, 4-NO_2-benzaldehyde, 2-CH_3-benzaldehyde,

Scheme (36). Acetalization of the aldehyde with acetic anhydride using SiO_2-Pr-SO_3H.

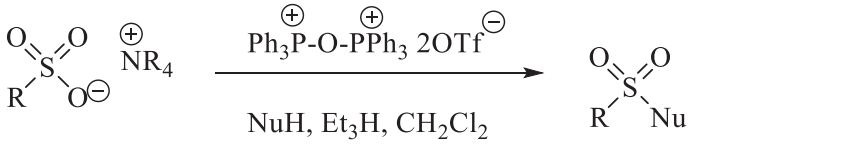
The synthesis of alkanesulfonyl, arenesulfonyl azide, and heteroarenesulfonyl azide derivatives was performed in the presence of PPh_3/TCCA under mild reaction conditions. High yield, short reaction time, direct formation, and use of inexpensive reagents are the other advantages of reaction [154]. Trichloroisocyanuric acid (TCCA), a better reactive *N*-halo reagent with triphenylphosphine (PPh_3) acted as a highly efficient catalyst for the formation of sulfonyl azides from sulfonic acid in excellent yields (Scheme **37**) [155].



R= Alkyl, Aryl

Scheme (37). Direct conversion of sulfonic acid to sulfonyl azides with PPh_3/TCCA/NaN_3 mixed reagent.

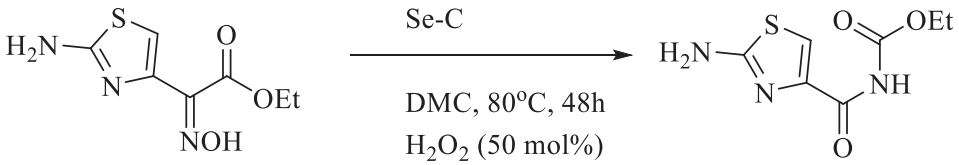
A simple synthesis of sulfonamides and activated sulfonate esters from the sulfonic acid in the presence of an activating agent, triphenylphosphine was described [156] (Scheme **38**). High yield production and good functional group tolerance were the advantages of the reaction.



R= C_6H_5, Me, Et_3H, NO_2-C_6H_5, MeO-C_6H_5 Nu= R-NH_2, PFPOH

Scheme (38). Sulfonate esters and Sulfonamindes from sulfonic acids.

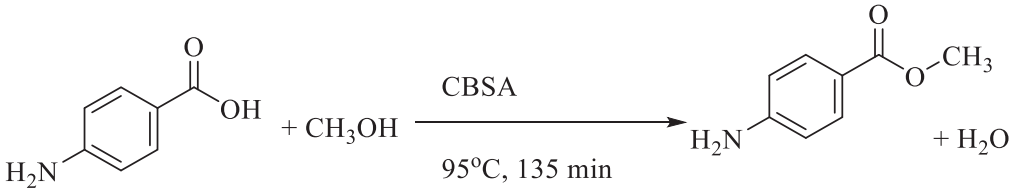
The application of selenium-doped carbon as a highly efficient solid acid catalyst in Beckmann rearrangement reaction was explained *via* a one-pot multi-component reaction of ethyl 2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetate, H_2O_2, and dimethyl carbonate for 48 hours at 80°C to form ethyl (2-aminothiazo--4-carbonyl)carbamate (Scheme **39**) [157].



Scheme (39). Preparation of ethyl (2-aminothiazole-4-carbonyl)carbamate by using selenium-doped carbon - based solid acid catalyst.

An eco-benign Fe_3O_4@cellulose-OSO_3H catalyzed protocol was developed for the synthesis of α-iminonitrile derivatives using air as an oxidant. It was an MCR strategy that involved condensation of diverse aldehydes, primary amines and trimethylsilylcyanide as reactants. The reaction occurred in mild reaction conditions and the catalyst was reused up to 10 cycles [158].

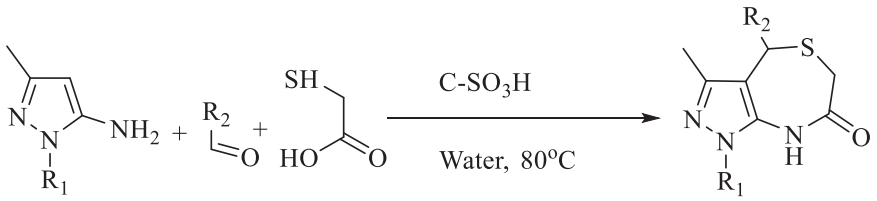
A greener and highly active carbon-based solid acid catalyst was synthesized from the modification of F-type fly ash in the presence of ortho-phosphoric acid. The synthesized catalyst was used for Fischer esterification reaction of 4-aminobenzoic acid and methanol to produce 4-aminobenzoate with excellent catalytic capability [159]. The study revealed that the recyclability of carbon-based solid acid catalyst retained the same catalytic capability till 5th cycles without any loss (Scheme **40**).



Scheme (40). Synthesis of 4-aminobenzoate by using carbon based solid acid catalyst.

A one-pot MCR strategy was developed for the synthesis of 4,8-dihydro-1*H*-pyrazolo[3,4-e] [1, 4]thiazepin-7(6*H*)-one derivative using carbon based solid acid catalyst (Scheme **41**). The catalyst was synthesized from polyvinyl alcohol and hydroxyethylsulfuric acid. The substituted aldehydes, substituent pyrazoles, and thioglycolic acid were used to afford a large number of derivatives with high to excellent yields (75-90%). The low catalyst loading (10 mg), water as a green

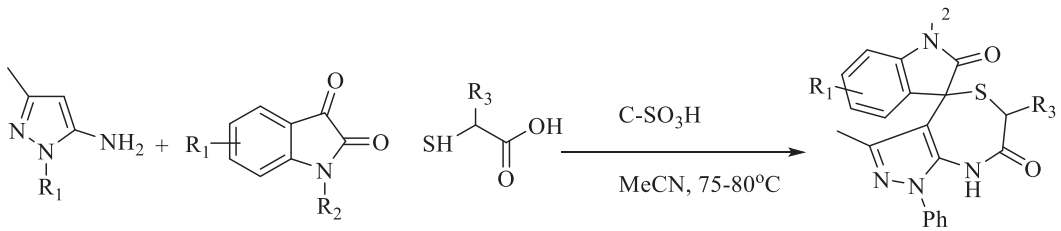
solvent, metal-free, mild reaction conditions are the advantages of the method [160].



R_1= C_6H_5, H
R_2= C_6H_5, 4-FC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 3-$NO_3C_6H_4$, 1-Napthal, i-Butyl, n-Octyl

Scheme (41). Synthesis of 4,8-dihydro-1H-pyrazolo[3,4-e] [1, 4]thiazepin-7(6H)-one derivatives by using carbon-based solid acid.

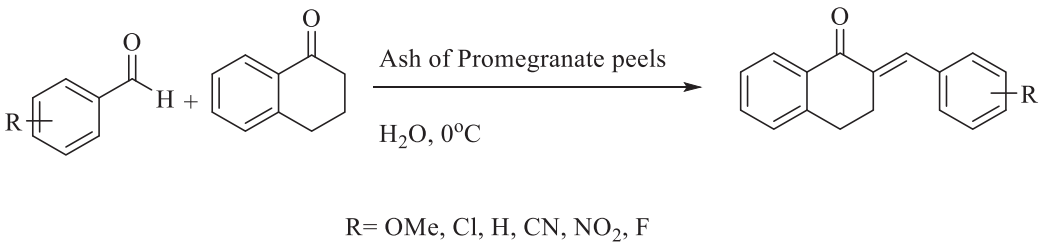
A novel, facile, and efficient methodology was developed for the synthesis of spiro[indoline-3,4'-pyrazolo[3,4-e] [1, 4]thiazepine] diones using carbon-sulfonic acid, synthesized from glycerol. The catalyst was recyclable and reused upto 4 runs and afforded high yields (72-91%) of targeted compounds (Scheme **42**) [161].



R_1= H, CH_3, OCH_3, Br, Cl
R_2= H, CH_2, Ph, Benzyl, Allyl
R_3= H, CH_3

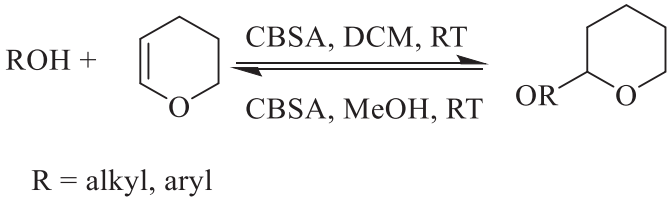
Scheme (42). Synthesis of spiro [indoline-3,40-pyrazolo[3,4-e] [1, 4] thiazepine] dione derivatives by using carbon-based solid acid.

An efficient, novel catalyst based on pomegranate peels was developed for the synthesis of 2-arylidene-1-tetralones using aldehydes, cycloalkanes and tetralone as precursors. The designed methodology has several benefits like five times reusability of catalyst, high to excellent yield (79-98%), short reaction time (25-35 min), eco-friendly (Scheme **43**) [162].



Scheme (43). Synthesis of 2-arylidene-1-tetralone derivatives by using Ash of pomegranate peels.

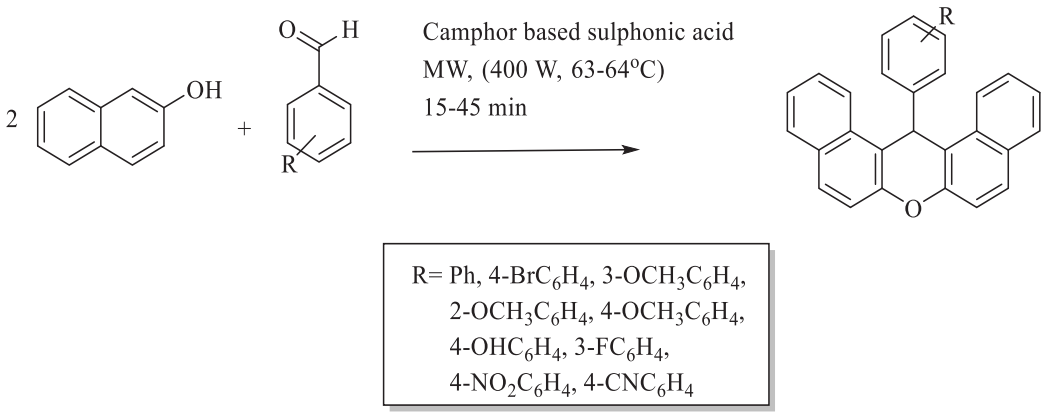
Glycerol pitch based carbon sulphonic acid catalyst was also used to catalyze the protection of tetrahydropyranyl and de-protection of phenol and alcohols [163]. The catalyst is the good replacement of H_2SO_4 and has good conversion efficiency against a wide range of alcohols irrespective of nature and hindrance present around it (Scheme **44**).



Scheme (44). Carbon-based solid acid-catalyzed tetrahydropyranylation and depyranylation of alcohols and phenols.

Dried rice straw wastes were used to synthesize carbon base solid acid by employing different temperature and reaction conditions. Initially, the biomass was dried at 100°C over the night and then kept in a tube furnace for 2 h. This dried mass was carbonized in the N_2 atmosphere to form a black mass that was treated with alcohol under sonication and then dried for 5h at 80°C. Now this sample was reacted with conc. H_2SO_4 and stirred at 300 rpm at different temperature for 3 h. The catalytic efficiency of the catalyst was analyzed by the hydration of α-pinene. The CBSA catalysts with the maximum acid density, large surface area, and pore volume (RS300-80) demonstrated the utmost selectivity of α-terpineol [164].

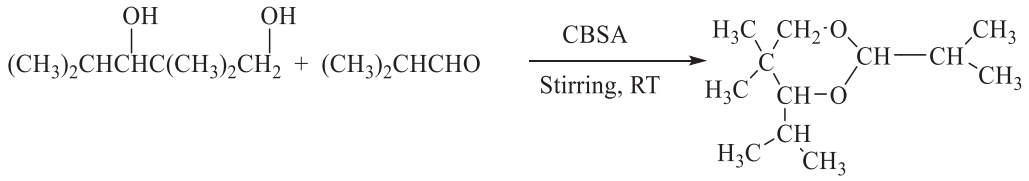
Similarly, an efficient protocol was developed and designed for the synthesis of 14-aryl/alkyl-14*H*-dibenzo[a,j]xanthenes using camphor based sulphonic acid (2 mol%) by the reaction of β -naphthol with aromatic/aliphatic aldehydes. Microwave irradiation at 400 W and 63-64°C has been employed and 54-95% yield was obtained (Scheme **45**) [165].



Scheme (45). Synthesis of 14-aryl-14H-dibenzo [a,j] xanthenes derivatives by different methods.

Carbon-based solid acid catalyst was prepared *via* carbonization and sulfonation using lignin. Initially, the alkaline lignin was carbonized and then sulfonation was done by adding carbonized material to ferrous sulfide solution at 105°C for 10 h. The catalytic efficiency of the synthesized catalyst was tested for the conversion of cellulose to levulinic acid using γ-varleroactone as a solvent system [166].

The synthesis of 2,4-diisopropyl-5,5-dimethyl-1,3-dioxane was performed through acetalization of isobutyralaldehyde with 2,2,4-trimethyl-1,3-pentanediol using novel carbon based solid acid catalyst. The simple workup process with high yield, easy, fast, low cost, recoverable and reusable catalyst up to 5 cyclesare the main benefits of this protocol (Scheme **46**) [167].



Scheme (46). Synthesis of 2,4-diisopropyl-5,5-dimethyl-1,3-dioxane.

Graphene oxide plays an important role as a carbon-based solid acid catalyst for the synthesis of organic compounds [168 - 172] and numerous graphene oxides and its complexes are used for the synthesis of heterocyclic compounds listed in Table **3**. The synthesis of 1,5-benzodiazepines took place *via* a one-pot three-component reaction of acetophenone, aromatic aldehydes, and benzene-1,--diamine in the presence of calcium ferrite/graphene oxide nanocomposites

(CF/GO) with ethanol-water as a solvent system under microwave irradiation at 100°C and 450W for 8-10 minutes. Additionally, the catalyst could be easily recovered up to five times with a small change in catalytic activity (Scheme **47**) [173].

Table 3. Various kinds of carbon-based solid catalysts in the synthesis of biscoumarin.

S.No	Catalyst	Synthesis of Catalyst	Reaction Condition	Advantages	References
1	Starch –sulfuric acid	Chlorosulfonic acid was added drop-wise at 0°C to starch with n-hexane and stirred for 2 hours. Then washed with acetonitrile and dried at RT.	Solvent-free, at 80°C.	85-97% yield. 14 derivatives. The catalyst was recovered by filtration after completion reaction.	[130]
2.	Sulfonated rice husk	$CHCl_3$ and chlorosulfonic acid were added to rice husk ash and HCl gas into the water as an absorbing solution, stirred for 2 hours at room temperature.	H_2O as a solvent. Heated at 80 °C for 10-70 min	87- 95% yield. 19 derivatives. The reusability of catalyst was also revealed.	[131]
3.	Cellulose sulphonic acid	Cellulose, n-hexane and chlorosulfonic acid were added drop-wise at 0°C during 2h. HCl gas was removed from the reaction. The reaction mixture was stirred for 2h and filtered.	H_2O as a solvent. Reflux for 100-150 min	80-90% 8 derivatives.	[132]
4.	Carbon-based solid acid from pistachio peel	Powder of green pistachio peel and conc. H_2SO_4 was mixed and stirred at room temperature for 1 hour then kept at 180°C for 12 hours in a teflon-lined autoclave.	Stirred at 80 °C for 3- 20 min. Solvent-free condition.	85-95% 15 derivatives The synthesized catalyst was reused up to 5 cycles.	[133]
5.	Magnetite-Containing Sulfonated Polyacrylamide	Bz_2O_2 was added to a solution of acrylamide, AMPS, and ethanol and were refluxed for 5 h. Afterwards, Fe_3O_4 nanoparticles were refluxed for 1 h.	Toluene as a solvent. 90°C for 15-33 min	94-97% 12 derivatives.	[134]

(Table 3) cont.....

S.No	Catalyst	Synthesis of Catalyst	Reaction Condition	Advantages	References
6.	Carbon-SO_3H	A mixture of glycerol (10 g) and concentrated sulfuric acid (40 g) were gently heated from ambient temperature to 180-200°C for 20 min, The reaction mixture was allowed to remain at that temperature for about 20-40 min (until foaming ceased) to achieve the polycyclic aromatic carbon compound. The crude product was allowed to be kept at room temperature and washed with hot water under agitation until the wash water demonstrated a pH=7 value. The partially crystalline product was filtered and dried in an oven at 120°C for 2-3 h.	Stirring at 80 °C	88-100% yield. 10 derivates each. The preparation catalyst was simple and easily reused six cycles. The molecular docking of synthesized compounds was also done.	[135, 136]

Table 4. Use of graphene oxide and its complex for the preparation of heterocyclic compounds.

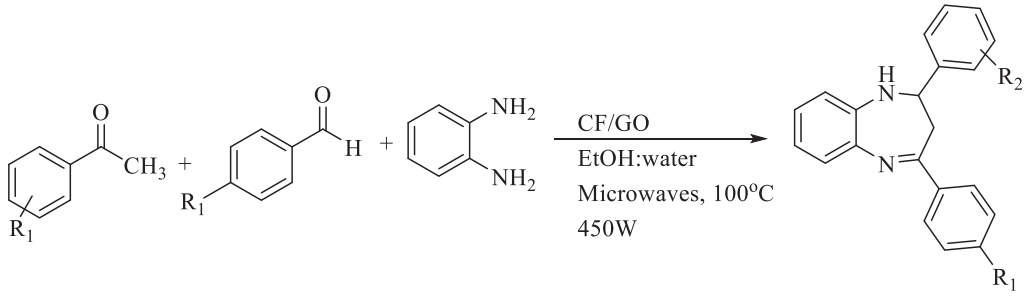
S. No.	Catalyst	Application of Catalyst	Reactant	Reaction Condition	Advantages	References
1.	Super-paramagnetic graphene oxide/Fe_3O_4/l-proline nano hybrid	Synthesis of 4,4′-(arylmethylene) bis(1H-pyrazo--5-ol) derivatives	3-methyl-1-phenyl-2-pyrazoline-5-one and aromatic aldehyde.	EtOH as solvent.	87-98% yield. Nanocatalyst could easily be recovered by applying an external magnet and reused for at least eight runs.	[174]
2.	Phosphorylated graphene oxide (PGO)	Synthesis of benzimidazole derivates.	Benzene-1,2- diamine and various aldehydes	EtOH as a solvent. Reflux at RT	Yields (87–94%) PGO showed interesting properties such as acidic character, large surface area, exceptional electrical conductivity, and enhanced dispersion in aqueous media.	[175]

(Table 4) cont.....

S. No.	Catalyst	Application of Catalyst	Reactant	Reaction Condition	Advantages	References
3.	Graphene oxide–chitosan (GO–chitosan) bionanocomposite	Synthesis of 2,4,5-trisubstituted imidazoles	Benzoin or benzyl, benzaldehyde, and NH_4OAc	Solvent free at 120 °C	95% yield The active and green nanocatalyst exhibited excellent recyclability.	[176]
4.	Graphene oxide–chitosan (GO–chitosan) bio-nanocomposite	Synthesis of 2,4,5-trisubstituted imidazoles	Benzoin or benzyl, benzaldehyde, and NH_4OAc	Solvent-free at 120 °C	95% yield. The active and green nanocatalyst exhibited excellent recyclability.	[177]
5.	Graphene oxide/ZnO nanocomposite (GO/ZnO)	Synthesis of 5-substituted-1H-tetrazole	Benzonitrite and NaN_3	DMF as a solvent. 120°C	62-82% yield The reusability was attributed to the high stability and turnover of catalyst.	[178]
6.	Magnetic amine-functionalized graphene oxide (Fe_3O_4–GO–NH_2)	Synthesis of pyrano[3,2-c]pyridine derivatives.	Malononitrile and 3,5-bis(benzylidene)4-piperidone.	Solvent-free. 80°C. 5-75 min	80-89% yield The large surface area of Fe_3O_4 –GO–NH_2 facilitated adsorption of reactants. The catalyst was recovered and reused seven times without considerable depletion of its activity.	[179]
7.	Monodispersed palladium nanoparticles supported on graphene oxide (Pd@GO)	Synthesis of 2-amino-4H-chromene derivatives.	Resorcinol, malanonitrile, and aromatic aldehydes.	EtOH as solvent. 80°C. 10-15 min	88-94% yield Catalyst was recovered by centrifugation and reused up to six times.	[180]
8.	Fe_3O_4-supported N-pyridin-4-amine-grafted graphene oxide	Synthesis of chromenes.	Dimedone, malononitrile, and aryl aldehydes	H_2O as solvent and Reflux	92-98% yield The catalyst could be reused at least six times. The slight decrease of catalytic activity after the fifth cycle.	[181]

(Table 4) cont.....

S. No.	Catalyst	Application of Catalyst	Reactant	Reaction Condition	Advantages	References
9.	Graphene Oxide	Synthesis of pyranocoumarin derivatives.	4-hydroxy-coumarin, aryl glyoxals, and malononitrile.	H_2O: EtOH Reflux 12-20 min	88-95% yield The catalyst could be easily recovered and reused for four runs with no appreciable loss in catalytic activity.	[182]
10.	Graphene Oxide nanoparticle	Synthesis of highly functionalized benzylpyrazolyl coumarin derivatives	Phenylhydrazine, ethylacetoacetate, aldehydes, and, 4-hydroxycoumarin	EtOH as a solvent.	82-93% yield The catalyst was reusable and non-toxic.	[183]
11.	Acidic magnetic graphene oxide nanosheets (Fe_3O_4–GO–SO_3H)	Synthesis of diverse 1-H spiro[isoindoline-1,2quinazoline]-3,4-(3-H)-diones	Isatoic anhydride, primary amines, and isatin	Solvent-free. 180°C	The catalyst provided high surface area and being acidic, afforded good yields in a short time. Moreover, the catalyst was separated easily using an external magnet and recycled up to four times without significant loss of activity.	[184]
12.	Silica-graphene oxide nanohybrid	Synthesis of quinoxalines.	1,2-diamine with substituted phenacyl bromide	Acetonitrile as a solvent. RT	88-92% yield The catalyst could be readily reused up to four runs.	[185]



R_1 = Cl, OCH_3, OH
R_2 = 4-Cl, 3-NO_2, 3-Br, 4-Br

Scheme (47). Synthesis of 1,5-benxodizepines by using calcium ferrite/graphene oxide.

CONCLUSION

Carbon-based solid acid catalysts have emerged as a promising approach for eco-friendly synthesis. There is an increased interest in the designing of carbon-based solid-acid catalyzed pathways for developing drugs with superior efficacy and safety profiles. Extensive research work has presently been carried out by diverse research groups using several rational and elegant approaches for the synthesis of these catalysts and their utility in organic transformations *viz.* Biginelli reaction, Knoevenagel condensation, Michael addition, coupling reactions, *etc.* In the chapter, we have summarized several CBSA catalyzed pathways for the heterocyclic syntheses of the past decades. Efforts have been made to investigate the role of carbon-based solid acid catalysts in the syntheses of various heterocycles. These catalysts have numerous noteworthy characteristics *viz.* inexpensive and simple preparation, provide large surface area, require low catalyst loading, suitable surface morphology, high dispersion, excellent activity, great selectivity, versatility, easy recovery, good recyclability, high stability, and eco-friendliness. Moreover, the presence of -SO_3H group in this catalyst augments their catalytic activity by improving the surface area and exposing active sites for the reactants. This generates high to excellent yields of desired products in short reaction time. Moreover, natural biodegradable compounds like cellulose, starch, glucose, rice-husk, peels of vegetables, biomass, *etc.* have also been used for their synthesis. In the end, we can say that these catalysts are truly a gift to the researchers for their role in various organic transformations.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirmed that this article has no conflict of interest.

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PROF. DR. ATTA-UR-RAHMAN, *FRS*

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