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Synthesis of dimethyl 1,2-dihydroisoquinolines through the reaction of isoquinoline and dimethyl acetylenedicarboxylate in the presence of amides

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

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.[1] It is known that groups such as triphenylphosphine,[2] pyridine,[3] amines[4] and isocyanides[5] can invoke zwitterion formation.

As part of our current studies on the development of new routes in heterocyclic synthesis,[6] we report the synthesis of 1,2-disubstituted 1,2-dihydroisoquinolines. The reaction of isoquinoline **1** and DMAD **2** in the presence of amides **3** proceeds smoothly in CH_2Cl_2 at room temperature to produce dimethyl 2-[1-[(alkyl)amino]-2(1*H*)-isoquinolinyl]-2-butenedioates **4** in excellent yields[7] (Scheme 1).

The products were characterized on the basis of their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of compounds **4a–f** displayed molecular ion peaks at appropriate values, which were consistent with 1:1:1 adducts of isoquinoline, DMAD and the amides.

The ^{1}H NMR spectrum of **4a** exhibited three singlets for the methoxy (δ 3.66 and 3.92 ppm) and olefinic (δ 5.71 ppm) protons, along with multiplets for the isoquinoline moiety. The proton-decoupled ^{13}C NMR spectrum of **4a** showed sixteen distinct resonances in agreement with the proposed structure. The spectral data of **4b–f** were also in agreement with the proposed structures.

Mechanistically, it is conceivable that the reaction involves initial formation of a 1:1 zwitterionic intermediate[1–5] **5** between isoquinoline and DMAD. This intermediate is protonated by amide **3** and then attacked by the conjugate base of the amide to produce **4** (Scheme 2).

Under similar conditions, the reaction of quinoline with DMAD in the presence of benzamide led to dimethyl 2-[1-[(phenylcarbonyl)amino]-2(1*H*)-quinolinyl]-2-butenedioate (**7**) in 95% yield (Scheme 3).

In conclusion, we have reported 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.

Keywords: Aminals; Amide; Quinoline; Isoquinoline; Acetylenic ester.
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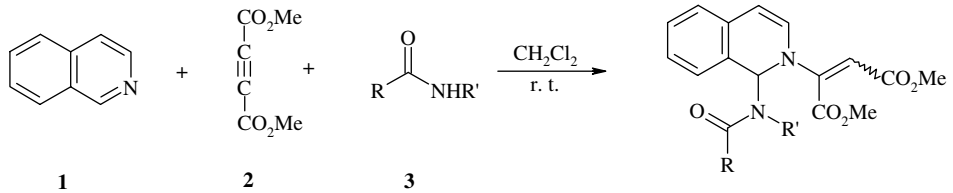
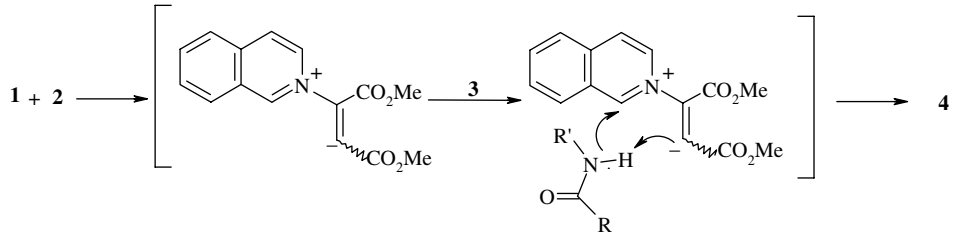


1 2 3

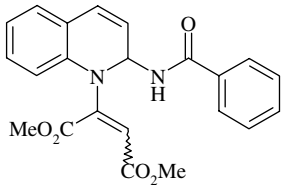
4	R	R'	Yield (%)
a	H	H	90
b	CH_2Cl	H	92
c	Ph	H	95
d	3-Pyridyl	H	98
e	Et	Me	93
f	Me	Ph	94

Scheme 1.



5 6

Scheme 2.



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Scheme 3.

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7. *General procedure for the preparation of compounds* **4** and **7**: To a stirred solution of DMAD (0.28 g, 2 mmol) and the amide (2 mmol) in CH_2Cl_2 (10 mL) 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 column chromatography (SiO_2; hexane/AcOEt 4:1) to afford the pure adducts. Compound **4a**: Grey powder, yield: 0.57 g (90%), mp 162–164 °C. IR (KBr): $\nu = 1717$, 1712, 1639 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 3.66$ and 3.92 (6H, 2s, 2MeO), 5.71 (1H, s, CH), 5.97 (1H, d, $^3J = 7.7$, CH), 6.34 (1H, d, $^3J = 7.7$, CH), 6.52 (1H, d, $^3J = 9.7$, NH), 6.93 (1H, d, $^3J = 9.7$, CH), 7.11 (1H, d, $^3J = 7.5$, CH), 7.23 (1H, t, $^3J = 7.0$, CH), 7.29 (1H, t, $^3J = 7.5$, CH), 7.32 (1H, d, $^3J = 7.2$, CH), 7.97 (1H, s, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 51.5$ and 53.5 (2MeO), 58.8, 94.6, 108.1, 124.7, 124.9, 126.8 and 128.0 (7CH), 128.5 and 128.6 (2C), 129.3 (CH), 148.5 (C), 158.8, 165.0 and 167.1 (3C=O). MS: 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**: Grey powder, yield: 0.67 g (92%), mp 162–164 °C. IR (KBr): $\nu = 1733$, 1697, 1633 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 3.69$ and 3.96 (6H, 2s, 2MeO), 4.01 (2H, AB system, $J_{AB} = 15.4$, CH_2), 5.69 (1H, s, CH), 6.05 (1H, d, $^3J = 7.6$, CH), 6.39 (1H, d, $^3J = 7.6$, CH), 6.89 (1H, d, $^3J = 9.6$, NH), 7.17 (1H, d, $^3J = 7.5$, CH), 7.26 (2H, t, $^3J = 7.0$, 2CH), 7.34 (2H, d, $^3J = 7.6$, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 42.2$ (CH_2), 51.5 and 53.5 (2MeO), 60.8, 94.7, 108.5, 124.7, 125.1, 126.7 and 128.01 (7CH), 128.2 (C), 128.5 (CH), 129.5 and 149.0 (2C), 164.1, 164.9 and 167.0 (3C=O). MS: m/z (%) = 364 (M^+, 5), 273 (40), 222 (65), 74 (100), 92 (48). 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%), mp 155–157 °C. IR (KBr): $\nu = 1728$, 1704, 1642 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 3.72$, 4.00 (6H, 2s, 2MeO), 5.90 (1H, s, CH), 6.08 (1H, d, $^3J = 7.7$, CH), 6.49 (1H, dd,

$^3J = 7.7$, $^4J = 1.1$, CH), 6.92 (1H, d, $^3J = 9.6$, NH), 7.19 (1H, d, $^3J = 5.3$, CH), 7.29 (1H, t, $^3J = 7.5$, CH), 7.35 (1H, t, $^3J = 7.5$, CH), 7.42–7.43 (2H, m, 2CH), 7.50 (1H, d, $^3J = 7.8$, CH), 7.51 (1H, t, $^3J = 7.7$, CH), 7.72 (1H, d, $^3J = 8.5$, CH), 7.73 (1H, d, $^3J = 8.5$, CH), 7.86 (1H, d, $^3J = 9.6$, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 51.8$ and 53.9 (2MeO), 61.3, 94.7 and 108.6 (3CH), 125.3 (2CH), 127.3 (CH), 127.7 (2CH), 128.3 (CH), 128.9 (2CH), 129.0 and 129.5 (2C), 129.6 and 132.5 (2CH), 133.6 and 149.3 (2C), 165.6, 165.9 and 167.7 (3C=O). MS: 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: 0.77 g (98%), mp 178–180 °C. IR (KBr): $\nu = 1720$, 1701, 1644 (C=O) cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 3.63$ and 3.90 (6H, 2s, 2MeO), 5.74 (1H, s, CH), 5.89 (1H, d, $^3J = 7.7$, CH), 6.32 (1H, d, $^3J = 7.6$, CH), 7.05 (1H, d, $^3J = 7.3$, CH), 7.11 (1H, d, $^3J = 9.2$, CH), 7.19–7.25 (3H, m, 3CH), 7.40 (1H, d, $^3J = 7.2$, CH), 7.67 (1H, d, $^3J = 9.2$, NH), 8.0 (1H, d, $^3J = 7.9$, CH), 8.46 (1H, d, $^3J = 5$, CH), 8.66 (1H, s, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 51.4$ and 53.5 (2MeO), 60.9, 94.5, 108.2, 123.4, 124.9, 125.0, 126.8 and 127.9 (8CH), 128.6, 128.7 and 129.1 (3C), 129.3 and 135.6, 148.0 (3CH), 148.7 (C), 152.4 (CH), 163.6, 165.0 and 167.0 (3C=O). MS: 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**: Grey powder, yield: 0.66 g (93%), mp 137–140 °C. IR (KBr): $\nu = 1739$, 1700, 1638 (C=O) cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.14$ (3H, t, $^3J = 7.5$, CH_3), 2.26 (2H, ABX_3 system, $\Delta\nu_{AB} = 78$, $J_{AB} = 16.0$, $J_{AX} = J_{BX} = 7.5$, CH_2), 2.62 (3H, s, CH_3), 3.65 and 3.95 (6H, 2s, 2MeO), 5.50 (1H, s, CH), 5.78 (1H, d, $^3J = 7.8$, CH), 6.40 (1H, d, $^3J = 7.8$, CH), 7.05 (1H, d, $^3J = 7.5$, CH), 7.19 (1H, t, $^3J = 7.3$, CH), 7.26 (1H, t, $^3J = 7.3$, CH), 7.36 (1H, d, $^3J = 7.5$, CH), 7.63 (1H, s, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 9.1$ (CH_3), 26.6 (CH_2), 28.9 (CH_3), 51.4 and 53.4 (2MeO), 63.3, 94.0, 106.1, 124.4 (4CH), 126.4 (C), 127.3, 127.9, 128.0 and 129.0 (4CH), 129.8 and 148.8 (2C), 165.3, 167.4 and 173.0 (3C=O). MS: 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**: Grey powder, yield: 0.88 g (94%), mp 190–192 °C. IR (KBr): $\nu = 1739$, 1700, 1638 (C=O) cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.68$ (3H, s, CH_3), 3.69 and 3.95 (6H, 2s, 2MeO), 5.20 (1H, d, $^3J = 7.7$, CH), 5.69 (1H, s, CH), 5.82 (1H, d, $^3J = 7.7$, CH), 6.00 (1H, d, $^3J = 7.5$, CH), 6.85 (1H, dd, $^3J = 8.0$, $^4J = 3.4$, CH), 6.98 (1H, t, $^3J = 7.3$, CH), 7.15 (1H, d, $^3J = 7.0$, CH), 7.25–7.34 (4H, m, 4CH), 7.55 (1H, dd, $^3J = 8.0$, $^4J = 3.4$, CH), 7.81 (1H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 22.2$ (CH_3), 51.4 and 53.4 (2MeO), 64.1, 93.5, 106.5, 124.4, 125.6, 127.1, 127.7 (7CH), 128.3 (C), 128.7, 128.9, 129.1, 129.2, 129.6, and 130.0 (6CH), 130.1, 137.6 and 149.2 (3C), 165.1, 167.4 and 169.4 (3C=O). Anal. Calcd for $C_{23}H_{22}N_2O_5$ (406.43): C, 67.97; H, 5.46; N, 6.89. Found: C, 67.89; H, 5.43; N, 6.91. Compound **7**: Brown powder, yield: 0.75 g (95%), mp 147–149 °C. IR (KBr): $\nu = 1730$, 1727, 1654 (C=O) cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 3.65$ and 3.69 (6H, 2s, 2MeO), 6.07 (1H, dd, $^3J = 8.2$, $^3J = 3.0$, CH), 6.30 (1H, d, $^3J = 9.0$, NH), 6.38 (1H, s, CH), 6.69 (2H, d, $^3J = 9.0$, 2CH), 7.05 (1H, t, $^3J = 7.2$, 2CH), 7.16 (2H, t, $^3J = 8.8$, 2CH), 7.30 (2H, t, $^3J = 7.1$, 2CH), 7.43 (1H, t, $^3J = 7.2$, CH), 7.62 (2H, d, $^3J = 7.3$, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 51.4$ and 52.8 (2MeO), 62.3, 103.3, 120.9, 123.4 and 124.2 (5CH), 125.0 (C), 126.2 (CH), 127.3 (2CH), 127.4 and 158.4 (2CH), 128.5 (2CH), 132.0 (CH), 133.4, 135.7 and 150.1 (3C), 165.1, 165.7 and 166.9 (3C=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.