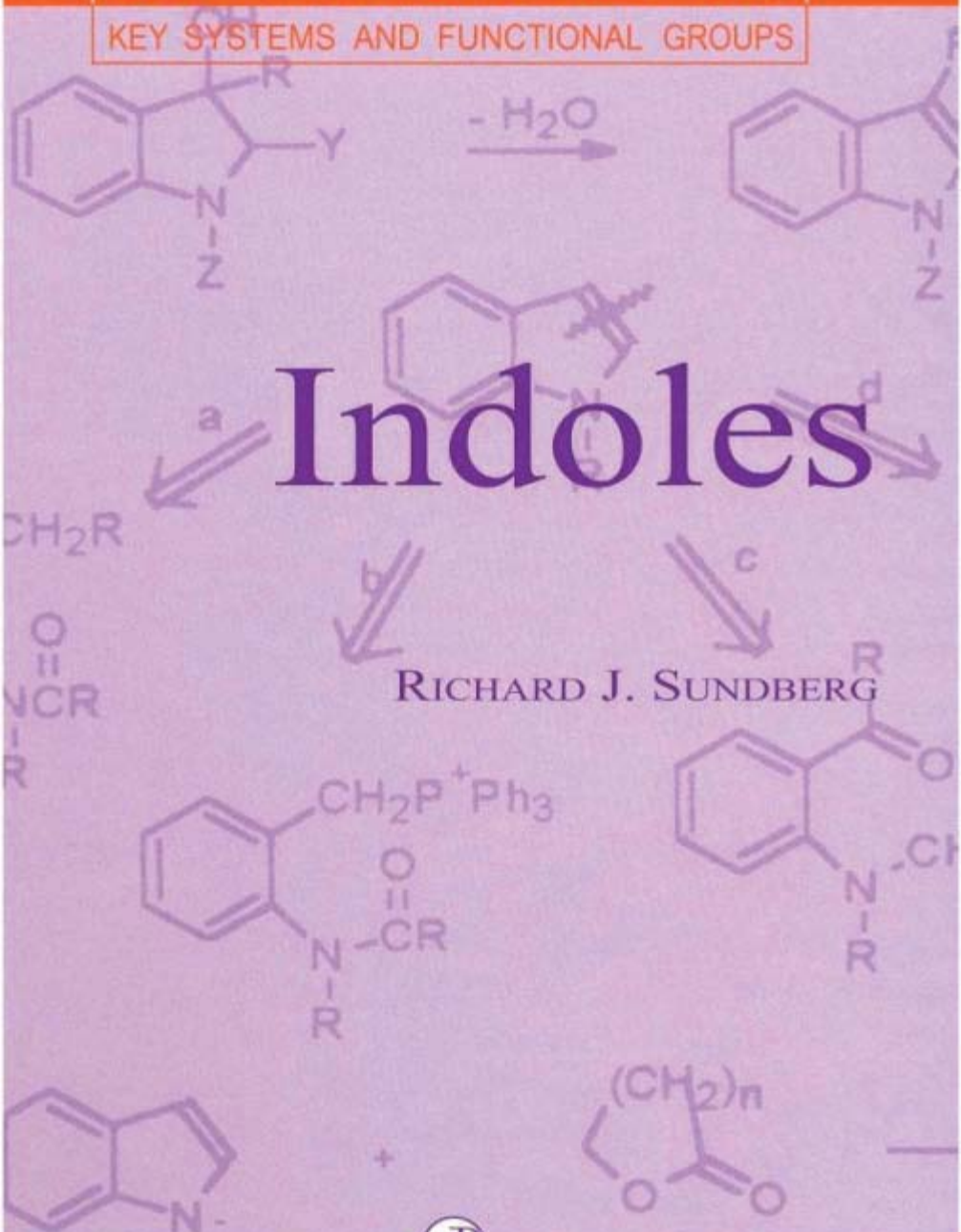
BEST SYNTHETIC METHODS

KEY SYSTEMS AND FUNCTIONAL GROUPS



Indoles

RICHARD J. SUNDBERG

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BEST SYNTHETIC METHODS

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Indoles

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Academic Press

Harcourt Brace & Company, Publishers

London San Diego New York Boston
Sydney Tokyo Toronto

ACADEMIC PRESS LIMITED
24–28 Oval Road
London NW1 7DX

US Edition published by
ACADEMIC PRESS INC.
San Diego, CA 92101

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A Catalogue record for this book is available from the British Library

ISBN 0-12-676945-1

This book is printed on acid-free paper

Typeset by Doyle Graphics, Tullamore, Co. Offaly, Ireland
and printed in Great Britain by Hartnolls Limited, Bodmin, Cornwall

Contents

Dedicated to Wayland E. Nolan in honour of his 70th birthday

Foreword

Best Synthetic Methods is now 10 years old, is a family of 16 volumes and has been well received by the majority of chemists as a valuable aid in their synthetic endeavours, be they academic or commercial. The focus of the series so far has been on special methods, reagents or techniques. This volume is the first of a new sub-series with a focus on heterocycles and their synthesis. It is amazing the extent to which each heterocyclic type has its own specialized synthetic methodology. Whether the chemist is endeavouring to make a heterocycle by ring synthesis or wishes to introduce specific substituents, it is the intention that this new development will serve their needs in a practical, authoritative, fully illustrative and compact manner. Richard Sundberg is an authority on indole chemistry and it is a pleasure to have such a noted heterocyclist to initiate this venture.

O.M.-C.

Preface

Synthesis of indole derivatives has been an active field of chemical research for well over a century. Synthetic interest has been driven by the wide range of indole derivatives which occur in nature and by the biological activity of many indole derivatives of both natural and synthetic origin. In this volume I have attempted to illustrate the most widely used of these synthetic methods. The underlying organization is on the basis of the retrosynthetic concept of identifying the bond(s) which are formed in the process. The chapters pertaining to ring construction (1–8) and substitutions (9–14) are focused on particular ring positions. The final two chapters consider indole-specific oxidation–reduction reactions and cycloaddition processes.

Even after 30 years of research activity in the field, my personal experience encompasses only a fraction of the methodologies included in the book. I have selected the methods and examples on the basis of utility and reliability as judged by frequency of application in the literature or by indications that specific procedures are especially convenient. I will welcome comments from chemists whose experience, good or bad, will help in recognizing the best of the many methods that are available.

Richard J. Sundberg
Charlottesville

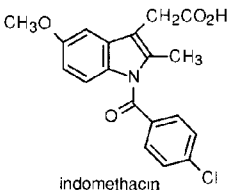
Detailed Contents

–1–

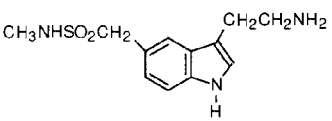
Introduction

The synthesis and reactivity of indole derivatives has been a topic of research interest for well over a century. The first preparation of indole dates from 1866 and the Fischer indole synthesis, which remains the most versatile method for preparing indoles, was first reported in 1883[1]. The principal commercial source of indole is extraction from coal tar, although the feasibility of industrial synthesis from starting materials such as aniline and ethylene glycol[2], *N*-ethylaniline[3] or 2-ethylaniline[4] has been demonstrated. Reports of several thousand individual indole derivatives appear annually in the chemical literature. The primary reason for this sustained interest is the wide range of biological activity found among indoles[5]. The indole ring appears in the amino acid tryptophan and metabolites of tryptophan are important in the biological chemistry of both plants and animals. Indole-3-acetic acid is a plant growth hormone[6] and 3-(2-aminoethyl)-5-hydroxyindole (serotonin) is one of the key neurotransmitters in animals[7]. Searches for specific agonists and antagonists of the receptors for these and other indole metabolites has been an active pursuit of pharmaceutical chemistry for nearly 50 years. The indole ring also appears in many natural products such as the indole alkaloids[8], fungal metabolites[9] and marine natural products[10].

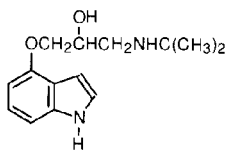
Among the indole derivatives which have found use as drugs are indomethacin, one of the first non-steroidal anti-inflammatory agents[11], sumatriptan, which is used in the treatment of migraine headaches[12] and pindolol[13], one of the β-adrenergic blockers.



indomethacin



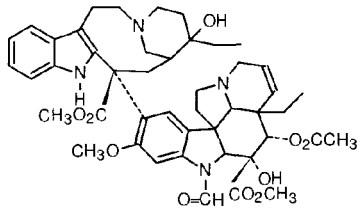
sumatriptan



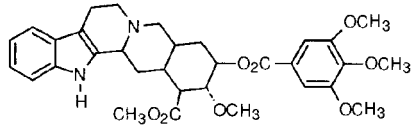
pindolol

(1.1)

Several of the naturally occurring indoles also have clinical importance. The dimeric *vinca* alkaloid vincristine and closely related compounds were among the first of the anti-mitotic class of chemotherapeutic agents for cancer[14]. The mitomycins[15] and derivatives of ellipticine[16] are other examples of compounds having anti-tumour activity. Reserpine, while not now a major drug, was one of the first compounds to show beneficial effects in treatment of mental disorders[17]

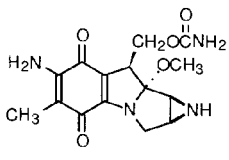


vincristine

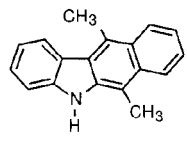


reserpine

(1.2)

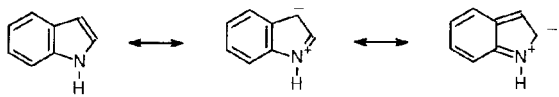


mitomycin C



ellipticine

Indole is classified as a π-excessive aromatic compound. It is isoelectronic with naphthalene, with the heterocyclic nitrogen atom donating two of the ten π-electrons.

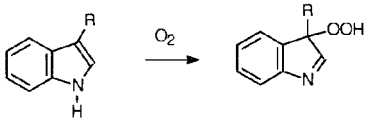


1.3A **1.3B** **1.3C**

(1.3)

The aromaticity of the ring is fundamental to the success of many synthetic methods. Most estimates of aromaticity ascribe a stabilization energy which is slightly less than naphthalene[18]. Most indole-forming reactions begin with materials which incorporate a benzene ring, and the additional stabilization resulting from the formation of the fused pyrrole ring provides a driving force for indole ring formation. The most fundamental properties of the indole ring are fully consistent with the expectation for such a heteroaromatic structure. Like pyrrole, indole is a very weak base; the conjugate acid is estimated to have

a $pK_a = -2.4$[19] because aromaticity is compromised by protonation at nitrogen. Instead, protonation occurs at C3. Indole itself and some of its simple derivatives are quite reactive toward strong acids as a result. As an electron-rich heteroaromatic, indole has a relatively high-energy HOMO and is subject to oxidative processes, including photosensitized electron transfer. Many indoles are readily oxidized by exposure to atmospheric oxygen, with the initial product being a 3-hydroperoxy-3*H*-indole.

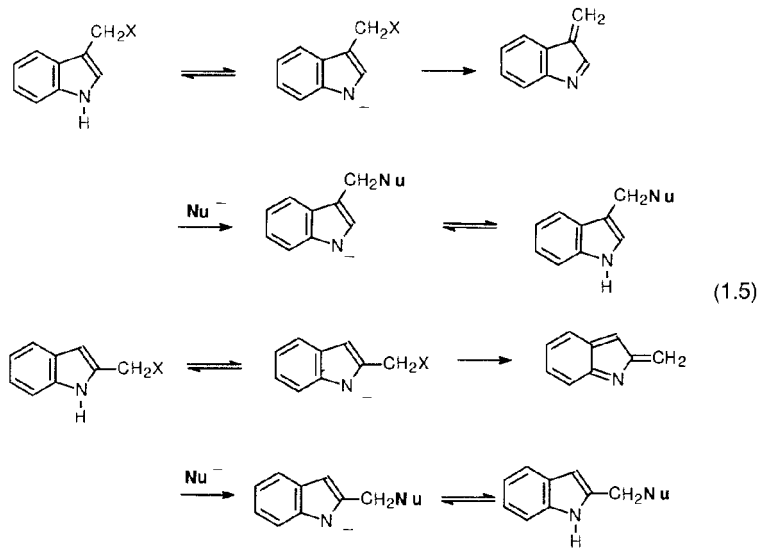


(1.4)

From the perspective of laboratory practice, the sensitivity of many indoles to acids, oxygen and light prescribes the use of an inert atmosphere for most reactions involving indoles and the avoidance of storage with exposure to light. This sensitivity is greatly attenuated by electron-withdrawing (EW) substituents.

Many synthetic methods have been developed for addition or modification of substituents on the indole ring. Electrophilic substitution occurs preferentially at C3, a result which is explicable in terms of the contribution of resonance structure **1.3B**, and is also consistent with various M.O. calculations which find the highest electron density and highest concentration of the HOMO at C3[20]. The C3 position is estimated to be 10^{13} more reactive than is benzene to electrophilic attack[21]. The C2 position is the second most reactive site toward electrophiles, but the most reliable means of achieving selective C2 substitution is by heteroatom-directed lithiation. The indole NH is weakly acidic, $pK = 16.7$ in water[19] and $pK = 20.9$ in DMSO[22], and the most nucleophilic site in the anion is N1. Selective N1 substitution therefore usually involves base-catalysed processes, including alkylation, acylation and conjugate addition. Regioselective substitution of the carbocyclic ring is problematic. The inherent selectivity is not high and so is strongly influenced by the specific substitution pattern. Usually, regiospecific substitution requires the prior synthesis of a functionalized intermediate. For example, the halo indoles are useful intermediates for introduction of carbocyclic substituents.

As is broadly true for aromatic compounds, the α- or benzylic position of alkyl substituents exhibits special reactivity. This includes susceptibility to radical reactions, because of the stabilization provided the radical intermediates. In indole derivatives, the reactivity of α-substituents towards nucleophilic substitution is greatly enhanced by participation of the indole nitrogen. This effect is strongest at C3, but is also present at C2 and to some extent in the carbocyclic ring. The effect is enhanced by N-deprotonation.



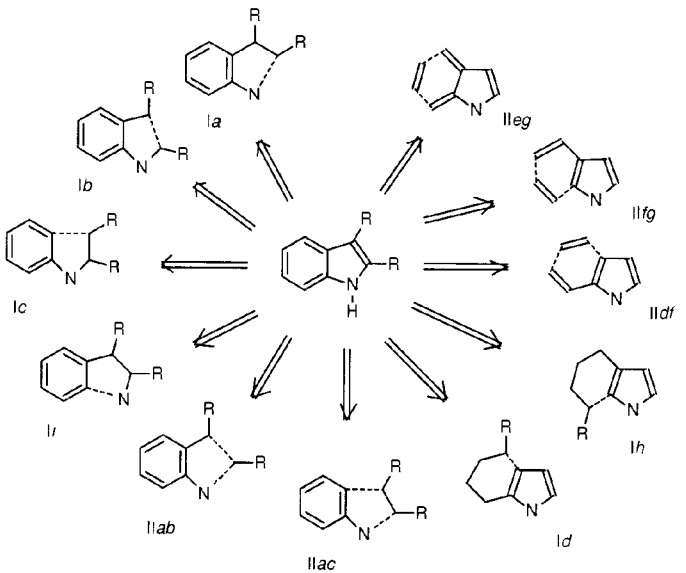
(1.5)

This reactivity pattern underlies a group of important synthetic methods in which an α-substituent is displaced by a nucleophile by an elimination–addition mechanism. Even substituents which are normally poor leaving groups, such as alkoxy and dialkylamino, are readily displaced in the indole series.

The material in the succeeding chapters describes both the synthesis of the indole ring and means of substituent modification which are especially important in indole chemistry. The first seven chapters describe the preparation of indoles from benzenoid precursors. Chapter 8 describes preparation of indoles from pyrroles by annelation reactions. These syntheses can be categorized by using the concept of bond disconnection to specify the bond(s) formed in the synthesis. The categories are indicated by the number and identity of the bond(s) formed. This classification is given in Scheme 1.1.

Chapters 9, 10 and 11 describe methods for substitution directly on the ring with successive attention to N1, C2 and C3. Chapters 12 and 13 are devoted to substituent modification as C3. Chapter 12 is a general discussion of these methods, while Chapter 13 covers the important special cases of the synthesis of 2-aminoethyl (tryptamine) and 2-aminopropanoic acid (tryptophan) side-chains. Chapter 14 deals with methods for effecting carbocyclic substitution. Chapter 15 describes synthetically important oxidation and reduction reactions which are characteristic of indoles. Chapter 16 illustrates methods for elaboration of indoles *via* cycloaddition reactions.

As for the other volumes in this series, examples of synthetic procedures have been given. These have been chosen to indicate the basic operations involved



SCHEME 1.1

in the individual syntheses. The procedures have been adapted from the published procedures for a succinct style of presentation. The original reference should be consulted for details which may not have been included.

There are a number of other sources of information available about the synthesis of indoles. The most comprehensive entrée to the older literature is through Volume 25, Parts I–III, of *The Chemistry of Heterocyclic Compounds*, which were published between 1972 and 1979[23]. Work to the early 1980s is reviewed in *Comprehensive Heterocyclic Chemistry*[24] and a second edition is forthcoming[25]. Other reviews emphasizing recent developments are also available[26–28].

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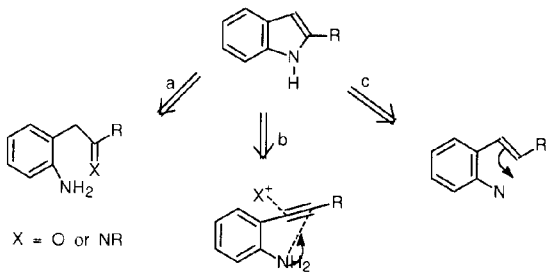
–2–

Category *Ia* Cyclizations

Category I*a* cyclizations involve formation of the N–C2 bond from a preformed intermediate which contains all the necessary atoms to construct the indole framework. One group of these cyclizations proceeds by addition–elimination at a carbonyl or imine group, as represented in retrosynthetic path **a**, Scheme 2.1. The starting materials are often aromatic nitro compounds, with the cyclization taking place following reductive conversion to a nucleophilic amino group. The carbonyl or imine double bond may be present in the starting material, but it can also be introduced during the synthetic process. Retrosynthetic path **b** involves activation of an acetylene bond to nucleophilic addition of the *endo-dig* type. Metal ions, especially Pd^{2+}, are effective catalysts, with the Pd^{2+} being removed after cyclization by protonolysis. Retrosynthetic path **c** corresponds to reaction between an electrophilic nitrogen species and an adjacent double bond. This pattern is realized synthetically by reductive conversion of *o*-nitrostyrenes to indoles.

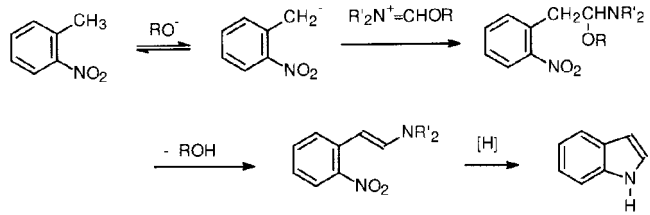


SCHEME 2.1

2.1 INDOLES FROM β-DIALKYLAMINO-*o*-NITROSTYRENES. THE LEIMGRUBER–BATCHO SYNTHESIS

The Leimgruber–Batcho synthesis is a two-step method which provides indoles that are substituted only in the benzene ring. The method was initially disclosed in a patent[1] and a representative procedure is available in *Organic Syntheses*[2]. A review of the reaction is available[3]. The reaction involves

condensation of an *o*-nitrotoluene with *N*,*N*-dimethylformamide dimethylacetal. In its first version the reaction was driven to completion by distillation of methanol. An improvement which has been widely adopted is to include pyrrolidine in the reaction mixture. Under these conditions the reaction is accelerated and the pyrrolidine is exchanged into the enamine product[4]. *tris*-Piperidinomethane is an alternative reagent which may be advantageous if the condensation with DMF dimethylacetal is sluggish[5]. The reaction depends on the nitro group both to acidify the methyl group and to stabilize the enamine product. The reaction is very versatile with respect to the range of carbocyclic substituents that can be used.



(2.1)

The second step of the synthesis involves reductive cyclization. A number of reducing agents have been used, the choice, at least in part, being dictated by the nature of the carbocyclic substituents. The reductive cyclization is usually done with hydrogen over a palladium catalyst or with Raney nickel and hydrazine. Not much is known about the exact sequence of the reduction but it is possible to obtain *N*-hydroxyindoles by choice of an appropriate reagent. Zinc-NH_4Cl is the preferred reductant for this purpose[6]. Use of $TiCl_3$ as reductant gives a mixture of the indole and N-hydroxyindole[7]. These results suggest that the cyclization can take place at the hydroxylamine reduction level. Table 2.1 gives some representative examples.

Procedures

7-Methoxyindole[8]

A. Condensation step

A solution of 2-nitro-3-methoxytoluene (5 g, 30 mmol), DMF dimethylacetal (4.25 ml, 32 mmol) and pyrrolidine (2.5 ml, 30 mmol) in DMF (50 ml) was stirred and heated at 130° C under nitrogen for 3 h. The solvent was removed *in vacuo* and the residue dissolved in isopropyl alcohol (50 ml). The enamine intermediate (3.98 g, 54%) was obtained as orange crystals.

B. Reductive cyclization

A mixture of 3-methoxy-2-nitro-β-pyrrolidinostyrene (10 g, 40 mmol) and Raney nickel (25 g) in methanol-THF (40 ml of each) was heated to 60°C and,

Table 2.1

Indoles prepared by the Leimgruber Batcho method

Entry	Substituents	Reagent	Reductant	Yield (%)	Ref.
1	4-Benzyloxy	$Me_2NCH(OMe)_2$/pyrrolidine	Raney Ni/NH_2NH_2	96	[2]
2	4-Benzyloxy	Tripiperidinomethane	Ni-B/NH_2NH_2	90	[9]
3	4-Cyano	$Me_2NCH(OMe)_2$	Fe	67	[10]
4	4-(2,2-Dimethoxyethyl)	$Me_2NCH(OMe)_2$/pyrrolidine	Raney Ni/NH_2NH_2	67	[11]
5	4-Methoxycarbonyl	$Me_2NCH(OMe)_2$	H_2Pd-C	82	[12]
6	5-Ethoxy	$[Me_2N]_2CHO$-*t*-Bu	Raney Ni/NH_2NH_2	53	[13]
7	6-Bromo	$Me_2NCH(OMe)_2$/pyrrolidine	Zn	62	[14]
8	6-Bromo	Tripiperidinomethane	$TiCl_3$	63	[15]
9	7-Carboxy	$Me_2NCH(OMe)_2$	Fe	80	[16]
10	4-Cyano-7-methoxy	$Me_2NCH(OMe)_2$	H_2/Pd-C	83	[17]
11	5,6-*bis*-(Benzyloxy)	Tripiperidinomethane	Fe, SiO_2	62	[18]
12	6-Chloro-5-methoxy	$Me_2NCH(OMe)_2$	Raney Ni/NH_2NH_2	68	[19]

with stirring, hydrazine hydrate (4 ml in 30 ml of THF) was added over 60 min. The reaction mixture was then cooled to room temperature and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue purified by chromatography through silica gel using 10% ether in hexane for elution. The fractions containing product were combined and evaporated to give the product as a clear oil (2.94 g, 50%).

4-Benzyloxyindole[9]

A. Condensation step

tris-Piperidinomethane (9.20 g, 34.7 mmol) and 2-benzyloxy-6-nitrotoluene (5.62 g, 23.1 mmol) were fused together under aspirator vacuum at 110°C and stirred for 6 h. The reaction mixture was cooled and abs. methanol (100 ml) was added. The bright-red product (7.31 g, 93%) crystallized and was collected by filtration.

B. Reductive cyclization

2-Benzyloxy-6-nitro-β-piperidinostyrene (5.00 g, 14.8 mmol) was added to a suspension of nickel boride in absolute ethanol which had been prepared from nickel acetate (15 mmol). The reaction mixture was heated to reflux. Hydrazine hydrate (1.5 g, 30 mmol) in abs. ethanol (25 ml) was added over a period of 15 min, during which vigorous gas evolution occurred. After cooling, the reaction mixture was filtered through Celite. [*CAUTION: Raney nickel can ignite during filtration.*] The filtrate was concentrated and the product purified by flash chromatography through silica gel using 1:1 toluene–cyclohexane for elution. The product (2.98 g, 90%) was obtained as a white solid.

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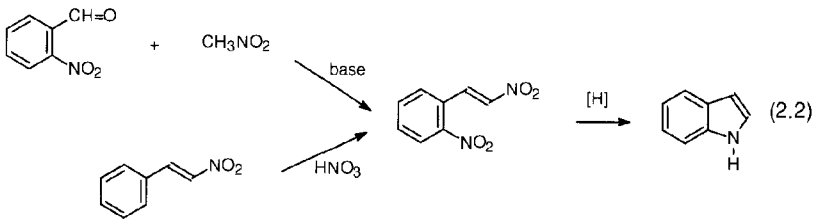
2.2 INDOLES FROM *o*,β-DINITROSTYRENES

A two-step synthesis of indoles from *o*-nitrobenzaldehydes proceeds by condensation with nitromethane followed by reductive cyclization. Like the Leimgruber Batcho method, the principal application of the reaction is to indoles with only carbocyclic substituents. The formation of the *o*,β-dinitrostyrenes is usually done under classical Henry condensation conditions but KF/18-crown-6 in propanol was found to be an advantageous reaction medium for acetoxy-substituted compounds[1]. The *o*,β-dinitrostyrenes can also be obtained by nitration of β-nitrostyrenes[2].



(2.2)

Several different reducing agents have been used in the reductive cyclization. Iron powder is the traditional choice but the work-up of such reactions is sometimes complicated by iron-containing precipitates. A procedure involving iron powder with a slurry with silica has been recommended[2]. Transfer hydrogenation using Pd/C and ammonium formate is also a convenient method for reduction[3]. There is little definitive evidence of the mechanism of the reductive cyclization of *o*,β-dinitrostyrenes. Certain reduction conditions lead to other products. For example, $NaBH_4$ leads to the reduction of only the styrene double bond[4] and formation of *o*-nitrophenylacetoximes has been observed occasionally[5]. Table 2.2 gives some typical procedures.

Procedures

5-Chloro-2,β-dinitrostyrene[6]

5-Chloro-2-nitrobenzaldehyde (122.9 g) and nitromethane (40.4 g) were dissolved in methanol (132 ml) and cooled to 10–15°C. A solution of NaOH (27.8 g) in water (67 ml) was added at such a rate that the temperature was maintained below 15°C by ice-bath cooling. The solution was kept in the ice bath for 2 h and the resulting mass was slurried with 700 ml of ice and water. The resulting

Table 2.2

Reductive cyclization of *o*,β-dinitrostyrenes

Entry	Substituents	Reductant	Yield (%)	Ref.
1	4-Chloro	Fe	85	[7]
2	4-Acetyloxy-5-benzyloxy	Fe/SiO_2	64	[8]
3	4,7-*bis*-Benzyloxy	Fe	63	[9]
4	4,7-Dimethoxy	$NaBH_4/Pd$-C	67	[5]
5	5,6-Diacetoxy	H_2/Pt-C	70	[10]
6	5,6-Dihydroxy	H_2/Pd-C	50	[11]
7	5-Methoxy-6-benzyloxy	Fe/SiO_2	91	[2]
8	5,6-Methylenedioxy	$NH_4^+HCO_2^-/Pd$-C	82	[3]
9	5,6,7-Trimethyl	H_2/Pd-C	43	[6]
10	5,6-*bis*-(Benzyloxy)-4.7-dimethyl	Fe/SiO_2	90	[12]
11	5,6-Dimethoxy-7-iodo-2-methyl	Fe	47	[13]

clear yellow solution was poured slowly into a mixture of 132 ml of conc. HCl and 198 ml of water. The addition product was obtained as a solid (72 g, 51%). The nitroalcohol (20 g) was added to a suspension of finely powdered anhydrous NaOAc (prepared by fusion and grinding) in acetic acid (90 ml). The mixture was refluxed for 5 min and after cooling it was poured into 600 ml of cold water. The product was obtained as an oil which solidified on standing at room temperature. The nitrostyrene was collected by filtration (17.6 g, 95%) and could be recrystallized from ethanol.

4,5-bis-*Benzyloxy-3,6-dimethyl-2,β-dinitrostyrene[12]*

3,4-*bis*-(Benzyloxy)-2,5-dimethylbenzaldehyde (50 mmol) and nitromethane (150 mmol) and dry NH_4OAc (150 mmol) were dissolved in acetic acid (150 ml) and heated at reflux for 1.5 h. The reaction mixture was cooled and poured into water (1 l). The product was collected by filtration, dissolved in CH_2Cl_2, washed with $NaHCO_3$, dried over Na_2SO_4 and passed through silica gel using CH_2Cl_2 for elution. The product (12.5 g, 64%) was purified by recrystallization from benzene-hexane. A solution of the β-nitrostyrene (3.89 g, 10 mmol) in dry acetic acid (40 ml) was heated to 60–65°C and $Cu(NO_3)_2$-$3H_2O$ was added in small portions over 30 min. The mixture was kept at 60–65°C for 1.25 h, cooled to room temperature and poured into water (400 ml). The product was collected as a solid and washed thoroughly with water. The dinitrostyrene was collected by filtration, dissolved in CH_2Cl_2, washed with $NaHCO_3$, dried over Na_2SO_4 and passed through silica gel using CH_2Cl_2 for elution. The product was recrystallized from benzene-cyclohexane and then ethanol (2.1 g, 48% yield).

5,6-bis-Benzyloxy-4,7-dimethylindole[12]

4,5-*bis*-(Benzyloxy)-3,6-dimethyl-2,β-dinitrostyrene (4 mmol), 70–270 mesh silica gel (10 g), acetic acid (24 ml) and electrolytic iron powder (4 g, 71 mmol) were dispersed in toluene (40 ml) and refluxed under nitrogen for 1 h. The mixture was cooled and then filtered. The solid was washed thoroughly with CH_2Cl_2. The combined filtrate and washings were washed successively with aq. $NaHSO_3$, water and aq. $NaHCO_3$. After drying over Na_2SO_4, the solution was evaporated *in vacuo*, and eluted through silica with CH_2Cl_2-hexane. The solvent was evaporated and the residue recrystallized from benzenecyclohexane to give 5,6-*bis*-(benzyloxy)-4,7-dimethylindole (1.28 g) in 90% yield.

Transfer hydrogenation[3]

The *o*,β-dinitrostyrene (1 mmol) and ammonium formate (10 mmol) were dissolved in methanol and 10% Pd/C (5% by wt) was added. The mixture was refluxed under nitrogen for 1 h. Formic acid (0.44 ml) was added and reflux was continued for 0.5–1 h until the completion of the reaction (tlc). The solution was filtered through Celite, evaporated *in vacuo* and eluted through silica gel with CH_2Cl_2.

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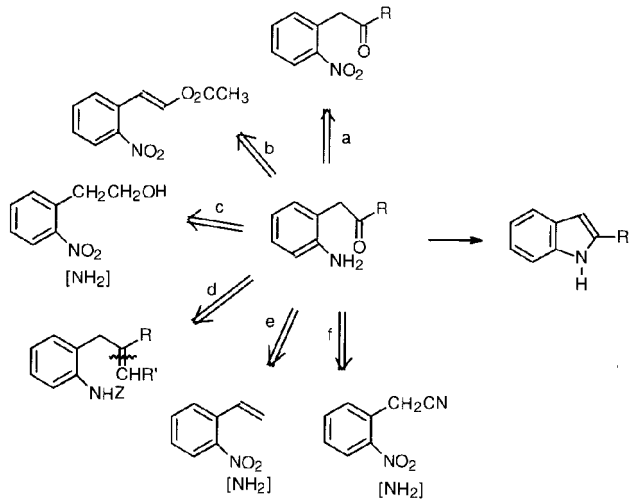
2.3 GENERATION AND CYCLIZATIVE CONDENSATION OF *o*-AMINOBENZYL ALDEHYDES AND KETONES

Both *o*-aminobenzyl aldehydes and ketones rapidly cyclize and undergo dehydration to indoles. The generation of these carbonyl compounds therefore represents a quite reliable route to indoles. The complication is that while there

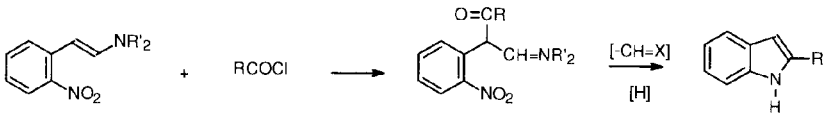


SCHEME 2.2

are numerous potential means of constructing the intermediates, none is entirely general. As a result, the specific synthetic route must be designed for the target compound within the context of the broad approach. Scheme 2.2 illustrates some of the approaches that have been used. A closely related group of reactions in which the intermediate benzyl carbonyl compound is not isolated will be described in Chapter 6.

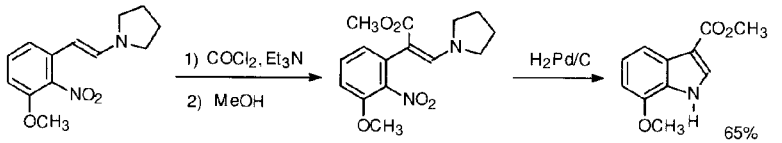
The final step can involve introduction of the amino group or of the carbonyl group. *o*-Nitrobenzyl aldehydes and ketones are useful intermediates which undergo cyclization and aromatization upon reduction. The carbonyl group can also be introduced by oxidation of alcohols or alkenes or by ozonolysis. There are also examples of preparing indoles from *o*-aminophenylacetonitriles by partial reduction of the cyano group.

One route to *o*-nitrobenzyl ketones is by acylation of carbon nucleophiles by *o*-nitrophenylacetyl chloride. This reaction has been applied to such nucleophiles as diethyl malonate[1], methyl acetoacetate[2], Meldrum's acid[3] and enamines[4]. The procedure given below for ethyl indole-2-acetate is a good example of this methodology. Acylation of *o*-nitrobenzyl anions, as illustrated by the reaction with diethyl oxalate in the classic Reissert procedure for preparing indole-2-carboxylate esters[5], is another route to *o*-nitrobenzyl ketones. The *o*-nitrophenyl enamines generated in the first step of the Leimgruber–Batcho synthesis (see Section 2.1) are also potential substrates for C-acylation[6,7]. Deformylation and reduction leads to 2-substituted indoles.



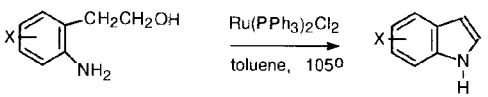
(2.3)

Acylation of the Leimgruber–Batcho enamines with phosgene followed by methanolysis and reductive cyclization generates methyl indole-3-carboxylates[8]



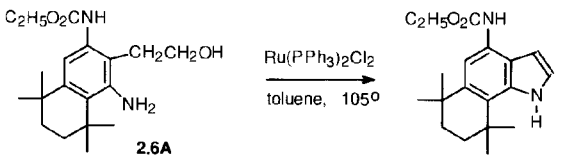
(2.4)

The reactant corresponding to retrosynthetic path **b** in Scheme 2.2 can be obtained by Meerwein arylation of vinyl acetate with *o*-nitrophenyldiazonium ions[9]. Retrosynthetic path **c** involves oxidation of a 2-(*o*-nitrophenyl)ethanol. This transformation has also been realized for 2-(*o*-aminophenyl)ethanols. For the latter reaction the best catalyst is $Ru(PPh_3)_2Cl_2$. The reaction proceeds with evolution of hydrogen and has been shown to be applicable to a variety of ring-substituted 2-(*o*-aminophenyl)ethanols[10].



(2.5)

This method has been successfully applied to the substituted indole **2.6B**, an analogue of the teleocidin type of protein kinase activators[11].

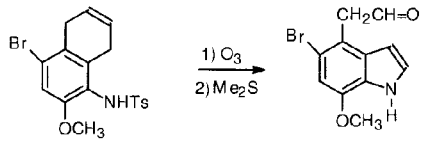


(2.6)

2-(*o*-Nitrophenyl)ethanols can be converted directly to indoles by use of a binary catalyst consisting of Pd/C or Rh/C and $Ru(PPh_3)_2Cl_2$[10]. The starting materials can be obtained by condensation of an *o*-nitrotoluene with formaldehyde. An illustrative procedure is given below for 4-chloroindole.

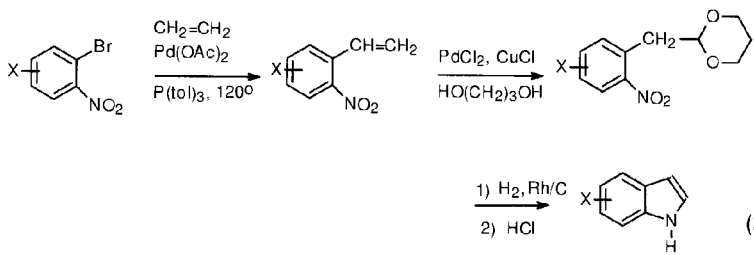
The oxidative generation of *o*-aminophenylacetaldehydes can be done by ozonolysis (retrosynthetic path **d** in Scheme 2.2) but this requires an elec-

tron-attracting substituent either on nitrogen or the ring to prevent further oxidation. An early example was reported by Plieninger[12] and the method has subsequently been used to prepare 4-substituted indoles[13] as in the case of an intermediate in the synthesis of the natural product rivularin D[14].



(2.7)

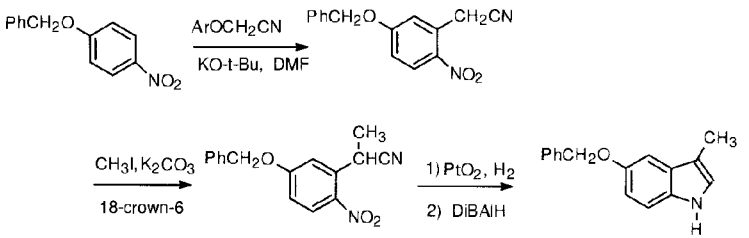
Retrosynthetic path **e** in Scheme 2.2 requires a regioselective oxidation of an *o*-nitrostyrene to the corresponding phenylacetaldehyde. This transformation has been accomplished by Wacker oxidation carried out in such a way as to ensure the desired regioselectivity. The required *o*-nitrostyrenes can be prepared by Heck vinylation. One procedure for oxidation uses 1,3-propanediol to trap the product as a 1,3-dioxane[15]. These can then be hydrogenated over Rh/C and cyclized by treatment with dilute HCl.



(2.8)

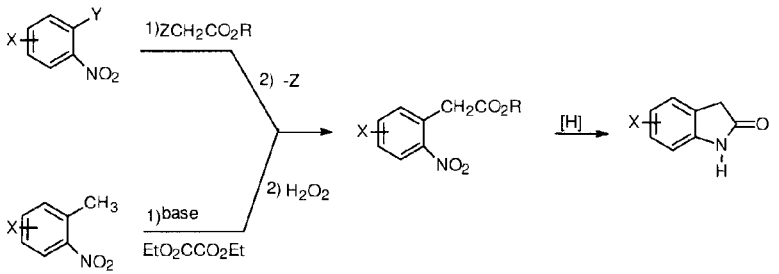
An alternative procedure involves use of alkyl nitrites and traps the desired product as an acetal[16].

o-Nitrobenzyl cyanides are also potential indole precursors. Reduction of the nitrile to the imine level and of the nitro group to the amine level permits cyclization and aromatization to indoles. Reduction has been carried out both in a single step[17–19] or by a two-step sequence[20]. One route to the *o*-nitrobenzyl cyanide starting materials is by the 'vicarious nucleophilic substitution' route developed by Makosza[18] which starts with a nitrobenzene. The cyanides can also be alkylated at the benzylic position so that it is also possible to introduce a 3-substituent as in the synthesis of 5-benzyloxy-3-methylindole[20].



(2.9)

The reduction of *o*-nitrophenyl acetic acids or esters leads to cyclization to oxindoles. Several routes to *o*-nitrophenylacetic acid derivatives are available, including nitroarylation of carbanions with *o*-nitroaryl halides[21,22] or triflate[23] and acylation of *o*-nitrotoluenes with diethyl oxalate followed by oxidation of the resulting 3-(*o*-nitrophenyl)pyruvate[24–26].



(2.10)

Procedures

Ethyl 4-(2-nitrophenyl)acetoacetate[3]

Thionyl chloride (11.5 g, 96.4 mmol) was added to 2-nitrophenylacetic acid (8.72 g, 48.2 mmol) and the suspension was warmed to 50°C and stirred until gas evolution was complete. The resulting solution was concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 (30 ml). This solution was added dropwise to a stirred solution of Meldrum's acid (6.94 g, 48.2 mmol) in CH_2Cl_2 (200 ml) under nitrogen at 0°C. The solution was stirred at 0°C for 1 h after the addition was complete and then kept at room temperature for an additional hour. The reaction solution was then worked up by successively washing with dil. HCl, water and brine and dried ($MgSO_4$). The dried solution was concentrated *in vacuo* and abs. ethanol (200 ml) was added to the residue. The mixture was

heated at reflux until gas evolution ceased. The ethanol was removed *in vacuo* and the residue triturated with a little ethanol and refrigerated overnight. The product solidified and was recrystallized from ethanol to give the product as a biege powder (10.28 g, 85%).

Ethyl indole-2-acetate[3]

Ethyl 4-(2-nitrophenyl)acetoacetate prepared as above (2.68 g, 10.7 mmol) was dissolved in acetone (30 ml) and placed in a separatory funnel. Aqueous NH_4OAc (288 ml, 4 M) was added, followed by aq. $TiCl_3$ (77 ml, 15% w/v). The mixture was shaken for 7 min. The resulting dark green solution was extracted with ether (4 × 100 ml) and the combined ether layers washed with water and brine. The solution was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography using CH_2Cl_2 for elution and gave the product (1.63 g) in 75% yield.

4-Chloroindole[10]

2-Chloro-6-nitrotoluene (25 g, 146 mmol) and 40% $PhCH_2N^+(CH_3)_3OH^-$ in methanol (Triton B, 1.8 ml), paraformaldehyde (60 mmol) and DMSO (60 ml) were mixed and stirred at 90°C for 2 h. The product was obtained by distillation (92% yield on basis of paraformaldehyde). The 2-(6-chloro-2-nitrophenyl)ethanol (10.2 g) was reduced by addition as a solution in ethanol (10 ml) to a suspension of zinc powder (42 g) and $CaCl_2$ (4.2 g) in 3:1 ethanol–water (200 ml). The mixture was heated at reflux for 8 h. The product was obtained in 45% yield by extraction with ether. The 2-(6-chloro-2-aminophenyl)ethanol (7 mmol) was added to a mixture of $RuCl_2(PPh_3)_2$ (2 mol%) in toluene under an argon atmosphere in a flask equipped with a gas burette. The mixture became homogeneous after being stirred for about 5 min and was then heated to 120°C in a preheated oil bath and kept at reflux for 6 h. The product was obtained in 92% yield.

6-Bromooxindole[26]

A. 4-Bromo-2-nitropyruvic acid

Diethyl oxalate (29.2 g, 0.20 mol) and 4-bromo-2-nitrotoluene (21.6 g, 0.10 mol) were added to a cooled solution of sodium ethoxide prepared from sodium (4.6 g, 0.20 mol) and ethanol (90 ml). The mixture was stirred overnight and then refluxed for 10 min. Water (30 ml) was added and the solution refluxed for 2 h to effect hydrolysis of the pyruvate ester. The solution was cooled and concentrated *in vacuo*. The precipitate was washed with ether and dried. The salt was dissolved in water (300 ml) and acidified with conc. HCl. The precipitate was collected, washed with water, dried and recrystallized from hexane-EtOAc to give 15.2 g of product.

B. 4-Bromo-2-nitrophenylacetic acid

The pyruvic acid (28.8 g, 0.10 mol) was dissolved in 1 N NaOH (300 ml) and stirred at 0°C. A solution of 30% H_2O_2 (11.3 ml, 0.10 mol) was added dropwise. The solution was stirred for 1 h at 5°C and then acidified with dil. HCl. The precipitate was collected by filtration, washed with water, dried and recrystallized from hexane-EtOAc to yield 22.2 g (85% yield) of the product.

C. 6-Bromooxindole

4-Bromo-2-nitrophenylacetic acid (26 g, 0.10 mol) was dissolved in a mixture of 50% H_2SO_4 (400 ml) and ethanol (600 ml) and heated to 90°C. Over a period of 1 h, zinc dust (26.2 g, 0.40 mol) was added slowly and then heating was continued for 2 h. The excess ethanol was removed by distillation. The solution was cooled and filtered. The filtrate was extracted with EtOAc. The filtered product and extract were combined, washed with 5% $NaCO_3$ and brine and then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue recrystallized from methanol to give 20.5 g (97% yield) of the oxindole.

6-Benzoyloxindole[22]

A. Diethyl 2-(4-benzoyl-2-nitrophenyl)propanedioate

Sodium hydride (9.3 g, 0.22 mol) was washed with petroleum ether and DMSO (200 ml) was added and the mixture was heated to 100°C. A solution of diethyl malonate (35.2 g, 0.22 mol) in DMSO (50 ml) was then added and stirred for 10 min to give a clear solution. A solution of 4-bromo-3-nitrobenzophenone (30.6 g, 0.10 mol) in DMSO (100 ml) was added and the resulting dark solution kept at 100°C for 1 h. The solution was poured into water (3 l) and extracted (2×) with ether. The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which crystallized. The solid was recrystallized from isopropyl alcohol to give 35.4 g (92% yield) of the product.

B. 6-Benzoyloxindole

A mixture of the above intermediate (23.1 g, 60 mmol) and tin powder (22.4 g, 190 mmol) in ethanol (150 ml) containing conc. HCl (65 ml) was heated at reflux for 2 h. The solution was filtered hot and on cooling the product crystallized. It was recrystallized from nitromethane to give 11.4 g (80% yield) of the oxindole.

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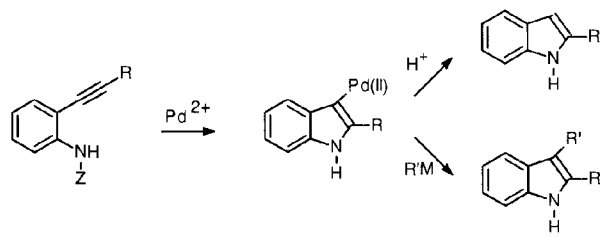
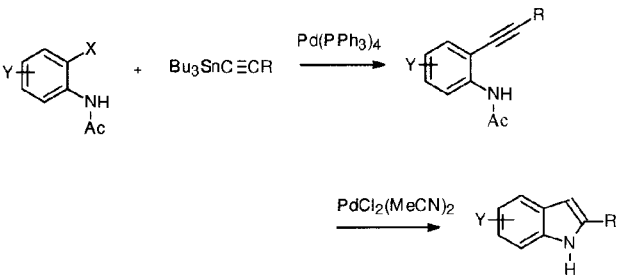
2.4 INDOLES FROM *o*-AMINO- OR *o*-NITROPHENYLACETYLENES

o-Aminophenylacetylenes or N-protected derivatives can be cyclized to indoles by an *endo-dig* addition. The most useful methods employ Pd(II) catalysts. Indol-3-ylpalladium intermediates are involved in the cyclization and this opens the possibility for tandem cyclization–substitution procedures which can introduce a 3-substituent. The ultimate starting materials are usually *o*-haloanilines which are coupled with acetylenes.



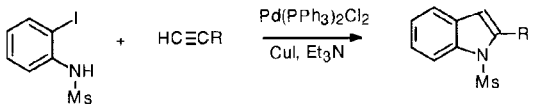
(2.11)

Rudisill and Stille developed a two-step procedure in which 2-bromo- or 2-trifluoromethanesulfonyloxyacetanilides were coupled with tri-*n*-butylstannylacetylenes in the presence of $Pd(PPh_3)_4$[1]. Cyclization was then effected with $PdCl_2(CH_3CN)_2$. The conditions are compatible with a variety of carbocyclic substituents so the procedure can provide 2-substituted indoles with carbocyclic substituents. The reported yield ranges from 40% to 97% for the coupling and from 40% to 82% for cyclization.



(2.12)

2-Iodo-*N*-(methanesulfonyl)anilines can be converted to 2-substituted indoles by reaction with terminal acetylenes in a one-pot process involving CuI, Et_3N and $Pd(PPh_3)_2Cl_2$ as the catalyst system[2]. Yields ranged from 40% to 70% for alkyl, aryl and several oxygenated alkyl substituents.



(2.13)

These Pd-catalysed procedures appear to be preferable to earlier ones in which Cu(I)[3] or Hg(II)[4] were used to induce cyclization. Some additional examples are given in Table 2.3.

Starting with 2-ethynylaniline, Cacchi and co-workers have prepared 2-aryl and 2-(cycloalkenyl)indoles by coupling followed by cyclization[7]. The reagents for the coupling step are $Pd(PPh_3)_4$:CuI:Et_2NH. The cyclization is

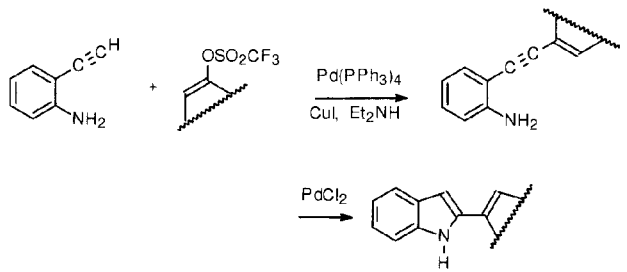
Table 2.3

Indoles *via* *o*-alkynylanilines

Entry	Substituents	Aromatic reactant	Reagent, catalyst	Yield[a] (%)	Ref.
1	2-Phenyl	2-Iodoaniline	Copper phenylacetylide	85	[5]
2	2-(3,4-Dihydro-6-methoxynaphth-1-yl)	2-Ethynylaniline	3,4-Dihydro-6-methoxy-1-trifluoromethanesulfonyloxy-naphthalene, (1) $Pd(PPh_3)_4$, CuI, Et_2NH (2) $PdCl_2$	91, 64	[7]
3	2-Butyl-5-methyl	2-Bromo-5-methylacetanilide	1-(Tri-*n*-butyl-stannyl)hexyne, (1) $Pd(PPh_3)_4$, (2) $PdCl_2(CH_3CN)_2$	81, 77	[1]
4	2-(Diethoxymethyl)-1-methanesulfonyl	2-Iodo-*N*-(methane-sulfonyl)aniline	3,3-Diethoxypropyne $Pd(PPh_3)_2Cl_2$, CuI	63	[2]
5	6-Methyl-5-(4-pyridyl)-7-aza-	2-Amino-3-iodo-6-methyl-5-(4-pyridyl)pyridine	Trimethylsilylethyne, $Pd(PPh_3)_2Cl_2$, CuI	96, 40	[6]

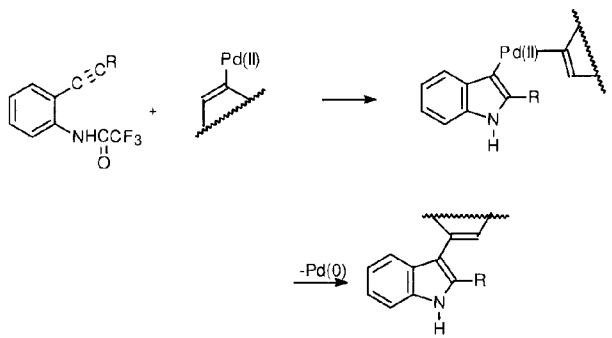
[a]Successive yields for coupling and cyclization or overall yield.

done using $PdCl_2$ in acetonitrile. This sequence was subsequently converted to a one-pot process by use of $PdCl_2$-mediated coupling/cyclization in a two-phase system consisting of CH_2Cl_2 and aq. $n\text{-}Bu_4N^+Br^-$ [8]. These conditions promote protonolysis of the indol-3-ylpalladium intermediate formed in the cyclization.



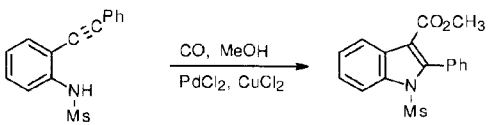
(2.14)

Tandem cyclization/3-substitution can be achieved starting with *o*-(trifluoroacetamido)phenylacetylenes. Cyclization and coupling with cycloalkenyl triflates can be done with $Pd(PPh_3)_4$ as the catalyst[9]. The Pd presumably cycles between the (0) and (II) oxidation levels by oxidative addition with the triflate and the reductive elimination which completes the 3-alkenylation. The *N*-protecting group is removed by solvolysis under the reaction conditions. 3-Aryl groups can also be introduced using aryl iodides[9].



(2.15)

Tandem cyclization and 3-carboxylation has been done with *o*-(methanesulfonamido)phenylacetylenes by conducting the reaction in methanol under a CO atmosphere[10].



(2.16)

Procedures

1-Acetyl-2-butyl-5-chloroindole[1]

A mixture of 2-bromo-4-chloroacetanilide (1.038 g, 4.36 mmol), tri(-*n*-butyl)-hexynylstannane (1.86 g, 5.01 mmol) and $Pd(PPh_3)_4$ (0.151 g, 0.131 mmol) in toluene (40 ml) was heated at 100°C for 1.5 h. The solvent was removed *in vacuo* and the residue eluted through silica gel with 4:1 hexane–EtOAc to give 2-(1-hexynyl)-4-chloroacetanilide (0.881 g) in 81% yield. To a solution of 2-(1-hexynyl)-4-chloroacetanilide (0.115 g, 0.46 mmol) in acetonitrile (6 ml) was added $PdCl_2(CH_3CN)_2$ (12 mg, 10 mol%). The mixture was heated at 80°C for 2 h. The solvent was removed *in vacuo* and the residue eluted through silica gel with 5:1 hexane–EtOAc to yield 95 mg (83% yield) of the product.

2-(3-α-Acetoxyandrost-16-en-17-yl)indole[8]

A solution of 3-α-acetoxyandrost-16-en-17-yl triflate (0.230 g, 0.49 mmol) in DMF (0.5 ml) and Et_2NH (2 ml) was prepared and, with stirring, 2-ethynylaniline (0.058 g, 0.49 mmol), $Pd(PPh_3)_4$ (11 mg, 2 mol%) and CuI (4 mg, 4 mol%) were added. The reaction mixture was stirred for 6 h at room temperature under a nitrogen atmosphere and then concentrated *in vacuo* with gentle warming. The residue was dissolved in CH_2Cl_2 (13 ml) and 0.5 N HCl (5 ml), $PdCl_2$ (5 mg, 6 mol%) and $Bu_4N^+Cl^-$ (15 mg, 10 mol%) were added. The mixture was stirred at room temperature for 48 h under nitrogen. The solvents were removed *in vacuo* and the residue purified by chromatography on silica gel using 4:1 hexane–EtOAc for elution to give the product (0.205 g) in 96% overall yield.

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2.5 REDUCTIVE CYCLIZATION OF *o*-NITROSTYRENES

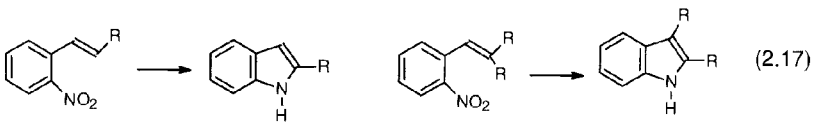
Several procedures have been explored for the reductive cyclization of *o*-nitrostyrenes. Triethyl phosphite accomplishes this transformation by 'deoxy-

Table 2.4

Indoles by reductive cyclization of *o*-nitrostyrenes

Entry	Substituents	Reagents	Yield (%)	Ref.
1	2-(Methoxycarbonyl)	$Pd(PPh_3)_2Cl_2$, CO, $SnCl_2$	60	[8]
2	2-Propyl	$P(OC_2H_5)_3$, 160°C	60	[1]
3	2-(2-Pyridyl)	$P(OC_2H_5)_3$, 160°C	65	[9]
4	2-(2-Pyridyl)	$Ru_3(CO)_{12}$, CO	63	[10]
5	2-[2-(3-Methylpyrid-2-yl)-dioxolan-2-yl	$P(OC_2H_5)_3$, 160°C	52	[11]
6	2-(5,6-Dimethoxyindol-2-yl)-3-phenylthio	$P(OC_2H_5)_3$, 160°C	>90	[12]
7	2-(Ethoxycarbonyl)-5,6-methylendioxy	$P(OC_2H_5)_3$, 160°C	86	[7]
8	Furo[3,2-b]	$P(OC_2H_5)_3$, 160°C	34	[13]

genation'[1,2]. More recently, a $PdCl_2$-PPh_3-$SnCl_2$ system has been found to effect cyclization using CO as the reductant[3]. There are several potential routes to *o*-nitrostyrenes, including Horner–Emmons–Wittig condensation with diethyl *o*-nitrobenzylphosphonate[1]. While these reductive cyclizations can formally be considered to be 'nitrenoid' in character, various observations suggest this to be an oversimplification[1,3]. It seems more likely that each of the reductants generates a specific electrophilic nitrogen intermediate which attacks the adjacent double bond. The structure of the reactive intermediate may vary with the reductant. An interesting feature of the phosphite deoxygenation method is that it can be applied to β,β-disubstituted *o*-nitrostyrenes, in which case one of the β-substituents migrates to become the indole 3-substituent[4–6]. Table 2.4 gives examples of reductive cyclizations of *o*-nitrostyrenes to indoles.



(2.17)

Procedures

Ethyl indole-2-carboxylate[7]

Ethyl *o*-nitrocinnamate (1 mmol) was dissolved in triethyl phosphite (5 mmol) and heated at 170°C for 3 h. The triethyl phosphite and triethyl phosphate were removed *in vacuo*. The residue was eluted through a column of silica gel using $CHCl_3$ and the product recrystallized from $CHCl_3$-hexane. The yield was 94%.

2-Phenylindole[3]

o-Nitrostilbene (2 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol) and dioxane (10 ml) were placed in a glass liner in a 50 ml stainless steel autoclave equipped for stirring. The apparatus was sealed, purged three times with CO (10 kg/cm^2) and pressurized to 20 kg/cm^2 with CO and heated quickly (within 10 min) to 100°C and maintained at that temperature for 16 h. The apparatus was then rapidly cooled and the gases discharged. The solvent was removed *in vacuo* and the product purified by medium pressure column chromatography on silica gel.

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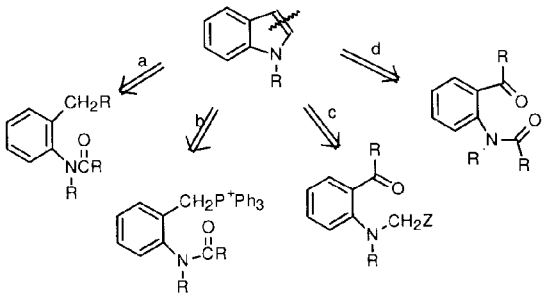
–3–

Category I*b* Cyclizations

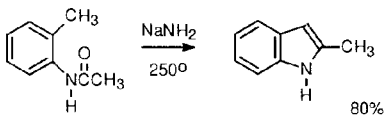
Category I*b* cyclizations effect closure of the C2 C3 bond. Scheme 3.1 depicts retrosynthetic transformations corresponding to syntheses in category I*b*. Included are three variations of the intramolecular aldol condensation and reductive coupling of *o*,*N*-diacylanilines.



SCHEME 3.1

3.1 INDOLES FROM *o*-ALKYLANILIDES – THE MADELUNG SYNTHESIS

The classical conditions for the Madelung indole synthesis are illustrated by the *Organic Syntheses* preparation of 2-methylindole which involves heating *o*-methylacetanilide with sodium amide at 250°C[1].



(3.1)

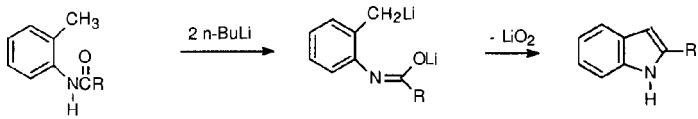
These conditions are so harsh that they are applicable only to indoles with the most inert substituents. Cyclization can be achieved at much lower temperatures by using alkyllithium reagents as the base. For example, treatment of *o*-methylpivalanilide with 3 eq. of *n*-butyllithium at 25°C gives 2-*tert*-butylindole in 87% yield[2]. These conditions can be used to make

Table 3.1

Indoles by base-mediated cyclization of *o*-alkylanilides

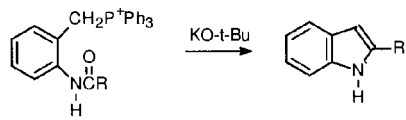
Entry	Substituents	Cyclization conditions	Yield (%)	Ref.
1	2-Methyl	$NaNH_2$, 250°C	80	[1]
2	2-Nonyl	$NaNH_2$, 250°C	81	[5]
3	2-(2-Indolyl)	K^+*t*-BuO$^-$, 25°C	80	[6]
4	2-(1-Methylpiperid-4-ylmethyl)	K^+*t*-BuO$^-$, 340°C	92	[7]
5	5-Chloro-2-phenyl	*n*-BuLi, −20/25°C	>90	[2]
6	2-Cyclohexyl-5-methoxy	*n*-BuLi, 25°C	40	[8]

2-arylindoles from benzanilides and have also been applied to the synthesis of azaindoles[3]. The reaction is presumed to proceed through a dilithiated intermediate which eliminates Li_2O[4]. Table 3.1 gives some examples.



(3.2)

A variation of the Madelung cyclization involves installing a functional group at the *o*-methyl group which can facilitate cyclization. For example, a triphenylphosphonio substituent converts the reaction into an intramolecular Wittig condensation. The required phosphonium salts can be prepared by starting with *o*-nitrobenzyl chloride or bromide[9]. The method has been applied to preparation of 2-alkyl and 2-arylindoles as well as to several 2-alkenylindoles. Table 3.2 provides examples.



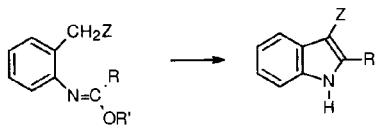
(3.3)

Table 3.2

2-Substituted indoles from *o*-carboxamidobenzylphosphonium salts

Entry	Substituents	Yield (%)	Ref.
1	2-Benzyl	64	[10]
2	2-(2-Methylprop-1-enyl)	93	[11]
3	2-(1-Methylethenyl)	65	[12]
4	2-(Ethoxycarbonylmethyl)	72	[13]
5	2-(4-Phenylbutyl)	78	[14]

Another variation of the Madelung synthesis involves use of an O-alkyl or O-silyl imidate as the C2 electrophile. The mechanistic advantage of this modification stems from avoiding competing N-deprotonation, which presumably reduces the electrophilicity of the amide group under the classical conditions. Examples of this approach to date appear to have been limited to reactants with a EW substituent at the *o*-alkyl group[15,16].

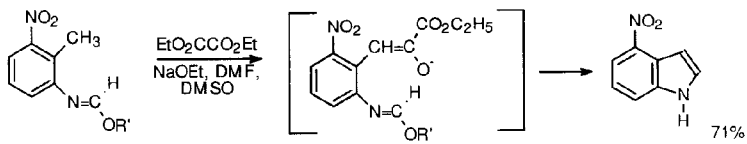


(3.4)

Z = $ArSO_2$; R =H; R' = C_2H_5

Z = CN; R = CH_3; R' $Si(CH_3)_3$

An *Organic Syntheses* preparation of 4-nitroindole may involve a related reaction. The condensation occurs in the presence of diethyl oxalate which may function by condensation at the methyl group. If this is the case, it must subsequently be lost by deacylation[17].



(3.5)

71%

Procedures

*2-(*tert*-Butyl)indole[2]*

A stirred solution of *o*-methylpivalanilide (50 mmol) in dry THF (100 ml) was maintained at 15°C under a nitrogen atmosphere. A 1.5 M solution of *n*-butyllithium in hexane (3 equiv.) was added dropwise. The solution was then maintained at room temperature for 16 h. The solution was cooled in an ice-bath and treated with 2 N HCl (60 ml). The organic layer was separated and the aqueous layer was further extracted with benzene. The combined layers were dried ($MgSO_4$). The product was obtained in 87% yield and recrystallized from ether-cyclohexane.

2-(4-Phenylbutyl)indole[14]

4-Phenylbutanoyl chloride (0.8 g, 4.9 mmol) was added dropwise to a stirred solution of *o*-aminobenzyltriphenylphosphonium chloride hydrochloride (1.6 g,

3.6 mmol) in DMF (3 ml) and pyridine (1 ml). The mixture was stirred overnight and then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and washed with 1 N HCl (2 × 10 ml) and brine (10 ml) and dried over Na_2SO_4. The solution was filtered and evaporated. The residue was triturated with ether (20 ml) to yield 1.8 g (90%) of the intermediate acylated phosphonium salt. A mixture of this material (4.5 g, 7.98 mmol) and KO-*t*-Bu (1.0 g, 8.9 mmol) was refluxed in toluene (50 ml) for 30 min. The cooled solution was filtered and then concentrated. The residue was purified by elution through silica gel with CH_2Cl_2. The yield was 1.55 g (78%).

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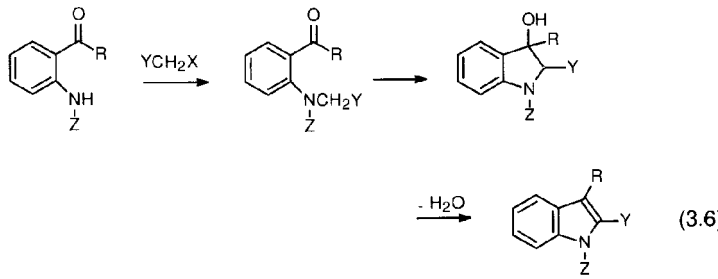
3.2 INDOLES FROM *o*-ACYLANILINE DERIVATIVES

Retrosynthetic path **b** in Scheme 3.1 corresponds to reversal of the electrophilic and nucleophilic components with respect to the Madelung synthesis and identifies *o*-acyl-*N*-alkylanilines as potential indole precursors. The known examples require an aryl or EW group on the *N*-alkyl substituent and these substituents are presumably required to facilitate deprotonation in the condensation. The preparation of these starting materials usually involves *N*-alkylation of an *o*-acylaniline. Table 3.3 gives some examples of this synthesis.

Table 3.3

Indoles from *o*-acylaniline derivatives

Entry	Substituents	Reactants	Conditions	Yield (%)	Ref.
1	2-Benzoyl	2-Aminophenyldioxolane, phenacyl bromide	(1) $NaHCO_3$ (2) HBr	60	[1]
2	6-Chloro-2-(ethoxycarbonyl)-3-(4-fluorophenyl)	N-[5-Chloro-2-(4-fluorobenzoyl]benzamide, methyl bromoacetate	(1) NaH (2) NaOMe	30	[2]
3	1-Benzoyl-5-chloro-2,3-diphenyl	N-(2-Benzoyl-4-chlorophenyl)-N-benzylbenzamide	(1) LDA (2) $POCl_3$, pyridine	72	[3]
4	5-Chloro-2-cyano-1-(4-methylphenyl-sulfonyl)-3-phenyl	N-(2-Benzoyl-4-chlorophenyl)-*p*-toluenesulfonamide, chloroacetronitrile	DMF, reflux	71	[4]



(3.6)

References

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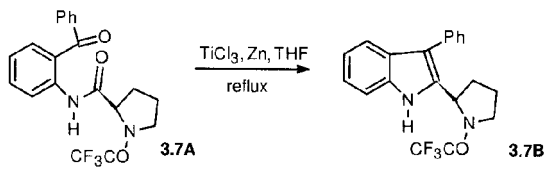
3.3 INDOLES FROM *o,N*-DIACYLANILINES

Retrosynthetic path **d** (Scheme 3.1) has recently been realized as an effective synthesis of 2,3-disubstituted indoles using low-valent titanium reagents to effect the reductive cyclization. Several aryl- and methyl-substituted compounds were prepared by using Ti-graphite prepared from K-graphite and $TiCl_3$[1,2]. An improved methodology which avoids the preparation of K-graphite was subsequently developed[3]. This procedure uses zinc powder to effect *in situ* reduction of $TiCl_3$.



3.7A **3.7B**

(3.7)

Procedure

S-3-Phenyl-2-[N-(trifluoroacetyl)pyrrolidin-2-yl]indole[3]

A mixture of compound **3.7A** (250 mg, 0.64 mmol), $TiCl_3$ (209 mg, 1.36 mmol) and zinc dust (178 mg, 2.72 mmol) in THF (20 ml) was heated at reflux for 1 h in an argon atmosphere. The solution was cooled to room temperature and

filtered through a short silica plug using EtOAc for elution. The product **3.7B** (206 mg) was obtained in 90% yield.

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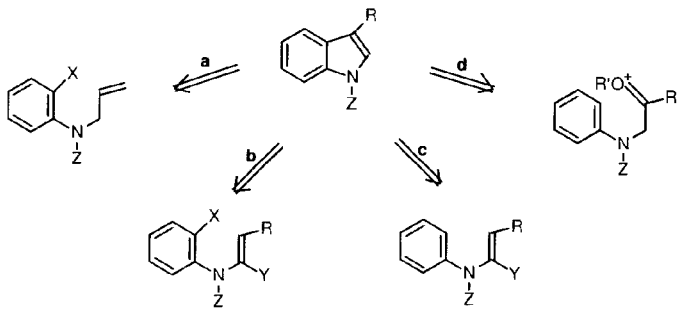
–4–

Category Ic Cyclizations

Category Ic cyclizations involve formation of the C3–C3a bond and require aniline derivatives with a nitrogen substituent appropriate for such reaction. Some, but not all, such cyclizations also require an *o*-substituent, frequently halogen. The retrosynthetic transformations corresponding to the most important of this group of syntheses are shown in Scheme 4.1



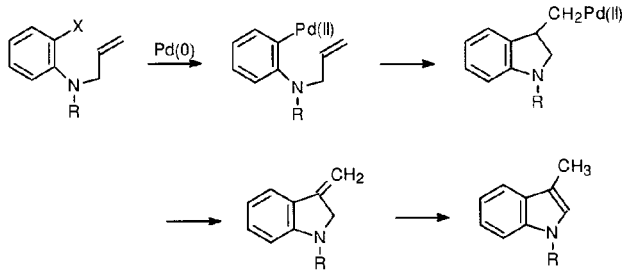
SCHEME 4.1

Retrosynthetic path **a** corresponds to Pd-catalysed *exo-trig* cyclization of *o*-halo-*N*-allylanilines. Path **b** involves the *endo-trig* cyclization of *o*-halo-*N*-vinyl anilines. Path **c** is a structurally similar cyclization which can be effected photochemically in the absence of an *o*-substituent. Retrosynthetic path **d** involves intramolecular Friedel–Crafts oxyalkylation followed by aromatization.

4.1 TRANSITION METAL-CATALYSED CYCLIZATION OF *N*-ALLYL- AND *N*-PROPARGYL ANILINES

The development of methods for aromatic substitution based on catalysis by transition metals, especially palladium, has led to several new methods for indole synthesis. One is based on an intramolecular Heck reaction in which an

o-halo-*N*-allylaniline is cyclized to an indole as represented by path **a** in Scheme 4.1. The first application of this reaction to indole synthesis was by Hegedus and co-workers[1]. The procedure involved extended heating of an *N*-allyl-*o*-iodoaniline with $Pd(OAc)_2$ and Et_3N in CH_3CN. The reaction presumably involves a Pd(0) species which undergoes oxidative addition with the aryl iodide. Cyclization then provides an unstable alkylpalladium intermediate which undergoes elimination regenerating Pd(0). The initial heterocyclic product is an *exo*-alkylideneindoline but under these conditions they isomerize to 3-alkylindoles.



(4.1)

An important reaction parameter is the choice of the base and Na_2CO_3 or NaOAc have been shown to be preferable to Et_3N in some systems[2]. The inclusion of NH_4Cl has also been found to speed reaction[2]. An optimization of the cyclization of *N*-allyl-2-benzyloxy-6-bromo-4-nitroaniline which achieved a 96% yield found Et_3N to be the preferred base[3]. The use of acetyl or methanesulfonyl as N-protecting groups is sometimes advantageous (see Entries 4 and 5, Table 4.1).

The indole skeleton can also be constructed by Pd-mediated cyclization of *N*-propargyl-*o*-haloanilines. The vinylpalladium intermediates formed in the cyclization are sufficiently stable to permit further reaction[4,5]. For example,

Table 4.1

Indoles by cyclization of *N*-allylaniline derivatives

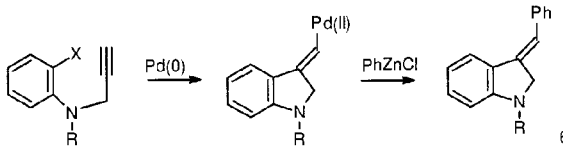
Entry	Substituents	Cyclization conditions	Yield (%)	Ref.
1	3-(2-Propyl)	$Pd(OAc)_2$, Et_3N	73	[1]
2	3-(1-Benzyloxycarbonylpyrrol-idin-2-ylmethyl)-5-(methane-sulfonamidomethyl)	$Pd(OAc)_2$, Et_3N	81	[6]
3	7-Benzyloxy-3-methyl-5-nitro	$Pd(OAc)_2$, Et_3N	96	[3]
4	1-Methanesulfonyl-6-methoxy-3-methylene-2,3-dihydro	$Pd(OAc)_2$, $AgCO_3$, PPh_3	80	[7]
5	1-Acetyl-5-(*N*-allylacetamido)-4,7-diacetoxy-3-methyl	$Pd(OAc)_2$, PPh_3, Et_3N	76	[8]

Table 4.2

Oxindoles by cyclization of *N*-alkenoylanilines

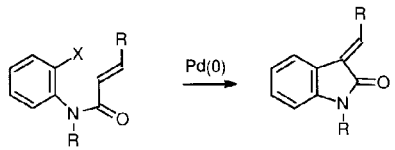
Entry	Oxindole substituents	Conditions	Yield (%)	Ref.
1	3-Benzylidene	$Pd(OAc)_2$, NaOAc	97	[2]
2	1-Methyl-*spiro*-3-cyclopent-2-ene	$Pd(OAc)_2$, PPh_3	91	[9]
3	1-Methyl-*spiro*-3-cyclohex-2-ene	$Pd_2(dba)_3$, Ag_3PO_4 *R*-BINAP	74 (80%ee)	[10]
4	1,3-Dimethyl-5-methoxy-3-(2-oxoethyl)	$Pd_2(dba)_3$, *S*-BINAP	84 (95%ee)	[11]
5	1,3-Dimethyl-5-methoxy	*n*-Bu_4Sn, AIBN	63	[12b]
6	3-Ethyl-5-methoxy-1-(α-methylbenzyl)	*n*-Bu_4Sn, AIBN	64 (2%ee)	[12d]
7	2-(Ethoxycarbonylmethyl)-1-methyl	TMSCl, *n*-BuLi	85	[13]

reaction with arylzinc chlorides gives 3-arylideneindolines. Similar reactions have been observed for alkyl and alkynylzinc chlorides and with the zinc enolate of ethyl acetate (Reformatsky reagent).



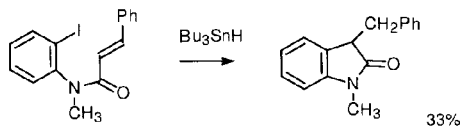
(4.2)

The Ic cyclization pattern has also proved useful for the preparation of oxindoles from *o*-haloalkenoylanilines. Table 4.2 gives some examples.

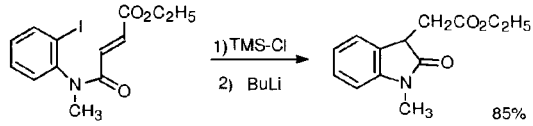


(4.3)

Besides Pd-catalysed cyclizations, both radical[12] and organolithium[13] intermediates can give oxindoles by *exo-trig* additions.



(4.4)



(4.5)

Procedure

7-Benzyloxy-3-methyl-5-nitroindole[3]

2-Benzyloxy-6-bromo-4-nitro-*N*-(2-propenyl)aniline (5.82 g, 16 mmol), *tetra-n*-butylammonium bromide (5.16 g, 16 mmol) and Et_3N (4.05 g, 40 mmol) were dissolved in DMF (15 ml). Palladium acetate (72 mg, 2 mol%) was added and the reaction mixture was stirred for 24 h. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with water, 5% HCl and brine, dried and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and filtered through silica to remove colloidal palladium. Evaporation of the eluate gave the product (4.32 g) in 96% yield.

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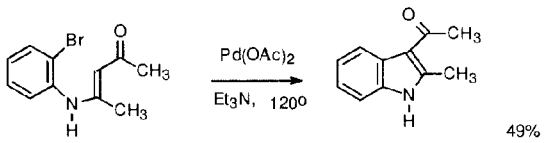
4.2 CYCLIZATION OF *N*-VINYL-*o*-HALOANILINES

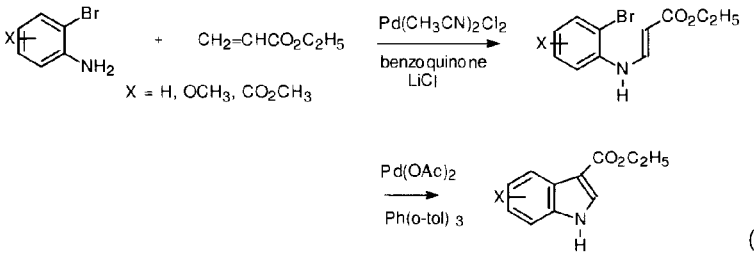
Intramolecular palladium-catalysed cyclizations can also be applied to *N*-vinylanilines. Usually the vinyl group carries an EW substituent which serves

to stabilize the enamine. β-(2-Bromoanilino)enones are cyclized to 3-acylindoles[1].



(4.6)

Esters of indole-3-carboxylic acid can be made in two steps starting with an *o*-bromoaniline and an acrylate ester[2].



(4.7)

References

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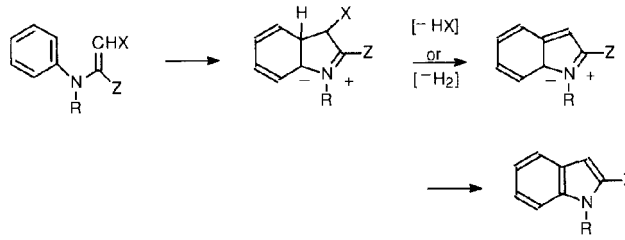
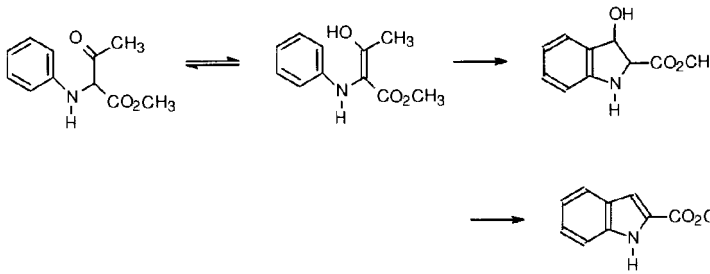
4.3 PHOTOCYCLIZATION OF *N*-VINYLANILINES

The photocyclization of *N*-vinylanilines is an example of a general class of photocyclizations[1]. If the vinyl substituent has a potential leaving group or the reaction is carried out so that oxidation occurs, the cyclization intermediate can aromatize to an indole.



(4.8)

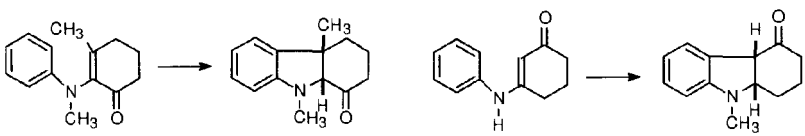
For example, α-anilino-β-ketoesters photocyclize to indole-2-carboxylate esters[2].



(4.9)

α-Anilinoacrylonitriles photocyclize to 2-cyano-2,3-dihydroindoles[3,4]. If the photocyclization is done under oxidative conditions, 2-cyanoindoles are obtained[5].

2-Anilinocyclohex-2-enones photocyclize to 1-oxo-1,2,3,4,4a,9a-hexahydrocarbazoles[6]. Similarly, 3-anilinocyclohex-2-enones give 4-oxo analogues[7].



(4.10)

Procedure

3-(4-Bromobutyl)-2-cyano-1-methylindole[5]

A solution of 7-bromo-2-(*N*-methylanilino)hept-2-enenitrile (145 mg, 0.52 mmol) in cyclohexane (60 ml) was placed in a quartz tube and purged with oxygen. The sample was irradiated for 8 h in a Rayonet Model RPR-100 Reactor using 254 nm light. An oxygen atmosphere was maintained during

photolysis. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography using EtOAc- hexane (2:98) for elution. The yield was 81%.

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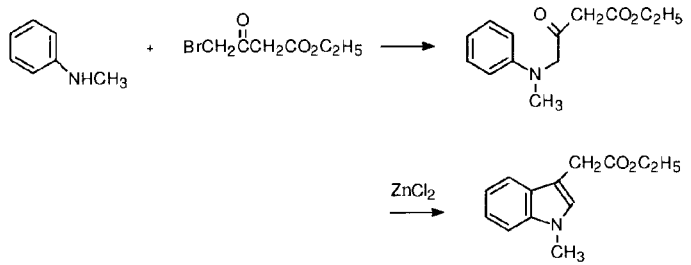
4.4 ELECTROPHILIC CYCLIZATION OF α-ANILINO ALDEHYDES AND KETONES

Another category Ic indole synthesis involves cyclization of α-anilino aldehydes or ketones under the influence of protonic or Lewis acids. This corresponds to retrosynthetic path **d** in Scheme 4.1. Considerable work on such reactions was done in the early 1960s by Julia and co-workers. The most successful examples involved alkylation of anilines with γ-haloacetoacetic esters or amides. For example, heating *N*-substituted anilines with ethyl 4-bromoacetoacetate followed by cyclization with $ZnCl_2$ gave indole-3-acetate ester[1]. Additional examples are given in Table 4.3.



(4.11)

N-(2,2-Diethoxyethyl)anilines are potential precursors of 2,3-unsubstituted indoles. A fair yield of 1-methylindole was obtained by cyclization of *N*-methyl-*N*-(2,2-diethoxyethyl)aniline with BF_3, but the procedure failed for indole itself[2]. Nordlander and co-workers alkylated anilines with bromoacetaldehyde diethyl acetal and then converted the products to *N*-trifluoroacetyl derivatives[3]. These could be cyclized to 1-(trifluoroacetyl)indoles in a mixture of trifluoroacetic acid and trifluoroacetic anhydride. Sundberg and

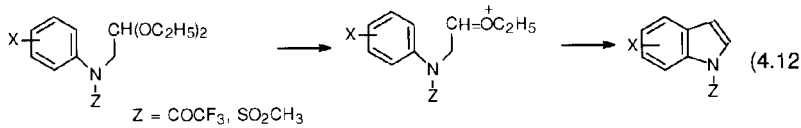
Table 4.3

Indoles by cyclization of α-anilino ketones and aldehydes

Entry	Substituents	Conditions	Yield (%)	Ref.
1	1-Ethyl-3-methyl	Ac_2O	53	[8]
2	3-(4-Fluorophenyl)-1-(2-propyl)	$ZnCl_2$	81	[5]
3	3-(1,3-*bis*-Ethoxycarbonyl-propyl)-1-methyl	$ZnCl_2$	64	[9]
4	6-Chloro-1-methanesulfonyl	$TiCl_4$, 110°C	55	[4]
5	4,6-Dimethyl-1-trifluoroacetyl	TFAA, TFA, 56°C	93	[3]
6	1,3-Dimethyl-5-methoxy	$ZnCl_2$	72	[10]
7	5-Methoxycyclohexa[b][a]	$MgCl_2$, *p*-anisidine	88	[11]
8	6,7-Dimethoxy-3-(ethoxycarbonylmethyl)-1-methyl-4-[2-(trimethylsilyl)ethoxycarbonylamido]	EtOH, reflux	87	[12]

[a]Systematic name 6-methoxy-1,2,3,4-tetrahydrocarbazole.

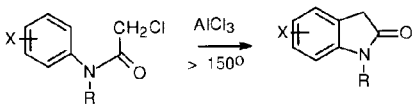
Laurino examined a similar method in which methanesulfonanilides were alkylated with bromoacetaldehyde diethyl acetal and then cyclized with $TiCl_4$[4]. These methods presumably involve generation of an electrophilic intermediate from the acetal functionality, followed by an intramolecular Friedel–Crafts reaction. As a consequence, the cyclization is favoured by ER substituents and retarded by EW groups on the benzene ring.



(4.12)

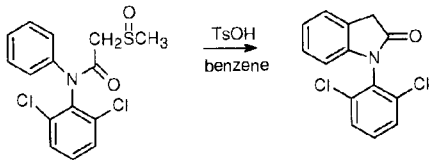
N-Phenacyl derivatives of *N*-acylmethylanilines can be cyclized in good yield using $ZnCl_2$ in alcoholic solution[5,6] or by exposure to solid $ZnCl_2$ or $AlCl_3$ [7]. Extended heating can cause rearrangement to the corresponding 2-substituted indole. Generally, these reactions cannot be applied to *N*-unsubstituted indoles because of competing formation of 2-arylindoles. The formation of 2-arylindoles from anilines and phenacyl halides will be discussed in Section 7.5. Table 4.3 gives some examples of preparation of indoles from α-anilinocarbonyl compounds.

Intramolecular Friedel–Crafts substitution has also figured prominently in the synthesis of oxindoles from α-haloacetanilides. Typical reaction conditions for cyclization involve heating with $AlCl_3$[13–17].



(4.13)

Milder conditions ($SnCl_4$, room temperature) suffice for α-chloro-α-thiomethylacetanilides, implying that it is the ionization of the halogen that is the difficult step in the chloroacetanilide cyclization[18,19]. Pummerer conditions can also be used for the cyclization of α-sulfinylacetanilides[19,20].



(4.14)

Procedure

1-Methyl-5-fluorooxindole[16]

N-Methyl-4-fluoro-α-bromoacetanilide

N-Methyl-4-fluoroaniline (49.5 g, 0.395 mol) was added dropwise over 30 min to bromoacetyl bromide (40 g, 0.198 mol) dissolved in benzene (250 ml) and the mixture was stirred overnight. The solution was filtered and washed with dil. HCl and then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated with toluene and filtered. The toluene was removed and the residue distilled under vacuum to give the product as an oil (14.4 g, 30%).

1-Methyl-5-fluorooxindole

The bromoacetanilide (14.4 g, 0.58 mol) was mixed with $AlCl_3$ (19.5 g, 0.146 mol) and heated to 220–225°C for 30 min. The hot solution was poured on to ice (600 g) and the precipitate was collected to give 8.6 g (85%) of the product.

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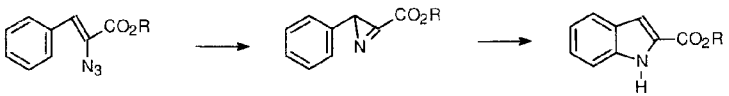
–5–

Category I*i* Cyclizations – The Hemetsberger Synthesis

The main example of a category I*i* indole synthesis is the Hemetsberger procedure for preparation of indole-2-carboxylate esters from α-azidocinnamates[1]. The procedure involves condensation of an aromatic aldehyde with an azidoacetate ester, followed by thermolysis of the resulting α-azidocinnamate. The conditions used for the base-catalysed condensation are critical since the azidoacetate enolate can decompose by elimination of nitrogen. Conditions developed by Moody usually give good yields[2]. This involves slow addition of the aldehyde and 3–5 equiv. of the azide to a cold solution of sodium ethoxide. While the thermolysis might be viewed as a nitrene insertion reaction, it has been demonstrated that azirine intermediates can be isolated at intermediate temperatures[3].



(5.1)

The procedure has been found to be compatible with a variety of carbocyclic substituents. Table 5.1 provides some examples of the reaction.

Procedure

Methyl 2,4,5-trimethoxy-α-azidocinnamate[11]

A solution of sodium methoxide (25% w, 115 ml, 532 mmol) in methanol (187 ml) was cooled to −8°C under nitrogen. A solution of 2,4,5-trimethoxybenzaldehyde (25 g, 128 mmol) and methyl azidoacetate (59 g, 513 mmol) in a 1:2 mixture of methanol–THF (50 ml + 100 ml) was added dropwise to the sodium methoxide solution with stirring at −8°C over a period of 45 min. The solution was stirred and kept below 5°C for 2 h. The mixture was then poured onto ice (1 kg) and stirred. The precipitate which resulted was collected by filtration, washed with water and dried over $CaCl_2$ in a vacuum desiccator. The dried precipitate was dissolved in EtOAc (600 ml) and dried over Na_2SO_4.

Table 5.1

Preparation of indole-2-carboxylate esters by the Hemetsberger method

Entry	Substituents	Ester	Conditions	Yield (%) (from ArCH=O)[a]	Ref.
1	4-Benzyloxy	Methyl	Xylene/reflux	33	[4]
2	4-Ethoxycarbonyl	Ethyl	Toluene/reflux	79	[5]
3	6-Methoxy	Methyl	Xylene/reflux	88	[6]
4	6-(1,1-Dimethylpropenoxy)	Ethyl	Toluene/reflux	60	[2]
5	6-(1-Methyl-1,3-dioxan-1-yl)	Methyl	Xylene/reflux	78	[7]
6	7-Bromo-4-methoxy	Methyl	Xylene/reflux	51	[8]
7	2-(*tert*-Butyldimethylsiloxymethyl)-7*H*-1,4-dioxino[2,3-e]	Methyl	Xylene/reflux	72, 75	[9]
8	4-Benzyloxy-5-methoxy-6-methyl	Methyl	Xylene/reflux	80, 96	[10]
9	4,6,7-Trimethoxy	Methyl	Xylene/reflux	74, 99	[11]
10	4-Ethyl-6.8-dimethylcyclopenta[f]	Ethyl	Toluene/reflux	86	[12]
11	5,7-Dibenzyloxy-4,6-difluoro	Methyl	Xylene/reflux	50	[13]

[a]Single yields are the overall yield from the aromatic aldehyde.

Evaporation of the solvent gave the product as bright yellow crystals (27.6 g) in 74% yield.

Methyl 4,6,7-trimethoxyindole-2-carboxylate[11]

The cinnamate ester prepared as above (23.2 g, 79 mmol) was added as a solid slowly to refluxing xylene (500 ml) over a period of 3 h at a rate that prevented accumulation of unreacted azidocinnamate in the solution (monitored by gas evolution through a gas bubbler). The solution was refluxed for an additional 2 h after gas evolution ceased. The reaction mixture was cooled and the solvent removed *in vacuo*. The residue was recrystallized from methanol to give pure product (20.7 g, 99% yield).

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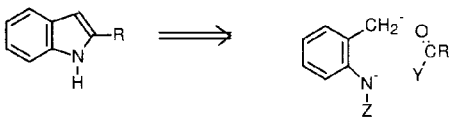
–6–

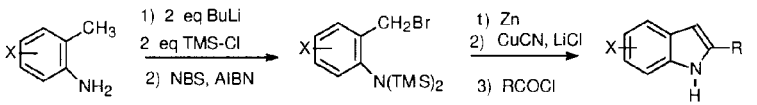
Category II*ab* Cyclizations

The main II*ab* synthetic pathway is illustrated in Scheme 6.1 and corresponds to C-acylation of an *o*-aminobenzyl carbanion equivalent. Acylation is normally followed by *in situ* cyclization and aromatization. This route is therefore closely related to the cyclizations of *o*-aminobenzyl ketones described in Section 2.3 but the procedures described here do not involve isolation of the intermediates.



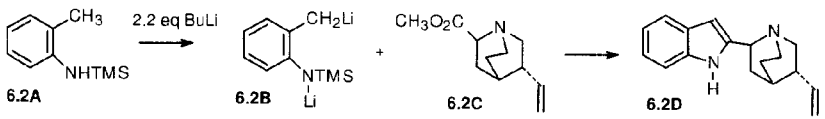
SCHEME 6.1

One type of *o*-aminobenzyl anion synthon is a mixed Cu/Zn reagent which can be prepared from *o*-toluidines by *bis*-trimethylsilylation on nitrogen, benzylic bromination and reaction with Zn and CuCN[1]. Reaction of these reagents with acyl halides gives 2-substituted indoles.



(6.1)

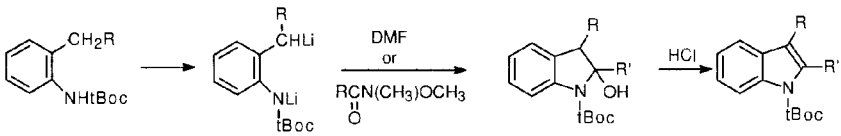
Another *o*-aminobenzyl anion equivalent is generated by treatment of *N*-trimethylsilyl-*o*-toluidine with 2.2 eq. of *n*-butyllithium. Acylation of this intermediate with esters gives indoles[2]. This route, for example, was used to prepare **6.2D**, a precursor of the alkaloid cinchonamine.



(6.2)

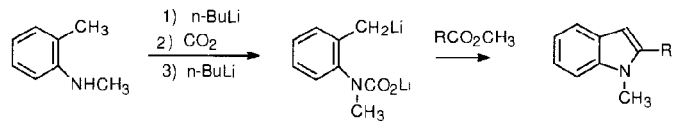
A more highly substituted analogue was successfully used in the preparation of the penitrem class of terpenoid indoles[3].

Another version of the *o*-aminobenzyl anion synthon is obtained by dilithiation of *N*-*t*-Boc-protected *o*-alkylanilines. These intermediates are *C*-acylated by DMF or *N*-methoxy-*N*-methyl carboxamides, leading to either 3- or 2,3-disubstituted indoles. In this procedure dehydration is not spontaneous but occurs on brief exposure of the cyclization product to acid[4]. Use of CO_2 as the electrophile generates oxindoles.



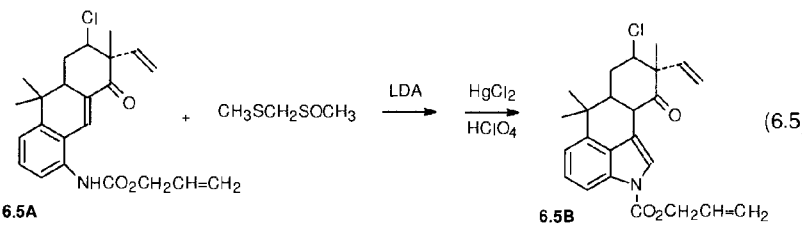
(6.3)

In a related procedure *N*-methyl-*o*-toluidine can be *N*-lithiated, carboxylated and *C*-lithiated by sequential addition of *n*-butyllithium, CO_2, and *n*-butyllithium[5]. The resulting dilithiated intermediate reacts with esters to give 1,2-disubstituted indoles.



(6.4)

In a more elaborate and specific synthesis, the terpenoid indole skeleton found in haplaindole G, which is isolated from a blue-green alga, was constructed by addition of a nucleophilic formyl equivalent to enone **6.5A**. Cyclization and aromatization to the indole **6.6B** followed Hg^{2-}-catalysed unmasking of the aldehyde group[6].



6.5A **6.5B**

(6.5)

Procedures

2-(5-Vinyl-1-azabicyclo[2.2.2]octan-2-yl)indole[2]

A solution of *N*-TMS-*o*-toluidine (200 mg, 1.12 mmol) in dry hexanes (8 ml) was cooled to 0°C and treated dropwise with a 2.5 M solution of *n*-BuLi in

hexanes (1.0 ml, 2.5 mmol). The pale yellow solution was heated at reflux for 6.5 h. The resulting solution (orange) was cooled to room temperature and added via a cannula to a cold (−78°C) solution of ethyl 5-vinyl-1-azabicyclo[2.2.2]octane-2-carboxylate (180 mg, 0.86 mmol) in THF (5 ml). The mixture was then allowed to warm to room temperature and diluted with ether (25 ml) and quenched with sat. aq. NaCl (10 ml). The product was isolated by extraction and purified by chromatography using 3:2 hexanes–acetone for elution. The yield was 63%.

*1-(*tert*-Butoxycarbonyl)-6-methoxyindole[4]*

A solution of *N*-(*tert*-butoxycarbonyl)-6-methoxy-2-methylaniline (11.9 g, 50 mmol) was cooled to −40°C and *s*-BuLi (96 ml of 1.3 M in cyclohexane, 125 mmol) was added. The mixture was stirred at −45°C to −55°C for 30 min and then allowed to warm slowly to −15°C over 60 min. The yellow solution was recooled to −45°C and DMF (5.8 ml, 75 mmol) was added. After 5 min the reaction mixture was diluted with water (250 ml) and the product was extracted with EtOAc (2 × 150 ml). The extract was washed with water (200 ml) and then concentrated *in vacuo*. The residue was dissolved in THF (100 ml) and 12 N HCl (2 ml) was added. The solution was stirred for 5 min at room temperature and then diluted with ether (250 ml). The solution was washed with water (250 ml), sat. aq. $NaHCO_3$ (250 ml), and brine (250 ml), dried (Na_2SO_4) and evaporated. The product was purified by chromatography using 2% EtOAc in hexane for elution. The yield (9.3 g) was 75%.

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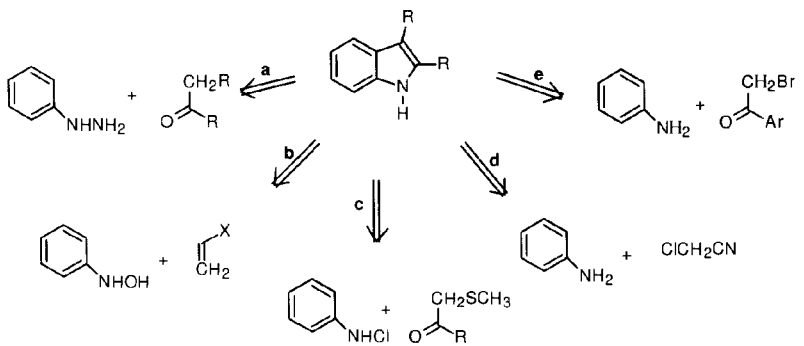
–7–

Category II*ac* Cyclizations

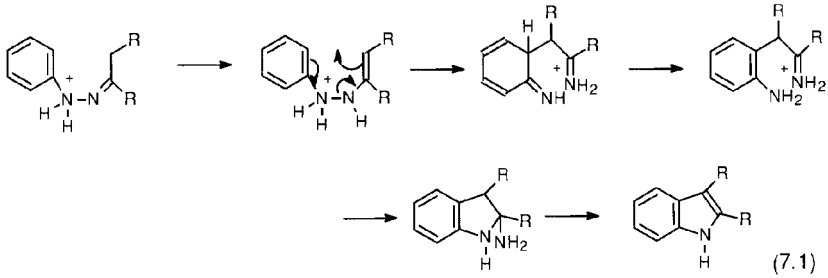
The II*ac* category is the most prevalent means for synthesis of 2-, 3- and 2,3-disubstituted indoles. This reaction pattern creates the indole ring from an aromatic compound and a second molecule which provides C2 and C3 and the attached substituents. This dissection allows for the synthesis to be quite general since the potential C2 and C3 substituents generally do not directly participate in the reaction. Some II*ac* syntheses require only a mono-substituted aromatic ring while others require a specific *o*-substitution pattern. The former type, of course, has the advantage of requiring a less complex starting material. Scheme 7.1 depicts some of the important indole syntheses which fall in category II*ac*. Path **a** is the Fischer cyclization, which is the most widely applied of all indole syntheses. Paths **b** and **c** are closely related methods, which, like the Fischer cyclization, depend on a sigmatropic rearrangement to effect *ortho*-substitution. In each of these reactions, an iminium or carbonyl bond is in place after the sigmatropic rearrangement to permit completion of the cyclization. Path **d** corresponds to the Sugasawa indole synthesis which proceeds by conversion of anilines to indoles by BCl_3-directed *ortho*-chloroacetylation, followed by a reductive cyclization. Path **f** dissects the indole ring to an aniline and α-haloketone. When the ketones are α-bromoacetophenones, this corresponds to the Bischler synthesis of 2-arylindoles.



SCHEME 7.1

7.1 FISCHER INDOLE SYNTHESIS

Retrosynthesis **a** in Scheme 7.1 corresponds to the Fischer indole synthesis which is the most widely used of all indole syntheses. The Fischer cyclization converts arylhydrazones of aldehydes or ketones into indoles by a process which involves *ortho*-substitution via a sigmatropic rearrangement. The rearrangement generates an imine of an *o*-aminobenzyl ketone which cyclizes and aromatizes by loss of ammonia.



(7.1)

The Fischer cyclization is usually carried out with a protic or Lewis acid which functions both to facilitate the formation of the enehydrazine by tautomerization and also to assist the N N bond breakage. The mechanistic basis of the Fischer cyclization has been discussed in recent reviews[1,2].

The Fischer cyclization has proved to be a very versatile reaction which can tolerate a variety of substituents at the 2- and 3-positions and on the aromatic ring. An extensive review and compilation of examples was published several years ago[3]. From a practical point of view, the crucial reaction parameter is often the choice of the appropriate reaction medium. For hydrazones of unsymmetrical ketones, which can lead to two regioisomeric products, the choice of reaction conditions may determine the product composition.

7.1.1 Reaction mechanism and catalysts

The mechanism of the Fischer cyclization outlined in equation 7.1 has been supported by spectroscopic observation of various intermediates[4] and by isolation of examples of intermediates in specialized structures[5]. In particular, it has been possible to isolate enehydrazines under neutral conditions and to demonstrate their conversion to indoles under the influence of acid catalysts[6].

Sigmatropic rearrangements are normally classified as concerted processes with relatively nonpolar transition states. However, the Fischer cyclization involves rearrangement of a charged intermediate and ring substituents have a significant effect on the rate of the rearrangement. The overall cyclization rate

is accelerated by ER substituents in the benzene ring[2,7]. The acceleration provided by acid catalysis is in the range 10^3–10^6[6,8]. This catalytic effect is due at least in part to acceleration of the sigmatropic rearrangement of intermediate. Both protic and Lewis acids have been shown to accelerate related sigmatropic reactions involving rupture of nitrogen–carbon bonds[9].

A variety of both protic and Lewis acids have been used to effect Fischer cyclizations. Hydrochloric acid or sulfuric acid in aqueous, alcohol or acetic acid solution are frequently used. Polyphosphoric acid and BF_3 in acetic acid have also been employed[10]. Zinc chloride is the most frequently used of the common Lewis acids. This choice is supported by comparative studies with $FeCl_3$, $AlCl_3$, $CoCl_2$ and $NiCl_2$, which found $ZnCl_2$ to be the most effective catalyst[11]. Zinc chloride can be used either as a solid mixture with the hydrazone reactant or in ethanol or acetic acid solution[12].

Fischer indolization can also be carried out under thermal conditions without a catalyst in solvents such as ethylene glycol[13], diethylene glycol[14], sulfolane[15] or pyridine (using the hydrazone hydrochloride)[16]. High temperature (275–350°C) heterogeneous cyclizations of arylhydazones to indoles have also been developed with special emphasis on the cyclization of acetaldehyde phenylhydrazone, a reaction which is difficult to achieve in solution. Vapour phase cyclization occurs using Al_2O_3, MgO and MgO/SiO_2[17]. Yields of 85% have been achieved using an alumina-MgF_2 catalyst[18]. This catalyst has also been used successfully to make substituted indoles. An acidic aluminium orthophosphate catalyst has been used to prepare several alkylindoles[19].

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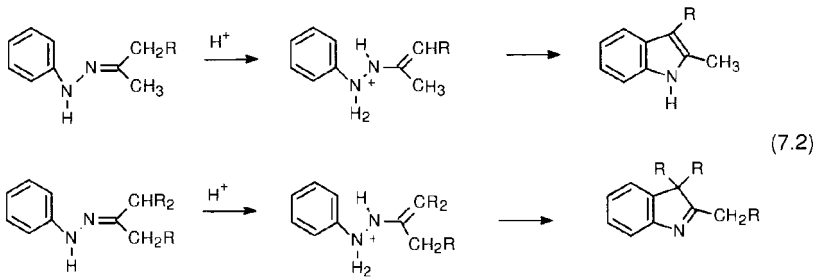
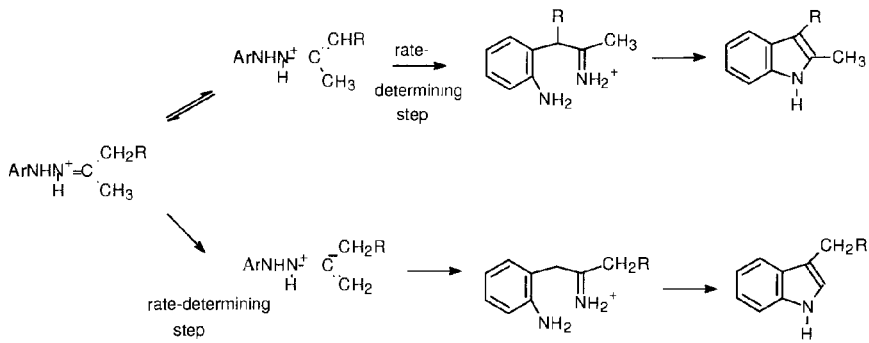
7.1.2 Regioselectivity

The issue of regioselectivity arises with arylhydrazones of unsymmetrical ketones which can form two different enehydrazine intermediates. Under the conditions used most commonly for Fischer cyclizations, e.g. ethanolic HCl, the major product is usually the one arising from the more highly substituted enehydrazine. Thus methyl ketones usually give 2-methylindoles and cyclization occurs in a branched chain in preference to a straight chain. This regioselectivity is attributed to the greater stability of the more substituted enhydrazine and its dominance of the reaction path.



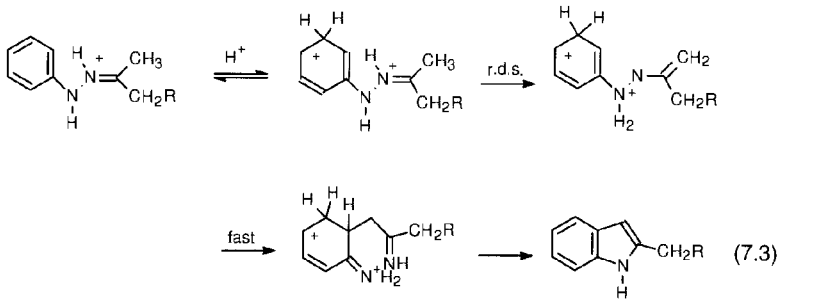
(7.2)

There are a number of cases in which it has been shown that more strongly acidic conditions can shift the direction of indolization from the more substituted group to the less subsituted one[1–6]. Mechanistic interpretation of this effect has suggested that either enehydrazine formation or its rearrangement can be rate-determining. Rate-determining enehydrazine formation could favour reaction through the less-substituted regioisomer while rate-determining rearrangement would proceed preferentially through the more substituted and thermodynamically preferred enehydrazine. These ideas are outlined in Scheme 7.2.



SCHEME 7.2

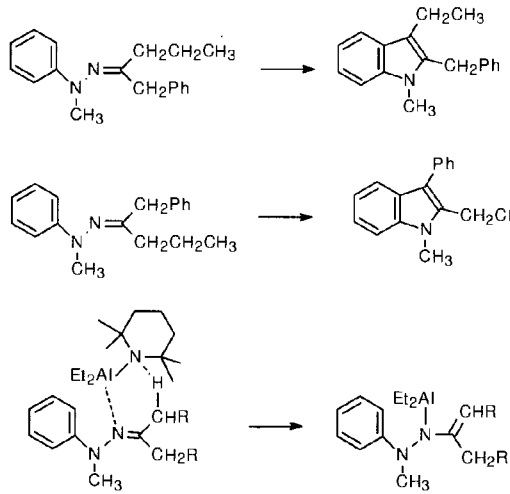
Recently the proposal has been advanced that rearrangement might occur through both mono- and di- protonated intermediates, with the latter favouring rate-determining enehydrazine formation and fast rearrangement[7]. A study of solvent and kinetic isotope effects has indicated that reaction in strongly acidic solution may proceed through an intermediate in which the aromatic ring is protonated. This non-aromatic cyclohexadienylium ion would be expected to have a much lower activation energy for sigmatropic rearrangement, permitting the enehydrazine formation to become rate-determining[7].



(7.3)

Very recent work has uncovered a different and promising approach to control of regioselectivity of Fischer indolization. It was found that use of dialkylaluminium amides, specifically diethylaluminium 2,2,6,6-tetramethylpiperidide (DATMP), promoted indolization of *N*-methylarylhydrazones[8]. The regioselectivity was dependent on the stereochemistry of the hydrazone. Thus for the *N*-methylphenylhydrazone of benzyl *n*-propyl ketone, the *Z*-isomer gave mainly 2-benzyl-3-ethyl-1-methylindole while the *E*-isomer gave mainly 1-methyl-3-phenyl-2-propylindole. The dependence on hydrazone stereochemistry could result from preferential *syn* deprotonation via a

DATMP complex. So far this methodology has been demonstrated only for *N*-alkylarylhydrazones.



(7.4)

Another issue of regioselectivity arises with *meta*-substituted arylhydrazones from which either 4- or 6-substituted indoles can be formed. Robinson has tabulated extensive data on this point[9]. A study comparing regioselectivity of cyclization as catalysed by HCl/EtOH and $ZnCl_2$ was carried out for several *m*-substituted arylhydrazones of diethyl ketone[10]. The results given in Table 7.1 show some dependence on catalyst but mixtures are obtained under all conditions studied.

Table 7.1

Regioselectivity in *m*-substituted arylhydrazones

Entry	Substituent	Reaction medium	6:4 Ratio
1	NO_2	$ZnCl_2$	3:7
2	NO_2	HCl, EtOH	1:1
3	Cl	$ZnCl_2$	0.8:1
4	Cl	HCl, EtOH	1.3:1
5	C_2H_5	$ZnCl_2$	1.2:1
6	C_2H_5	HCl, EtOH	1.8:1
7	CH_3O	$ZnCl_2$	1:1
8	CH_3O	HCl, EtOH	5.4:1

Data from Reference 10 of Section 7.1.2.

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7.1.3 Other reaction media

In addition to the more traditional reaction media discussed in Section 7.1.1, there are a number of other reaction systems which have been investigated. Some of their specific characteristics are outlined in the succeeding paragraphs.

Polyphosphoric acid trimethylsilyl ester (PPSE)[1] can be used in sulfolane, CH_2Cl_2 or nitromethane. It is similar to polyphosphoric acid but the overall conditions are milder and the work-up more convenient. PPSE has been used in the cyclization of *bis*-arylhydrazones of cyclohexane-1,2-diones to give indolo[2,3-a]carbazole analogues[2].

A mixture of methanesulfonic acid and P_2O_5 used either neat or diluted with sulfolane or CH_2Cl_2 is a strongly acidic system. It has been used to control the regioselectivity in cyclization of unsymmetrical ketones. Use of the neat reagent favours reaction into the less substituted branch whereas diluted solutions favour the more substituted branch[3].

A solution of trifluoroacetic acid in toluene was found to be advantageous for cyclization of pyruvate hydrazones having nitro substituents[4]. *p*-Toluenesulfonic acid or Amberlyst-15 in toluene has also been found to give excellent results in preparation of indole-2-carboxylate esters from pyruvate hydrazones[5,6]. Acidic zeolite catalysts have been used with xylene as a solvent to convert phenylhydrazines and ketones to indoles both in one-flask procedures and in a flow-through reactor[7].

Phosphorus trichloride in benzene is reported to effect mild and fast cyclization. It has been used for synthesis of 2,3-dialkyl- and 2,3-diarylindoles[8–11]. Table 7.2 presents some typical Fischer indolization reactions using both the traditional and more recently developed reaction conditions.

Table 7.2

Representative Fischer indole cyclizations

Entry	Substituents	Cyclization conditions	Yield (%)	Ref.
1	2-Phenyl	$ZnCl_2$, 170°C	70–80	[12]
2	2-Ethoxycarbonyl	TsOH, toluene	85	[5]
3	2-(1,1-Dimethyl-2-propenyl)	$ZnCl_2$, diglyme	45	[13]
4	3-(2-Propyl)	BF_3, EtOH	60	[14]
5	Cyclohexa[b][a]	HOAc	75–85	[15]
6	3-Methyl-2-phenyl	Polyphosphate ester	64	[16]
7	5-Chloro-2-(ethoxycarbonyl)	Amberlyst-15, toluene	70	[5]
8	2-(Ethoxycarbonyl)-5-nitro	Polyphosphoric acid, xylene	83	[17]
9	2,5-Dimethyl-3-(4-fluorophenyl)	H_2SO_4, EtOH	80	[18]
10	5-Chloro-3-ethyl-2-propyl	Zeolite, xylene	77	[7]
11	2,3-Diphenyl-5-methyl	PCl_3, CH_2Cl_2	80	[10]
12	3-Ethyl-2-methyl-5-nitro	Conc. HCl	69	[19]
13	3-Methyl-5-[*N*-(2-propenyl)-acetamido]-7-benzyloxy	TsOH, THF	90	[4]
14	5-Bromo-2-(ethoxycarbonyl)-7-(4-methylphenylsulfonyloxy)	Polyphosphoric acid	41	[20]
15	3,3-Dimethyl-2-phenyl-3*H*	Acetic acid	66	[21]

[a]Systematic name 1,2,3,4-tetrahydrocarbazole.

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7.1.4 Synthesis of Indoles with Functionalized Substituents

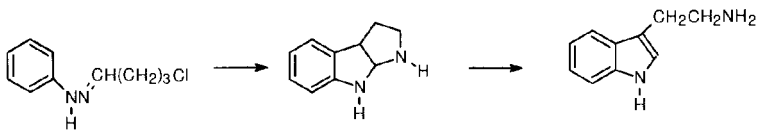
One of the virtues of the Fischer indole synthesis is that it can frequently be used to prepare indoles having functionalized substituents. This versatility extends beyond the range of very stable substituents such as alkoxy and halogens and includes esters, amides and hydroxy substituents. Table 7.3 gives some examples. These include cases of introduction of 3-acetic acid, 3-acetamide, 3-(2-aminoethyl)- and 3-(2-hydroxyethyl)- side-chains, all of which are of special importance in the preparation of biologically active indole derivatives. Entry 11 is an efficient synthesis of the non-steroidal anti-inflammatory drug indomethacin. A noteworthy feature of the reaction is the

Table 7.3

Fischer indole cyclizations incorporating functionalized substituents

Entry	Substituents	Conditions	Yield (%)	Ref.
1	3-[2-(3-Pyridyl)ethyl]	MeOH, HCl	56	[2]
2	3-(6-Isopropyl-8-methylene-6-azabicyclo[3.2.1]oct-3-en-7-yl)methyl	4% H_2SO_4	64	[3]
3	3-[2-(*N*,*N*-Dimethylamino-carbonyl)methyl]-2-phenyl	$ZnCl_2$, 170°C	78	[4]
4	1-(4-Chlorobenzyl)-2-(2-ethoxy-carbonyl-2-methylpropyl)-3-methyl	EtOH, cat. H_2SO_4	68	[5]
5	3-[2-Acetamido-2,2-bis-(ethoxy-carbonyl)ethyl]-7-chloro	5% H_2SO_4	99	[6]
6	*N*,*N*-Dimethyl-2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine	4% H_2SO_4	76	[7]
7	7-Bromo-6-fluoro-3-(2-hydroxyethyl)	$ZnCl_2$	48	[8]
8	3-(2-Aminoethyl)-5-cyano	EtOH, HBr	35	[9]
9	2-(Diethoxyphosphonylmethyl)-3-hexyl	EtOH, HCl	90	[10]
10	3-(*t*-Butylthio)-2-[2-(methoxy-carbonyl)-2-methylpropyl]-5-(2-propenyloxy)	HOAc, NaOAc	31	[11]
11	3-(Carboxymethyl)-1-(4-chlorobenzoyl)-5-methoxy-2-methyl	HOAc	96	[12]

installation of a 1-acyl substituent prior to cyclization. Entry 8 is an example of the Grandberg method for tryptamine synthesis in which 4-chlorobutanal reacts with an arylhydrazine[1]. The α-nitrogen of the hydrazone is alkylated during the reaction and becomes the tryptamine nitrogen.



(7.5)

Procedures

N,N-*Dihexyl-2-phenylindole-3-acetamide from 3-phenyl-3-oxopropanoic Acid[4]*

3-Phenyl-3-oxopropanoic acid (25 mmol) and Et_3N (87.5 mmol) were dissolved in THF (150 ml) and cooled to −40°C. Ethyl chloroformate (27.5 mmol) was added dropwise to this solution and then the reaction mixture was stirred for 30 min at −20°C. Di-*n*-hexylamine (27.5 mmol) was added to the suspension and it was stirred at room temperature for an additional hour. The reaction mixture was diluted with water (100 ml) and extracted with ether (400 ml). The extract was washed with aq. 5% HCl (100 ml) and brine (2 × 100 ml) and dried over Na_2SO_4. The crude amide was obtained by removal of the solvent *in vacuo* and phenylhydrazine (25 mmol) was added. The mixture was heated to 100°C for 30 min. The residue was held *in vacuo* to remove the water formed and then powdered $ZnCl_2$ (125 mmol) was added. The mixture was heated at 170°C with manual stirring for 5 min. The cooled residue was dissolved in acetone (100 ml) and diluted with ether (500 ml). Water (100 ml) was added. The organic layer was separated and washed successively with 5% aq. HCl (100 ml) and brine (2 × 100 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOAc-hexane. The yield was 79%.

2-Acetamido-2-(7-chloroindol-3-ylmethyl)propanedioic acid dimethyl ester[6]

A. Hydrazone formation

A solution of 2-chlorophenylhydrazine hydrochloride (89.5 g, 0.50 mol) in water (800 ml) was neutralized with 1 N NaOH and extracted with benzene (800 ml). The solution was dried ($MgSO_4$) and filtered. Acetic acid (10.7 ml) and dimethyl 2-acetamido-2-(3-oxopropyl)propanedioate (122.5 g, 0.50 mol) were dissolved in benzene (200 ml) and added. This mixture was stirred for 1 h at 50°C and then kept at 4°C for 2 days. The hydrazone precipitated. Additional product was recovered by concentration of the filtrate to about

one-fourth its volume and diluting with pentane. Pure product (153 g, 83%) was obtained by recrystallization from MeOH/water (70:30).

B. Cyclization

The hydrazone prepared above (153 g. 0.42 mol) was heated at reflux for 5 h in 5% H_2SO_4 (750 ml). The solution was cooled to 4°C and after 12 h the precipitate was collected by filtration. Recrystallization from MeOH/water (70:30) gave the product (145 g, 99%).

N,N-*Dimethyl-2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine[7]*

A solution of 4% aq. H_2SO_4 (30 l) was heated to 50°C over 30–60 min. Nitrogen was bubbled through the solution during this time. 4-(Cyanomethyl)phenylhydrazine hydrochloride (1080 g, 4.77 mol) was added as a solid to the heated mixture. After it had dissolved, *N,N*-dimethyl-4,4-dimethoxybutanamine (965 g, 5.98 mol) was added over a period of 30 min. The mixture was then heated at reflux for 2 h. The reaction mixture was cooled and diluted with portions of 30% aq. NH_4OH (21 total) over 0.5 h at a rate to maintain the temperature at 25–30°C. The product was then extracted into isopropyl acetate (3 × 10 l). The solution was concentrated to 31 which led to a precipitate which was isolated by filtration and washed with cold isopropyl acetate to give 827.4 g (76%) of product.

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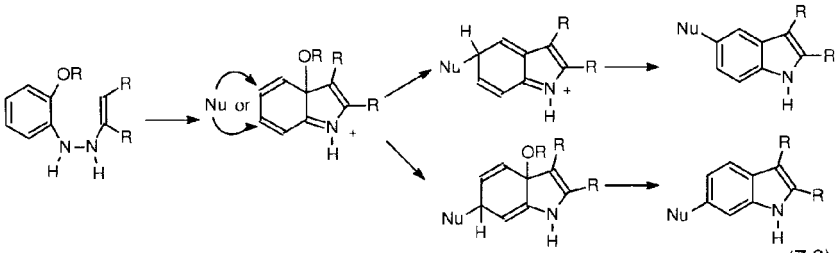
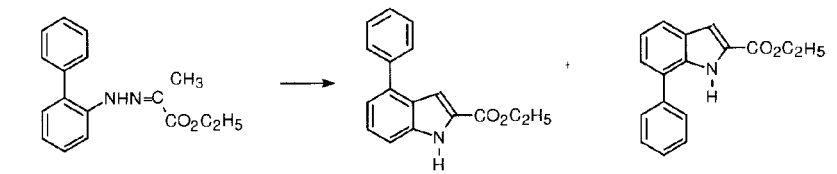
7.1.5 Anomalous reactions

Anomalous Fischer cyclizations are observed with certain *o*-substituted arylhydrazones, especially 2-alkoxy derivatives[1]. The products which are formed can generally be accounted for by an intermediate which would be formed by *ipso*-substitution during the sigmatropic rearrangement step. Nucleophiles from the reaction medium, e.g. Cl^- or the solvent, are introduced at the 5- and/or 6-position of the indole ring. Even carbon nucleophiles, e.g. ethyl acetoacetate, can be incorporated if added to the reaction solution[2]. The use of 2-tosyloxy or 2-trifluoromethanesulfonyloxy derivatives has been found to avoid this complication and has proved useful in the preparation of 7-oxygenated indoles[3].



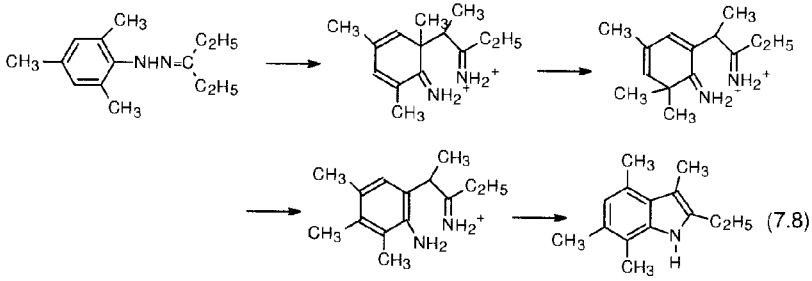
(7.6)

ipso-Substitution has also been observed with alkyl and aryl substituents and can lead to substituent migration. For example, 4-substituted indoles have been isolated from the cyclization of *o*-methyl and *o*-phenylphenylhydrazones of ethyl pyruvate. Formation of these by-products can be minimized by variation of the cyclization conditions and the use of *p*-toluenesulfonic acid in benzene or acetic acid was the preferred system[4].



(7.7)

Similarly, the *N*-mesitylhydrazone of acetophenone gives 2-phenyl-4,5,7-trimethylindole as a minor product (10%)[5]. 2,4,6-Trialkylphenylhydrazones have also been observed to give 5,6,7-trialkylindoles as the result of a formal 3a → 6 shift[6]. These reactions probably occur via a 1,5-shift followed by a 1,2-shift.



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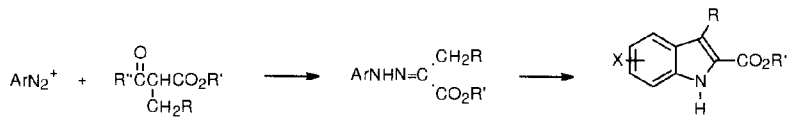
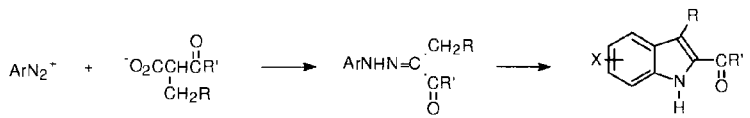
7.1.6 The Japp–Klingemann route to arylhydrazones

The Japp–Klingemann coupling of aryldiazonium ions with enolates and other nucleophilic alkenes provides an alternative route to arylhydrazones. The reaction has most frequently been applied to β-ketoesters, in which deacylation follows coupling and the indolization affords an indole-2-carboxylate ester.



(7.9)

If, instead of an ester, the Japp–Klingemann reaction is done with a salt of a β-ketoacid, decarboxylation occurs and the eventual product is a 2-acylindole.



(7.10)

Table 7.4

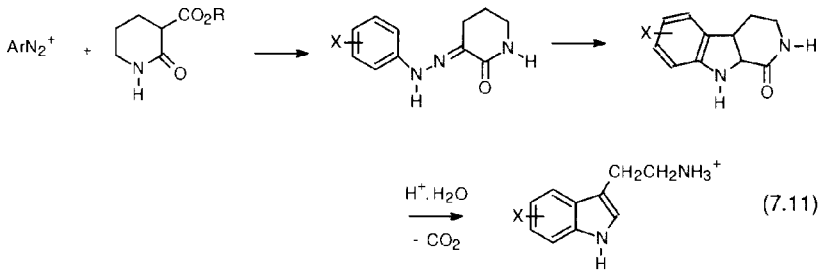
Japp–Klingemann coupling/Fischer cyclization

Entry	Substituents	Coupling reactant	Cyclization conditions	Yield (%)	Ref.
1	2-(Ethoxycarbonyl)-7-nitro	Ethyl 2-methyl-3-oxobutanoate	PPA	78	[5]
2	6-Formamido-5-methoxy-2-(methoxycarbonyl)	Methyl 2-methyl-3-oxobutanoate	HCO_2H	72	[6]
3	2-Acetyl-5-chloro-3-phenyl	Ethyl 2-benzyl-3-oxobutanoate	Conc. HCl	50–90	[7]
4	3-(4-Fluorophenyl)-2-(methoxycarbonyl)-5-methyl	Methyl 2-(4-fluorophenyl)-3-oxobutanoate	H_2SO_4	58	[8]
5	5-Benzyloxy-2-(ethoxycarbonyl)-3-(2-phthalimidoethyl)	Ethyl 2-(3-phthalimidopropyl)-3-oxobutanoate	HCl, EtOH	51	[9]
6	4-Carboxy-3-(2-carboxyethyl)-7-chloro-2-(ethoxycarbonyl)	2-Ethoxycarbonylcyclopentanone	BF_3-HOAc	63, 81	[1]
7	5-Bromo-2-carboxy-3-(3-carboxypropyl)	2-Cyanocyclopentanone	HCl, EtOH[a]	80	[10]

[a]The reaction involves subsequent hydrolysis of a 2-cyano group to 2-carboxy.

Table 7.4 gives some examples of indoles obtained from hydrazones prepared by Japp–Klingemann coupling. Entry 6 presents a case where coupling with 2-ethoxycarbonylcyclopentanone is followed by ring cleavage to generate a precursor of an indole-3-propanoic acid. This reaction was successfully performed on a large scale (5 kg of product) using BF_3 in acetic acid as the reaction medium[1].

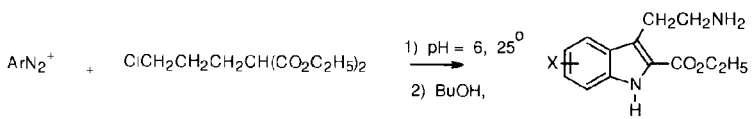
A special application of the Japp–Klingemann/Fischer sequence is in the preparation of tryptamines from piperidone-3-carboxylate salts, a method which was originally developed by Abramovitch and Shapiro[2]. When the piperidone is subjected to Japp–Klingemann coupling under mildly alkaline conditions decarboxylation occurs and a 3-hydrazonopiperidin-2-one is isolated. Fischer cyclization then gives 1-oxotetrahydro-β-carbolines which can be hydrolysed and decarboxylated to afford the desired tryptamine.



(7.11)

The decarboxylation is frequently the most troublesome step in this sequence. Attempts at simple thermal decarboxylation frequently lead to recyclization to the lactam. The original investigators carried out decarboxylation by acidic hydrolysis and noted that rings with ER substituents were most easily decarboxylated[2]. It appears that ring protonation is involved in the decarboxylation under hydrolytic conditions. Quinoline–copper decarboxylation has been used successfully after protecting the exocyclic nitrogen with a phthaloyl, acetyl or benzoyl group[3].

A variation on the tryptamine synthesis is to use diethyl (3-chloropropyl)-malonate as the substrate for a one-pot Japp–Klingemann/Fischer procedure. The chloropropyl group alkylates the α-nitrogen, forming the tryptamine side-chain. The precise stage at which the alkylation occurs is unclear[4].



(7.12)

Procedures

4-Carboxy-7-chloro-2-(ethoxycarbonyl)indole-3-propanoic acid[1]

Water (12 l) and crushed ice (12 kg) were added to a suspension of 3-amino-4-chlorobenzoic acid (5.0 kg) in conc. HCl (6 l). The mixture was stirred and kept at 0–2°C by adding more ice during addition of a solution of $NaNO_2$ (2.05 kg) in water (3 l). Stirring was continued at 0–2°C for 1 h after the addition was complete. NaOAc hydrate (5 kg) was added, followed by ethyl 2-oxocyclopentanecarboxylate (4.55 kg). An oil separated which eventually solidified. After 30 min the precipitate was collected as an orange solid and washed with ice-water. The solid was then added to 80% acetic acid (30 l) and the mixture was stirred at 95–100°C for 1 h. The solution was cooled and the intermediate hydrazone was collected by filtration and dried (6.6 kg, 63%). The hydrazone (6.6 kg) was suspended in glacial acetic acid (25 l) and BF_3-acetic acid complex (4.5 l) was added. The mixture was heated to 90°C with stirring. At this point an exothermic reaction began and the heat source was removed. The solution was allowed to spontaneously reflux until the exotherm subsided and then heated to reflux again for 4 h. The solution was cooled and filtered. The solid product was washed with water and dried to give the product (5.1 kg, 81%).

Methyl 3-(4-fluorophenyl)-5-methylindole-2-carboxylate[8]

To a solution of *p*-toluidine (119.4 g, 1.1 mol) in conc. HCl (580 ml) was added over 1.5 h at 0–5°C a solution of $NaNO_2$ (84.6 g, 1.2 mol) in water (500 ml). This solution was added in one portion with stirring, to a mixture of methyl 2-(4-fluorobenzyl)-3-oxobutanoate (250 g, 1.1 mol), KOH (220 g, 3.9 mol) water (500 ml), ethanol (1.25 ml) and ice (2 kg). After 2 h at room temperature, the reaction solution was extracted with ether (2 × 2 l). The organic phases were combined, washed with water (3 l), dried (Na_2SO_4) and evaporated to give the crude hydrazone (330 g) which was used without further purification. The hydrazone was dissolved in MeOH (2.25 l) containing conc. H_2SO_4 (100 ml) and the solution was heated at reflux for 18 h. The solution was cooled and partially evaporated *in vacuo*. The product (180 g) was obtained in 58% yield.

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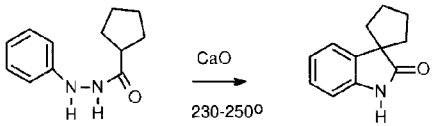
7.1.7 Oxindoles from *N*-acylphenylhydrazines

Oxindoles can be prepared from *N*,β-acylphenylhydrazines by a reaction which is analogous to the Fischer cyclization. This is known as the Brunner reaction. The reaction is typically conducted under strongly basic conditions. For example, heating *N*-phenylcyclopentanecarbonylhydrazide with CaO gives a 70% yield of spiro-cyclopentane oxindole[1].



(7.13)

Calcium hydride has also been used as the base[2,3]. A comparison of the effect of metal cations indicated that yields increase in the order $K^+ < Na^+ < Li^+$ and a procedure in which *n*-BuLi serves as the base has been developed[4].

Procedure

3,3,7-Trimethyloxindole[3]

Ground, predried CaH (11.0 g, 0.26 mol) was added to a mixture of *N*-(2-methylphenyl)-2-methylpropanoylhydrazide (25.0 g, 0.13 mol) in tetralin (500 ml). The mixture was slowly heated over 2 h to about 200°C and kept at that temperature for 30 min. The reaction mixture was slowly cooled to room temperature and a solution of aq. methanol (100 ml, 50% by vol) was carefully added at 0–5°C. After H_2 evolution ceased, the pH was adjusted to 1 with conc. HCl and the mixture heated at reflux for 1 h. Then 3 N NaOH was added to bring the pH to 5. A precipitate formed and was collected and dried to give 20.1 g (89% yield) of the product.

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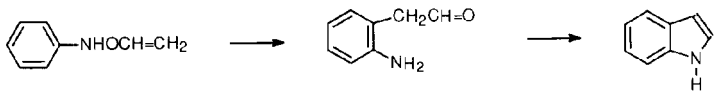
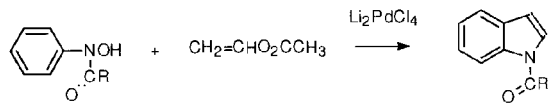
7.2 INDOLES FROM *N*-ARYL-*O*-HYDROXYLAMINES

The oxygen analogue of the Fischer cyclization requires the formation of *O*-vinyl derivatives of *N*-arylhydroxylamines. These are readily converted to indoles but are less readily accessible than the arylhydrazones used for the Fischer cyclization.



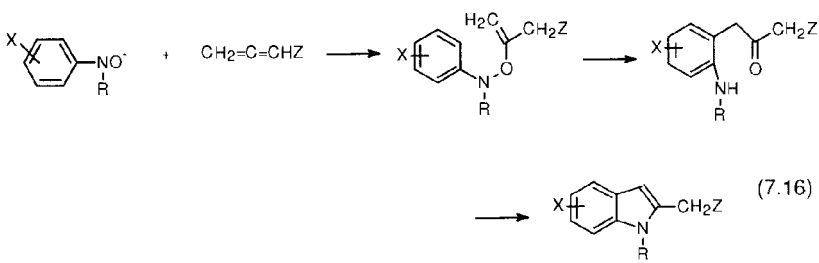
(7.14)

One route to *O*-vinyl derivatives involves $LiPdCl_4$-catalysed exchange with vinyl acetate[1]. Rearrangement and cyclization occur concurrently to give 1-acylindoles.



(7.15)

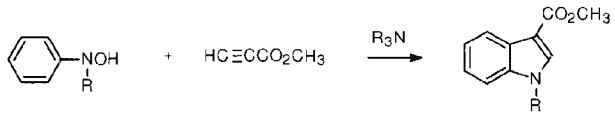
Addition of arylhydroxylamines to electrophilic allenes such as methyl propadienoate or 1-methanesulfonyl-1,2-propadiene is another route to *O*-vinyl derivatives[2]. The addition step is carried out by forming the salt of the hydroxylamine using NaH and the addition is catalysed with LiO_2CCF_3. The intermediate adducts are cyclized by warming in formic acid. Yields are typically 80% or better.



(7.16)

N-Substituted arylhydroxylamines add to methyl propynoate and rearrangement occurs to give indole-3-carboxylate esters[3]. With unsubstituted

arylhydroxylamines addition occurs a second time and the products are *N*-(β-carbomethoxyvinyl)indoles[4].



(7.17)

R = CH_2Ph, CO_2CH_2Ph

Procedure

1-Benzyl-3-methyl 6-methoxyindole-1,3-dicarboxylate[3]

N-Benzyloxycarbonyl-3-methoxyphenylhydroxylamine (1.84 g, 6.74 mmol) and methyl propynoate (1.2 ml, 13.5 mmol) were dissolved in dry CH_2Cl_2 (20 ml). *N*-Methylmorpholine (0.74 ml, 6.73 mmol) was added at room temperature. The temperature of the solution rose to 40°C. Stirring was continued for 1 h and the solvent removed. The product was purified by elution through silica gel using 1:1 CH_2Cl_2–hexane. The product was recrystallized from methanol. The yield was 1.51 g (66%).

References

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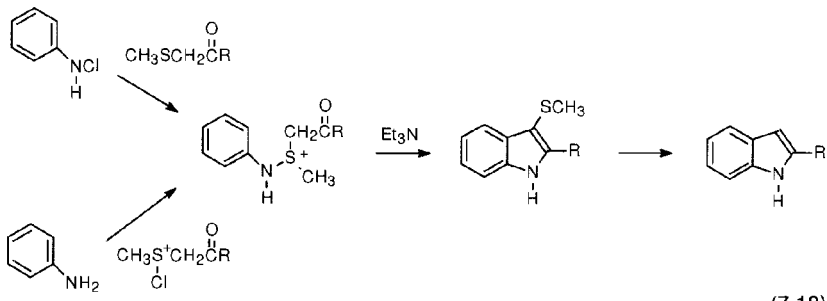
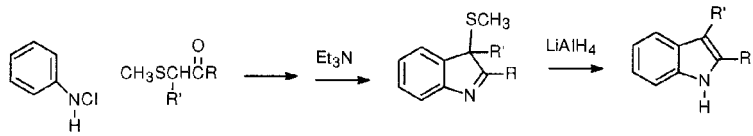
7.3 REARRANGEMENT OF ANILINOSULFONIUM YLIDES – THE GASSMAN SYNTHESIS

Gassman and co-workers developed a synthetic route from anilines to indoles and oxindoles which involves [2,3]-sigmatropic rearrangement of anilinosulfonium ylides. These can be prepared from *N*-chloroanilines and α-thiomethylketones or from an aniline and a chlorosulfonium salt[1]. The latter sequence is preferable for anilines with ER substituents. Rearrangement and cyclization occurs on treatment of the anilinosulfonium salts with Et_3N. The initial cyclization product is a 3-(methylthio)indole and these can be desulfurized with Raney nickel. Use of 2-(methylthio)acetaldehyde generates 2,3-unsubstituted indoles after desulfurization[2]. Treatment of 3-methylthioindoles with trifluoroacetic acid/thiosalicylic acid is a possible alternative to Raney nickel for desulfurization[3].



(7.18)

When longer chain α-methylthio substituents or α-methylthiocycloalkanones are used, 3-methylthio-3*H*-indole intermediates are isolated. These can be converted to 2,3-disubstituted indoles by reduction with $LiAlH_4$[4].



(7.19)

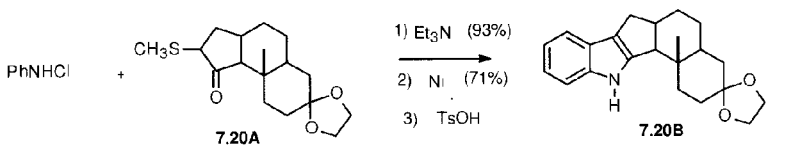
The Gassman method has proven to be adaptable to complex structures, such as the intermediate **7.20B** used in the synthesis of the indole diterpenes paspalicine and pasalinine[5]. Table 7.5 gives some other examples.

Table 7.5

Indoles from anilinosulfonium salts

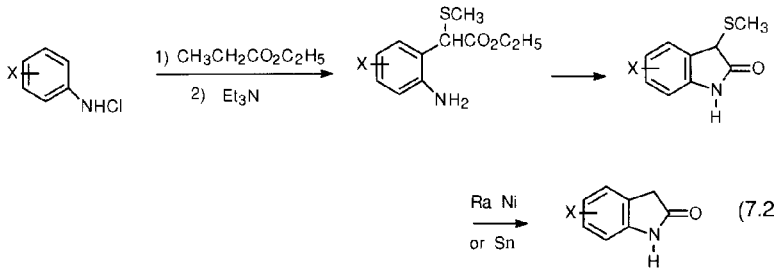
		Yield (%)		
Entry	Substituents	Cycl.	Desulf.	Ref.
1	2-Ethyl-3-methyl	81		[4]
2	5-(Ethoxycarbonyl)-2-methyl	50–70		[6]
3	5-Chloro-2-methyl	72	74	[1a]
4	5-Cyano-2-methyl	85	83	[3]
5	7-Methoxy-2-methyl	45	87	[1b]
6	4,5-Difluoro-2-methyl	93	86	[7]
7	2-Methylbenzo[e]	76	88	[2]
8	2-Methyl-3-(methylthio)-1,7-trimethylene[a]	39		[8]

[a]Systematic name: 1-(Methylthio)-2-methyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-ij]quinoline.



(7.20)

The Gassman synthesis has been a particularly useful method for the synthesis of oxindoles[1b,8]. Use of methylthioacetate esters in the reactions leads to 3-(methylthio)oxindoles which can be desulfurized with Raney nickel. Desulfurization can also be done by reduction with zinc or tin[10,11].



(7.21)

There are two sequences in which the reaction can be carried out. For most anilines the first step is *N*-chlorination which can be done with *t*-butyl hypochlorite[9]. However, for anilines with ER substituents it may be preferable to halogenate the thioester. The halogenation can be done with Cl_2[1b] or SO_2Cl_2[12]. For some anilines simply adding *t*-butyl hypochlorite to a mixture of the aniline and thioester is satisfactory (Entries 1, 4, Table 7.6).

Procedure

7-Benzoyl-3-methyloxindole[15]

Chlorination, rearrangement and cyclization

A solution of 2-aminobenzophenone (98 g, 0.50 mol) and methyl 2-(methylthio)propanoate (74 g, 0.50 mol) in CH_2Cl_2 (2 l) was cooled to $-70°C$ and 95% *t*-butyl hypochlorite (56 g, 0.5 mol) was added dropwise at such a rate that the temperature did not rise above $-65°C$. One hour after the addition was complete, Et_3N was added and the mixture was allowed to come to room temperature. The solution was mixed with 3 N HCl (800 ml) and stirred for 1 h. The organic layer was separated, dried (Na_2SO_4) and filtered. The solution was evaporated *in vacuo* and the residue triturated with ether. Filtration gave the 3-(methylthio)oxindole intermediate (92 g) in 62% yield.

Table 7.6

Oxindoles by the Gassman method

Entry	Substituents	Reagent sequence	Yields (%)	Ref.
1	7-Cyclohexanonyl	1: 2-Cyclohexanoylaniline, ethyl thiomethyl acetate 2: *t*-BuOCl 3: Et_3N 4: Tin powder	58, 88	[11]
2	7-(4-Chlorobenzoyl)-5-methoxy	1: Cl_2, Ethyl methylthioacetate 2: 2-(4-chlorobenzoyl)-4-methoxyaniline 3: Et_3N 4: Raney Ni	74, 90	[13]
3	7-Methoxy-4-methyl-3-methylthio	1: Methyl methylthioacetate, SO_2Cl_2 2: 2-Methoxy-5-methylaniline 3: 1,8-*bis*-(Dimethylamino)naphthalene	81,	[14]
4	7-Benzoyl-3-methyl	1: Ethyl methylthiopropanoate, 2-aminobenzophenone, *t*-BuOCl 2: Et_3N 3: Raney Ni	62, 89	[15]
5	5-[2-Chloro-4-(trifluoromethyl)phenoxy)-3-methylthio	1: Cl_2, Ethyl methylthioacetate 2: 4-[2-Chloro-4-(trifluoromethyl)phenoxyl]aniline 3: Et_3N	49,	[16]
6	5-Methoxy-4,7-*bis*-(methoxymethyl)-6-methyl-3-methylthio	1: Cl_2, Ethyl methylthioacetate 2: 4-Methoxy-2,5-*bis*-(methoxymethyl)-3-methylaniline 3: Et_3N 4: Xylene, 120°C	74,	[17]
7	5-(2-Chloro-1-oxopropyl)-3-spiro[thiolane-2,3'-	1: 4-(2-Chloro-1-oxopropyl)aniline, *t*-BuOCl 2: Methyl thiolane-2-carboxylate 3: Et_3N	57,–	[18]

Desulfurization

The above intermediate (8 g, 0.03 mol) in THF (80 ml) was stirred with Raney nickel (40 g) for 2 h and then carefully filtered. [*CAUTION: Raney nickel can ignite during filtration.*] Conc. HCl (2 drops) was added to the filtrate and it was evaporated *in vacuo*. Recrystallization of the residue from 2-propanol gave the product (6.0 g) in 89% yield.

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7.4 INDOLES FROM ANILINES *via o*-CHLOROACETYLATION–THE SUGASAWA SYNTHESIS

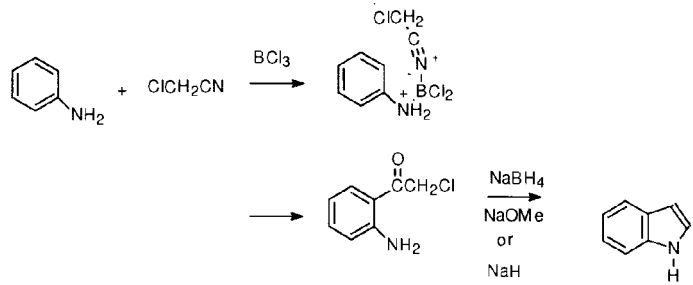
Boron trichloride, usually in conjunction with an additional Lewis acid, effects *o*-chloroacetylation of anilines. The resulting products are converted to indoles by reduction with $NaBH_4$[1]. The strength of the Lewis acid required depends upon the substitution pattern on the ring. With ER substituents no additional

Table 7.7

Indoles *via* o-chloroacetylanilines

Entry	Substituents	Acylation conditions	Yield (%) Acyl.	Cycl.	Ref.
1	5-Methyl	$BCl_3/ZnCl_2$	62	81	[2]
2	7-Propyl	$BCl_3/AlCl_3$	59	48	[3]
3	5-Methoxy-7-methyl	$BCl_3/TiCl_4$	25	86	[4]
4	5-Chloro-1-(1-methylpiperid-4-yl)	BCl_3	93	69	[5]
5	6,7-Dibromo-4-methoxy	$BCl_3/TiCl_4$	90	90	[6]
6	5,6,7-Trimethoxy	BCl_3	85	72	[7]

catalyst may be required but in other cases $TiCl_4$ or $AlCl_3$ is needed. Table 7.7 gives some examples of indoles prepared in this way.



(7.22)

Procedure

6,7-Dibromo-4-methoxyindole[6]

Chloroacetylation

A solution of 2,3-dibromo-5-methoxyaniline (32 g, 0.17 mol) in CH_2Cl_2 (300 ml) was stirred and cooled in an ice bath. Boron trichloride (1 M in CH_2Cl_2, 180 ml, 0.18 mol), chloroacetonitrile (14.3 g, 0.19 mol) and $TiCl_4$ (1 M in CH_2Cl_2, 190 ml, 0.19 mol) were added. The resulting mixture was refluxed for 1.5 h. The solution was cooled to room temperature and poured carefully on to a mixture of ice and 20% aq. HCl (700 ml). The organic layer was separated and the CH_2Cl_2 removed by distillation. The residue was heated to 90°C on a water bath for 30 min. The solution was cooled and the solid collected by filtration. It was partitioned between ether (1.4 l) and 1 N NaOH (500 ml). The ether layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from ethanol to give 2-amino-3,4-dibromo-6-methoxy-α-chloroacetophenone (55 g) in 90% yield.

Reductive cyclization

The above product (24 g, 0.067 mol) was dissolved in 90:10 dioxane–water (300 ml) and sodium borohydride (92.5 g, 0.067 mol) was added. The mixture was refluxed for 4 h. The cooled solution was poured into 0.1 N HCl (1.1 l). A solid precipitated and was collected by filtration, dried and recrystallized from ether hexane to give 6,7-dibromo-4-methoxyindole (18.5 g, 90%).

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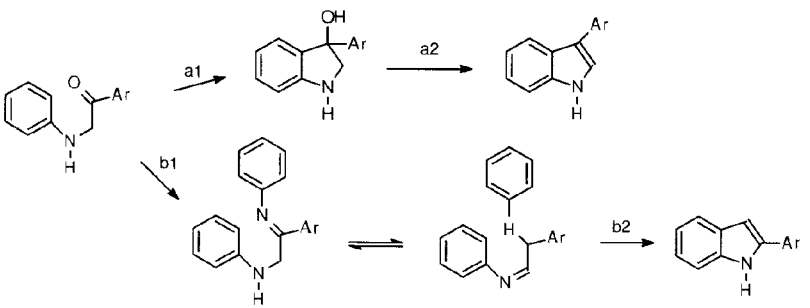
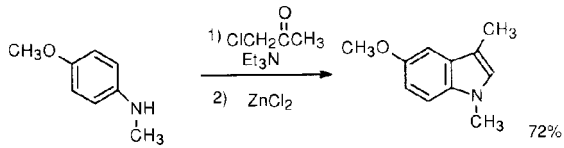
7.5 THE BISCHLER INDOLE SYNTHESIS

Anilines react with α-haloacetophenones to give 2-arylindoles. In a typical procedure an *N*-phenacylaniline is heated with a two-fold excess of the aniline hydrobromide to 200–250°C[1]. The mechanism of the reaction was the subject of considerable investigation in the 1940s[2]. A crucial aspect of the reaction seems to be the formation of an imine of the acetophenone which can isomerize to an aldimine intermediate. This intermediate apparently undergoes cyclization more rapidly (path **b1** → **b2**) than its precursor (Scheme 7.3). Only with very reactive rings, e.g. 3,5-dimethoxyaniline, has the alternative cyclization (path **a1** → **a2**) to a 3-arylindole been observed and then only under modified reaction conditions[3].



SCHEME 7.3

There is an experimental variation in which an *N*-phenacylpyridinium salt is heated with an aniline[4]. This reaction can also be readily accommodated to the mechanism involving an imine intermediate. There are a few examples of use of other types of α-halokctones[5,6] but most of the synthetic applications have been to 2-arylindoles.



(7.23)

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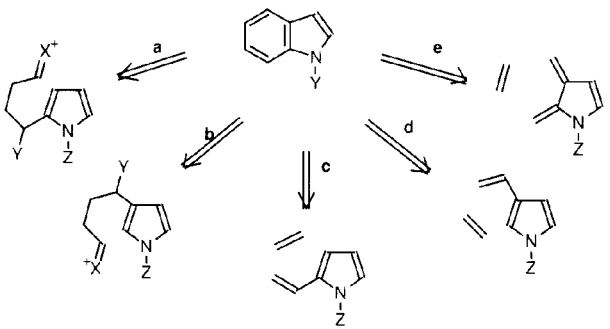
–8–

Indoles by Annelation of Pyrroles

Indoles are usually constructed from aromatic nitrogen compounds by formation of the pyrrole ring as has been the case for all of the synthetic methods discussed in the preceding chapters. Recently, methods for construction of the carbocyclic ring from pyrrole derivatives have received more attention. Scheme 8.1 illustrates some of the potential disconnections. In paths **a** and **b**, the syntheses involve construction of a mono-substituted pyrrole with a substituent at C2 or C3 which is capable of cyclization, usually by electrophilic substitution. Paths **c** and **d** involve Diels–Alder reactions of 2- or 3-vinylpyrroles. While such reactions lead to tetrahydro or dihydroindoles (the latter from acetylenic dienophiles) the adducts can be readily aromatized. Path **e** represents a category II*eg* cyclization based on 2 + 4 cycloadditions of pyrrole-2,3-quinodimethane intermediates.

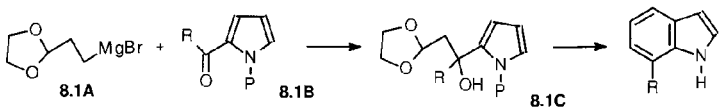


SCHEME 8.1

8.1 CATEGORY I*d* AND CATEGORY I*h* CYCLIZATIONS

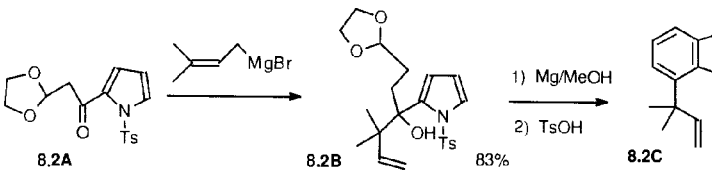
These two methods are closely related but differ in the point of initial attachment of the substituent from which the carbocyclic indole ring is constructed. One strategy for building up 2-substituted pyrroles capable of

cyclization to indoles involves addition of a Grignard reagent to a 2-acylpyrrole. For example the dioxolanyl group of the Grignard reagent **8.1A** provides a potential aldehyde substituent capable of electrophilic substitution at C3. Furthermore, substitution by the electrophilic aldehyde group creates a hydroxyl group which can be eliminated during aromatization. This method provides a potentially general route to 7-alkyl and 7-arylindoles[1]. In most examples the pyrroles were protected by *N*-tosyl groups and 6% H_2SO_4 in isopropanol was found to be a useful cyclization medium.



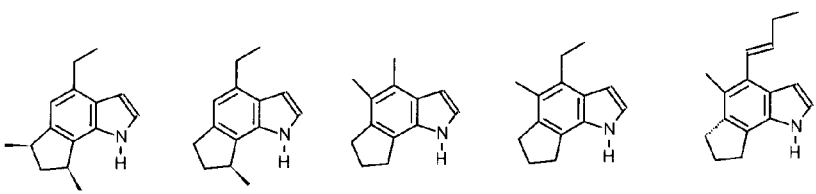
8.1A **8.1B** **8.1C** **8.1D** (8.1)

An alternative strategy is to put a 3-(-2-dioxolanyl)ethanoyl substituent in place first and then add the C7-substituent by a Grignard addition. This approach was applied to the synthesis of **8.2C** but in this case it was found necessary to remove the tosyl protecting group prior to cyclization[1].



8.2A **8.2B** 83% **8.2C** 74% (8.2)

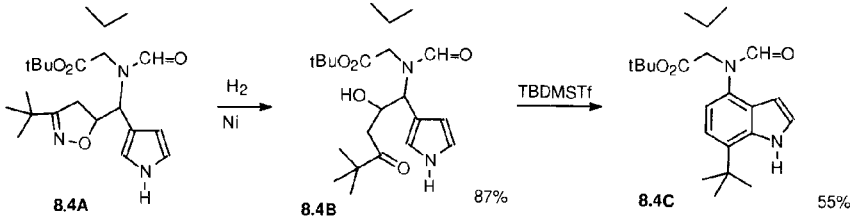
4-Substituted indoles can be obtained by the same general method starting with 3-acylpyrroles[2]. The precise methodology for construction of the substituent can be adapted as necessary for more complex structures. For example, enantioselective syntheses of both *cis* and *trans*-trikentin A and herbindoles A, B and C have been accomplished by using the annelation methodology[3].



cis-trikentin A trans-trikentin A herbindole A herbindole B herbindole C

(8.3)

The category I*d* cyclization has also been applied to 4-aminoindoles of the type found in the indolelactam tumour promoters such as lyngbyatoxin A and pendolmycin. In a synthesis of analogues of lyngbyatoxin A the isoxazoline **8.4A** was constructed as a key intermediate[4]. Reductive cleavage of the isoxazoline ring generated **8.4B** which was cyclized by reaction with *tert*-butyldimethylsilyl triflate (Entry 6, Table 8.1). The cyclization of a thioamide was a key step in the synthesis of pendolmycin[5] (Entry 7, Table 8.1).



(8.4)

Procedure

4-Cyclohexyl-1-(4-methylphenylsulfonyl)indole[2]

To a solution of 3-cyclohexanoyl-1-(4-methylphenylsulfonyl)pyrrole (85 mg) in THF (3 ml) at −20°C under argon was added the Grignard reagent prepared from 2-(1,3-dioxan-2-yl)ethyl bromide (0.60 ml) and Mg (90 mg) in THF (3.4 ml). After 15 min the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. After washing and purification by TLC, the intermediate carbinol was obtained (108 mg, 97%). A portion (73 mg) of this product was dissolved in 6% H_2SO_4 in isopropanol (4.5 ml). The solution was refluxed for 30 min. After cooling and dilution with water, the solution was extracted with CH_2Cl_2. After washing and purification by TLC the indole was obtained in 82% yield.

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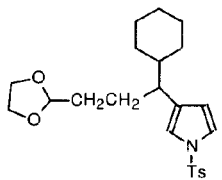
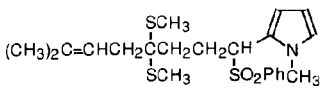
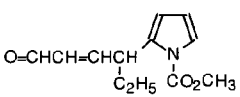
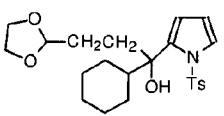
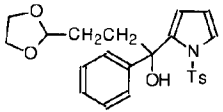
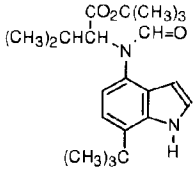
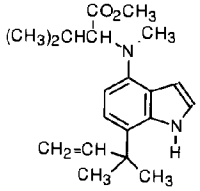
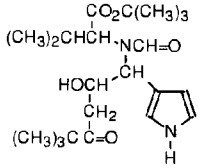
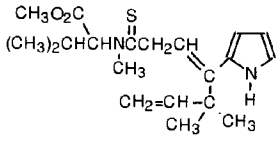
Table 8.1

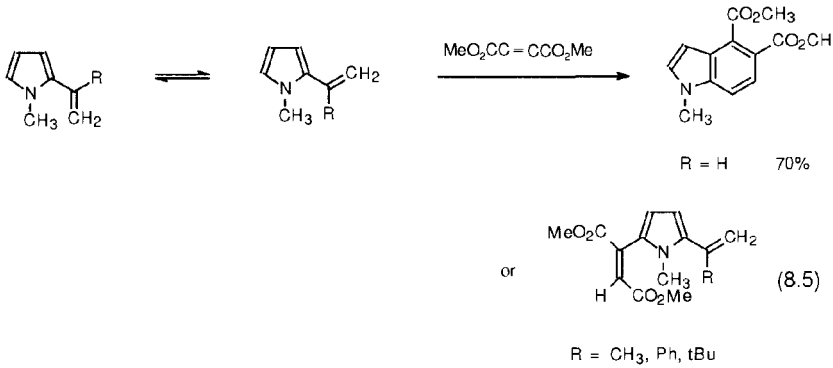
Synthesis of indoles by electrophilic annelation of pyrroles

Entry	Product	Reactant	Conditions	Yield (%)	Ref.
1	4-Cyclohexyl-1-(4-methylphenylsulfonyl)-indole		H_2SO_4, propanol	82	[1]
2	1-Methyl-4-(3-methylbut-2-enyl)-indole		*p*-TsOH	35	[6]
3	7-Ethyl-1-methoxycarbonylindole		*p*TsOH, benzene	89	[7]
4	7-Cyclohexyl-1-(4-methylphenylsulfonyl)-indole		H_2SO_4, propanol	69	[2]

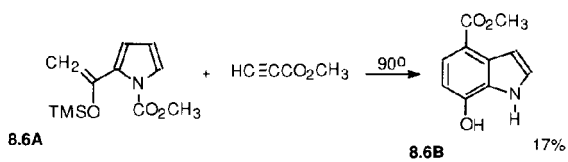
5	7-Phenyl-1-(4-methylphenylsulfonyl)-indole		H_2SO_4, propanol	70	[1]
6			TBDMSOTf	54	[4]
7			CH_3I, DMF	73	[5]

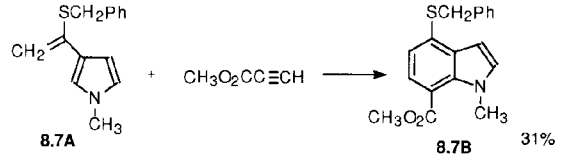
8.2 CATEGORY II*df* AND CATEGORY II*fh* CYCLIZATIONS – DIELS–ALDER REACTIONS OF VINYLPYRROLES

As illustrated in Scheme 8.1, both 2-vinylpyrroles and 3-vinylpyrroles are potential precursors of 4,5,6,7-tetrahydroindoles via Diels–Alder cyclizations. Vinylpyrroles are relatively reactive dienes. However, they are also rather sensitive compounds and this has tended to restrict their synthetic application. While 1-methyl-2-vinylpyrrole gives a good yield of an indole with dimethyl acetylenedicarboxylate, α-substituents on the vinyl group result in direct electrophilic attack at C5 of the pyrrole ring. This has been attributed to the steric restriction on access to the necessary *cisoid* conformation of the 2-vinyl substituent[1].



Donor substituents on the vinyl group further enhance reactivity towards electrophilic dienophiles. Equations 8.6 and 8.7 illustrate the use of such functionalized vinylpyrroles in indole synthesis[2,3]. In both of these examples, the use of acetyleneic dienophiles leads to fully aromatic products. Evidently this must occur as the result of oxidation by atmospheric oxygen. With vinylpyrrole **8.6A**, adducts were also isolated from dienophiles such as methyl acrylate, dimethyl maleate, dimethyl fumarate, acrolein, acrylonitrile, maleic anhydride, *N*-methylmaleimide and naphthoquinone. These tetrahydroindole adducts could be aromatized with DDQ, although the overall yields were modest[3].





(8.7)

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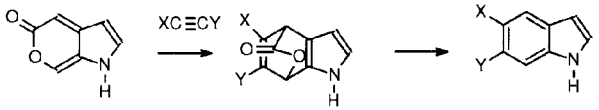
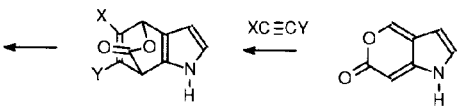
8.3 CATEGORY IIeg CYCLIZATIONS – CYCLOADDITIONS INVOLVING PYRROLE-2,3-QUINODIMETHANE INTERMEDIATES AND EQUIVALENTS

This category corresponds to the construction of the carbocyclic ring by 2 + 4 cycloaddition with pyrrole-2,3-quinodimethane intermediates. Such reactions can be particularly useful in the synthesis of 5,6-disubstituted indoles. Although there are a few cases where a pyrrolequinodimethane intermediate is generated, the most useful procedures involve more stable surrogates. Both 1,5-dihydropyrano[3,4-b]pyrrol-5(1*H*)-ones[1] and 1,6-dihyropyrano[4,3-b]pyrrol-6-(1*H*)-ones[2] can serve as pyrrole-2,3-quinodimethane equivalents. The adducts undergo elimination of CO_2.



1,5-dihydropyrano[3,4-b]pyrrol-5-one

(8.8)



1,6-dihydropyrano[4,3-b]pyrrol-6-one

Reactions with mono-substituted alkynes usually give mixtures of both 5- and 6-substituted indoles, although certain combinations of substituents result in good regioselectivity. Table 8.2 provides some examples.

Table 8.2

Indoles by cycloaddition with pyrrole-2,3-quinodimethane equivalents

Entry	Product	Reactants	Yield (%)	Ref.
1	4-Ethyl-4-methyl-1-(phenylsulfonyl)indole	4-Ethyl-7-methyl-1-phenylsulfonyl-1,5-dihydropyrano-[3,4-b]pyrrol-5-one; phenyl vinyl sulfoxide	60	[3]
2	5,6-*bis*-(Methoxycarbonyl)indole	1,6-Dihydropyrano[4,3-b]pyrrol-6-one; dimethyl acetylenedicarboxylate	82	[2]
3	1-(Isobutoxycarbonyl)-5-(ethoxycarbonyl)-6-trimethylsilylindole	1-(Isobutoxycarbonyl)-1,5-dihydropyrano[3,4-b]pyrrol-5-one; ethyl 3-trimethylsilylpropynoate	77[a]	[2]
4	5,6-*bis*-(Methoxycarbonyl)-7-methyl-1-phenylsulfonylindole	7-Methyl-1-phenylsulfonyl-1,5-dihydropyrano[3,4-b]pyrrol-5-one; dimethyl acetylenedicarboxylate	70	[1]
5	6-(Methoxycarbonyl)-7-methyl-1-(phenylsulfonyl)-5-trimethylsilylindole	7-Methyl-1-phenylsulfonyl-1,5-dihydropyrano[3,4-b]pyrrol-5-one; ethyl 3-trimethylsilylpropynoate	53	[1]
6	1-(Isobutoxycarbonyl)-4-methylbenzo[f]indole	1-(Isobutoxycarbonyl)-4-methyl-1,6-dihydropyrano[4,3-b]-pyrrole-6-one; benzyne	84	[2]

[a]The regioisomer was isolated in 13% yield.

Procedure

5-Ethyl 1-isobutyl 6-(trimethylsilyl)indole-1,5-dicarboxylate[2]

A mixture of *iso*-butyl 1,6-dihydropyrano[4,3-b]pyrrol-6-(1*H*)-one-1-carboxylate (80 mg, 0.34 mmol) and ethyl 3-(trimethylsilyl)propynoate (173 mg, 1.02 mmol) in chlorobenzene (10 ml) was refluxed for 20 h. The solvent was removed *in vacuo* and the residue purified by chromatography to give the product (98 mg, 79%) and its regioisomer (13 mg, 11%).

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–9–

Synthetic Modification of Indoles by Substitution at Nitrogen

Synthetic methodology for introduction of substituents on indole has historically been dominated by electrophilic substitution. Since the 3-position is the most reactive on the indole ring, this position is the easiest one at which to accomplish electrophilic substitution. The nitrogen atom can be made the most reactive nucleophilic site by deprotonation, so procedures for N1 substitution normally involve base-catalysed nucleophilic substitution or conjugate addition reactions. Base-catalysed conditions are also used for introduction of acyl and sulfonyl substituents. Phase transfer catalysis has been found useful for both alkylation and acylation. 1-Substitution is also important for introduction of protecting groups. The most versatile methods for C2 substitution involve organometallic intermediates obtained by C2 lithiation. Several *N*-protecting and/or directing groups have been developed in conjunction with methods for lithiation.

9.1 ALKYLATION

The indole-NH is weakly acidic with *pK* values of 16.7 and 20.9 having been determined in water[1] and DMSO[2], respectively. While the neutral indole ring is not very nucleophilic at nitrogen, the anion is a good nucleophile. Procedures for *N*-alkylation therefore normally are done under conditions where the nitrogen is deprotonated. One method is to use one or more equivalent of a strong base in a polar aprotic solvent[3]. Both sodium hydride and alkali metal hydroxides have been used as bases. Another method involves phase transfer catalysis[4]. An older procedure involves deprotonation by $NaNH_2$ in liquid NH_3[5]. This method is reliable but somewhat less convenient than the other methods. The reaction conditions can also be influenced by ring substituents. 3-Acyl substituents, for example, facilitate the deprotonation reaction and allow the use of weaker bases. The alkylating reagents must be able to undergo S_N2 substitution. Primary alkyl, benzyl and allyl halides and sulfonates are usually excellent electrophiles. There are fewer examples of use of secondary systems and the reaction is slower and accompanied by dehydro-

Table 9.1

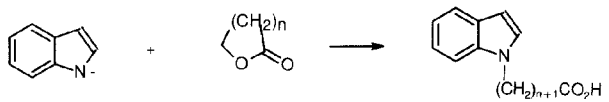
N-Alkylation of indoles

Entry	Substituents	Conditions	Yield (%)	Ref.
A Homogeneous basic solution				
1	1-Methyl	CH_3I, $NaNH_2$, $NH_{3\ liq.}$	85–95	[5]
2	1-Methyl	CH_3I, NaH, DMF	86	[8]
3	1-Benzyl	$PhCH_2Br$, DMSO, KOH	95	[3b]
4	1-Ethyl	C_2H_5I, acetone, KOH	88	[3c]
5	1-Cyclopentyl-3-formyl	*c*-C_5H_9Cl, DMF, K_2CO_3	58	[6]
6	1-Methyl-3-(2-methylpropanoyl)	CH_3I, DMSO, NaH	89	[9]
7	1-(2-Trimethylsilylethoxymethyl)	$(CH_3)_3SiCH_2CH_2OCH_2Cl$, NaH	96	[7]
B Phase transfer conditions				
8	1-Ethyl	$(C_2H_5O)_2SO_2$, benzene, 50% NaOH, $(C_4H_9)_4N^+HSO_4^-$ (5 mol%)	95	[4a]
9	1-(2-Propenyl)	$CH_2{=}CHCH_2Br$, ether, KO-*t*-Bu, 18-crown-6 (10 mol%)	78	[4d]
10	1-(*n*-Butyl)	C_4H_9Br, benzene, 50% NaOH, $(C_4H_9)_4N^+HSO_4^-$ (5 mol%)	93	[4f]
C Conjugate addition				
11	1-[(2-Ethoxycarbonyl)ethyl]	KH, $CH_2{-}CHCO_2C_2H_5$	72	[10]
12	5-Chloro-1-(2-cyanoethyl)	Triton B, $CH_2{=}CHCN$	na	[11]
13	1-Propanoamide	NaOMe, pyridine, $CH_2{=}CHCONH_2$	39	[12]
14	1-[2-(4-Pyridyl)ethyl]	NaOEt, $CuSO_4$, 4-vinylpyridine	57	[13]

halogenation[3]. Good results were reported for *N*-alkylation of indole-3-carboxaldehyde using cyclopentyl chloride in DMF with K_2CO_3 as the base[4]. Among the alkyl substituents which have been used as protecting groups in multistep synthesis is the 2-(trimethylsilyl)ethoxymethoxy (SEM) group. It can be introduced by reaction of the corresponding chloride with the sodium salt of indole and can be removed by fluoride ion[7]. Table 9.1 gives some representative alkylation procedures.

Indoles can also be alkylated by conjugate addition under alkaline conditions. Under acidic conditions, alkylation normally occurs at C3 (see Section 11.1). Table 9.1 includes examples of alkylation by ethyl acrylate, acrylonitrile, acrylamide and 4-vinylpyridine.

Indoles can also be alkylated by lactones[14]. Base-catalysed reactions have been reported for β-propiolactone[15], γ-butyrolactone[10] and δ-valerolactone[10]. These reactions probably reflect the thermodynamic instability of the *N*-acylindole intermediate which would be formed by attack at the carbonyl group relative to reclosure to the lactone. The reversibility of the *N*-acylation would permit the thermodynamically favourable *N*-alkylation to occur.



(9.1)

Procedure

2,3-Dimethylindole-1-propanenitrile[16]

A solution of 2,3-dimethylindole (145 g, 1 mol) in dry dioxan containing hydroquinone (100 mg) was treated with *N,N,N*-trimethylbenzylammonium ethoxide (5 ml of a 40% solution in MeOH) and warmed to 35°C. Freshly distilled acrylonitrile (150 ml, 2.5 mol) was added at a rate such that the temperature did not rise above 40°C. The solution was then stirred overnight and diluted with 10% aq. acetic acid (1 l). The solution was extracted with CH_2Cl_2 and the extract was washed with water and dried ($MgSO_4$). The extract was then mixed with silica gel (800 g) and the solvent removed *in vacuo*. The silica was placed in a Soxhlet extractor and extracted with cyclohexane. The extract deposited the product as colourless needles (125 g, 63% yield).

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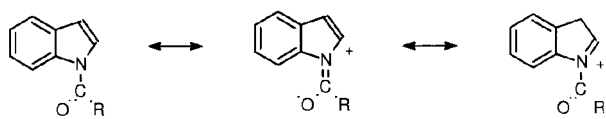
9.2 ACYLATION AND SULFONYLATION

The mechanistic principles underlying *N*-acylation and sulfonylation are the same as for *N*-alkylations. The reaction conditions are designed so that the indole anion is the reactive nucleophile. The usual acylating agents are acid anhydrides, acyl chlorides or chloroformate esters and sulfonyl chlorides are used for sulfonylation. The *tert*-butoxycarbonyl group is introduced using di-*tert*-butyl dicarbonate[1] or *tert*-butyl phenyl carbonate[2]. The *N*-acyl derivatives of indoles are less stable to hydrolysis than normal amides because of the diminished capacity of the indole nitrogen to act as an electron donor toward the carbonyl group.



(9.2)

Nevertheless, they are stable to standard work-up and purification methods. The benzenesulfonyl group can be introduced using base and an aprotic solvent[3] or under phase transfer conditions[4]. Table 9.2 gives some representative examples of acylation and sulfonylations.

Procedures

1-(tert-Butoxycarbonyl)indole[1]

Indole (10 mmol) was added to dry CH_3CN (20 ml) and the mixture stirred while DMAP (122 mg, 1.00 mmol) and di-*tert*-butyl dicarbonate (2.62 g, 12 mmol) were added. Evolution of gas was noted and stirring was continued

Table 9.2

Acylation and sulfonylation of indoles

Entry	Substituents	Conditions	Yield (%)	Ref.
1	1-Acetyl	$(CH_3CO)_2O$, DMF, K_2CO_3	na	[3]
2	1-Benzoyl	PhCOCl, DME, NaOH	83	[4]
3	1-*tert*-Butoxycarbonyl	$(CH_3)_3COCO_2C_6H_5$, THF, NaH	78	[5]
4	1-Phenylsulfonyl	$C_6H_5SO_2Cl$, benzene, 50% NaOH, $(C_4H_9)_4N^+HSO_4^-$ (10 mol%)	96	[6]

for 1 h or until the reaction was judged to be complete by TLC. The solvent was removed *in vacuo* and the residue purified by being eluted through silica gel with CH_2Cl_2-hexanes.

1-(Benzyloxycarbonyl)indole[2]

To a stirred ice-cooled suspension of indole (12.0 g, 0.102 mmol), $Bu_4N^+Br^-$ (1.16 g, 3.6 mmol) and powdered NaOH (5.24 g, 0.13 mol) in CH_2Cl_2 (100 ml) there was added over a period of 50 min a solution of benzyl chloroformate (15 ml, 0.11 mol) in CH_2Cl_2 (50 ml). After stirring for an additional 10 min, the reaction mixture was diluted with water (200 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The extracts were dried (Na_2SO_4) and evaporated. The residue crystallized on cooling and was recrystallized from ether to give pure product in 84% yield.

1-(Phenylsulfonyl)indole[6, adapted]

Indole (25.0 g, 0.213 mol) was dissolved in CH_2Cl_2 (200 ml). Powdered NaOH (17.1 g, 0.426 mol) and *n*-$Bu_4N^+HSO_4^-$ (0.103 g, 0.3 mmol) were added. The solution was stirred for 1 h. The solution was then cooled in an ice bath and $PhSO_2Cl$ (30 ml, 0.234 mol) was added dropwise over 30 min. The solution was then stirred overnight. The solution was mixed with water (300 ml) and CH_2Cl_2 (300 ml) and the layers separated. The CH_2Cl_2 was washed with 10% aq. NaCl and dried (Na_2SO_4). The solution was filtered and concentrated *in vacuo* to give crude product which was triturated with MeOH to yield 44.9 g (82% yield) of product.

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–10–

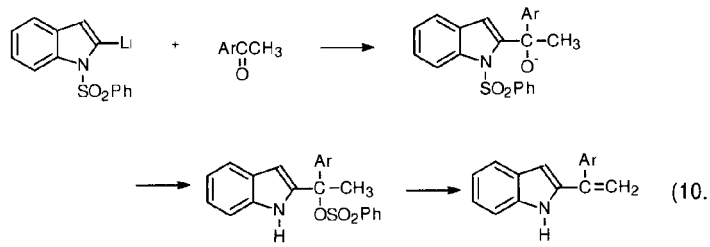
Introduction of Substituents at C2

The most versatile procedures for C2 substitution are based on lithiation, which is selective for C2 because of the influence of the heteroatom. 1-Alkylindoles such as 1-methylindole are readily lithiated and undergo typical reactions with electrophiles. For syntheses requiring *N*-unsubstituted indoles, removable protecting groups are used. The most widely used are phenylsulfonyl[1–3], *tert*-butoxycarbonyl[4] and carboxy[5]. For cases where protective groups must be removed under highly selective conditions, the 1-(2-trimethylsilylethoxymethyl) (SEM) group may be useful[6]. These groups can by introduced as described in the preceding chapter. The original procedure for lithiation of 1-phenylsulfonylindole used *t*-butyllithium because *n*-butyllithium caused competing reaction at the sulfonyl group[1]. Subsequently it was shown that LDA could readily effect lithiation[2,3]. More recently other workers have reported good results using *n*-butyllithium directly[7,8]. Lithiation of *tert*-butoxycarbonylindole is done using *t*-butyllithium in THF at $-78°C$[4]. The lithiocarboxy protecting group is introduced by allowing *N*-lithioindole to react with solid CO_2 in THF. The salt is then lithiated at C2 with an equivalent of *t*-butyllithium[5].

10.1 ALKYLATION AND HYDROXYALKYLATION

Lithiated indoles can be alkylated with primary or allylic halides and they react with aldehydes and ketones by addition to give hydroxyalkyl derivatives. Table 10.1 gives some examples of such reactions. Entry 13 is an example of a reaction with ethylene oxide which introduces a 2-(2-hydroxyethyl) substituent. Entries 14 and 15 illustrate cases of addition to aromatic ketones in which dehydration occurs during the course of the reaction. It is likely that this process occurs through intramolecular transfer of the phenylsulfonyl group.

Synthetic procedures involving other types of intermediates can be based on 2-lithiation. An indirect 2-alkylation can be carried out via indol-2-ylborates which can be prepared by addition of 2-lithioindoles to trialkylboranes.



(10.1)

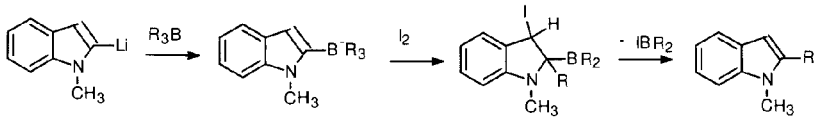
Treatment of the borates with iodine leads to boron → C2 migration of an alkyl group[9]. This reaction has not been widely applied synthetically but it might be more applicable for introduction of branched alkyl groups than direct alkylation of an indol-2-yllithium intermediate.

Table 10.1

Alkylation and hydroxalkylation of 2-lithioindoles

Entry	Substituents	Electrophile	Yield (%)	Ref.
A Alkylation				
1	1-(Phenylsulfonyl)-2-methyl	CH_3I	85	[3]
2	1-Carboxy-2-methyl	CH_3I	68	[5]
3	2-(4-Bromobutyl)-1-(phenylsulfonyl)	$Br(CH_2)_4Br$	76	[8]
4	2-(*E,E*-Farnesyl)-1-phenylsulfonyl	*E,E*-Farnesyl bromide	70	[12]
B Hydroxyalkylation				
5	1-(Phenylsulfonyl)-2-(1-hydroxyethyl)	$CH_3CH{=}O$	93	[3]
6	1-(Phenylsulfonyl)-2-[hydroxy-(4-methoxyphenyl)methyl]	4-Methoxybenzaldehyde	65	[1]
7	1-(Phenylsulfonyl)-2-[hydroxy-(pyrid-2-yl)methyl]	Pyridine-2-carboxaldehyde	32	[1]
8	1-(Phenylsulfonyl)-2-[1-hydroxy-1-phenylpropyl]	Ethyl phenyl ketone	na	[2]
9	1-Carboxy-2-[hydroxy(4-methoxyphenyl)methyl	4-Methoxybenzaldehyde	72	[5]
10	1-(Phenylsulfonyl)-2-[1-hydroxy-1-(methoxycarbonyl)ethyl]	Methyl pyruvate	64	[13]
11	1-(Dimethylaminomethyl)-2-[hydroxy(phenyl)methyl]	Benzaldehyde	77	[14]
12	2-[1-[3-(*t*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)]-1-hydroxymethyl]-1-(phenylsulfonyl)	3-(*t*-Butoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxaldehyde	71[a]	[7]
13	2-(2-Hydroxyethyl)-1-(phenylsulfonyl)	Ethylene oxide	69	[15]
C Hydroxyalkylation/dehydration				
14	2-(2-Methyl-1-phenylpropenyl)	Isobutyrophenone	68	[15]
15	2-(2-Methylphenylethenyl)	*o*-Methylacetophenone	33	[16]

[a]Product is a 4:1 mixture of stereoisomers.



(10.2)

Indol-2-ylcopper reagents can also be prepared from 2-lithioindoles and they have some potential for the preparation of 2-substituted indoles. 1-Methylindol-2-ylcopper can be prepared by reaction of 2-lithio-1-methylindole with CuBr[10]. It reacts with aryl iodides to give 2-aryl-1-methylindoles. Mixed cyanocuprate reagents can be prepared using CuCN[11]. The cyanocuprate from 1-methylindole reacts with allyl bromide to give 2-allyl-1-methylindole.

Procedures

1-[1-(Phenylsulfonyl)indol-2-yl]ethanol[3]

A solution of 2-lithio-1-(phenylsulfonyl)indole was prepared by adding 1-(phenylsulfonyl)indole (11.7 mmol) dissolved in THF (30 ml) to a solution of LDA prepared from $(i\text{-Pr})_2NH$ (1.12 eq) and n-BuLi (1.05 eq) in THF (30 ml) at $-75°C$. The solution was stirred at $-70°C$ for 1 h and then warmed slowly to 5°C over 1 h. The solution was recooled to $-78°C$. A solution of acetaldehyde (1.00 g, 22.7 mmol) in THF (5 ml) was added rapidly by syringe. The reaction mixture was then allowed to come slowly to room temperature and poured into 1% HCl (350 ml). The solution was extracted with CH_2Cl_2 (3×250 ml) and the combined extract was washed with water (400 ml) and brine (2×400 ml) and then dried over K_2CO_3. The solvent was evaporated *in vacuo* and the residue purified by chromatography to give the product (3.28 g, 93%).

Methyl α-hydroxy-α-methyl-1-(phenylsulfonyl)indole-2-acetate[13, as subsequently modified]

Dry THF (150 ml) was added to a flame-dried flask protected from the atmosphere and $(i\text{-Pr})_2NH$ (10.2 ml, 0.073 mol) was added. The flask was cooled to 0°C using an ice-bath. *n*-Butyllithium (0.068 mol) was added as a hexane solution and the solution stirred at 0°C for 30 min. The solution was then cooled to $-78°C$. A solution of 1-(phenylsulfonyl)indole (14.0 g, 0.055 mol) was dissolved in THF (50 ml) and cooled to $-78°C$. The indole solution was cannulated into the LDA solution over 15–20 min and the mixture stirred at $-78°C$ for an additional 45 min. The solution was then

brought to 0°C and stirred for 1 h before being recooled to −78°C. A solution of methyl pyruvate (14.7 ml, 0.163 mol) was dissolved in THF (50 ml) and cannulated into the solution of 2-lithio-1-(phenylsulfonyl)indole over a period of 15–20 min. The solution was stirred at −78°C for 30 min and then allowed to come gradually to room temperature over 2 h. The reaction mixture was poured into sat. NH_4Cl (400 ml) and the phases separated. The aqueous phase was extracted further with ether (3 × 150 ml). The original organic phase was washed with water (3 × 150 ml) and the organic phases combined and dried ($MgSO_4$). The solvent was removed *in vacuo*. The residual oil was crystallized by trituration with ether to give 14.3 g (73%) of product.

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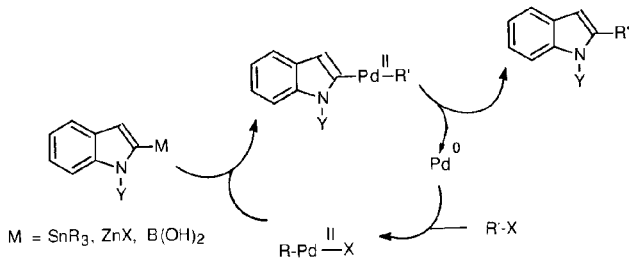
10.2 ARYLATION AND VINYLATION

Lithiation at C2 can also be the starting point for 2-arylation or vinylation. The lithiated indoles can be converted to stannanes or zinc reagents which can undergo Pd-catalysed coupling with aryl, vinyl, benzyl and allyl halides or sulfonates. The mechanism of the coupling reaction involves formation of a disubstituted palladium intermediate by a combination of ligand exchange and oxidative addition. Phosphine catalysts and salts are often important reaction components.



(10.3)

Several groups have developed procedures for Pd-mediated coupling based on this general chemistry. The variety of such procedures and the range of compounds for which they are applicable suggest that Pd-catalysed coupling is currently the most versatile method for introduction of 2-substituents which cannot be prepared directly from organolithium intermediates.

Several *N*-protecting groups were examined in developing procedures based on the coupling of indol-2-yltri-*n*-butylstannanes. The 1-methyl and 1-(2-trimethylsilylethoxymethyl) (SEM) derivatives reacted readily with aryl and vinyl halides, whereas the 1-*tert*-butoxycarbonyl derivative was less reactive[1,2]. The SEM protecting group is removed by $BuN_4^+F^-$, providing access to

Table 10.2

Palladium-catalysed 2-arylation, 2-allylation and 2-vinylation

Entry	Indole	Reagents	Yield (%)	Ref.
1	1-Methyl-2-(tri-*n*-butylstannyl)indole	4-Bromobenzonitrile, $Pd(PPh_3)_2Cl_2$	91	[2]
2	1-(Phenylsulfonyl)indol-2-ylzinc chloride	Iodobenzene, $Pd(PPh_3)_2Cl_2$	57	[4]
3	1-(Phenylsulfonyl)indol-2-ylzinc chloride	2-Bromo-4-methylpyridine, $Pd(PPh_3)_2Cl_2$	92	[5]
4	1-(*tert*-Butoxycarbonyl)-2-(tri-*n*-butylstannyl)indole	4-Bromobenzonitrile, $Pd(PPh_3)_2Cl_2$	66	[2]
5	1-Carboxyindol-2-ylzinc chloride	Iodobenzene, $Pd(PPh_3)_4$	74	[3]
6	1-(Trimethylsilylethoxymethyl)-2-(tri-*n*-butylstannyl)indole	2-Methyliodobenzene, $Pd(PPh_3)_4$	93	[1]
7	1-(Trimethylsilylethoxymethyl)-2-(tri-*n*-butylstannyl)indole	3-Bromopropene, $Pd_2(dba)_3$, tri-(2-furyl)phosphine	93	[1]
8	1-(Trimethylsilylethoxymethyl)-2-(tri-*n*-butylstannyl)indole	2-Bromopropene, $Pd(PPh_3)_2Cl_2$	62	[2]

deprotected 2-substituted indoles. Both $PdCl_2(CH_3CN)_2$ and $Pd(PPh_3)_4$ have been used as catalysts with somewhat better results being reported for the latter[1]. For coupling with allylic bromides $Pd_2(dba)_3$ with trifurylphosphine as the phosphine ligand gave the best results[1].

Indol-2-ylzinc halides are also useful reagents for Pd-catalysed cross-coupling. One route to these intermediates is *via* lithiation and metal–metal exchange using *N*-(*t*-Boc) protection[3]. 1-(Phenylsulfonyl)indol-2-yl zinc iodide has been prepared directly from the 2-iodoindole by reaction with active zinc[4]. Entries 2, 3 and 4 in Table 10.2 give examples of these procedures.

Procedures

2-(2-Methylphenyl)-1-(2-trimethylsilylethoxymethyl)indole[1]

1-(SEM)indol-2-yltri-*n*-butylstannane (1.0 mmol) was added to a solution of 2-iodotoluene (1.3 mmol) and $Pd(PPh_3)_4$ (0.01 mmol) in dry DMF (5 ml) using a syringe. The mixture was stirred at 110°C until the reaction was judged to be complete by TLC (2 h). The reaction solution was cooled to room temperature, diluted with water (20 ml) and extracted with ether. The extract was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography to give the product in 93% yield.

1-(tert-Butoxycarbonyl)-2-(4-cyanophenyl)indole[2]

A mixture of 1-(*t*-Boc)indol-2-yl-tri-*n*-butylstannane (1.2 mmol) and 4-bromobenzonitrile (1.0 mmol) and $Pd(PPh_3)_2Cl_2$ (0.02 mmol) in dry dioxane (5 ml) was heated at 100°C overnight under nitrogen. The reaction mixture was cooled, diluted with EtOAc and stirred for 15 min with 15% aq. KF. The precipitate was removed by filtration and washed with EtOAc. The EtOAc layer was separated, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica. The yield was 66%.

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10.3 ACYLATION AND CARBOXYLATION

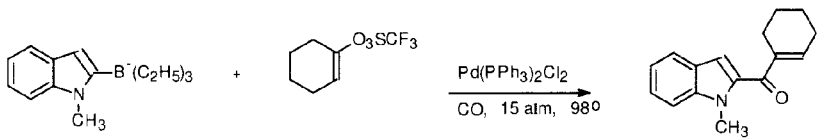
The simplest procedures for 2-acylation involve reaction of an *N*-protected 2-lithioindole with an acyl halide, anhydride or ester. Such reactions typically give good yields of 2-acylindoles. Table 10.3 presents some examples. Aryl

Table 10.3

Acylation and carboxylation of 2-lithioindoles

Entry	2-Lithioindole	Electrophile	Yield (%)	Ref.
1	1-(Phenylsulfonyl)	Benzoyl chloride	65	[3]
2	1-(Phenylsulfonyl)	Pyridine-3-carbonyl chloride	60	[3]
3	1-(Phenylsulfonyl)	Benzoic anhydride	72	[4]
4	1-(Phenylsulfonyl)	Isonicotinic anhydride	75	[5]
5	1-(Phenylsulfonyl)	Pyridine-3,4-dicarboxylic acid anhydride	83	[6]
6	1-(*tert*-Butoxycarbonyl)	Dimethyl oxalate	66	[7]
7	1-(Phenylsulfonyl)	Ethyl chloroformate	75	[3]
8	1-(Phenylsulfonyl)	Carbon dioxide	63	[3]
9	1-(Phenylsulfonyl)	Dimethylformamide	50	[8]
10	1-(Lithiocarboxy)	Carbon dioxide	70	[9]
11	1-(Lithiocarboxy)-3-methyl	Ethyl chloroformate	70	[10]
12	1-(Lithiocarboxy)-3-methyl	Dimethylformamide	51	[10]
13	5-Methoxy-1-(phenylsulfonyl)	Dimethyl oxalate	54	[11]
14	1-(Phenylsulfonyl)	Pyridine-2-carbonitrile	36	[3]

nitriles have also been used occasionally (Entry 14). Palladium-catalysed carbonylation via stannanes can also be done but this adds an additional step if the original starting point is 2-lithiation[1]. 2-Acylindoles have also been prepared by Pd-catalysed carbonylation using indol-2-ylborates and vinyl triflates[2].



(10.4)

Procedure

Methyl 5-methoxy-α-oxo-1-(phenylsulfonyl)indole-2-acetate[11]

tert-Butyllithium (16 ml of 1.7 M solution, 27.1 mmol) in pentane was added dropwise to a solution of 5-methoxy-1-(phenylsulfonyl)indole (6.0 g, 20.1 mmol) in THF (50 ml) at −10°C. The solution was stirred for 20 min at −5°C and then for 20 min at room temperature. This solution was then transferred to a dropping funnel and added dropwise to a solution of dimethyl oxalate (10.0 g, 35.5 mmol) in THF (35 ml) at 0°C. After being stirred for 1 h at room

temperature, the reaction mixture was treated with 5% aq. NH_4Cl. The layers were separated and the water layer extracted with EtOAc. The combined organic layers were washed with water and brine and dried. The solvent was removed *in vacuo* and the residue crystallized from MeOH to give 4.18 g (54%) of product.

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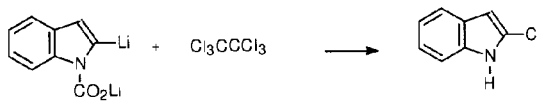
10.4 INTRODUCTION OF OTHER FUNCTIONAL GROUPS

N-Protected 2-lithioindoles can, in principle, be used to introduce a range of other functional groups at C2 by applying synthetic methods applicable to aryllithium intermediates. Among cases for which procedures have been developed are halogenation using hexachloroethane, 1,2-dibromo-1,1,2,2-tetrachloroethane and 1,2-diodoethane[1]. The *N*-carboxy protecting group was used.



(10.5)

Similar halogenations have been done on 2-lithio-1-phenylsulfonylindole[2]. 2-Lithio-1-phenylsulfonylindole is readily converted to the 2-(trimethylsilyl) derivative[2,3]. 2-Trialkylstannylindoles can also be prepared via 2-lithioindoles[4,5]. 2-Sulfonamido groups can be introduced by reaction of a 2-lithioindole with sulfur dioxide, followed by conversion of the sulfinic acid group to the sulfonyl chloride with *N*-chlorosuccinimide[6].

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Introduction of Substituents at C3

There are a wide variety of methods for introduction of substituents at C3. Since this is the preferred site for electrophilic substitution, direct alkylation and acylation procedures are often effective. Even mild electrophiles such as alkenes with EW substituents can react at the 3-position of the indole ring. Techniques for preparation of 3-lithioindoles, usually by halogen–metal exchange, have been developed and this provides access not only to the lithium reagents but also to other organometallic reagents derived from them. The 3-position is also reactive toward electrophilic mercuration.

11.1 ALKYLATION

The susceptibility of indoles to electrophilic attack makes direct 3-alkylation by carbocations or ion pairs a feasible reaction. However, the indole ring is quite reactive to protic and Lewis acids so that only procedures which generate carbocations under relatively mild conditions are likely to produce good yields. Alkylation is sometimes carried out directly on the neutral heterocycle but it is also possible to use salts of indoles. Synthetic procedures for 3-alkylation usually involve magnesium salts prepared by reaction of the indole with a Grignard reagent. The magnesium salts tend to give 3-substitution, rather than 1-substitution, presumably because the tight coordination of magnesium at nitrogen reduces its nucleophilicity. There have been several studies of the ratio of *N*:*C* alkylation of indole salts[1–3]. *C*-Alkylation is favoured in the order $Mg^{2+} > Li^{+} > Na^{+} > K^{+}$[3]. Improved donor character of the solvent promotes ion pair dissociation of the indole salts and favours *N*-alkylation[2,3]. *C*-Alkylation is favoured by more reactive alkylating agents such as allylic and benzylic halides[1,3]. *C*-Alkylation is more favourable for iodides than for tosylates, but this effect is rather small[3].

Table 11.1 lists some of the reaction conditions which have given preparatively useful yields of 3-alkylation. Entries 1–3 are typical alkylations using a magnesium salt and an alkyl halide. Even 2,3-disubstituted indoles are alkylated at C3 under these conditions (Entry 7). Entry 5 represents a more recently developed method in which an allylic alcohol and indole react in the

Table 11.1

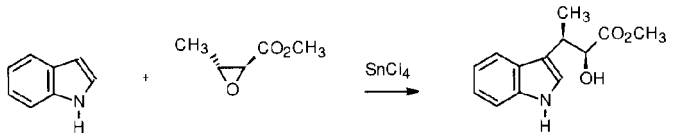
3-Alkylation of indoles

Entry	Indole reactant	Alkylating reactant	Yield (%)	Ref.
1	Indol-1-ylmagnesium bromide	3-Bromopropene, benzene, 10–14 h at 20°C	70	[4]
2	Indol-1-ylmagnesium bromide	Methyl 2-(bromomethyl)-propenoate, THF, −20°C → 30°C	56	[5]
3	6-Methoxyindol-1-ylmagnesium bromide	3-(1-Chloroethyl)pyridine	40	[6]
4	Indole	1-Bromo-3-methylbut-2-ene. HOAc, NaOAc, H_2O, 23°C, 1 h	56	[7]
5	Indole	3-Methylcyclohex-2-enol, 3 M $LiClO_4$, 0.01 eq. HOAc	82	[8]
6	Benzyl indole-5-carboxylate	Methyl 4-(bromomethyl)-3-methoxybenzoate, DMF, 80°C	45	[9]
7	2,3-Dimethylindol-1-ylmagnesium bromide	3-Bromopropyne, ether, 38°C	64	[10]
8	2,3-Dimethylindol-1-yllithium	Iodoethane, THF, −78°C → 25°C	45–70	[11]
9	1,2,3,4-Tetrahydrocarbazol-9-ylmagnesium bromide	*N*,*N*-Dimethyl-3-chloropropanamine	50	[12]

presence of 3 M $LiClO_4$ and a small amount of acetic acid. This reaction presumably involves generation of allylic perchlorate ion pairs. Alkylation occurs at the less substituted allylic terminus. Entry 6 involves solvolysis of a benzyl bromide. Earlier examples of 'solvolytic' alkylation of indole include a reaction with isopentenyl bromide in acetate buffer (Entry 4). Entries 8 and 9 are examples of alkylation of lithium salts of 2,3-dialkylindoles which occurs at C3 to give 2,3,3-trisubstituted 3*H*-indoles.

Carbocations stabilized by functional groups can also effect 3-alkylation of indoles. From a synthetic point of view the most important are *N*,*N*-dialkylmethyleneiminium ions which can be generated under Mannich conditions from formaldehyde and secondary amines[13]. The products, 3-(*N*,*N*-dialkylaminomethyl)indoles, are useful synthetic intermediates (see Chapter 12).

Epoxides and aziridines are also capable of electrophilic subsitution of indoles. Indolylmagnesium bromide and cyclohexene oxide react to give 3-(*trans*-2-hydroxycyclohexyl)indole[14]. Reaction of indoles with epoxides also occurs in the presence of Lewis acids. For example, indole reacts with methyl 2*S*,3*R*-epoxybutanoate at C3 with inversion of configuration[15].



(11.1)

Lewis acids such as zinc triflate[16] and BF_3[17] have been used to effect the reaction of indole with *N*-protected aziridine-2-carboxylate esters. These alkylations by aziridines constitute a potential method for the enantioselective introduction of tryptophan side-chains in a single step. (See Chapter 13 for other methods of synthesis of tryptophans.)

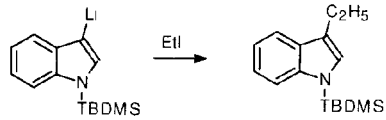
3-Alkylation can also be accomplished with electrophilic alkenes. There is a dichotomy between basic and acidic conditions. Under basic conditions, where the indole anion is the reactive nucleophile, *N*-alkylation occurs. Under acidic conditions *C*-alkylation is observed. The reaction of indole with 4-vinylpyridine is an interesting illustration. Good yields of the 3-alkylation product are obtained in refluxing acetic acid[18] whereas if the reaction is done in ethanol containing sodium ethoxide 1-alkylation occurs[19]. Table 11.2 gives some examples of 3-alkylation using electrophilic alkenes.

It is also possible to effect 3-alkylation via reactions of 3-lithioindoles. 3-Lithioindoles are not as easily available nor quite as easy to use as the 2-isomers. They are ordinarily prepared by halogen–metal exchange between a haloindole and an alkyllithium reagent. The stability of the 3-lithioindoles depends on the nitrogen substituent. With a 1-phenylsulfonyl substituent rearrangement to the more stable 2-lithioindole occurs at temperatures of $-40°C$ and above[24]. This problem can be avoided by use of a *tert*-butyldimethylsilyl (TBDMS) protecting group. 3-Lithio-1-TBDMSindole can be prepared from 3-bromo-1-TBDMSindole and is stable up to room temperature[25]. The steric bulk of the protecting group evidently retards rearrangement of lithium to C2. 3-Lithioindoles prepared by halogen metal exchange undergo typical alkylation reactions[25,26].

Table 11.2

3-Alkylation by conjugate addition

Entry	Indole reactant	Electrophile	Yield (%)	Ref.
1	Indole	But-3-en-2-one, 4:1 AcOH, Ac_2O, $25°C \rightarrow 90$ C	75	[20]
2	Indole	But-3-en-2-one, BF_3, EtOH, $-20°C$	86	[21]
3	Indole	But-3-en-2-one, CH_2Cl_2, montmorillonite clay, 40°C	75	[22]
4	Indole	Nitroethene, benzene, 0°C then 25°C for 20 h	80	[23]



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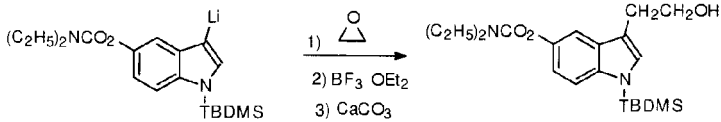
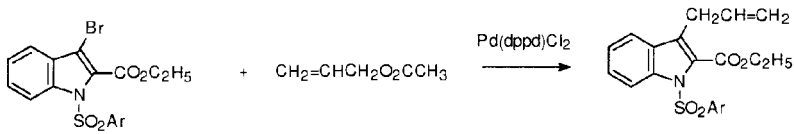


(11.3)

There are also palladium-catalysed procedures for allylation. Ethyl 3-bromo-1-(4-methylphenylsulfonyl)indole-2-carboxylate is allylated at C3 upon reaction with allyl acetate and hexabutylditin[27]. The reaction presumably involves a π-allyl-Pd intermediate formed from the allyl acetate, oxidative addition, transmetallation and cross coupling.



(11.4)

Procedures

3-(2-Propenyl)indole[4]

A 20% excess of ethylmagnesium bromide was prepared from magnesium (6.5 g) in ether (80 ml) by adding ethyl bromide (30 g) in ether (30 ml). Indole (25.8 g) in benzene (50 ml) was then added slowly with stirring and stirring was continued for 20 min after addition was complete. A solution of allyl bromide (29.2 g) in benzene (20 ml) was then added slowly. The mixture was stirred overnight and then diluted with ether and the product isolated and purified by distillation (22.7 g, 70% yield).

Methyl 4-[[5-(benzyloxycarbonyl)indol-3-yl]methyl]-3-methoxybenzoate[9]

A solution of benzyl indole-5-carboxylate (1.0 g, 3.98 mmol) and methyl 4-(bromomethyl)-3-methoxybenzoate (2.06 g, 7.97 mmol) in dry DMF (10 ml) was heated at 80°C for 24 h. The reaction solution was cooled, poured into water (100 ml) and the product extracted with EtOAc (3 × 75 ml). The extract was washed with water and brine and dried over $MgSO_4$. The product was obtained by evaporation of the solvent and purified by chromatography on silica gel using 1:4 EtOAc/hexane for elution. The yield was 1.11 g (32%) and some of the indole (30%) was recovered unreacted.

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11.2 VINYLATION, ARYLATION AND ALKYNYLATION

The best procedures for 3-vinylation or 3-arylation of the indole ring involve palladium intermediates. Vinylations can be done by Heck reactions starting with 3-halo or 3-sulfonyloxyindoles. Under the standard conditions the active catalyst is a Pd(0) species which reacts with the indole by oxidative addition. A major consideration is the stability of the 3-halo or 3-sulfonyloxyindoles and usually an EW substituent is required on nitrogen. The range of alkenes which have been used successfully is quite broad and includes examples with both ER and EW substituents. Examples are given in Table 11.3. An alkene which has received special attention is methyl α-acetamidoacrylate which is useful for introduction of the tryptophan side-chain. This reaction will be discussed further in Chapter 13.

Table 11.3

3-Vinylation of indoles

Entry	Indole reactant	Reagent, conditions	Yield (%)	Ref.
A Heck reactions				
1	1-Acetyl-3-bromoindole	Methyl acrylate, $Pd(OAc)_2$, Ar_3P, Et_3N, DMF	50	[1]
2	1-(Phenylsulfonyl)-3-trifluoromethyl-sulfonyloxyindole	Styrene, $Pd(PPh_3)_2Cl_2$, $EtN(i\text{-}Pr)_2$, DMF	75	[2]
3	4-Bromo-3-iodo-1-(4-methylphenyl-sulfonyl)indole	*N*-Vinylphthalimide, $Pd(OAc)_2$, Et_3N	77	[3]
4	4-Bromo-3-iodo-1-(4-methylphenyl-sulfonyl)indole	Ethyl α-acetamidoacrylate, $Pd(OAc)_2$, Et_3N	60	[4]
B Oxidative vinylations				
5	1-(Phenylsulfonyl)indole	Ethyl acrylate. AgOAc (2 eq.), $Pd(OAc)_2$, (10 mol%)	98 (at 32% conv.)	[5]
6	1-(2,6-Dichlorobenzoyl)indole	Acrylonitrile, $Pd(OAc)_2$	52 (at 47% conv.)	[6]
7	Ethyl 1-Benzylindole-2-carboxylate	Methyl acrylate, $PdCl_2$, $Cu(OAc)_2$	84	[7]
8	4-Bromo-1-(4-methylsulfonyl)indole	Methyl α-(*t*-butoxycarbonylamino)acrylate, $Pd(OAc)_2$, chloranil	87	[8]
C Vinyl stannane coupling				
9	3-Bromo-1-(methanesulfonyl)indole	*Z*-(2-Ethoxyvinyl)tri-*n*-butylstannane, $Pd(PPh_3)_2Cl_2$	83	[9]
D Boronic acid coupling				
10	1-(4-Methylphenylsulfonyl)indole-3-boronic acid	1-Benzyl-3-trifluoromethanesulfonyloxy-1,2,5,6-tetrahydropyridine, $Pd(PPh_3)_4$	92	[10]

Because Pd(II) salts, like Hg(II) salts, can effect electrophilic metallation of the indole ring at C3, it is also possible to carry out vinylation on indoles without 3-substituents. These reactions usually require the use of an equiv. of the Pd(II) salt and also a Cu(II) or Ag(I) salt to effect reoxidation of the Pd. As in the standard Heck conditions, an EW substitution on the indole nitrogen is usually necessary. Entry 8 of Table 11.3 is an interesting example. The oxidative vinylation was achieved in 87% yield by using one equiv. of $Pd(OAc)_2$ and one equiv. of chloranil as a co-oxidant. This example is also noteworthy in that the 4-bromo substituent was unreactive under these conditions. Part B of Table 11.3 lists some other representative procedures.

3-Vinylation can also be done by Pd-catalysed cross-coupling in which one component is used as a halide or triflate and the other as a stannane (Stille reaction) or boronic acid (Suzuki reaction). Entry 9, Table 11.3, is an example of the use of a vinylstannane with a haloindole. Indole-3-boronic acids, which can be prepared by mercuration/boration, undergo coupling with vinyl triflates (Entry 10).

Arylation reactions can involve generation of either a nucleophilic (e.g. stannane, organozinc, boronic acid) or electrophilic (e.g. halide or triflate) derivative of indole. A complementary reagent provides the 3-substituent and palladium is used to catalyse coupling. Coupling proceeds by oxidative addition of the electrophilic component on Pd(0) and ligand exchange with the nucleophilic component to generate a diarylpalladium(II) intermediate which undergoes reductive elimination. In most of the cases reported to date, the indole has served as the nucleophilic component. 1-TBDMSindol-3-ylzinc chloride, which can be prepared by metal–metal exchange from the lithio intermediate, has been successfully coupled with various heteroaryl halides[11]. 1-(Phenylsulfonyl)indol-3-ylzinc iodide, which can be prepared by reaction of 1-(phenylsulfonyl)-3-iodoindole and activated zinc, also gives good yields in aryl–aryl coupling reactions[12].

3-Indolyltrialkylstannanes are also potential reagents for Pd-catalysed coupling. 3-(Tri-*n*-butylstannyl)-1-tosylindole can be prepared by Pd-catalysed

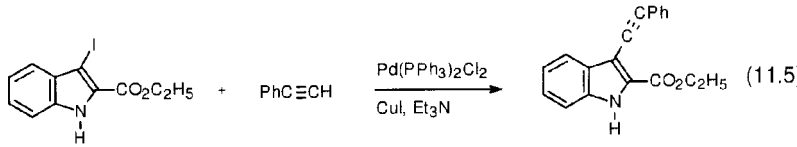
Table 11.4

3-Arylation of indoles

Entry	Indole reactant	Arylation reagent	Catalyst	Yield (%)	Ref.
1	1-(4-Methylphenylsulfonyl)-3-(tri-*n*-butylstannyl)indole	2-Naphthyl triflate	$Pd_2(dba)_3$, $AsPh_3$, DMF	87	[13]
2	1-(*t*-Butyldimethylsilyl)-3-indolylzinc chloride	2-Bromopyridine	$PdCl_2(PPh_3)_2$, DiBAlH, THF	95	[11]
3	1-(Phenylsulfonyl)-3-indolylzinc iodide	Iodobenzene	$Pd(PPh_3)_4$	83	[12]

stannylation of 3-iodo-1-tosylindole. It reacts with aryl and heteroaryl halides or aryl and vinyl triflates to give coupling products[13]. The best catalyst for these couplings was *tris*-(dibenzylideneacetone)dipalladium (Pd_2dba_3) with *tris*-(2-furyl)phosphine or triphenylarsine as the added ligand. Examples of these reactions are given in Table 11.4.

Palladium also catalyses coupling of haloindoles with acetylenes. The reaction is carried out in the presence of Cu(I) and presumably involves a copper acetylide as an intermediate[14].



(11.5)

Procedures

4-Bromo-3-(2-methoxycarbonylethenyl)-1-(4-methylphenylsulfonyl)indole[3]

4-Bromo-3-iodo-1-(4-methylphenylsulfonyl)indole (0.476 g, 1.00 mmol), methyl acrylate (0.108 g, 1.25 mmol), Et_3N (0.127 g, 1.25 mmol) and $Pd(OAc)_2$ (11 mg, 0.050 mmol) were mixed in a tube, purged with argon and the tube was sealed and heated to 100°C for 1 h. After cooling, it was opened and mixed with CH_2Cl_2 (50 ml). The solution was washed with water and dried (Na_2SO_4). The residue was purified by chromatography on silica using 1:3 benzene–hexane for elution. The yield was 0.350 g (81%).

3-Phenyl-1-(phenylsulfonyl)indole[12]

Activated zinc was prepared from lithium naphthalenide (12 mmol) and $ZnCl_2$ (6.3 mmol) in THF. The mixture was centrifuged and the solvent decanted. The zinc was resuspended in dry THF and 3-iodo-1-(phenylsulfonyl)indole (766 mg, 2 mmol) was added. The solution was stirred at room temperature for 2 h. The mixture was centrifuged and the supernatant solution was added to a solution of iodobenzene (410 mg, 2 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) in THF (2 ml). The mixture was stirred for 18 h and then filtered through Celite. The product was isolated from the filtrate by extraction with $CHCl_3$ and dried over $MgSO_4$ and purified by silica gel chromatography using hexane–EtOAc for elution (9:1). The yield was 550 mg (83%).

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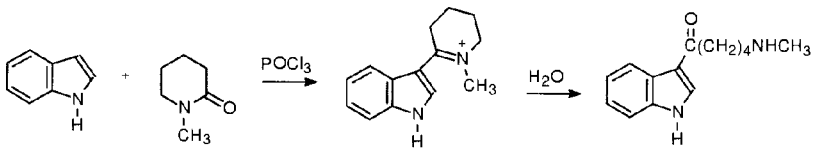
11.3 ACYLATION AND CARBOXYLATION

Acylation of the indole ring at C3 can be carried out using carboxylic acid chlorides or Vilsmeier–Haack reagents. If the indole ring does not have EW substituents, 3-acylation is usually done by reaction of the magnesium salt with an acyl chloride. Recently, excellent results have been obtained using zinc salts prepared by metal–metal exchange from the magnesium salts[1]. For indoles with EW substituents, use of a Friedel–Crafts catalyst is necessary. For example, 1-(phenylsulfonyl)indole can be acylated in good yields by reactions with acyl chlorides using $AlCl_3$ in CH_2Cl_2[2]. Oxalyl chloride is sufficiently reactive to acylate simple indoles in the absence of a catalyst. This acylation is the starting point for a versatile method of synthesis of tryptamines via indole-3-glyoxamides (see Section 13.1). Other examples of acylation procedures are given in Table 11.5.

Vilsmeier–Haack conditions have been used most frequently for formylation but are also applicable to longer acyl chains[3]. Reactions with lactams generate 3-(iminyl)indoles which can be hydrolysed to generate ω-aminoacyl groups as in equation 11.6 [4].



(11.6)

Section C of Table 11.5 gives some examples of Friedel–Crafts and Vilsmeier–Haack acylations of indoles.

Chlorosulfonyl isocyanate has been used to introduce 3-carboxamide groups. The initial product, an *N*-chlorosulfonylcarboxamide, is treated with tri-*n*-butylstannane to form the primary carboxamide[15]. 3-Cyano groups can also be introduced using chlorosulfonyl isocyanate. The intermediate *N*-chlorosulfonylindole-3-carboxamide is converted to 3-cyanoindole on reaction with triethylamine[16] or DMF[17].

Table 11.5

3-Acylation of indole derivatives

Entry	Indole reactant	Acylation conditions	Yield (%)	Ref.
A Acylation of indole salts				
1	Indol-1-ylmagnesium bromide	Cyclopentanecarbonyl chloride	49	[5]
2	Indol-1-ylzinc chloride	3-Methylbut-2-enoyl chloride	70	[1]
3	5-Benzyloxyindol-1-ylmagnesium bromide	Acetyl chloride	65	[6]
4	5-(Dibenzylamino)indol-1-ylmagnesium bromide	1-(Benzyloxycarbonyl)pyrrolidine-2-carbonyl chloride	44	[7]
5	6-(4-Fluorophenyl)indol-1-ylzinc chloride	3-(Pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-c]thiazole-7-carbonyl chloride	>45	[8]
B Acylation under Friedel–Crafts conditions				
6	1-(Phenylsulfonyl)indole	But-2-enoyl chloride, $AlCl_3$	98	[9]
7	Ethyl indole-2-carboxylate	3-(Methoxycarbonyl)propanoyl chloride, $AlCl_3$, nitrobenzene	95	[10]
8	Ethyl indole-2-carboxylate	4-Methoxybenzoic acid, TFAA, H_3PO_4	74	[11]
C Vilsmeier–Haack acylation				
9	Indole	DMF, $POCl_3$	95	[12]
10	6-Methoxyindole	DMF, $POCl_3$	95	[13]
11	4-Benzyloxyindole-2-(*N*,*N*-dimethyl-carboxamide)	DMF, $POCl_3$	60	[14]
12	Indole	*N*,*N*-Dimethylpropanoamide, $POCl_3$	85	[3]
13	Indole	*N*-Methylpiperidone, $POCl_3$	32	[4]

Procedures

3-(Cyclopentanecarbonyl)indole[5]

Phenylmagnesium bromide (2.8 mol) was prepared in anhydrous ether (2 l) from bromobenzene (440 g, 2.9 mol) and magnesium turnings (68.0 g 2.8 g-atom). To this solution was added dropwise a solution of indole (328 g, 2.8 mol) in benzene (800 ml). The resulting solution was stirred for 10 min and then a solution of cyclopentanoyl chloride (322 g, 2.4 mol) in benzene (800 ml) was added dropwise. The solution was stirred for 1 h and then water (1 l) was added carefully. The precipitate which formed was collected by filtration and dried to give 169 g of crude product. Additional product (97 g) was obtained by evaporation of the organic layer of the filtrate. The combined products were recrystallized from toluene to give 250 g (49% yield) of pure product.

3-Acetyl-1-(phenylsulfonyl)indole[2]

A suspension of $AlCl_3$ (20.00 g, 0.15 mol) in CH_2Cl_2 (250 ml) was stirred at 25°C. Acetic anhydride (7.6 g, 0.075 mol) was added and the mixture was stirred for 15 min, resulting in a clear solution. A solution of 1-(phenylsulfonyl)indole (6.43 g, 0.025 mol) in CH_2Cl_2 (50 ml) was added dropwise. The mixture was then stirred for 2 h and poured on to crushed ice (400 ml). The mixture was extracted with CH_2Cl_2 (3 × 100 ml) and washed with brine (100 ml), sat. aq. $NaHCO_3$ (100 ml) and brine (100 ml), dried (K_2CO_3) and evaporated *in vacuo* to give the product (7.39 g, 98%).

Indole-3-carboxaldehyde[12]

$POCl_3$ (5 ml, 0.05 mol) was added dropwise to DMF (16 g, 0.22 mmol) at a temperature of 10–20°C. Indole (5.85 g, 0.50 mmol) in DMF (4 ml) was then added slowly with stirring at a temperature of 20–30°C. The mixture was kept at 35°C for 45 min and then poured on to crushed ice and the clear solution treated at 20–30°C with aq. NaOH (20%, 0.24 mol) at such a rate that the solution was always acidic. The last quarter was added all at once and the solution quickly boiled for 1 min. The product was collected by filtration, washed with water and dried to yield 6.93 g (95% yield) of product.

6-Methoxyindole-3-carboxaldehyde[13]

$POCl_3$ (86.8 g, 0.57 mol) was added dropwise to DMF (164 g, 2.24 mol) at 0°C and the mixture stirred for 1 h. A solution of 6-methoxyindole (75.0 g, 0.57 mol) in DMF (75 ml) was then added over a period of 75 min and stirring was continued for 2 h at 35°C after the addition was complete. Ice (250 g) was

added to the warm solution and the mixture was transferred to a larger flask to which a solution of NaOH (225.6 g, 5.64 mol in 1 l of water) was added slowly with mechanical stirring. The mixture was then heated rapidly to reflux and evolution of dimethylamine was observed. The mixture was cooled and refrigerated overnight. The precipitate was collected by filtration and washed with water (3 × 500 ml). The solid was then resuspended in water (2 l) and collected by filtration. The moist solid was dissolved in hot ethanol (2 l) and boiled with charcoal for 5 min. The solution was filtered and concentrated. The product was obtained as a gold powder (84.8 g, 95%).

3-Cyanoindole[16]

To a stirred solution of indole (5.857 g, 50 mmol) in abs. CH_3CN (150 ml) at 0°C was added chlorosulfonyl isocyanate (4.35 ml, 50 mmol) dissolved in CH_3CN (50 ml) over about 45 min. A precipitate of 3-(*N*-chlorosulfonyl-aminocarbonyl)indole formed. After stirring for 1 h, Et_3N (6.82 ml, 49 mmol) was added over 45 min, maintaining the temperature near 0°C. The resulting solution was warmed to room temperature and stirred for 2 h. The solvent was then removed *in vacuo* and the residue mixed with $CHCl_3$ and ice-cold sat. aq. $NaHCO_3$. The $CHCl_3$ layer was separated, dried (Na_2SO_4) and evaporated to yield crude product. The product was heated with EtOAc (3 × 200 ml) and the combined solution treated with charcoal. Evaporation of the EtOAc provided 6.803 g (96%) of product.

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11.4 OTHER FUNCTIONAL GROUPS

The halogenation of the indole ring in the 3-position is a facile process and so long as appropriate recognition is taken as to the stability limitations of the product, good yields can be obtained. While introduction of a 1- or 2-EW substituent attenuates reactivity, halogenation still occurs readily. Indole, 1-methylindole and 2-methylindole can be brominated or iodinated by reaction with the halogens in DMF[1]. Other reagents which have been used for halogenation of indoles include pyridinium bromide perbromide[2], *N*-chlorosuccinimide[3], sulfuryl chloride[4] and 2,4,4,6-tetrabromocyclohexadienone[5]. A recently developed procedure involves use of *N*-bromosuccinimide in a slurry of silica in CH_2Cl_2[6]. Table 11.6 gives some examples of these reactions.

3-Sulfenylation of indoles can be carried out with sulfenyl halides[7], disulfides[7–9] or with *N*-methylthiomorpholine[10]. With disulfides the indoles are converted to lithium[8] or zinc[9] salts prior to sulfenylation. Thiophenols and iodine convert indoles to 3-(arylthio)indoles[11].

Direct 3-silylation of *N*-substituted indoles has been effected by reaction of the indoles with trimethylsilyl triflate in the presence of triethylamine[12]. The trimethylsilyl group has also been introduced via 3-lithio-1-(phenylsulfonyl)-indole[13].

Procedure

3-Bromoindole[2]

A solution of indole (4.0 g, 0.034 mol) in pyridine (40 ml) was cooled to 0°C and pyridinium bromide perbromide (10.8 g, 0.034 mol) was added slowly so that the reaction temperature did not rise above 2°C. When the addition was

Table 11.6

Halogenation of indoles

Entry	Substituents	Halogenation reagent	Position	Yield (%)	Ref.
1	None	Pyridinium bromide perbromide	3	64	[2,3]
2	None	*N*-Chlorosuccinimide, MeOH	3	84	[3]
3	None	2,4,4,6-Tetrabromocyclohexadienone	3	88	[5]
4	1-Methyl	Br_2, DMF	3	94	[1]
5	2-Methyl	I_2, DMF	3	98	[1]
6	2-Methyl	NBS, CH_2Cl_2, silica	3	98	[6]
7	3-Methyl	NBS, CH_2Cl_2, silica	2	90	[6]
8	3-Bromo	Br_2, CH_2Cl_2	2	76	[3]
9	4,7-Dibromo	SO_2Cl_2 (2 eq.)	2,3	88	[4]

complete the reaction solution was poured into cold ether and filtered. The filtrate was washed successively with dil. HCl, dil. NaOH and water. The ether solution was dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from *n*-heptane to give 4.3 g (64% yield) of 3-bromoindole. Heating the recrystallization solution above 60°C causes decomposition of the product. The recrystallized 3-bromoindole can be stored under pentane at −20°C.

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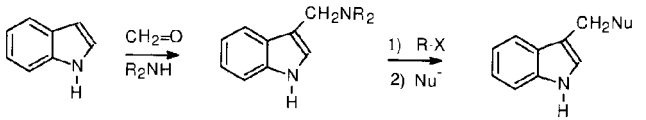
Modification of 3-Alkyl Substituents by Nucleophilic Substitution

An important method for construction of functionalized 3-alkyl substituents involves introduction of a nucleophilic carbon synthon by displacement of an α-substituent. This corresponds to formation of a benzylic bond but the ability of the indole ring to act as an electron donor strongly influences the reaction pattern. Under many conditions displacement takes place by an elimination–addition sequence[1]. Substituents that are normally poor leaving groups, e.g. alkoxy or dialkylamino, exhibit a convenient level of reactivity. Conversely, the 3-(halomethyl)indoles are too reactive to be synthetically useful unless stabilized by a ring EW substituent. 3-(Dimethylaminomethyl)indoles (gramine derivatives) prepared by Mannich reactions or the derived quaternary salts are often the preferred starting material for the nucleophilic substitution reactions.

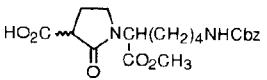
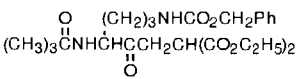


(12.1)

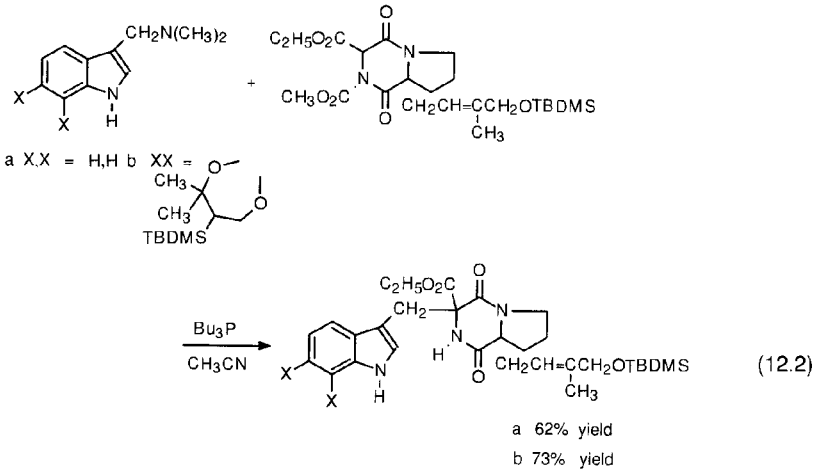
A number of early studies demonstrated that stabilized carbanions such as those from dialkyl malonates, β-ketoesters, α-nitroesters and nitroalkanes were alkylated by gramine and its derivatives. The cyanide group can also be easily introduced by nucleophilic substitution. Table 12.1 gives some examples of these reactions. The procedures typically involve heating the nucleophilic anion and the gramine derivative. In some procedures gramine is converted to the salt prior to the reaction (e.g. Entries 7 and 8) but in other procedures the salt is formed *in situ* by including an alkylating reagent, typically dimethyl sulfate, in the reaction mixture (Entries 1, 2, and 3). The alkylation of dimethyl malonate, nitromethane and similar anions was found to be improved by inclusion of tri-*n*-butylphosphine in the reaction mixture[2]. For example, heating gramine and diethyl acetamidomalonate in acetonitrile in the presence of 40 mol% tri-*n*-butylphosphine resulted in a quantitative yield of the alkylation product, while no reaction occurred in the absence of the phosphine. It is postulated that the phosphine traps the methyleneindolenine intermediate and

Table 12.1

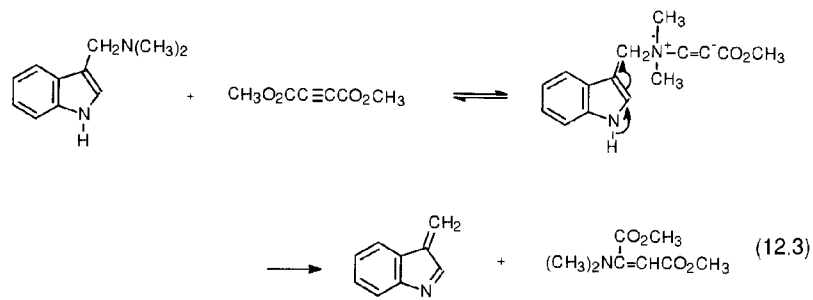
Alkylation using gramine derivatives

Entry	Indole reactant	Nucleophile	Conditions	Yield (%)	Ref.
1	Gramine	Nitromethane	$(MeO)_2SO_2$, NaOMe	86	[4]
2	Gramine	Methyl 2-nitropropanoate	Xylene, reflux	81	[5,6]
3	Gramine	Diethyl acetamidomalonate	$(MeO)_2SO_2$, NaOEt	95	[7]
4	Gramine	Diethyl formamidomalonate	$(MeO)_2SO_2$, NaOEt	99	[7,8]
5	Gramine	3-Cyanopenta-2,4-dione sodium enolate	$(MeO)_2SO_2$	79	[9]
6	Gramine	Diethyl 2-(ethoxycarbonyl)-butanedioate	(1) Na, toluene (2) aq. NaOH	na	[10]
7	Gramine	2-Cyano-4-oxopentanecarbo-nitrile	DMAD	71	[9]
8	Gramine methiodide		DBU, DMF	25	[11]
9	Gramine methiodide		NaOMe	76	[12]
10	3-[1-(2-Propylamino-ethyl)]indole	Methyl nitroacetate	Et_3N, toluene, reflux	85	[13]
11	5-Benzyloxygramine	Ethyl 2-nitropropanoate	Xylene, reflux	90	[6]
12	7-Benzoylgramine	Diethyl malonate	NaH, xylene	46	[14]
13	5-Nitro-3-(diethylamino-methyl)indole	Ethyl nitroacetate	Xylene, 92°C	86	[15]
14	4-(3-Hydroxy-3-methyl-1-butenyl)-3-(dimethyl-aminomethyl)indole	Methyl nitroacetate	Tributylphosphine	80	[16]
15	4-(3-Methylbut-2-enyl)-3-(dimethylamino)indole	Diethyl formamidomalonate	Toluene, NaOH	78	[17]

promotes subsequent addition, perhaps through a pentavalent phosphorane. The phosphine catalyst method has proven useful for the alkylation of rather complex structures such as illustrated by equation 12.2.

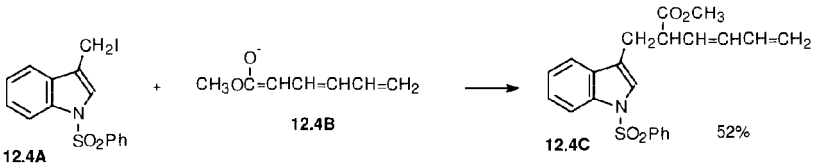


Dimethyl acetylenedicarboxylate (DMAD) has also been used to catalyse gramine alkylations (see Entry 7). It may function by both activating the dialkylamino leaving group and deprotonating the nucleophile[3].

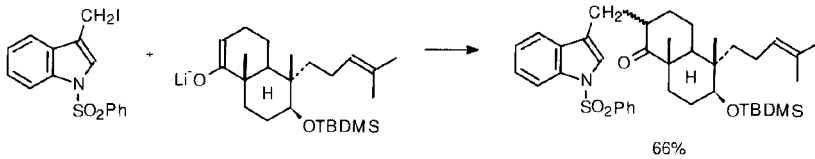


The simple 3-halomethylindoles are too unstable to be useful reagents for synthesis. However, stabilization by an EW nitrogen substituent gives more suitable compounds. 1-Benzoyl- and 1-(phenylsulfonyl) derivatives of 3-(bromomethyl)indole can be prepared by radical bromination with NBS[19,20]. These compounds are capable of alkylating typical nucleophiles such as imidazole, cyanide or azide ion, and enolates of compounds such as diethyl malonate[19]. Reaction with triethyl phosphite gives a phosphonate ester which can be used in Wadsworth–Emmons condensations[20]. 1-(Phenylsulfonyl)-3-(iodomethyl)indole gives 52% of the C2 alkylation product **12.4C** on

reaction with the lithium enolate of methyl sorbate[21]. This iodide has also been used in the alkylation of a ketone enolate in the course of synthesis of the indolyl terpene emeniveiol (equation 12.5)[22].



(12.4)



(12.5)

Procedures

In situ *quaternization method: ethyl 2-(ethoxycarbonyl)-2-formamido-3-(indol-3-yl)propanoate[7,8]*

Sodium metal (0.23 g, 10 mmol) was dissolved in abs. EtOH (30 ml). Gramine (1.74 g, 10 mmol) and diethyl formamidomalonate (2.03 g, 10 mmol) were added, followed by slow addition of dimethyl sulfate (2.52 g). The solution was allowed to stand at room temperature for 4 h, during which a precipitate formed. The mixture was poured into water and the product collected by filtration (99% yield).

In situ *quaternization method: 3-(2-nitroethyl)indole[4]*

A solution of NaOMe was prepared from sodium (4.35 g, 0.19 g-atom) and MeOH (300 ml). This was added to a stirred solution of gramine (30 g, 172 mmol) and dimethyl sulfate (43.4 g, 344 mmol) in 1:1 CH_3NO_2–MeOH (500 ml). The reaction mixture was stirred for 24 h. Nearly all of the solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2. The solution was washed with 5% NH_3, 1 N HCl and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was purified by chromatography using $CHCl_3$-hexane to give the product (28.0 g, 86%) along with a little 3-[2-nitro-2-(indol-3-ylmethyl)ethyl]indole (2.8 g, 5%).

Prior quaternization method: 4-acetyl-4-cyano-5-(indol-3-yl)pentan-2-one[9]

To a solution of gramine (4.35 g, 25 mmol) in dry THF (30 ml) under nitrogen was slowly added dimethyl sulfate (3.24 g, 25 mmol) in dry THF (25 ml). A pink gum formed. In a separate flask, 3-cyanopenta-2,4-dione (4.23 g, 25 mmol) in dry THF was added slowly to THF (15 ml) and NaH (0.6 g, 25 mmol) at 0°C. When the addition was complete, the cooling bath was removed and the solution of the anion (purple) was slowly transferred by cannula to the first flask. The mixture was shaken to disperse the gummy precipitate sufficiently to permit stirring. Stirring was then continued for 16 h. The solvent was evaporated and the residue was partitioned between $CHCl_3$ (25 ml) and 2 M HCl (25 ml). The aqueous layer was extracted with additional $CHCl_3$ (2 × 15 ml) and the combined $CHCl_3$ layers washed with water, brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by chromatography using petroleum ether/EtOAc for elution. The product was obtained as an oil (6.22 g, 79%).

Tri-n-butylphosphine catalysis: 3-(2-methyl-2-nitropropyl)indole[2]

A solution of gramine (87.3 mg, 0.50 mmol) and 2-nitropropane (33.7 mg, 0.38 mmol) in CH_3CN (3 ml) was treated with n-Bu_3P (18.6 mg, 0.14 mmol). The mixture was refluxed for 4 h. The solvent was removed *in vacuo* and the residue was acidified with 0.5 N aq. HCl and extracted with 95:5 CH_2Cl_2–MeOH. The extract was washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by TLC to yield 138.5 mg (99% yield) of the product.

Indole-3-acetonitrile[18]

A solution of gramine methosulfate (30.0 g, 0.10 mol) and NaCN (15.0 g, 0.30 mol) in water (300 ml) was heated to 65–70°C for 1 h. A colourless oil separated as the reaction proceeded. The solution was cooled and saturated with Na_2SO_4 and extracted with ether (400 ml). The ether was removed *in vacuo* and the residue purified by high vacuum distillation to give the product in 94% yield.

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Introduction of the Tryptamine and Tryptophan Side-Chains

The appearance of the 2-(indol-3yl)ethylamine (tryptamine) unit in both tryptophan-derived natural products and in synthetic materials having potential pharmacological activity has generated a great deal of interest in the synthesis of such compounds. Several procedures which involve either direct 3-alkylation or tandem 3-functionalization/modification have been developed. Similarly, methodology applicable to preparation of tryptophan analogues has been widely explored.

13.1 INTRODUCTION OF THE TRYPTAMINE SIDE-CHAIN

There are several procedures in which the reactivity of the indole ring towards electrophilic subsitution at C3 is used as the basis for introducing the tryptamine side-chain. A procedure developed by Speeter and Anthony involves acylation by oxalyl chloride followed by reaction with an amine to give an indol-3-ylglyoxamide[1]. The glyoxamides are then reduced to tryptamines. In the original procedure $LiAlH_4$ was used but alternative methods using diborane and alane are also successful. The borane reductions generate amine–borane complexes from which the amine is liberated using CsF or acidic hydrolysis. Table 13.1 lists some examples of these reactions.

Tryptamines can also be obtained from nitroethyl and nitrocthenyl indoles. 3-(2-Nitroethyl)indoles can be obtained in moderate to good yield by 3-alkylation with nitroethylene. The effective generation of this reactive alkene is the key to the success of the procedures. Ranganathan and co-workers generated nitroethylene from a mixture of nitroethanol and phthalic anhydride heated to 175–180°C. Nitroethylene was obtained by distillation at partial vacuum. Reaction of nitroethylene with indole gave 3-(2-nitroethyl)indole in 80% yield[8]. Another procedure involves *in situ* generation of nitroethylene from 2-nitroethyl acetate. This can be done in refluxing xylene in the presence of a radical chain inhibitor (e.g. *tert*-butylcatechol)[9].

3-(2-Nitroethenyl)indoles can be prepared by reaction of an indole with 2-(dimethylamino)-1-nitroethene in TFA[10]. 3-(2-Nitroethenyl)indoles can

Table 13.1

Synthesis of tryptamines from indoles *via* glyoxamides

Entry	Indole substituent	Amine	Reductant	Yield (%)	Ref.
1	None	Indoline	AlH_3	93,97	[2]
2	5-Benzyloxy	*N*,*N*-Dibenzylamine	$LiAlH_4$	91,92	[1]
3	5-Nitro	Dimethylamine	BH_3-THF	36,54	[3]
4	6-Chloro	NH_3	$LiAlH_4$	83,41	[4]
5	6-Chloro-5-methoxy	NH_3	BH_3-$S(CH_3)_2$	85,76[a]	[5]
6	5,6-Dimethoxy	1-Phenylethyl-amine	AlH_3	75,85	[6]
7	Oxano[3,2-c]	Dimethylamine	BH_3-$S(CH_3)_2$	78,54	[7]

[a]Isolated as *N*-acetyl derivative.

also be made by condensation of indole-3-carboxaldehydes with nitroalkanes. Condensation is typically carried out with NH_4OAc/Ac_2O[11]. The nitroethenyl indoles can be reduced to tryptamines with $LiAlH_4$. In addition to $LiAlH_4$, AlH_3 has been used for reduction[9]. Stepwise reduction, first to the nitroalkane using Wilkinson's catalyst and then to the tryptamine by hydrogenation over Pd/C, has also been reported[12]. The examples in Table 13.2 illustrate these procedures.

Tryptamines can also be prepared from gramine via indole-3-acetonitriles. This procedure was found advantageous for C-halo tryptamines[9].

Procedures

3-(2-Dimethylaminoethyl)-5-nitroindole[3]

Glyoxamide formation

To a stirred mixture of 5-nitroindole (10.00 g, 61.7 mmol) and phthalimide (4.00 g) in anhydrous ether (250 ml) was added dropwise oxalyl chloride (17.0 ml, 0.194 mmol). The reaction mixture was stirred under nitrogen for 72 h. The mixture was then chilled in ice and a solution of dimethylamine (80 ml) condensed in ether (80 ml) at −78°C was added cautiously with vigorous stirring. Stirring was continued for 1 h after the addition was complete. The ether was then removed by evaporation and the residue partitioned between water (500 ml) and CH_2Cl_2 (500 ml). The pH was adjusted to 3 with conc. HCl. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 × 500 ml). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallization of the residue from methanol gave the glyoxamide (5.74 g, 36%).

Table 13.2

Synthesis of tryptamines *via* nitroethyl and nitroethenyl indoles

Entry	Indole substituent	Reactant	Reductant	Yield (%)	Ref.
A Nitroethylation via nitroethene					
1	None	Nitroethene		80, –	[8]
2	5-Methoxy	2-Nitroethyl acetate		66, –	[9]
3	4-(4-Hydroxy-3-methyl-1-butenyl)	Nitroethene	-	53,	[11]
B Nitroethenylation with dimethylaminonitroethene					
4	2-Methyl	Dimethylaminonitroethene	(1) H_2, $RhCl(PPh_3)_3$ (2) H_2, Pd/C	80, 93	[10]
5	6-Benzyloxy	Dimethylaminonitroethene	$LiAlH_4$	95, 98	[12]
6	2-Cyclohexyl-5-methoxy	Dimethylaminonitroethene	$LiAlH_4$	60, 42[a]	[13]
C From indole-3-carboxaldehydes by condensation with nitroalkanes					
7	None	Nitropropane, NH_4OAc, Ac_2O	$LiAlH_4$	34, 40	[14]
8	1-Cyclopentyl	Nitromethane, NH_4OH	$LiAlH_4$	60, 58	[15]
9	4,7-Dibenzyloxy	Nitromethane, NH_4OAc, Ac_2O	$LiAl_4$	98, 100	[16]
10	6-Chloro-5-methoxy	Nitroethane, NH_4OAc, Ac_2O	AlH_3	47, 97	[9]

[a]Isolated as acetyl derivative.

Reduction with diborane

To a stirred solution of the glyoxamide (5.36 g, 20.5 mmol) in anhydrous THF (55 ml) was added 1.0 M diborane in THF (78.8 ml, 78.8 mmol). The resulting solution was stirred at room temperature under nitrogen for 16 h. A saturated solution of $NaHCO_3$ (200 ml) was added carefully to the reaction solution and the mixture was extracted with ether (3 × 150 ml). The ether extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*, leaving the amine–borane complex. This solid was added to a mixture of abs. ethanol (150 ml), CsF (6.9 g) and Na_2CO_3 (6.9 g). The resulting mixture was heated at reflux under nitrogen for 16 h. The solution was cooled, filtered through Celite and the filtrate concentrated *in vacuo*. The oil was purified by chromatography using CH_2Cl_2-MeOH-aq. NH_3 for elution to give the product (2.58 g, 54%) as a yellow solid.

3-(2-Aminoethyl)-6-benzyloxy-1-methylindole[12,13]

Nitroethenylation

To a stirred ice-cooled solution of 2-(dimethylamino)-1-nitroethene (1.67 g, 14.4 mmol) in TFA (7.2 ml) was added 6-benzyloxy-1-methylindole (3.42 g, 14.4 mmol). The solution was allowed to warm to room temperature and poured into ice water. The product was extracted using EtOAc to give 6-benzyloxy-1-methyl-3-(2-nitroethenyl)indole (4.2 g, 95%).

Reduction

The previous product was added to $LiAlH_4$ (6 eq.) in THF. The solution was heated at reflux for 1 h. The excess hydride was destroyed by dropwise addition of water and the resulting mixture filtered through Celite. The filtrate was diluted with EtOAc, washed with brine and dried (Na_2SO_4). The product was an oil (3.4 g, 98%).

3-(2-Aminobutyl)indole[14]

Condensation step

A solution of crystalline NH_4OAc (66 g), Ac_2O (18 ml) and AcOH (60 ml) was stirred for 20 min at 50°C. A mixture of indole-3-carboxaldehyde (87.0 g, 0.6 mol) and 1-nitropropane (300 ml) in AcOH (300 ml) was added. The mixture was refluxed for 3 h, cooled, diluted with water (360 ml) and chilled to 10°C. The solid which was collected was recrystallized from 40% ethanol to give 44.5 g (34%) of 3-(2-nitro-1-butenyl)indole.

Reduction

Anhydrous THF (300 ml) was treated with $LiAlH_4$ (1.7 g). After reaction subsided, additional $LiAlH_4$ (30.0 g) was added carefully and the mixture was

stirred for 1.5 h. A solution of the nitrobutenylindole (36.0 g, 0.17 mol) in THF (285 ml) was added dropwise over 3 h and the mixture gradually brought to reflux. The suspension was heated at reflux for an additional 2 h and kept overnight at room temperature. Moist ether (500 ml) was added cautiously, followed by addition of 70 ml of water and 100 ml of THF. When reaction ceased, 20 ml of conc. NaOH was added. The mixture was stirred for 1 h and filtered. The solid was washed with ether (1.5 l). The filtrate and washings were combined, dried over K_2CO_3 (50 g) and concentrated. The residual oil was dissolved in MeOH (100 ml) and AcOH (12 ml) was added. The mixture was evaporated and the residue dissolved in EtOAc (250 ml) and MeOH (30 ml). This solution was evaporated to about one-third volume, and 2 ml of AcOH was added. The product (17.0 g, 40%) precipitated on cooling.

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13.2 INTRODUCTION OF THE TRYPTOPHAN SIDE-CHAIN

One effective method for synthesis of tryptophan derivatives involves alkylation of formamido- or acetamido- malonate diesters by gramine[1,2]. Conversion to tryptophans is completed by hydrolysis and decarboxylation. These reactions were discussed in Chapter 12. An enolate of an α-nitro ester is an alternative nucleophile. The products can be converted to tryptophans by reduction[3,4].

A versatile tryptophan synthesis which proceeds directly from indoles as starting materials was developed by Gilchrist[5]. The alkylation reagent is the

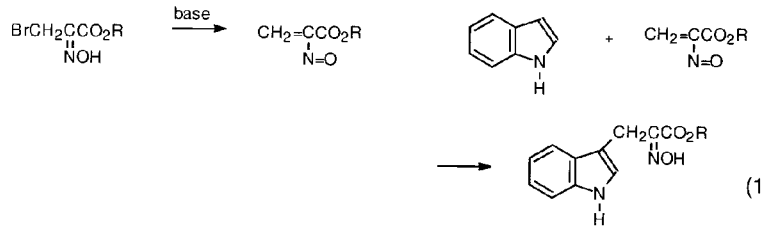
Table 13.3

Introduction of the tryptophan side-chain

Entry	Indole substituents	Reactants	Yield (%)	Ref.
A By reaction with ethyl β-bromopyruvate oxime				
1	2-Cyclohexyl	(1) Ethyl β-bromopyruvate oxime, Na_2CO_3 (2) Zn, HOAc; HCl; $(t\text{-Boc})_2O$	99, 83[a]	[7]
2	4-(Ethoxycarbonyl)methyl	(1) Ethyl β-bromopyruvate oxime, Na_2CO_3 (2) Al-Hg	72, 88	[8]
3	5-Bromo-2-(3-phenylpropyl)	(1) Ethyl β-bromopyruvate oxime, Na_2CO_3 (2) Zn, HOAc; NaOH	63, 55	[9]
4	4-[*N*-Methyl-*N*-(1-benzyloxycarbonyl-2-methylpropyl)amino]	(1) Ethyl β-bromopyruvate oxime, Na_2CO_3 (2) Al-Hg	45, >42	[10]
5	4-[*N*-(1-(*t*-Butoxycarbonyl-2-methylpropyl)-*N*-methylamino]-7-(1,1-dimethyl-2-propenyl)	(1) Ethyl β-bromopyruvate oxime, Na_2CO_3 (2) Al/Hg	57, 90	[11]
B By palladium-catalysed reaction with amidoacrylate esters				
6	4-Bromo-3-iodo-1-(4-methylphenylsulfonyl)	(1) Methyl α-acetamidoacrylate, $Pd(OAc)_2$ (2) H_2, $RhCl(PPh_3)_3$	60. 98	[12]
7	4-Fluoro-3-iodo-1-(4-methylphenylsulfonyl)	(1) Methyl α-acetamidoacrylate, Pd/C	77,	[13]
8	3-Bromo-2-(ethoxycarbonyl)	(1) Methyl α-(*t*-butoxycarbonylamino)acrylate, $Pd(PPh_3)_2Cl_2$	66,	[14]

[a]Isolated as *t*-Boc derivative.

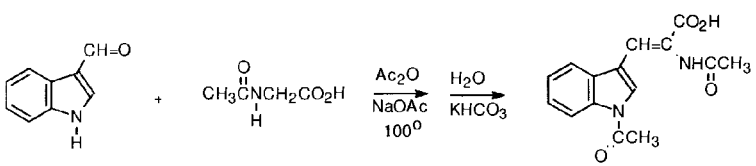
oxime of ethyl bromopyruvate which generates α-nitrosoacrylate *in situ*. This intermediate reacts with indoles to give 2-oximino-3-(indol-3-yl)propanoates which can be reduced to tryptophans. This method has proved to be a useful way of preparing both 2- and C-substituted derivatives of tryptophan. Table 13.3 includes some examples.



(13.1)

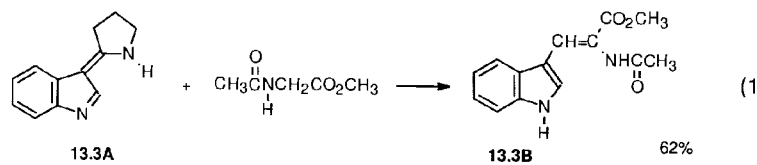
If the oximino intermediates are O-alkylated and then reduced with BH_3-$N(CH_3)_3$, N-alkoxy tryptophans can be obtained[6].

Tryptophans can also be prepared by reduction of α,β-dehydrotryptophans. These can be obtained by a classical azlactone type synthesis from derivatives of indole-3-carboxaldehyde. These reactions usually rquire an *N*-EW substituent and the yields are modest[15].



(13.2)

Better results have been obtained using the 3-(2-pyrrolidinylidene)indolenine intermediate **13.3A** which can be prepared from indole-3-carboxaldehyde and pyrrolidine[16].

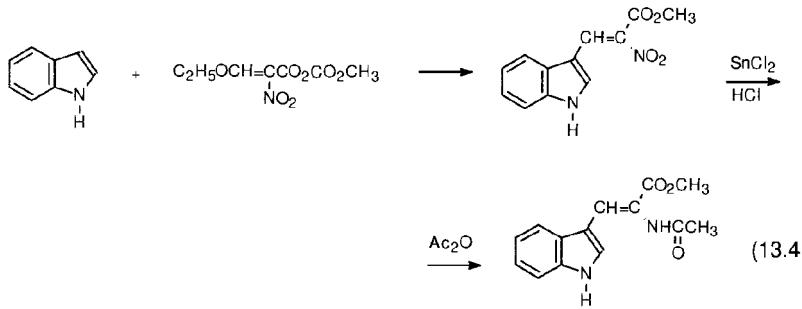


(13.3)

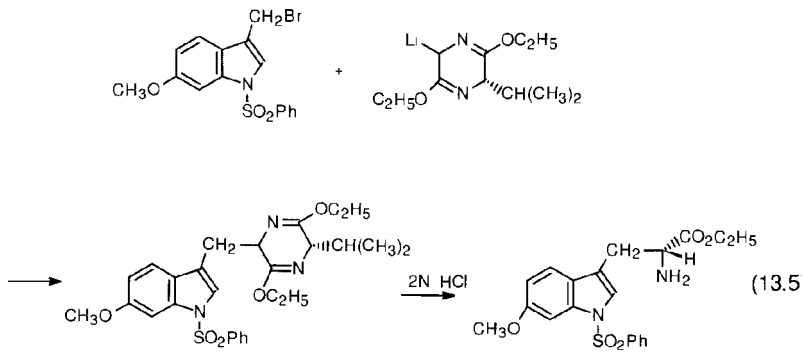
Use of α-acetamidoacrylate esters in the Heck reaction allows for the introduction of a dehydroalanine side-chain. The dehydrotryptophans can be reduced catalytically, and this reduction can be done enantioselectively[17].

Standard Heck conditions were used to introduce the dehydroalanine side-chain with 4-bromo-3-iodo-1-(4-methylphenylsulfonyl)indole[12]. Using 4-fluoro-3-iodo-1-(4-methylphenylsulfonyl)indole as the reactant, Merlic and Semmelhack found that addition of 2 eq. of LiCl or KCl improved yields in reactions carried out with 10% Pd/C as the catalyst[13]. The addition of the dehyroalanine side chain can also be done by stoichiometric Pd-mediated vinylation (see Section 11.2). A series of C-substituted dehydrotryptophans was prepared in 40–60% yield by this method[14].

The tryptophan side-chain can also be introduced using methyl 2-ethoxy-1-nitroacrylate as an electrophile[17b]. Vinylation occurs at room temperature by addition elimination. Reduction by $SnCl_2$ followed by acylation generates N^{β}-acyl-α,β-dehydrotryptophans.



Enantioselective synthesis of tryptophans has been accomplished *via* alkylation of 2,5-diethoxy-3,6-dihydropiperazines by the method developed by Schöllkopf[18]. For example, *D*(+)-6-methoxytryptophan ethyl ester was prepared using 1-(phenylsulfonyl)-3-(bromomethyl)-6-methoxyindole for alkylation[19].



Procedures

5-Benzyloxytryptophan[3]

Alkylation of ethyl nitromalonate

5-Benzyloxygramine (28.0 g, 0.10 mol) and ethyl nitromalonate (20.5 g, 0.10 mol) were dissolved in toluene (225 ml). The solution was heated at reflux with a vigorous stream of nitrogen passing through the solution. During the heating, precipitation of a solid occurred, which made stirring difficult, but it disappeared on continued heating. The reaction was continued until evolution of dimethylamine was complete (about 4 h). The cooled solution was washed with 2 N HCl (2 × 100 ml), 1 N NaOH (2 × 100 ml) and water. The solution was dried ($MgSO_4$) and decolorized with Magnesol.

Partial hydrolysis and decarboxylation

The toluene solution from the previous step was treated with an ethanol solution of NaOEt (0.1 mol in 100 ml) at 0°C. When about a quarter of the solution had been added a thick precipitate formed and ether (100 ml) was added to maintain a fluid slurry. The remainder of the NaOEt was added and the slurry was stirred overnight. The solid was collected and washed with ether. It was then mixed with ether (200 ml) and 2 N HCl (75 ml) and shaken in a separatory funnel until the solid dissolved. The ether layer was washed with 2 N H HCl (2 × 50 ml) and water and dried over $MgSO_4$. The solution was decolorized with Magnesol and evaporated to give the α-nitro ester as a red oil.

Reduction and hydrolysis

Ethyl 2-nitro-3-(5-benzyloxyindol-3-yl)propanoate (3.7 g, 0.01 mol) was dissolved in abs. ethanol (50 ml) and hydrogenated over PtO catalyst (1.0 g) until H_2 uptake ceased (about 1.75 h). The solution was purged with nitrogen and 20% aq. NaOH solution (4.0 g) was added. A hydrogen atmosphere was re-established and the hydrolysis was allowed to proceed overnight. The solution was diluted with water (20 ml) and filtered. The pH of the filtrate was adjusted to 6 with HOAc and heated to provide a solid precipitate. The mixture was cooled and filtered to provide 5-benzyloxytryptophan (2.64 g).

N^{β}-(tert)-*Butoxycarbonyl-2-cyclohexyl tryptophan ethyl ester*

A solution of 2-cyclohexylindole (100 mmol) in CH_2Cl_2 containing Na_2CO_3 (7.5 g) was treated with a solution of ethyl 3-bromo-2-(hyroxyimino)propanoate (7.35 g, 35 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred under nitrogen for 16 h, filtered through Celite, and concentrated *in vacuo*. The

intermediate was purified by chromatography (99% yield). The intermediate (13 mmol) was dissolved in AcOH (100 ml) and zinc dust (3.4 g) was added in portions over 30 min. The reaction was slightly exothermic but was not cooled. The mixture was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in 1 N HCl and evaporated to provide the tryptophan hydrochloride salt as a foam. This salt was dissolved in *t*-butanol (50 ml) and water (5 ml) and treated with Et_3N (2.3 ml, 16 mmol) and di-*tert*-butyl dicarbonate (3.4 g, 16 mmol). After stirring overnight, the reaction mixture was evaporated *in vacuo*, dissolved in EtOAc, washed with 1 N HCl, 1 M Na_2CO_3 and brine. The solution was dried (Na_2SO_4), filtered and concentrated. The product was purified by silica gel chromatography, using $CHCl_3$ for elution (83% yield).

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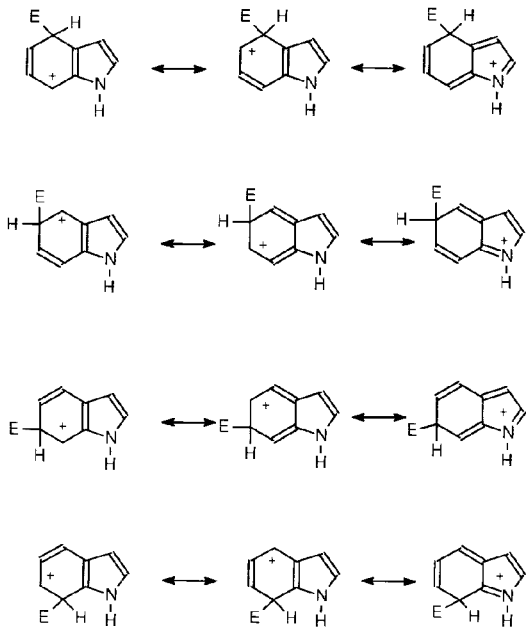
–14–

Introduction of Substituents on the Carbocyclic Ring

Introduction of substituents on the carbocyclic ring relies primarily on electrophilic substitution and on organometallic reactions. The former reactions are not under strong regiochemical control. The nitrogen atom can stabilize any of the C-ring σ-complexes and both pyrrole and benzo ring substituents can influence the substitution pattern, so that the position of substitution tends to be dependent on the specific substitution pattern (Scheme 14.1).

Reactions via organometallic intermediates achieve position selectivity on the basis of prior substitution, for example through halogen–metal exchange

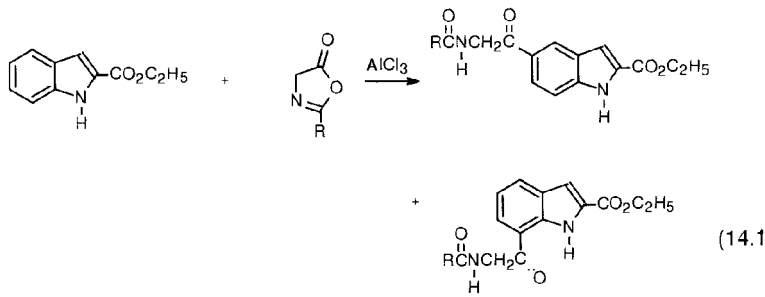


SCHEME 14.1

of C-haloindoles or by directed metallation, and thus are ultimately dependent on a preceding synthetic manipulation for regioselectivity.

14.1 ELECTROPHILIC SUBSTITUTION

Electrophilic substitution on the carbocyclic ring requires deactivation of the heterocyclic ring and this is usually achieved by the presence of an EW substituent at N1, C2 or C3 or a combination thereof. For example, ethyl indole-2-carboxylate can give either C3 or C5,7 acylation, depending upon reaction conditions[1,2]. Use of excess $AlCl_3$ favours carbocylic subsitution. This may reflect stoichiometric complexation at the ethoxycarbonyl group which further deactivates the heterocyclic ring. Ethyl indole-3-carboxylate gives a mixture of 5-, 6- and 7-substitution products on reaction with $CH_3COCl/AlCl_3$[3]. In some instances the regioselectivity seems to be governed by the specific acylating agent. For example $ClCH_2COCl$ and $Cl_2CHCOCl$ give good yields of 6-acylation products on $AlCl_3$-catalysed reaction with 1-acylindoles[4]. Acetyl chloride does not exhibit this regioselectivity. Under certain conditions ethyl indole-2-carboxylate can be acylated at C5 in preference to C3(5). This regioselectivity is observed for acid chlorides with EW substituents (see Entry 3, Table 14.1 for example). Azlactones have been found to give predominantly C5/C7 substitution with ethyl indole-2-carboxylate[2]. At the moment the mechanistic basis of these regioselectivities is not clear.



(14.1)

The presence of activating substituent on the carbocyclic ring can, of course, affect the position of substitution. For example, Entries 4 and 5 in Table 14.1 reflect such orientational effects. Entry 6 involves using the *ipso*-directing effect of a trimethylsilyl substituent to achieve 4-acetylation.

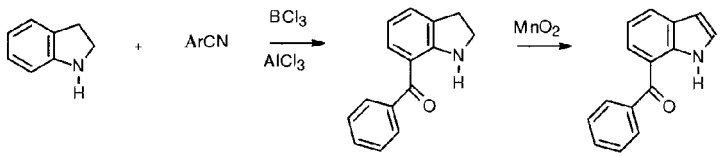
The stronger directing effects present in the indoline ring can sometimes be used to advantage to prepare C-substituted indoles. The aniline type of nitrogen present in indoline favours 5,7-substitution. After the substituent is introduced the indoline ring can be aromatized by dehydrogenation (see Section 15.2 for further discussion). A procedure for 7-acylation of indoline

Table 14.1

Electrophilic carbocyclic substitution

Entry	Substituents	Reagents	Yield (%)	Ref.
1	1-Acetyl-6-chloroacetyl	Chloroacetyl chloride, $AlCl_3$	80	[4]
2	6-Acetyl-1-benzoyl-2,3-dimethyl	Acetyl chloride, $AlCl_3$	70	[2]
3	2-(Ethoxycarbonyl)-5-(4-nitrobenzoyl)	4-Nitrobenzoyl chloride, $AlCl_3$	73	[7]
4	2-(Ethoxycarbonyl)-7-methoxy-3-methyl-4-propanoyl	Propanoyl chloride, $AlCl_3$	93	[8]
5	7-Methoxy-4-(methoxycarbonyl)-1-phenylsulfonyl	(1) ClCOCOCl, $AlCl_3$ (2) MeOH	75	[9]
6	1,4-Diacetyl	Acetyl chloride, $AlCl_3$	95	[10]

depends upon a chelation effect. Nitriles are known to have a preference for *ortho*-acylation when reaction is carried out on a preformed BCl_3 complex[11].



(14.2)

1-Acetylindoline-2-sulfonic acid, which can readily be obtained from indole by addition of sodium sulfite followed by acetylation, is a useful intermediate for introduction of 5-substituents by electrophilic substitution[12]. The substituted indoline-2-sulfonic acid can be reconverted to the substituted indole by treatment with base.

Procedures

6-Chloroacetyl-1-(2,2-dimethylpropanoyl)indole[4]

To a suspension of $AlCl_3$ (89 g, 0.67 mol) in 1,2-dichloroethane (600 ml) chloroacetyl chloride (56 ml, 0.70 mol) was added dropwise at 0°C. After the addition was complete the mixture was kept at ambient temperature for 15 min, at which time 1-(2,2-dimethylpropanoyl)indole (30 g, 0.15 mol) was added over 3 h. After completion of the addition, the mixture was stirred for 15 min and then poured into ice-cold water. The mixture was extracted with 1,2-dichloroethane. The extract was washed with water (3×) and aq. 5% $NaHCO_3$ (3×), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was

crystallized to give the product (25 g, 60% yield). Additional product (5.4 g, 13% yield) and a small amount of the 4-chloroacetyl isomer (1.7 g, 4% yield) was obtained by chromatography of the mother liquor.

7-Benzoylindole[13]

Acylation

A solution of indoline (120 g, 1.0 mol) and benzonitrile (124 g, 1.2 mol) in toluene (555 ml) was heated to boiling and 90 ml of toluene was distilled off to effect azeotropic drying. In a separate flask BCl_3 (130 g, 1.1 mol) was added to dry toluene (745 ml) at 5°C. This solution was kept at 5–10°C while the indoline-benzonitrile solution was added over 2.5 h. The temperature was maintained at 5–10°C and $AlCl_3$ (147 g, 1.1 mol) was added in portions over 45 min. The reaction mixture was then refluxed for 16 h. The reaction mixture was cooled to 8°C and water (188 ml) was added with continued stirring, resulting in separation of a heavy gum. There was then added 2 N HCl (800 ml) and the reaction mixture was heated to reflux for 2.5 h. During heating, a tan granular precipitate formed. After cooling, it was collected by filtration, washed with water and pressed dry. The damp solid was resuspended in water (1.1 l) and the suspension made basic with 25% NaOH solution while keeping the temperature below 20°C. Stirring was then continued for 4 h. The resulting yellow solid was collected by filtration, washed with water and dried to give 179 g (80%) of 7-benzoylindoline.

Aromatization

7-Benzoylindoline (223 g, 1.0 mol) was dissolved in CH_2Cl_2 (2.23 l) and MnO_2 (261 g, 3.0 mol, Diamond–Shamrock grade M) was added. The mixture was heated at reflux and agitated for 18 h. The reaction mixture was filtered and the solid washed with hot CH_2Cl_2 (200 ml). Evaporation of the solvent left 7-benzoylindole.

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14.2 RING METALLATION

Carbocyclic substitution can also be achieved by first introducing a reactive organometallic substituent. Preparation of organolithium reagents can be done by one of the conventional methods, especially halogen–metal exchange or directed lithiation. Table 14.2 gives examples.

A study of conditions for halogen–metal exchange of the C-bromoindoles found that the best results were obtained if the indole was first converted to its potassium salt by reaction with KH in ether at 0°C. Halogen–metal exchange was then done with *t*-butyllithium at −78°C[1]. Attempts to use excess *t*-butyllithium on the neutral indole were not as reproducible or effective and this was attributed to complications resulting from both incomplete *N*-deprotonation and heterogeneity. Using optimal lithiation conditions, electrophiles such as DMF, *N*-methyl-*N*-methoxycarboxamides and dimethyl disulfide gave good yields of C-substituted indoles[1,2]. Directed lithiation should also be an appropriate procedure for preparation of C-substituted indoles. Most examples in the literature have been the result of specific synthetic objectives rather than comprehensive studies of directed lithiation. Nevertheless, they indicate the potential of the methodology. One of the issues which must be considered is competition with 2-lithiation. A study of 5-methoxy-1-methylindole observed competition between C2, C4 and C6 lithiation[3]. Such competition can be influenced by proper choice of substituents. Bulky *N*-silyl substituents can retard C2 lithiation. For example, while 1-methyl-3-(dimethylaminomethyl)-indole is lithiated at C2, use of an *N*-(tri-isopropylsilyl) protecting group leads to C4 lithiation[4]. 5-(Dimethylcarbamoyloxy)-1-(*tert*-butyldimethylsilyl)-indole is cleanly lithiated at C4[5]. 1-*tert*-Butoxycarbonylindoline is lithiated at C7 and this permits introduction of various electrophiles at the 7-position[6]. These lithiated intermediates permit the introduction of various functional groups by reaction with electrophiles or they can be converted to other organometallic reagents for Pd-catalysed coupling (see Section 14.3 for examples).

Directed thallation has been useful for synthesis of some 4- and 7-substituted indoles. Electrophilic thallation directed by 3-substituents is a potential route to 4-substituted indoles. 3-Formyl[7], 3-acetyl[8] and 3-ethoxycarbonyl[7] groups can all promote 4-thallation. 1-Acetylindoline is the preferred starting

Table 14.2

Introduction of carbocyclic substituents *via* lithioindoles

Entry	Indole reactant	Reagents	Substituent	Yield (%)	Ref.
A Substitution via halogen metal exchange					
1	Potassio 4-bromoindole	(1) *s*-BuLi; (2) DMF	4-Formyl	57	[1]
2	Potassio 6-bromoindole	(1) *s*-BuLi; (2) $(CH_3S)_2$	6-Methylthio	94	[2]
3	Potassio 7-bromoindole	(1) *s*-BuLi; (2) DMF	7-Formyl	61	[1]
B Substitution by directed lithiation					
4	3-(Dimethylaminomethyl)-1-(tri-isopropylsilyl)-indole	(1) *t*-BuLi; (2) DMF	4-Formyl	57	[4]
5	3-(Dimethylaminomethyl)-1-(tri-isopropylsilyl)-indole	(1) *t*-BuLi; (2) CH_3I	4-Methyl	69	[12]
6	5-(*N,N*-Dimethylcarbamoyloxy-1-(*tert*-butyldimethyl-silyl)indole	(1) *s*-BuLi, TMEDA; (2) C_2Cl_6	4-Chloro	90	[5]
C Substitution by thallation					
7	3-Acetylindole	(1) $Tl(O_2CCF_3)_3$; (2) KI	4-Iodo	75	[8]
8	Indole-3-carboxaldehyde	(1) $Tl(O_2CCF_3)_3$; (2) $CuBr_2$	4-Bromo	58	[10]

material for 7-thallation[7]. The thallium can then be replaced by various functional groups including halogen[8–10], nitro[7] and azido[7], or subjected to Pd-catalysed coupling[11].

Procedure

Indole-7-carboxaldehyde[1]

Potassium hydride (1 eq.) was washed with hexanes and suspended in anhydrous ether at 0°C. 7-Bromoindole was added as a solution in ether. After 15 min, the solution was cooled to −78°C and *t*-butyllithium (2 eq.) which had been precooled to −78°C was added by cannula. A white precipitate formed. After 10 min DMF (2 eq.) was added as a solution in ether. The reaction mixture was allowed to warm slowly to room temperature and when reaction was complete (TLC) the suspension was poured into cold 1 M H_3PO_4. The product was extracted with EtOAc and the extract washed with sat. $NaHCO_3$ and dried ($MgSO_4$). The product was obtained by evaporation of the solvent and purified by chromatography on silica gel (61% yield).

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14.3 PALLADIUM-CATALYSED SUBSTITUTION

Indoles with carbocyclic halogen or triflate substituents are potential starting materials for vinylation, arylation and acylation via palladium-catalysed processes[1]. Indolylstannanes, indolylzinc halides and indolylboronic acids are also potential reactants. The principal type of substitution which is excluded from such coupling reactions is alkylation, since saturated alkyl groups tend to give elimination products in Pd-catalysed processes.

Heck type vinylation of 4-bromo-1-(4-methylphenylsulfonyl)-indole proceeds in good yield with such alkenes as methyl acrylate, styrene and *N*-vinylphthalimide using $Pd(OAc)_2$ (5 mol%) and tri-*o*-tolylphosphine as the

Table 14.3

Carbocylic vinylation and arylation

Entry	Indole reactant	Reagents	Yield (%)	Ref.
A Vinylation under Heck conditions				
1	7-Iodo	Methyl acrylate, $Pd(OAc)_2$, Et_3N	90	[7]
2	5-Trifluoromethanesulfonyloxy	Methyl α-acetamidoacrylate, $Pd(OAc)_2$, *n*-Bu_3N, LiCl, *bis*-(diphenylphosphinoferrocene)	38	[8]
3	4-Bromo-1-(4-methylphenylsulfonyl)	Methyl α-acetamidoacrylate, $Pd(PPh_3)_2Cl_2$, NaOAc, Et_3N	90	[2]
4	4-Bromo-3-[2-(*t*-butoxycarbonylamino)-2-(ethoxycarbonyl)ethenyl]-1-(4-methylphenylsulfonyl)	2-Methylbut-3-en-2-ol, $Pd(PPh_3)_2Cl_2$, Ag_2CO_3, Et_3N	83	[3]
B Arylation by palladium-catalysed coupling				
5	5-Bromo	2-(*t*-Butoxy)-5-(tri-*n*-butylstannyl)furan, $PhCH_2Pd(PPh_3)_2Cl$	60	[9]
6	5-Boronic acid	Bromobenzene, $Pd(PPh_3)_4$	87	[10]
7	6-Bromo	4-Fluorobenzeneboronic acid, $Pd(PPh_3)_4$	90	[11]
8	8-Bromo	4-Fluorobenzeneboronic acid, $Pd(PPh_3)_4$	74	[5]
9	3-Formyl-4-(*bis*-trifluoroacetoxythallio)	Benzeneboronic acid, $Pd(OAc)_2$	60	[6]

catalyst system[1]. Methyl α-acetamidoacrylate also gives good results[2]. The Heck reaction has also been used to introduce 4-(3-hydroxy-3-methyl-1-butenyl) substituents[1,3]. 4-Haloindoles can be coupled with acetylenes via Pd-catalysed processes[4]. Table 14.3 gives examples of these reactions.

The Suzuki coupling of arylboronic acids and aryl halides has proven to be a useful method for preparing C-aryl indoles. The indole can be used either as the halide component or as the boronic acid. 6-Bromo and 7-bromoindole were coupled with arylboronic acids using $Pd(PPh_3)_4$[5]. No protection of the indole NH was necessary. 4-Thallated indoles couple with aryl and vinyl boronic acides in the presence of $Pd(OAc)_2$[6]. Stille coupling between an aryl stannane and a haloindole is another option (Entry 5, Table 14.3).

Procedures

Methyl 1-(4-methylphenylsulfonyl)indole-4-(α-acetamido)propenoate[2]

A mixture of 4-bromo-1-(4-methylphenylsulfonyl)indole (88 mg, 0.25 mmol), methyl α-acetamidoacrylate (91 mg, 0.64 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol) and NaOAc (82 mg, 0.98 mmol) in Et_3N (0.8 ml) and DMF (0.4 ml) was heated to 120°C in a sealed tube for 2 h. The tube was opened and the contents diluted with EtOAc and filtered through Celite. The EtOAc was washed successively with 10% HCl, sat. $NaHCO_3$ and brine and then dried ($MgSO_4$). The residue was purified by elution through silica gel with 10:1 benzene–EtOAc to give the product as a yellow solid (93 mg, 90%).

6-(4-Fluorophenyl)indole[5]

A solution of 6-bromoindole (0.10 mol) in toluene (200 ml) was treated with $Pd(PPh_3)_4$ (5 mol%) and stirred for 30 min. A solution of 4-fluorophenylboronic acid (0.25 M, 0.15 mol) in abs. EtOH was added, followed immediately by sat aq. $NaHCO_3$ (10 eq.). The biphasic mixture was refluxed for several hours and then cooled to room temperature. The reaction mixture was poured into sat. aq. NaCl (200 ml) and the layers separated. The aq. layer was extracted with additional EtOAc (200 ml) and the combined organic layers dried (Na_2SO_4), filtered and concentrated *in vacuo*. The solution was filtered through silica gel using hexane-CH_2Cl_2-hexane for elution and evaporated. Final purification by recrystallization gave the product (19 g, 90%).

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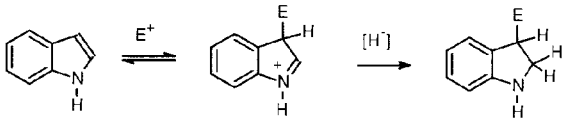
–15–

Selective Reduction and Oxidation Reactions

15.1 REDUCTION OF INDOLES TO INDOLINES

While catalytic reduction of the indole ring is feasible, it is slow because of the aromatic character of the C2–C3 double bond. The relative basicity of the indole ring, however, opens an acid-catalysed pathway through 3*H*-indolenium intermediates.



(15.1)

A traditional method for such reductions involves the use of a reducing metal such as zinc or tin in acidic solution. Examples are the procedures for preparing 1,2,3,4-tetrahydrocarbazole[1] or ethyl 2,3-dihydroindole-2-carboxylate[2] (Entry 3, Table 15.1). Reduction can also be carried out with acid-stable hydride donors such as acetoxyborane[4] or $NaBH_3CN$ in TFA[5] or HOAc[6]. Borane is an effective reductant of the indole ring when it can complex with a dialkylamino substituent in such a way that it can be delivered intramolecularly[7]. Both $NaBH_4$-HOAc and $NaBH_3CN$-HOAc can lead to N-ethylation as well as reduction[8]. This reaction can be prevented by the use of $NaBH_3CN$ with temperature control. At 20°C only reduction occurs, but if the temperature is raised to 50°C N-ethylation occurs[9]. Silanes can also be used as hydride donors under acidic conditions[10]. Even indoles with EW substituents, such as ethyl indole-2-carboxylate, can be reduced[11,12].

Procedures

Ethyl 2,3-dihydroindole-2-carboxylate[2]

Ethyl indole-2-carboxylate (45.2 g, 0.238 mmol) was dissolved in abs. EtOH (450 ml) in a 1 l polyethylene container and cooled in a dry ice–ethanol bath. The solution was saturated with dry HCl gas until the volume increased to 875 ml. Granular tin metal (84.2 g, 0.710 mmol) was added to the slurry and

Table 15.1

Reduction of indoles to 2,3-dihydroindoles

Entry	Indole substituents	Reduction conditions	Yield (%)	Ref.
1	None	$NaBH_3CN$, HOAc, 50°C	60[a]	[9]
2	None	Zn, H_3PO_4	64	[10]
3	2-(Ethoxycarbonyl)	Sn, HCl, EtOH	62	[2]
4	1,2-Dimethyl	$NaBH_3CN$, HOAc	92	[5]
5	2-(Ethoxycarbonyl)-1-methyl	Et_3SiH, TFA	67	[12]
6	5,6-Dimethoxy	$NaBH_3CN$, HOAc	86	[14]
7	3-(2-Benzyloxycarbonylethyl)-5-methoxy	$NaBH_3CN$, HOAc	87	[6]
8	5,6-Dimethoxy-2-methyl-3-[2-(4-phenylpiperazino)ethyl]	Et_3SiH, TFA	80	[11b]
9	2-(Methoxycarbonyl)pyrrolo[3,2-e]	$NaBH_3CN$, HOAc	79	[15]
10	5-Hydroxy-6-1-(Methoxycarbonyl)-(phenylsulfonyl)-8-methyl-pyrrolo[3,2-e]	Et_3SiH, TFA	80	[13]
11	5-Benzyloxy-2-(benzyloxycarbonyl)-4-methoxypyrrolo[3,2-e]	$NaBH_3CN$, HOAc	>63	[16]

[a]The product is 1-ethyl-2,3-dihydroindole.

the container was sealed in a precooled 1.4 l autoclave which had all surfaces coated with silicone oil. The sealed autoclave was kept at room temperature for 36 h and then vented. The reaction mixture was filtered through sintered glass and chilled to −15°C overnight. A yellow crystalline tin complex (73.6 g) was obtained. This complex was dissolved in abs. EtOH (750 ml), cooled and treated with anhydrous ammonia until the pH reached 8. The EtOH was evaporated and the residue slurried with ether and filtered. The solid was washed with several portions of ether. The ether filtrate and washes were combined and extracted with 1:1 water–saturated brine (300 ml) to remove basic tin salts. The ether layer was dried ($MgSO_4$) and evaporated to leave an oil which spontaneously crystallized. Recrystallization from hexane gave pure product (28.5 g, 62%).

Benzyl 2,3-dihydro-1-benzoyl-5-methoxyindole-3-propanoate[6]

A solution of benzyl 5-methoxyindole-3-propanoate (26.0 g, 0.084 mol) in HOAc (500 ml) was cooled as $NaBH_3CN$ (26 g, 0.41 mol) was added. The resulting mixture was stirred at room temperature for 3.5 h and then poured into cold water (2 l). The mixture was extracted with several portions of CH_2Cl_2 and the extracts were washed with aq. $NaHCO_3$ and dried over Na_2SO_4. Removal of the solvent gave the crude product as a viscous oil. This

material was dissolved in $CHCl_3$ and cooled in ice. Pyridine (8 ml, 0.10 mol) and then benzoyl chloride (11.5 ml, 0.10 mol) were added. The mixture was stirred for 1 h at room temperature. The reaction mixture was washed with water, aq. $NaHCO_3$ and brine and then dried (Na_2SO_4). The solvent was removed and the residue was dissolved in EtOAc and eluted through a short Florisil column using additional EtOAc. Evaporation of the eluate and crystallization of the residue from toluene/hexane gave the product (30.2 g, 87%).

Ethyl 3-acetyl-5-hydroxy-8-methyl-6-(phenylsulfonyl)-1,2,3,6-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-1-carboxylate

To a stirred ice-cold solution of ethyl 3,6-dihydro-5-hydroxy-8-methyl-6-(phenylsulfonyl)benzo[1,2-b:4,3-b']dipyrrole-1-carboxylate (368 mg, 0.85 mmol) in TFA (3 ml) was added Et_3SiH (1.5 ml). After 15 min the solution was allowed to come to room temperature and stirred for an additional 2 h. The solution was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2 (10 ml), washed with aq. $NaHCO_3$ and dried over $MgSO_4$. The solution was mixed with Ac_2O (1 ml) and CH_2Cl_2 (1 ml) and kept at room temperature for 2 h. The reaction mixture was evaporated and the residue purified by chromatography on silica gel using CH_2Cl_2–EtOAc (3:1) for elution. The product (271 mg) was obtained in 71% yield.

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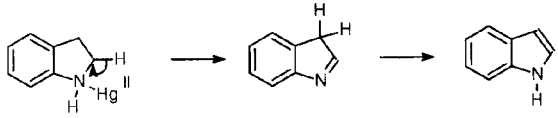
15.2 AROMATIZATION OF INDOLINES

Aromatization of indolines is important in completing synthetic sequences in which the directive effects of the indoline ring have been used to achieve selective carbocyclic substitution[1]. Several methods for aromatization have been developed and some of these are illustrated in Table 15.2. A range of reagents is represented. One type of procedure represents use of oxidants which are known to convert amines to imines. Aromatization then provides the indole. Such reagents must not subsequently oxidize the indole. Mercuric acetate (Entry 1) is known to oxidize other types of amines and presumably reacts by an oxidative deprotonation α- to the complexed nitrogen.



(15.2)

The perruthenate procedure (Entry 2) is also based on a general amine to imine oxidation. The iodosobenzene method (Entry 3) is an application of a

Table 15.2

Aromatization of indolines by dehydrogenation

Entry	Substituents	Reagent	Yield (%)	Ref.
1	None	$Hg(OAc)_2$	72	[4]
2	None	$R_4N^+RuO_4^-$, *N*-methylmorpholine-*N*-oxide	50–75	[5]
3	None	Iodosobenzene	38	[6]
4	2-Methyl	O_2, Co(salen)	79	[2]
5	5-Propyl	$Mn(OAc)_3$	60	[7]
6	7-Benzoyl	MnO_2	>90	[8]
7	3-(1-Acetylpiperid-4-yl)-5-nitro	MnO_2	47	[9]
8	1-Benzoyl-4-[2-(*N*,*N*-dipropylamino)ethyl]-5-methoxy	O_2, KO-*t*-Bu	41	[10]
9	3,4-Dihydrobenzo[cd]indol-5(1*H*)one	$(PhSeO)_2O$	57	[11]
10	4,5,6-Tribromo	O_2, Co(salen)	86	[12]

method for conversion of cyclic secondary amines to imines. None of these three methods has yet been tested extensively with substituted indolines. The Co(salen) catalytic oxidation was found to be satisfactory for several 2- and 3-alkylindoles[2] and has been applied to 6-nitro[2] and 7-nitroindoline[3]. The other reagents included in Table 15.2 have been applied to specific substituted indoles.

Procedure

Catalytic oxidation using Co(salen)[3]

To a solution of indoline (20 mM in MeOH) was added Co(salen) (0.10 equiv.) and O_2 was bubbled through the suspension at 25°C. After 1 h the suspension became homogeneous and the solvent was removed *in vacuo* and the product purified by chromatography on silica gel.

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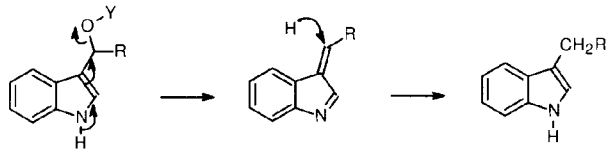
15.3 REDUCTIVE DISPLACEMENT OF α-SUBSTITUENTS

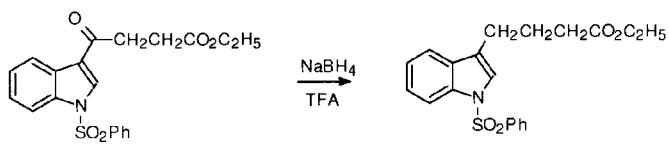
3-Acyl groups on the indole ring can generally be reduced directly to 3-alkyl groups. The reduction proceeds through the intermediate indol-3-ylcarbinol stage and carbinols prepared by other means are also susceptible to reductive deoxygenation. The facility of these reductive displacements depends upon the susceptibility of indol-3-ylcarbinols to elimination.



(15.3)

The reaction is assisted by nitrogen-deprotonation and is therefore somewhat less facile for 1-subsituted indoles. 2-Acylindoles and indol-2-ylcarbinols are also susceptible to reductive deoxygenation but the reactivity is somewhat less than for 3-substituted indoles because nitrogen participation is diminished at the 2-position. Among the reducing agents which have been used successfully for deoxygenation of 3-acylindoles are $LiAlH_4$[1,2] and diborane[3–5]. Diborane is the more electrophilic of the two reagents and while $LiAlH_4$ often results in formation of carbinols from *N*-substituted 3-acylindoles, diborane usually gives complete reduction. Monti and co-workers developed a procedure which avoids competing reduction of the indole ring which involves quenching excess diborane with acetone[3]. Reduction with $NaBH_4$ normally gives carbinols from 1-substituted 3-acylindoles[6]. The partial reduction of acylindoles to carbinols has also been done with $LiBH_4$, although the generality of this procedure has not been demonstrated[7]. The use of $LiAlH_4$, BH_3 and AlH_3 for reduction of indole-3-glyoxamides to tryptamines was discussed in Section 13.1.

3-Acyl-1-(phenylsulfonyl)indoles can be reduced to 3-alkyl-1-(phenylsulfonyl)indoles using $NaBH_4$-TFA[8]. The active reductant is presumably a trifluoroacetoxyborane[9]. The presence of the electron-attracting phenylsulfonyl substituent would be expected to require electrophilic assistance in the elimination step. The $NaBH_4$-TFA reagent is selective enough to permit some functional groups in the side-chain to survive, as in equation 15.4[10].



(15.4)

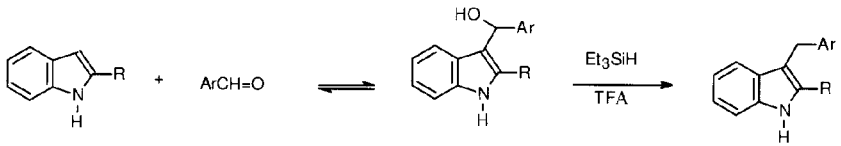
The reduction of several 2-acyl-1-(phenylsulfonyl)indoles to the corresponding 2-alkyl compounds was achieved using BH_3-$H_2NC(CH_3)_3$-$AlCl_3$[10].

Indol-3-ylcarbinols can also be reduced using Et_3SiH-TFA. Aryl indolyl-3-ylcarbinols can be formed *in situ* from 2-alkylindoles and benzaldehydes. These reactions, when run in tandem, provide a versatile route to 3-benzylindoles[11]. Indole itself undergoes reduction to indoline under these conditions. Indol-3-ylcarbinols can also be generated by organometallic additions to 3-acylindoles[12].

Table 15.3

Reductive deoxygenation of 2-acyl and 3-acylindoles

Enty	Indole substituents	Reduction conditions	Yield (%)	Ref.
A 2-Acylindoles				
1	2-Propanoyl-1-(phenylsulfonyl)	BH_3-$H_2NC(CH_3)_3$. $AlCl_3$	75	[10]
B 3-Acylindoles				
2	3-Acetyl	$LiAlH_4$	72	[1]
3	3-Benzoyl-1-methyl	B_2H_6	80–85	[3]
4	3-Acetyl-1-(phenylsulfonyl)	$NaBH_4$-TFA	99	[8]
5	3-Acetyl-5-hydroxy-2-methyl	B_2H_6	82	[4]
6	3-[1-Hydroxy-1-(3-methyl-pyrid-2-yl)methyl]-1-methyl-	Pd/C, H_2	88	[13]



(15.5)

Table 15.3 gives some examples of reductive deoxygenation of 2-acyl and 3-acyl indoles.

Procedures

3-Ethyl-5-hydroxy-2-methylindole[4]

A solution of 1.05 M diborane in THF (25 ml, 26 mmol) was added slowly to a stirred suspension of 3-acetyl-5-hydroxy-2-methylindole (1.0 g, 5.3 mmol) in THF (10 ml). After hydrogen evolution ceased, the mixture was heated at reflux for 1 h, cooled and poured into acetone (75 ml). The mixture was heated briefly to boiling and then evaporated *in vacuo*. The residue was heated with methanol (50 ml) for 20 min. The solution was concentrated and 3 N HCl (40 ml) was added. The mixture was extracted with ether and the extracts dried ($MgSO_4$) and evaporated to yield a yellow oil. Vacuum sublimation or recrystallization yielded pure product (0.76 g, 82%).

Ethyl 4-[1-(phenylsulfonyl)-indol-3-yl]butanoate[10]

$NaBH_4$ pellets (10–12 eq.) were added to TFA (25 ml) over 30 min. Ethyl 4-[1-(phenylsulfonyl)indol-3-yl]-4-oxobutanoate (1.5 mmol) was then added as

a solution in CH_2Cl_2. The mixture was stirred overnight and diluted with water (75 ml). The product was isolated by an extraction sequence and purified by silica gel chromatography using 1:1 hexane–CH_2Cl_2 for elution (85% yield).

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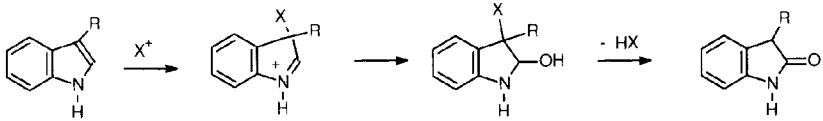
15.4 OXIDATION OF INDOLES TO OXINDOLES

The conversion of indoles to oxindoles can be achieved in several ways. Reaction of indoles with a halogenating agent such as NCS, NBS or pyridinium bromide perbromide in hydroxylic solvents leads to oxindoles[1]. The reaction proceeds by nucleophilic addition to a 3-haloindolenium intermediate.

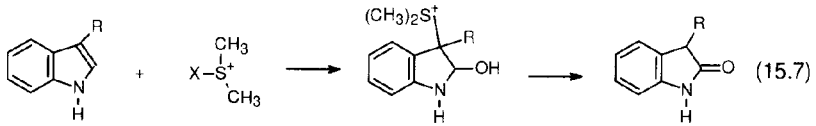


(15.6)

Use of an excess of the halogenating agent results in halogenation at the 3-position of the oxindole[3,4]. The halogenation and hydrolysis can be carried out as two separate steps. One optimized procedure of this type used NCS as the halogenating agent and it was found that 70% phosphoric acid in 2-methoxyethanol was the most effective medium for hydrolysis[2]. If the halogenation is carried out in pyridine, the intermediate is trapped as an

N-(indol-2-yl)pyridinium salt which can subsequently be hydrolysed to an oxindole[5].

The oxidation of 3-substituted indole to oxindoles can also be done with a mixture of DMSO and conc. hydrochloric acid[6–9]. This reaction probably involves a mechanism similar to the halogenation with a protonated DMSO molecule serving as the electrophile[10].



(15.7)

Procedures

7-Benzoyloxindole[2]

A CH_2Cl_2 of 7-benzoylindole (245 g, 1 mol) was chlorinated with *N*-chlorosuccinimide (119 g, 0.87 mol) at 15–20°C by adding a quarter of the reagent at 0.5 h intervals. One hour later, the solution was washed with water (2.5 l × 2). The water layer was re-extracted with CH_2Cl_2 (200 ml). After washing with an equal volume of water, the extract was combined with the original CH_2Cl_2 layer and distilled to remove the CH_2Cl_2. The residual 7-benzoyl-3-chloroindole was dissolved in 2-methoxyethanol (1.8 l) and heated to 100°C. With stirring, H_3PO_4 (70%, 1.3 l) was added. A phosphate salt separated but stirring was continued. The mixture was maintained at reflux for 4–8 h, using TLC to monitor reaction progress. Upon completion, the mixture was treated with charcoal (20–40 g) at reflux for 15 min and then filtered hot. The filtrate was kept at 70°C while warm (65–70°C) water (2.3 l) was added with stirring. Precipitation began during the addition. The slurry was cooled slowly to 5°C and kept for 12 h. Filtration then gave 7-benzoyloxindole (199 g, 84% yield).

1,3-Dimethyl-5-methoxyoxindole[8]

A solution of 1,3-dimethyl-5-methoxyindole (4.5 g, 0.026 mol) in DMSO (27 ml) was maintained at 5°C as conc. HCl (23 ml, 0.77 mol) was added dropwise over 15 min. Stirring was continued for 3 h at room temperature and the reaction mixture was then poured into ice-water (100 ml). The mixture was neutralized with $NaHCO_3$ to pH 7 and extracted with EtOAc (100 ml × 2). The EtOAc was removed *in vacuo* and the residue purified by chromatography on silica using hexane–EtOAc (7:3) for elution. The yield was 4.35 g (88%).

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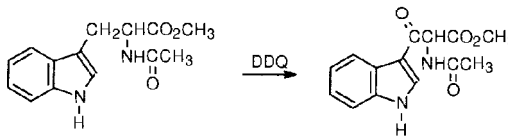
15.5 SELECTIVE OXIDATION OF SUBSTITUENTS

Because of the susceptibility of the indole ring to oxidation, most of the classical methods for oxidation of aromatic substituents are not appropriate for indole derivatives. There are, however, procedures that can effect conversion of 3-alkyl groups to 3-acyl groups and of 2-alkyl subsitutents to hydroxyalkyl or acyl. The preferred reagent for oxidation of 3-alkylindoles to 3-acylindoles is dichlorodicyanoquinone (DDQ). It has been used both with substituted indoles and fused ring analogues. For example, *N,O*-protected tryptophans can be oxidized in good yield[1].



(15.8)

Generally speaking though, yields are best for the fused ring derivatives. The reactions are usually carried out in 10% aq. THF and probably proceed through 3-alkylideneindolenine intermediates. Table 15.4 gives several examples. Selenium dioxide has also been used for oxidations leading to 3-acylindoles (Entry 9).

Selective oxidations of 2-alkyl groups usually involve an initial attack at C3 followed by an allylic rearrangement which places the substituent at the α-carbon of the C2 substituent. The overall pattern of α-2C oxidation has been observed with several oxidants including oxygen[10] and peroxysulfate[11] but the most reliable reagent for preparative purposes is diiodinepentaoxide[12]. A few oxidations have also been reported using $Mn(OAc)_3$ (Entry 13).

Table 15.4

α-Oxidation of 2- and 3-alkylindoles

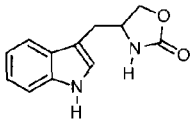
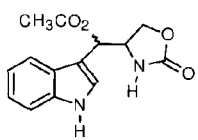
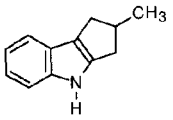
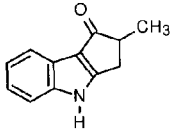
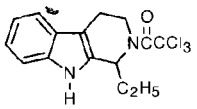
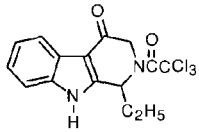
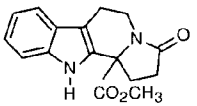
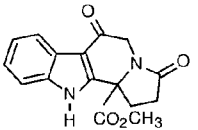
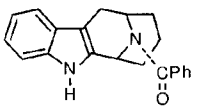
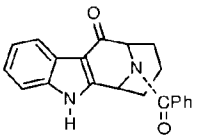
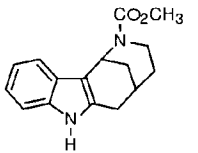
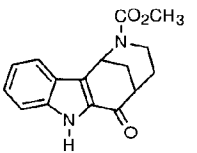
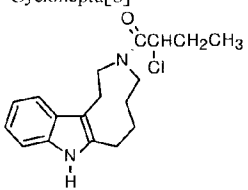
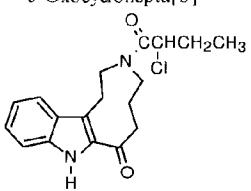
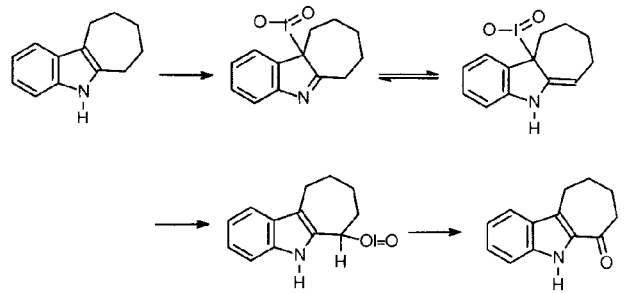
Entry	Indole	Product	Oxidation conditions	Yield (%)	Ref.
1	1,2.5-Trimethyl	2,5-Dimethylindole-3-carboxaldehyde	DDQ, THF, H_2O	30[a]	[1]
2	3-(2-Benzyloxycarbonylamino)ethyl	3-(2-Benzyloxycarbonylamino)-1-oxoethyl	DDQ	>73	[2]
3			DDQ, HOAc, THF	98	[3]
4	Tetrahydrocarbazole	4-Oxotetrahydrocarbazole	DDQ, THF, H_2O	82	[1]
5			DDQ, THF, H_2O	31	[4]
6	Methyl 1.2,3,4-tetracarbazole-2-acetate	Methyl 4-oxo-1,2,3,4-tetrahydro-carbazole-2-acetate	DDQ, THF, H_2O	85	[5]
7			DDQ, acetone, H_2O −78°C	77	[6]

Table 15.4 (*Continued*)

α-Oxidation of 2- and 3-alkylindoles

Entry	Indole	Product	Oxidation conditions	Yield (%)	Ref.
8			DDQ, THF, H_2O	78	[7]
9			SeO_2, dioxane	90	[8]
10			SeO_2, dioxane	72	[9]
11	Cyclohepta[b]	5-Oxocyclohepta[b]	I_2O_5	99	[12]
12			I_2O_5	65	[13]
13	2,3-Dimethyl-1-phenylsulfonyl	2-Acetoxymethyl-3-methyl-1-phenylsulfonyl	$Mn(OAc)_3$, AcOH	58	[14]

[a]Some 3,5-dimethylindole-2-carboxaldehyde (8%) is also formed.



(15.9)

Procedures

Methyl 4-oxo-1,2,3,4-tetrahydrocarbazole-2-acetate[5]

A solution of methyl 1,2,3,4-tetrahydrocarbazole-2-acetate (5.94 g) in THF (195 ml) containing water (15 ml) was cooled to 0°C and DDQ (11.22 g) dissolved in deoxygenated THF (75 ml) was added. The solution was maintained at 0°C for 2 h and then evaporated *in vacuo*. The residue was dissolved in EtOAc and washed thoroughly with aq. $NaHCO_3$ solution to remove dichlorodicyanohydroquinone. The EtOAc was then dried ($MgSO_4$) and evaporated to give methyl 4-oxo-1,2,3,4-tetrahydrocarbazole-2-acetate (5.23 g) in 85% yield.

Oxidation of cycloalkan[b]indoles with diiodinepentaoxide[12]

I_2O_5 (400 mg 1.20 mmol) was added to a solution of a cycloalka[b]indole (1.00 mmol) in 80% aqueous THF (25 ml). The mixture was stirred at room temperature and the solvent removed *in vacuo*. The residue was extracted into EtOAc and the extract washed with water, 5% NaS_2O_3, saturated $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was evaporated and the residue purified by silica gel chromatography.

References

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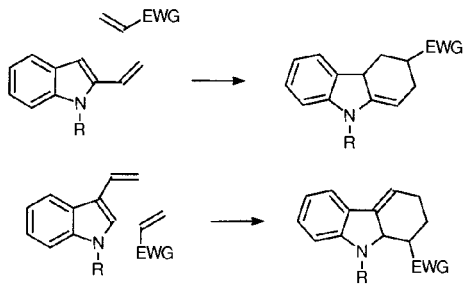
–16–

Synthetic Elaboration of Indole Derivatives using Cycloaddition Reactions

Two types of cycloaddition reactions have found application for the synthetic elaboration of indoles. One is Diels–Alder reactions of 2- and 3-vinylindoles which yield partially hydrogenated carbazoles. The second is cycloaddition reactions of 2,3-indolequinodimethane intermediates which also construct the carbazole framework. These reactions are discussed in the following sections.

16.1 DIELS–ALDER REACTIONS OF 2- AND 3-VINYLINDOLES

While both 2- and 3-vinylindole have been synthesized and characterized[1,2], they are quite reactive and susceptible to polymerization. This is also true for simple 1-alkyl derivatives which readily undergo acid-catalysed dimerization and polymerization[3]. For this reason, except for certain cases where *in situ* generation of the vinylindoles is practical, most synthetic applications of vinylindoles involve derivatives stabilized by EW-nitrogen substituents[4].

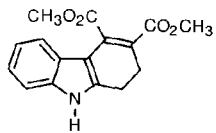
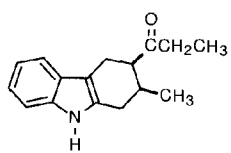
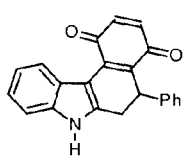
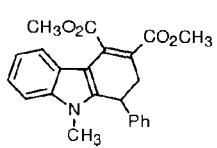


(16.1)

Most examples of Diels–Alder reactions reported for both 2-vinyl and 3-vinylindoles involve typical electrophilic dienophiles such as benzoquinone, *N*-phenylmaleimide and dimethyl acetylenedicarboxylate (see Table 16.1). These symmetrical dienophiles raise no issues of regioselectivity. While there are fewer examples of use of mono-substituted dienophiles, they appear to react

Table 16.1

Diels–Alder reactions of 2-vinyl and 3-vinylindoles

Entry	Indole substituents	Dienophile	Product	Yield (%)	Ref.
A 2-Vinylindoles					
1	2-Ethenyl	$CH_3O_2CC{\equiv}CCO_2CH_3$		46	[1]
2	2-(1-Propenyl)	Pent-1-en-3-one		46	[8]
3	2-(2-Phenylethenyl)	Benzoquinone		49	[8]
4	1-Methyl-2-(1-phenylethenyl)	$CH_3O_2CC{\equiv}CCO_2CH_3$		37	[9]

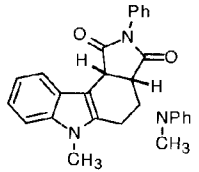
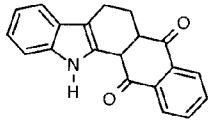
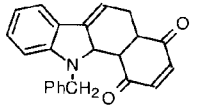
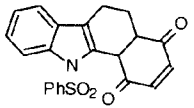
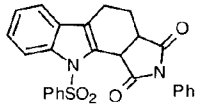
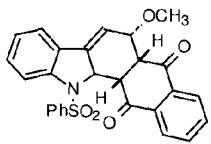
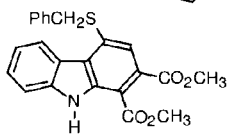
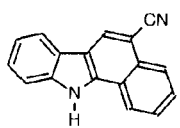
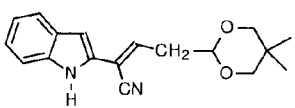
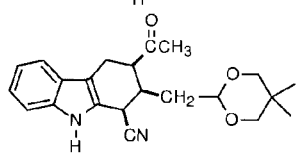
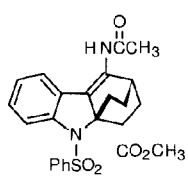
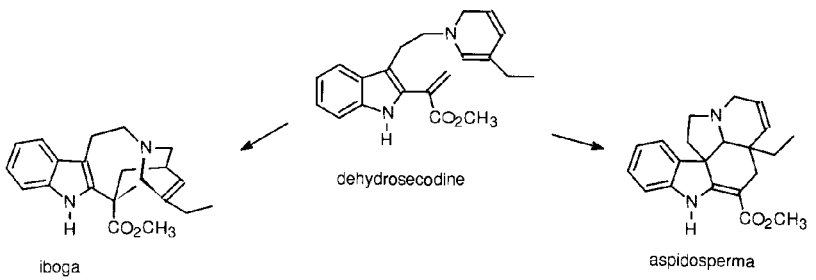
5	1-Methyl-2-[(2-(*N*-methyl-*N*-phenylamino)ethenyl)]	*N*-Phenylmaleimide		30	[10]
B 3-Vinylindoles					
6	3-Ethenyl	Naphthoquinone		91	[2]
7	1-Benzyl-3-ethenyl	Benzoquinone		86	[6]
8	3-Ethenyl-1-(phenylsulfonyl)	Benzoquinone		50	[11]
9	3-Ethenyl-1-(phenylsulfonyl)	*N*-Phenylmaleimide		60	[7]

Table 16.1 (*Continued*)

Entry	Indole substituents	Dienophile	Product	Yield (%)	Ref.
10	3-(2-Methoxyethenyl)-1-(phenylsulfonyl)	Naphthoquinone		86	[12]
11	3-(1-Benzylthio)	$CH_3O_2CC{\equiv}CCO_2CH_3$		70	[13]
12	3-(2-Cyanoethenyl)	Benzyne		15	[14]
13		But-1-en-3-one		70	[15]
14	4-Acetamido-9-(phenylsulfonyl)-1,2-dihydrocarbazole	Methyl acrylate		86	[16]

in a predictable fashion. 2-Vinylindoles appear to have the highest electron density at C3 of the indole ring. For 3-vinylindoles the β-carbon of the vinyl group has the highest HOMO density and bonds to the more electron-poor β-carbon of the dienophile[5]. While the initial adducts with exocyclic unsaturation are sometimes observed[5,6], in most cases an isomerization provides the rearomatized indole. Table 16.1 gives some examples of these reactions.

2-Vinylindoles have been of interest in the synthesis of both *aspidosperma* and *iboga* alkaloids. The structural relationship between these two groups can be illustrated by two alternative intramolecular Diels–Alder reactions of the putative (biosynthetic?) intermediate dehydrosecodine[17]. Despite several efforts[18–20], the closest synthetic approach to dehydrosecodine that has been achieved is release of the *N*-benzyl derivative from a $Cr(CO)_3$ complex[21]. Under these conditions, the *aspidosperma* pathway dominates over the *iboga*. Addition of a 4-silyloxy substituent to the dihydropyridine ring makes the *iboga* pathway the preferred one[22]. The retrosynthetic concept embodied in the disconnection of both the *aspidosperma* and *iboga* structures to dehydrosecodine has been used to develop syntheses of both types of alkaloids[23,24].



(16.2)

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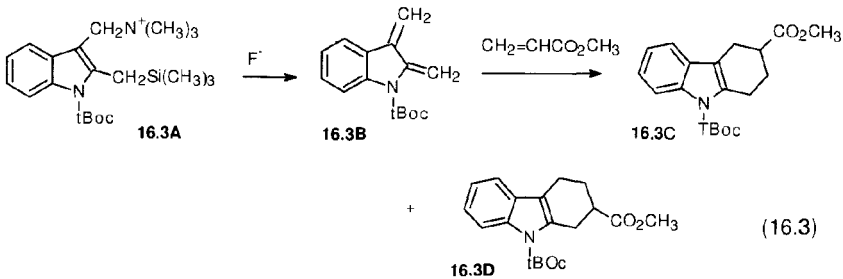
16.2 GENERATION AND REACTIONS OF INDOLE-2,3-QUINODIMETHANE INTERMEDIATES

Indole-2,3-quinodimethane is, as would be expected, an extraordinarily reactive diene. Its generation in the presence of an alkene or alkyne leads to 2 + 4 cycloaddition to form a carbazole ring structure[1]. Several procedures for generation of the intermediate or *N*-protected analogues have been developed. Procedures in which a synthetic equivalent, particularly derivatives of pyrano[3,4-b]indol-3-one, is used are also valuable. 1-Acylindole-2,3-quinodimethanes can be generated from the corresponding 2,3-*bis*-(bromomethyl)-indoles by reductive eliminated through reaction with NaI[2,3]. The gramine derivative **16.3A** is also a potential indole-2,3-quinodimethane precursor[4]. As illustrated by examples in Table 16.2, the intermediates can be trapped by typical electron-poor dienophiles.



(16.3)

Table 16.2

Synthesis of carbazoles from indoles by quinodimethane intermediates

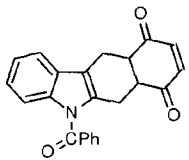
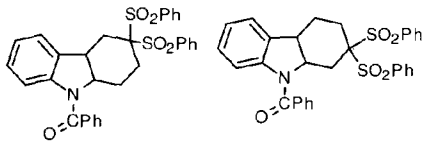
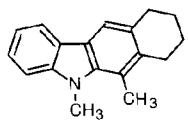
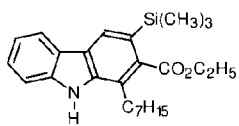
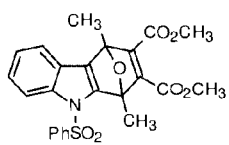
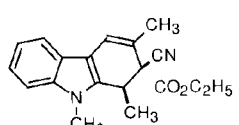
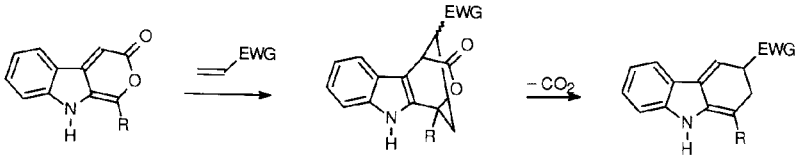
Entry	Quinodimethane precursor	Dienophile	Product	Yield (%)	Ref.
1	2,3-*bis*-(Bromomethyl)-1-benzoylindole	Benzoquinone		90	[2]
2	2,3-*bis*-(Bromomethyl)-1-benzoylindole	1,1-*bis*-phenylsulfonyl-ethene	 1:1 mixture	67	[13]
3	1-Methylpyrano[3,4-b]indol-3-one	But-3-en-2-one	1-Methyl-3-acetyl-1,2,3,9a-tetrahydro-carbazole	48	[14]
4	1-Methylpyrano[3,4-b]indol-3-one	Ethyl acrylate	Methyl 9-methylcarbazole-3-carboxylate and methyl 9-methylcarbazole-2-carboxylate (2:1 mixture)	75	[8]
5	1,4-Dimethylpyrano[3,4-b]-indol-3-one	Ethyl acrylate	Methyl 1,4-dimethylcarbazole-3-carboxylate and methyl 1,4-dimethylcarbazole-2-carboxylate (30:1 mixture)	65	[8]
6	1,9-Dimethylpyrano[3,4-b]-indol-3-one	Vinyl acetate	1,9-Dimethylcarbazole	97	[10]

Table 16.2 (*Continued*)

Synthesis of carbazoles from indoles by quinodimethane intermediates

Entry	Quinodimethane precursor	Dienophile	Product	Yield (%)	Ref.
7	1,9-Dimethylpyrano[3,4-b]-indol-3-one	(1) Cyclohexene (2) Ambient conditions		93	[10]
8	1-Heptylpyrano[3,4-b]indol-3-one	$EtO_2C{\equiv}CSi(Me)_3$		74	[9]
9	1,3-Dimethyl-4-(phenylsulfonyl)furo[3,4-b]indole	$MeO_2C{\equiv}CCO_2Me$		100	[15]
10	4-Benzyl-1-(*tert*-butyldimethylsilyloxy)furo[3,4-b]indole	(1) $CH_2{=}CHCO_2Me$ (2) $BF_3{-}OEt_2$	Methyl-9-benzyl-4-hydroxycarbazole-3-carboxylate	87	[16]
11	1,9-Dimethylpyrano[3,4-b]-indole-3-one	Ethyl α-cyanobut-2-enoate		97	[17]

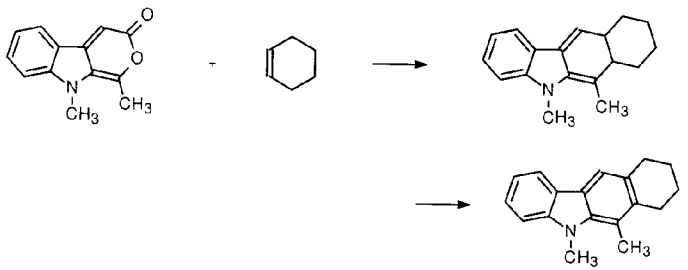
Pyrano[3,4-b]indol-3-ones are the most useful equivalents of the indol-2,3-quinodimethane synthon which are currently available for synthetic application. These compounds can be synthesized readily from indole-3-acetic acids and carboxylic anhydrides[5,6]. On heating with electrophilic alkenes or alkynes, adducts are formed which undergo decarboxylation to 1,2-dihydrocarbazoles or carbazoles, respectively.



(16.4)

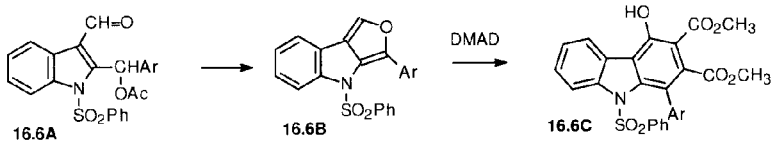
The regioselectivity of the reaction appears to be determined by a balance of electronic and steric factors. For acrylate and propiolate esters, the carboxylate group is found preferentially at C3 of the carbazole product[6–8]. Interestingly, a 4-methyl substituent seems to reinforce the preference for the EW group to appear at C3 (compare Entries 4 and 5 in Table 16.2). For disubstituted acetylenic dienophiles, there is a preference for the EW group to be at C2 of the carbazole ring[6]. This is reinforced by additional steric bulk in the other substituent[6,9].

Alkynes lacking activating EW groups can give adducts too, but the yields are lower than for electrophilic alkynes[6]. Alkenes with donor substituents can also react with pyrano[3,4-b]indol-3-ones. Vinyl acetate, for example, gives a very high yield of 1,9-dimethylcarbazole (Entry 6). There are fewer examples of reactions with unactivated alkenes although cyclohexene has been found to give an adduct which eventually is aromatized to 5,6-dimethyl-7,8,9,10-tetrahydrobenzo[b]carbazole[10].



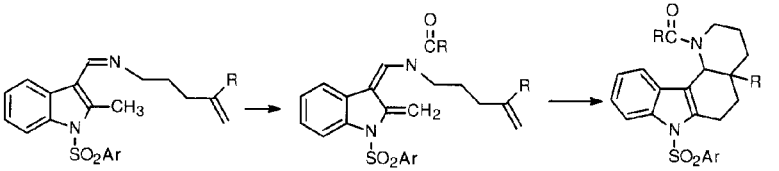
(16.5)

Furo[3,4-b]indoles are also potential indolequinodimethane equivalents[11,12]. For example, **16.6A** generates a furo[3,4-b]indole *in situ* which is trapped by dimethyl acetylenedicarboxylate generating the carbazole **16.6C**[12].



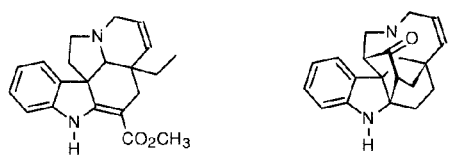
(16.6)

As was the case with reactions of vinylindoles, the most elaborate synthetic targets approached by the indole-2,3-quinodimethane route have been alkaloids[18]. The route has been applied to *aspidosperma*[19] and kopsine[20] structures. The fundamental reaction pattern is illustrated in equation 16.7. An indole-2,3-quinodimethane is generated by *N*-acylation of an *N*-(pent-4-enyl)-imine of a 2-methyl-3-formylindole. Intramolecular 2 + 4 cycloaddition then occurs.



(16.7)

In the case of the *aspidosperma* structure, the 5-membered C-ring is constructed from the *N*-acyl substituent. For the kopsine skeleton, an allyl group is installed and used to form the C6–C20 bridge.



(16.8)

Procedures

Mixture of 2-butanoyl- and 3-butanoyl-1-methylcarbazole[6]

A mixture of 1-methylpyrano[3,4-b]indol-3-one (414 mg, 2.08 mmol) and hex-1-yn-3-one (988 mg, 10.29 mmol) in bromobenzene (30 ml) was heated to reflux for 3 h. The solvent was removed *in vacuo* and the residue purified by chromatography on silica gel to give an inseparable mixture of the isomeric products (463 mg, 1:2.8 ratio, 87%).

3-Acetyl-1-methylcarbazole[7]

A solution of 1-methylpyrano[4,3-b]indol-3-one (1 mmol) and methyl vinyl ketone (5 ml) in toluene (5 ml) containing 5% Pd/C (40 mg) was heated for 48 h in a sealed tube at 110°C. The reaction mixture was evaporated *in vacuo* and the residue purified by silica gel chromatography to give the product in 80% yield.

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