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Synthesis of 2-butenedioates viamulticomponent reaction of isoquinoline

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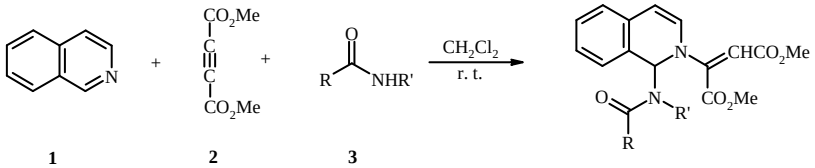
Abstract: Isoquinoline reacts smoothly with dimethyl acetylenedicarboxylate (DMAD) in the presence of amides to produce dimethyl (E)-2-[1-[aryl(alkyl)carbonylamino]-2(1H)-isoquinolinyl]-2-butenedioates. Also, quinoline reacts with DMAD in the presence of benzamide to produce dimethyl (E)-2-[1-[(phenylcarbonyl)amino]-2(1H)-quinolinyl]-2-butenedioate.

Keywords: Three-component reactions; amide; quinoline; isoquinoline; acetylenic ester.

Introduction

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 acidic hydrogen atoms leads to a 1:1 zwitterionic intermediate that can undergo further transformations culminating in a stabilized product [1]. It has been known from the studies of various groups that triphenylphosphine [2], pyridine [3], amines [4], and isocyanides [5] can invoke the zwitterions formation.

As part of our current studies on the development of new routes in heterocyclic synthesis [6], in this paper, we report on the synthesis of 1,2-disubstituted dihydro-isoquinolines. Thus, the reaction of isoquinoline and DMAD in the presence of amides (**1**) proceeds smoothly in CH_2Cl_2 at room temperature to produce dimethyl (*E*)-2-[1-[(alkyl)amino]-2(1*H*)-isoquinolinyl]-2-butenedioate (**2**) in excellent yields[7] (Scheme 1).



1 **2** **3**

4	R	R'	Yield (%)
a	H	H	90
b	CH_2Cl	H	92
c	Ph	H	95
d	3-Pyridyl	H	98
e	Et	Me	93
f	Me	Ph	94

Scheme 1: Synthesis of compound **4**

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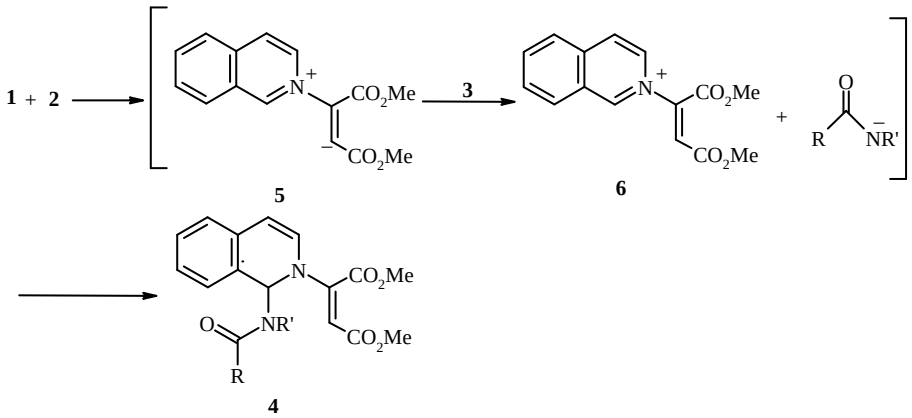
Results and Disscusion

The products were characterized on the basis of their elemental analyses and their IR, ^{1}H-NMR and ^{13}C- NMR spectra.

The mass spectrum of 4**a** displayed the molecular ion (M^{+}) peak at *m*/*z* = 392, which isconsistent with the 1:1:1 adduct of isoquinoline, DMAD and formamide. The ^{1}H NMR spectrum of 4**a** exhibited two singlets for methoxy (δ 3.66 and 3.92 ppm) and olefinic (δ 5.70 ppm) proton, along with multiplets at δ 6.33-7.32 ppm for the isoquinoline moiety. The proton-decoupled ^{13}C NMR spectrum of 4**a** showed sixteen distinct resonances in agreement with the proposed structure. Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate[8]**5** between isoquinoline and DMAD, which is protonated by **3** to produce *N*-vinylazinium salt **6**. Intermediate **6** is attacked by the conjugate base of the amide to produce **4** (Scheme 2).



Scheme 2: Proposed mechanism of compounds **4**

Conclusion

In conclusion, we report a novel transformation involving DMAD and isoquinoline or quinoline in the presence of amides which affords 1,2-disubstituted nitrogen-containing heterocycles. The advantage of the present procedure is that the reaction is performed under neutral conditions by simply mixing the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of aminal heterocyclic compounds.

Experimental

Chemicals used in this work were purchased from Fluka and used without further purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *BrukerDRX-500 AVANCE* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; □ in ppm, *J* in Hz. EI-MS (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 for the Preparation of Compounds* **4** and 7.To a stirred solution of 0.28 g DMAD (2 mmol) and the amide (2 mmol) in 10 mL CH_2Cl_2 was added the *N*-heterocycle (2 mmol) at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by CC (SiO_2; hexane/AcOEt 4:1) to afford the pure title compounds.Compound **4a**: Gray powder, yield: 0.57 g (90%), m.p. 162-164°C. IR (KBr): ν = 1717, 1712, 1639 (C=O) cm^{-1}. ^{1}H-NMR: δ= 3.66 and 3.92 (2 *s*, 2 MeO), 5.70 (*s*, CH), 5.97 (*d*, ^{3}J= 7.7, CH), 6.34 (*t*, ^{3}J= 7.7,CH), 6.52 (*d*, ^{3}J= 9.6, NH), 6.93 (*d*, ^{3}J= 9.8, CH), 7.11 (*d*, ^{3}J= 7.5, CH), 7.22-7.32 (*m*, 3 CH), 7.97 (*broads*, CH). ^{13}C-NMR:δ= 51.4 and 53.5 (2 MeO), 58.8, 93.5, 108.0, 124.5, 124.9, 126.7 and 127.9 (7 CH), 128.2 (C), 128.5 (CH), 129.3 (C), 149.5 (CH), 165.2, 167.5 and 169.5 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 316 (M^{+}, 10), 129 (40), 68 (65), 59 (100), 39 (48). Anal. Calcd for $C_{16}H_{16}N_2O_5$ (316.31): C, 60.76; H, 5.10; N, 8.86. Found: C, 60.72; H, 5.13; N, 8.77.

Compound **4b**: Gray powder, yield: 0.57 g (90%), m.p. 162-164°C. IR (KBr): ν = 1733, 1697, 1633 (C=O) cm^{-1}. ^{1}H-NMR: δ= 3.69 and 3.96 (2 *s*, 2 MeO), 4.06 (*s*, CH_2), 5.69 (*s*, CH), 6.05 (*d*, ^{3}J= 7.7, CH), 6.39 (*d*, ^{3}J= 7.5,CH), 6.88 (*d*, ^{3}J= 9.6, NH), 7.17 (*d*, ^{3}J= 7.5, CH), 7.25-7.35 (*m*, 4 CH). ^{13}C-NMR:δ= 41.9 (CH_2), 51.4 and 53.5 (2 MeO), 60.8, 94.6, 108.4, 124.5, 125.5, 126.6 and 127.5 (7 CH), 128.0, 128.5 and 129.4 (3 C), 149.5 (CH), 164.2, 164.9 and

166.9 (3 C=O). Anal. Calcd for $C_{17}H_{17}ClN_2O_5$ (364.78): C, 55.97; H, 4.70; N, 7.68. Found: C, 55.86; H, 4.35; N, 7.62.

Compound **4c**: Pale orange powder, yield: 0.74 g (95%), m.p. 155-157 °C. IR (KBr): ν = 1728, 1704, 1642 (C=O) cm^{-1}.^{1}H-NMR: δ= 3.72, 4.00 (2 *s*, 2 MeO), 5.90 (*s*, CH), 6.08 (*d*, ^3J= 7.7, CH), 6.48 (*t*, ^3J= 7.1,CH), 6.92 (*d*, ^3J= 9.6, NH), 7.18 (*d*, ^3J= 5.3, CH), 7.21 (*d*, ^3J= 2.3, CH), 7.28 (*t*, ^3J= 2.3, CH), 7.34 (*t*, ^3J= 7.5, CH), 7.40 (*t*, ^3J= 7.5, 2 CH), 7.50 (*t*, ^3J= 7.8, CH), 7.51 (*t*, ^3J= 7.7, CH), 7.72 (*d*,^3J= 1.4, 2 CH). ^{13}C-NMR:δ= 51.8 and 53.8 (2 MeO), 61.3, 94.7 and 108.6 (3 CH), 125.3 (2 CH), 127.3 (CH), 127.7 (2 CH), 128.3 (CH), 128.8 (2 CH), 128.9 and 129.4 (2 C), 129.6 and 132.4 (2 CH), 133.6 and 149.3 (2 C), 165.6, 165.9 and 167.7 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 392 (M^+, 2), 169 (24), 69 (100), 59 (60), 43 (30). Anal. Calcd for $C_{22}H_{20}N_2O_5$ (392.41): C, 67.34; H, 5.14; N, 7.14. Found: C, 67.32; H, 5.15; N, 7.20**.**

Compound **4d**: Yellow powder, yield: 0.85 g (91%), m.p. 178-180°C. IR (KBr): ν = 1720, 1701, 1644 (C=O) cm^{-1}. ^{1}H-NMR: δ= 3.63 and 3.90 (2 *s*, 2 MeO), 5.74 (*s*, CH), 5.90 (*d*, ^3J= 7.7, CH), 6.32 (*d*, ^3J= 7.6,CH), 7.05 (*d*, ^3J= 7.3, NH), 7.11 (*d*, ^3J= 9.2, CH), 7.19-7.25 (*m*, 3 CH), 7.39 (*d*, ^3J= 7.2, CH), 7.67 (*d*,^3J= 8.9, CH), 7.95 (*d*, ^3J= 6.3, CH), 8.46 (*d*, ^3J= 4.6, CH), 8.66 (*s*, CH). ^{13}C-NMR:δ= 51.4 and 53.5 (2 MeO), 60.8, 94.5, 108.2, 123.4, 24.8, 124.9, 126.8 and 127.8 (8 CH), 128.6, 128.8 and 129.0 (3 C), 129.3 and 135.5 (2 CH), 14.0 (C), 148.7 and 152.3 (2 CH), 163.6, 165.0 and 167.0 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 393 (M^+, 10), 287 (100), 272 (62), 167 (46), 149 (95), 129 (55), 106 (58). Anal. Calcd for $C_{21}H_{19}N_3O_5$ (393.39): C, 64.12; H, 4.87; N, 10.68. Found: C, 64.10; H, 4.85; N, 10.70.

Compound **4e**: Gray powder, yield: 0.66 g (93%), m.p. 137-140 °C. IR (KBr): ν = 1739, 1700, 1638 (C=O) cm^{-1}. ^{1}H-NMR: δ= 1.13 (*t*, ^3J= 7.8, CH_3), 2.15-2.35 (*m*, CH_2), 2.62 (s, CH_3), 3.65 and 3.95 (2 *s*, 2 MeO), 5.50 (*s*, CH), 5.78 (*d*, ^3J= 7.8, CH), 6.40 (*d*, ^3J= 7.8, CH), 7.00 (*d*, ^3J= 7.5, CH), 7.18-7.27 *(m*, 2 CH), 7.36 (*d*, ^3J= 7.6, CH), 7.63 (*s*, CH). ^{13}C-NMR:δ= 9.1 (CH_3), 26.5 (CH_2), 28.9 (CH_3), 51.4 and 53.4 (2 MeO), 63.3, 94.0 , 106.1, 124.5 (4 CH), 126.0 (C), 127.2, 127.9, 128.0 and 129.0 (4 CH), 129.8 and 148.8 (2 C), 165.6, 167.3 and 172.3 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 358 (M^+, 10), 129 (30), 70 (40), 59 (80), 57 (100), 42 (42).Anal. Calcd for $C_{19}H_{22}N_2O_5$ (358.39): C, 63.68; H, 6.19; N, 7.82. Found: C, 62.93; H, 6.2; N, 7.80.

Compound **4f**: Gray powder, yield: 0.88 g (94%), m.p. 190-192 °C. IR (KBr): ν = 1739, 1700, 1638(C=O) cm^{-1}. ^{1}H-NMR: δ= 1.67 (s, CH_3), 3.67 and 3.94 (2 *s*, 2 MeO), 5.20 (*d*, ^3J= 7.7, CH), 5.68 (*s*, CH), 5.82 (*d*, ^3J= 7.7, CH), 6.00 (*d*, ^3J= 7.7, CH), 6.85-7.56 (m, 8 CH), 7.81 (*s*, CH) ppm. ^{13}C-NMR:δ= 22.2 (CH_3), 51.8 and 53.5 (2 MeO), 64.0, 93.4 and 106.4 (3 CH), 124.3 (2 CH), 125.6 (CH), 127.0 (2 CH), 127.7 (CH), 128.2 and 128.7 (2 C), 128.8, 129.1 and 129.6 (3 CH), 129.9, 130.1 and 149.2 (3 C), 165.1, 167.4 and 169.3 (3 C=O). Anal. Calcd for $C_{23}H_{22}N_2O_5$ (406.43): C, 67.97; H, 5.64; N, 6.89. Found: C, 67.89; H, 5.43; N, 6.91.

Compound **7**: Brown powder, yield: 0.71 g (90%), m.p. 147-149 °C. IR (KBr): ν = 1730, 1727, 1654, (C=O) cm^{-1}. ^{1}H-NMR: δ= 3.65 and 3.69 (2 *s*, 2 MeO), 6.07 (*dd*, ^3J = 7.3, ^3J = 6.2, CH), 6.30 (*d*, ^3J= 6.2,NH), 6.38 (*s*, CH), 6.78 (*d*, ^3J= 7.1, 2 CH), 7.05 (*t*, ^3J= 7.6, 2 CH), 7.16 (*t*, ^3J= 8.8, 2 CH), 7.30 (*t*, ^3J= 7.1, 2 CH), 7.41 (*t*, ^3J= 7.6, CH), 7.62 (*t*, ^3J= 7.3, 2 CH). ^{13}C-NMR:δ= 51.4 and 52.8 (2 MeO), 62.3, 103.3, 120.9, 123.4 and 124.2 (5 CH), 125.0 (C), 126.2 (CH), 127.2 (2 CH), 127.4 (CH), 128.5 (2 CH), 132.0 (CH), 133.4, 135.7 and 150.1 (3 C), 165.1, 165.7 and 166.9 (3 C=O). Anal. Calcd for $C_{22}H_{20}N_2O_5$ (392.41): C, 67.34; H, 5.14; N, 7.14. Found: C, 67.30; H, 5.10; N, 7.15.

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