

Multicomponent reactions of dimethyl methoxymalonate and dialkyl acetylenedicarboxylate in the presence of *N*-Nucleophiles: one-pot synthesis of 2*H*-pyridinyl-2-butenedioates in water

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Abstract An efficient synthesis of 2*H*-pyridinyl-2-butenedioate derivatives via reaction of dimethyl methoxymalonate and dialkyl acetylenedicarboxylate in the presence of *N*-nucleophiles in water as a solvent is described.

Keywords *N*-heterocycles · Acetylenic ester · Three-component reaction · Dimethyl methoxymalonate

Introduction

Multicomponent reactions (MCRs), with three or more reactants combined in a one-pot procedure to give a single product, have become increasingly popular during the last decade [1–5]. They are economically and environmentally advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus are finding increased use in the discovery process for new drugs and agrochemicals [6–8]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9].

The fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. Usually, the addition of nucleophiles devoid of an acidic hydrogen atom leads to a 1:1 zwitterionic intermediate that can undergo further transformations culminating in a stabilized product [10]. It is known that groups such as triphenylphosphine [11–13], pyridine [14],

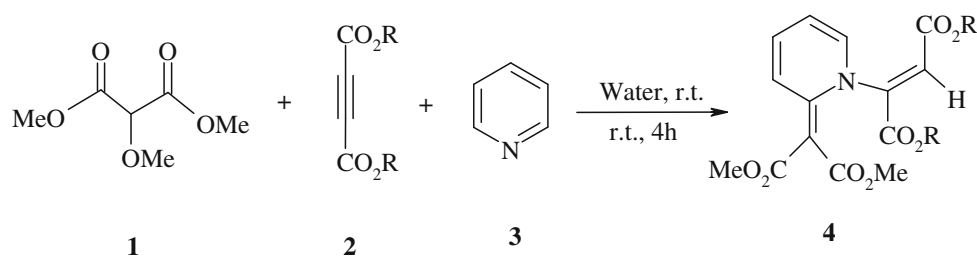
amines [15,16], and isocyanides [17] can invoke zwitterion formation. As part of our current studies on the development of new routes in heterocyclic synthesis [18–20], we report an efficient synthesis of 2*H*-pyridinyl-2-butenedioate derivatives (Scheme 1).

Results and discussion

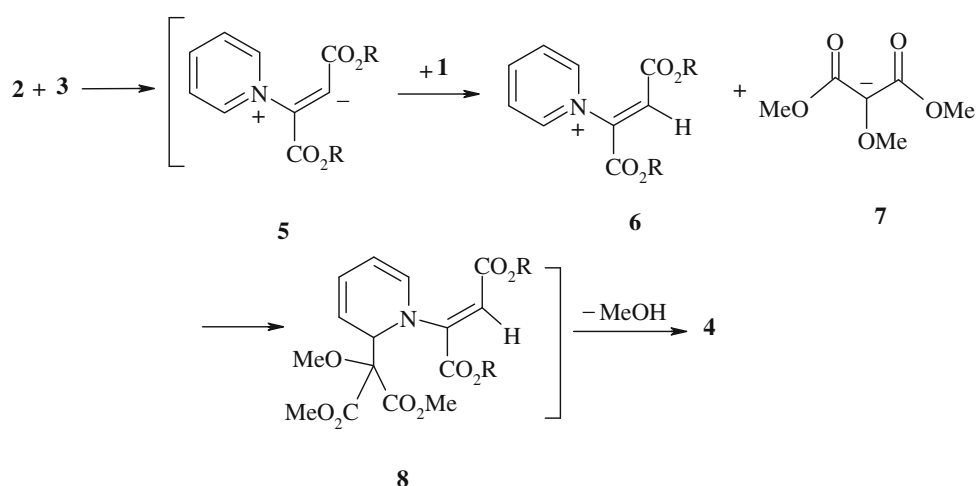
The reaction of dimethyl methoxymalonate **1** and dialkyl acetylenedicarboxylates **2** in the presence of pyridine **3** proceeds smoothly in water as a solvent at room temperature to produce dialkyl 2-{2-[2-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-pyridinyl}-2-butenedioates (**4**) in excellent yields (Scheme 1). Structures of compounds were characterized on the basis of their elemental analyses and their IR, ¹H NMR and ¹³C NMR spectra. The mass spectra of compounds **4a–d** displayed molecular ion signals at appropriate values, which were consistent with 1:1:1 adducts of dimethyl methoxymalonate, dialkyl acetylenedicarboxylates, and pyridine. For example, the ¹H NMR spectrum of **4a** exhibited four singlets for the methoxy (δ = 3.73, 3.77, 3.81, and 3.94 ppm) and olefinic (6.04 ppm) proton, along with multiplets for the pyridine moiety. The proton-decoupled ¹³C NMR spectrum of **4a** showed 16 distinct resonances in agreement with the proposed structure. NMR spectroscopy was employed to distinguish between (*Z*)-**4** and (*E*)-**4**. The (*Z*) and (*E*) configuration of the carbon–carbon double bonds in **4** are based on the chemical shift of the olefinic proton [21]. The ¹H NMR spectra of (*Z*)-**4** showed olefinic proton at 6.98–7.06 ppm, while the (*E*)-**4** isomer exhibited the olefinic proton at 6.16–6.30 ppm.

Mechanistically, it is conceivable that the reaction involves initial formation of a 1:1 zwitterionic intermediate [14–17] **5** between pyridine and dialkyl acetylenedicarboxylates. This

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Scheme 1 Synthesis of 2*H*-pyridinyl-2-butenedioate derivatives

2, 4	R	Yield/ % of 4
a	Me	92
b	Et	90
c	<i>t</i> Bu	84
d	isopropyl	85

Scheme 2 Proposed mechanism for the one-pot synthesis of 2*H*-pyridinyl-2-butenedioates

intermediate is protonated by dimethyl methoxymalonate **1** and then attacked by the conjugate base of the dimethyl methoxymalonate to produce **8**. Intermediate **8** is converted to the final product **4** by loss of methanol (Scheme 2).

Under similar conditions, the reaction of dimethyl methoxymalonate **1** with dialkyl acetylenedicarboxylates **2** in the presence of isoquinoline led to dialkyl 2-{2-[2-(methoxycarbonyl)-2-oxoethylidene]-2(1*H*)-isoquinolinyl]-2-butenedioates (**9**) in good yield. Also, the reaction of **1** with (**2a**, DMAD) in the presence of quinoline produces dimethyl 2-{2-[2-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-quinolinyl]-2-butenedioates (**10**) in excellent yield (Scheme 3).

In conclusion, the reaction of pyridine, isoquinoline, and quinoline with dialkyl acetylenedicarboxylates in the presence of dimethyl methoxymalonate led to dialkyl 2-{2-[2-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-pyridinyl]-2-butenedioates, dialkyl 2-{2-[2-(methoxycarbonyl)-2-oxoethylidene]-2(1*H*)-isoquinolinyl]-2-butenedioates and Dimethyl 2-{2-[2-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-quinolinyl]-2-butenedioate in good yields. The functionalized *N*-heterocyclic compounds that are reported in this work may be considered as potentially useful synthetic

intermediates. The present procedure has the advantage that the reaction is performed in water as a solvent, and the starting materials can be used without prior activation or modification.

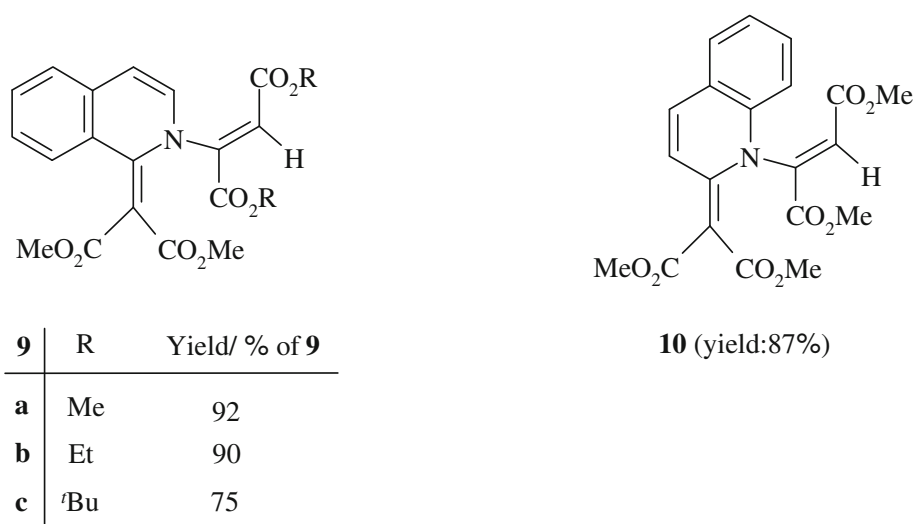
Material and methods

Isoquinoline, quinoline, pyridine, dimethyl methoxymalonate, and acetylenic compounds were obtained from *Fluka* and were used without further purification. IR spectra: *Shimadzu IR-460* spectrometer. ¹H and ¹³C NMR spectra: *Bruker DRX-500 Avance* instrument; in CDCl₃ at 500.1 and 125.7 MHz, respectively; δ in parts per million, *J* in hertz. EIMS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General procedure

Pyridine, quinoline or isoquinoline (2 mmol) was added slowly to a mixture of dialkyl acetylenedicarboxylates (2 mmol) and dimethyl methoxymalonate (0.32 g, 2 mmol) in

Scheme 3 Synthesis of 2*H*-pyridinyl-2-butenedioate derivatives using isoquinoline and quinoline



5 mL of water at room temperature. The reaction mixture was stirred for 4 h. The completion of reaction was confirmed by TLC (EtOAc–hexane 2:1). The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using hexane/EtOAc (3:1) to afford the pure title compounds.

*Dimethyl-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-pyridinyl]-2-butendioate (4a)*

Yellow oil, yield: 0.63 g (90%). IR (KBr) (ν_{\max} /cm^{−1}): 3430, 1760, 1734, 1700, 1640, and 1255 cm^{−1}. ¹H NMR: δ = 3.73 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.94 (s, 3H, OMe), 6.04 (s, 1H, CH), 6.86 (d, 1H, ³*J* = 7.8 Hz, CH), 7.54 (t, 2H, ³*J* = 7.8 Hz, 2CH), 8.65 (d, 1H, ³*J* = 7.4 Hz, CH) ppm. ¹³C NMR: δ = 51.5 (OMe), 52.5 (OMe), 52.9 (OMe), 53.8 (OMe), 95.4 (C), 115.9 (CH), 124.2 (CH), 124.6 (C), 137.1 (CH), 138.5 (CH), 149.7 (CH), 143.6 (C), 164.3 (C=O), 165.7 (C=O), 169.5 (C=O), 169.7 (C=O) ppm. MS: *m/z* (%) = 351 (M⁺, 10), 304 (54), 260 (70), 187 (68), 31 (100). Anal. Calc. for C₁₆H₁₇NO₈(351.31): C, 54.70; H, 4.88; N, 3.99; found: C, 54.59; H, 4.75; N, 3.83%.

*Diethyl-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-pyridinyl]-2-butendioate (4b)*

Yellow oil, yield: 0.67 g (89%). IR (KBr) (ν_{\max} /cm^{−1}): 3440, 1728, 1691, 1661, and 1624 cm^{−1}. ¹H NMR: δ = 1.31 (t, 3H, ³*J* = 7.2 Hz, Me), 1.40 (t, 3H, ³*J* = 7.3 Hz, Me), 3.57 (s, 3H, OMe), 3.59 (s, 3H, OMe), 4.22 (q, 2H, ³*J* = 7.3 Hz, OCH₂), 4.25 (q, 2H, ³*J* = 7.2 Hz, OCH₂), 6.00 (s, 1H, CH), 6.82 (d, 1H, ³*J* = 7.4 Hz, CH), 7.53 (t, 2H, ³*J* = 7.4 Hz, 2CH), 8.68 (d, 1H, ³*J* = 7.2 Hz, CH) ppm. ¹³C NMR: δ = 14.5 (Me), 14.7 (Me), 51.5 (OMe), 52.3 (OMe), 60.2 (OCH₂), 61.6 (OCH₂), 89.2 (C), 115.5 (CH), 124.3 (CH),

136.7 (2CH), 138.4 (CH), 144.6 (C), 149.7 (C), 164.1 (C=O), 164.8 (C=O), 165.4 (C=O), 169.2 (C=O) ppm. MS: *m/z* (%) = 379 (M⁺, 15), 320 (40), 261 (30), 237 (62), 45 (100). Anal. Calc. for C₁₈H₂₁NO₈(379.36): C, 56.99; H, 5.58; N, 3.69 found: C, 56.82; H, 5.45; N, 3.58%.

*Di(tert-Butyl)-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-pyridinyl]-2-butendioate (4c)*

Yellow oil, yield: 0.74 g (85%). IR (KBr) (ν_{\max} /cm^{−1}): 3345, 1750, 1739, 1719, and 1635 cm^{−1}. ¹H NMR: δ = 1.35 (s, 9H, C(Me)₃), 1.42 (s, 9H, C(Me)₃), 3.53 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.94 (s, 1H, CH), 7.28 (d, 1H, ³*J* = 7.8 Hz, CH), 7.57 (t, 1H, ³*J* = 7.4 Hz, CH), 8.24 (t, 1H, ³*J* = 7.4 Hz, CH), 9.47 (d, 1H, ³*J* = 8.2 Hz, CH) ppm. ¹³C NMR: δ = 28.3 (C(Me)₃), 28.6 (C(Me)₃), 51.2 (OMe), 52.0 (OMe), 81.2 (C(Me)₃), 82.8 (C(Me)₃), 98.2 (C), 114.7 (CH), 120.4 (CH), 125.7 (CH), 128.3 (CH), 137.7 (CH), 141.7 (C), 147.3 (C), 163.9 (C=O), 164.3 (C=O), 166.8 (C=O), 167.7 (C=O) ppm. MS: *m/z* (%) = 435 (M⁺, 10), 249 (40), 149 (58), 58 (100). Anal. Calc. for C₂₂H₂₉NO₈(435.47): C, 60.68; H, 6.71; N, 3.22 found: C, 60.57; H, 6.64; N, 3.14%.

*Diisopropyl-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-1(2*H*)-pyridinyl]-2-butendioate (4d)*

Yellow oil, yield: 0.71 g (87%). IR (KBr) (ν_{\max} /cm^{−1}): 3342, 1745, 1725, 1712, and 1657 cm^{−1}. ¹H NMR: δ = 1.21 (d, 6H, ³*J* = 7.3 Hz, 2 Me), 1.35 (d, 6H, ³*J* = 7.4 Hz, 2 Me), 3.72 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.25 (m, 1H, CH), 4.65 (m, 1H, CH), 6.25 (s, 1H, CH), 6.87 (d, 1H, ³*J* = 7.5 Hz, CH), 7.45 (t, 1H, ³*J* = 7.4 Hz, CH), 7.85 (t, 1H, ³*J* = 7.4 Hz, CH), 9.24 (d, 1H, ³*J* = 8.2 Hz, CH) ppm. ¹³C NMR: δ = 22.4 (2 Me), 23.7 (2 Me), 50.9 (OMe), 51.7 (OMe), 69.5 (CH), 70.8 (CH), 97.4 (C), 117.2 (CH), 125.6 (CH), 127.9

(CH), 138.4 (CH), 140.2 (C), 149.8 (C), 164.2 (C=O), 165.2 (C=O), 167.0 (C=O), 169.5 (C=O) ppm. Anal. Calc. for $C_{20}H_{25}NO_8$ (407.41): C, 58.96; H, 6.18; N, 3.44 found: C, 58.87; H, 6.00; N, 3.37%.

Dimethyl-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-2(1H)-isoquinoliny]-2-butendioate (9a)

Yellow oil, yield: 0.74 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3410, 1738, 1720, 1697, and 1233cm^{-1} . ^1H NMR: δ = 3.67 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.94 (s, 3H, OMe), 6.45 (s, 1H, CH), 6.87 (d, 1H, 3J = 7.5 Hz, CH), 7.14 (d, 1H, 3J = 7.4 Hz, CH), 7.27–7.56 (m, 3H, 3 CH), 8.57 (d, 1H, 3J = 7.5 Hz, CH) ppm. ^{13}C NMR: δ = 52.1 (OMe), 52.3 (OMe), 53.4 (OMe), 54.2 (OMe), 95.4 (C), 110.3 (CH), 118.5 (CH), 120.4 (CH), 125.2 (CH), 126.5 (CH), 128.2 (CH), 132.7 (CH), 133.0 (C), 135.4 (C), 140.2 (C), 148.7 (C), 162.8 (C=O), 163.7 (C=O), 164.6 (C=O), 167.8 (C=O) ppm. MS: m/z (%) = 401 (M^+ , 10), 345 (45), 167 (58), 129 (94), 31 (100). Anal. Calc. for $C_{20}H_{19}NO_8$ (401.37): C, 59.85; H, 4.77; N, 3.49 found: C, 59.72; H, 4.65; N, 3.35%.

Diethyl-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-2(1H)-isoquinoliny]-2-butendioate (9b)

Yellow oil, yield: 0.77 g (90%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3370, 1765, 1730, 1710, 1663, and 1237cm^{-1} . ^1H NMR: δ = 1.22 (t, 3H, 3J = 7.4 Hz, Me), 1.29 (t, 3H, 3J = 7.3 Hz, Me), 3.74 (3H, s, OMe), 3.82 (s, 3H, OMe), 4.18 (q, 2H, 3J = 7.3 Hz, OCH_2), 4.24 (q, 2H, 3J = 7.3 Hz, OCH_2), 6.48 (s, 1H, CH), 7.54–7.66 (m, 4H, 4CH), 7.78 (d, 1H, 3J = 7.6 Hz, CH), 7.91 (d, 1H, 3J = 9.8 Hz, CH) ppm. ^{13}C NMR: δ = 14.2 (Me), 14.8 (Me), 52.8 (OMe), 53.0 (OMe), 60.4 (OCH_2), 61.2 (OCH_2), 98.8 (C), 110.4 (CH), 115.6 (CH), 120.4 (CH), 125.4 (CH), 126.4 (CH), 128.4 (CH), 131.5 (CH), 132.0 (C), 136.2 (C), 141.3 (C), 150.3 (C), 164.4 (C=O), 166.2 (C=O), 166.7 (C=O), 167.4 (C=O) ppm. MS: m/z (%) = 429 (M^+ , 10), 311 (48), 266 (70), 129 (100), 45 (98). Anal. Calc. for $C_{22}H_{23}NO_8$ (429.42): C, 62.01; H, 5.46; N, 3.62 found: C, 62.00; H, 5.45; N, 3.65%.

Di(tert-Butyl)-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-2(1H)-isoquinoliny]-2-butendioate (9c)

Yellow oil, yield: 0.73 g (75%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3340, 1745, 1732, 1721, and 1647cm^{-1} . ^1H NMR: δ = 1.29 (s, 9H, $\text{C}(\text{Me})_3$), 1.1.35 (s, 9H, $\text{C}(\text{Me})_3$), 3.75 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.53 (s, 1H, CH), 7.32–7.71 (m, 4H, 4CH), 7.83 (t, 1H, 3J = 7.4 Hz, CH), 8.24 (d, 1H, 3J = 7.4 Hz, CH) ppm. ^{13}C NMR: δ = 27.8 ($\text{C}(\text{Me})_3$), 28.4 ($\text{C}(\text{Me})_3$), 50.8 (OMe), 51.7 (OMe), 79.5 ($\text{C}(\text{Me})_3$), 80.4 ($\text{C}(\text{Me})_3$), 98.4 (C), 111.2 (CH), 115.8 (CH), 121.0 (CH), 126.4 (CH), 127.0 (CH),

128.6 (CH), 132.7 (CH), 133.4 (C), 137.2 (C), 142.0 (C), 150.2 (C), 164.0 (C=O), 165.2 (C=O), 167.1 (C=O), 168.6 (C=O) ppm. MS: m/z (%) = 485 (M^+ , 10), 412 (56), 339 (62), 129 (100), 57 (98). Anal. Calc. for $C_{26}H_{31}NO_8$ (485.53): C, 64.32; H, 6.44; N, 2.88 found: C, 64.28; H, 6.37; N, 2.80%.

Dimethyl-2-[2-[2-methoxy-1-(methoxycarbonyl)-2-oxoethylidene]-1(2H)-quinoliny]-2-butendioate (10)

Pale yellow oil, yield: 0.70 g (87%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3414, 1730, 1725, 1692, and 1245cm^{-1} . ^1H NMR: δ = 3.75 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.34 (s, 1H, CH), 6.82 (d, 1H, 3J = 7.4 Hz, CH), 7.24 (d, 1H, 3J = 7.6 Hz, CH), 7.28–7.62 (m, 3H, 3CH), 8.64 (d, 1H, 3J = 7.6 Hz, CH) ppm. ^{13}C NMR: δ = 51.7 (OMe), 52.4 (OMe), 52.7 (OMe), 53.7 (OMe), 92.8 (C), 113.4 (CH), 120.2 (CH), 121.9 (CH), 126.0 (CH), 127.4 (CH), 129.4 (CH), 131.4 (CH), 132.8 (C), 136.0 (C), 139.4 (C), 150.2 (C), 163.0 (C=O), 164.8 (C=O), 165.4 (C=O), 168.6 (C=O) ppm. MS: m/z (%) = 401 (M^+ , 10), 345 (45), 167 (58), 129 (94), 31 (100). Anal. Calc. for $C_{20}H_{19}NO_8$ (401.37): C, 59.85; H, 4.77; N, 3.49 found: C, 59.72; H, 4.65; N, 3.35%.

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