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Synthesis of isoquinoline derivatives through the reaction of acetylenic compounds in the presence of amides

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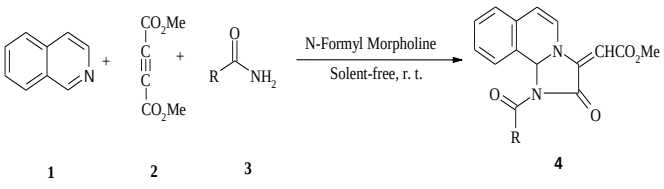
Abstract: Isoquinoline reacts smoothly with dimethyl acetylenedicarboxylate (DMAD) in the presence of amides to produce isoquinoline derivatives. Also, quinoline reacts with DMAD in the presence of benzamide to produce dimethyl quinoline derivatives.

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 N-formylmorpholine at room temperature to produce isoquinoline derivatives 4 in excellent yields (Scheme **1**).



1 **2** **3** **4**

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

Scheme 1: Synthesis of isoquinoline derivatives

Result and Discussion

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

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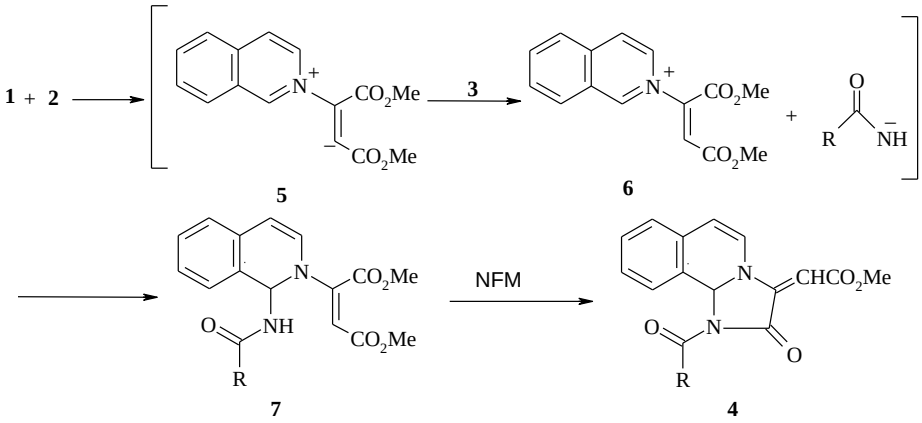
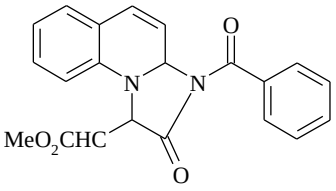
molecular ion (M^+) peak at *m*/*z* = 361, which is consistent with the 1:1:1 adduct of isoquinoline, DMAD and formamide. The ^{1}H NMR spectrum of 4**a** exhibited two singlets for methoxy (δ 3.66 and 3.92 ppm) and olefinic (δ 5.70 ppm) proton, along with multiplets at δ 6.33-7.32 ppm for the isoquinoline 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 [7] **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 **7**. In the presence of NFM intermediate **7** eliminated methoxy group and produce product **4** (Scheme **2**).



Scheme 2: Proposed mechanism for the synthesis of **4**

Under similar conditions, the reaction of quinoline with DMAD in the presence of benzamide led to quinoline derivatives (**5**).



5

The ^{1}H-NMR spectrum of **5** exhibited two methoxy groups (δ = 3.65 and 3.69, 2 *s*), a hydrogen (δ = 6.07, *dd*) for aminal CH, along with multiplets at δ = 6.78-7.62 for the aromatic moiety. The proton-decoupled ^{13}C-NMR spectrum of **7** showed 22 distinct resonances in agreement with the proposed structure.

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

General:

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: *Bruker DRX-500 AVANCE* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ 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 5. To a stirred solution of 0.28 g DMAD (2 mmol) and the amide (2 mmol) in 10 mL NFM 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*, ^3J = 7.7, CH), 6.34 (*t*, ^3J = 7.7, CH), 6.52 (*d*, ^3J = 9.6, NH), 6.93 (*d*, ^3J = 9.8, CH), 7.11 (*d*, ^3J = 7.5, CH), 7.22-7.32 (*m*, 3 CH), 7.97 (*broad s*, 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*, ^3J = 7.7, CH), 6.39 (*d*, ^3J = 7.5, CH), 6.88 (*d*, ^3J = 9.6, NH), 7.17 (*d*, ^3J = 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 $C_{22}H_{20}N_2O_5$ (361.41): 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 **5**:*

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.

References

[1] Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 424.
[2] (a) Johnson, A. W.; Tebby, J. C. *J. Chem. Soc.* **1961**, 2126. (b) Tebby, J. C.; Wilson, I. F.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2133. (c) Butterfield, P. J.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1189.
[3] (a) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1932**, *16*, 498. (b) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125. (c) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.(London)* **1964**, 2676.
[4] (a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952. (b) Winterfeldt, E.; Dillinger, H. J. *Chem. Ber.* **1966**, *99*, 1558.
[5] Winterfeldt, E.; Schumann, D.; Dillinger, H. J. *Chem. Ber.* **1969**, *102*, 1656.
[6] (a) Yavari, I.; Adib, M.*Tetrahedron* **2001**, *57*, 5873. (b) Yavari, I.; Adib, M.; Sayahi, M. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2343. (c) Yavari, I.; Adib, M.; Jahani- Moghaddam, F.; Bijanzadeh, H. R. *Tetrahedron* **2002**, *58*, 6901.(d) Yavari, I.; Sabbaghan, M.; Hossaini, Z. *Synlet.* **2006**, 2501. (e) Yavari, I; Hossaini, Z; Sabbaghan, M. *Tetrahedron Lett* .**2006**, 47, 6037.
[7] Perillo, I.; Repetto, E.; Caterina,M. C.; Massa, R.; Gutkind, G.; Salerno, A. *Eur. J. Med. Chem.*, **2005**, *40*, 811**.**
[8] Diaz, J. L.; Miguel, M.; Lavilla, R., *J. Org. Chem.* **2004**, *69*, 3550**.**