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Green synthesis of isoquinoline derivatives using multicomponent reactions of amides

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Abstract: Isoquinoline that is produced from the reaction of phthalaldehyde and methyl amine reacts smoothly with dialkyl acetylenedicarboxylate in the presence of amides to produce isoquinoline derivatives. The advantages of this procedure than to reported methods are short time of reaction, high yields of product, easy separation of product, clean mixture of reaction and green media for performing reaction.

Keywords: Four-component reactions, Amide, Isoquinoline.

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. The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis [6]. Bridgehead *N*-heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity [7, 8]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [9].

Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [10].
They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions As part of our current studies on the development of new routes in heterocyclic synthesis, in this paper, we report on the synthesis of isoquinolines derivatives in good yields.
In this research isoquinoline was produced insitue from the reaction of phthalaldehyde **1** and methyl amine **2**.

Thus, the reaction of synthesized isoquinoline and activated acetylenic compounds **3** in the presence of amides **4** proceeds smoothly in H_2O at room temperature to produce 2-butenedioate **5** in excellent yields (Scheme **1**).

Results and discussion

As part of our current studies on the development of new routes in heterocyclic systems, in this letter we describe a simple synthesis of functionalized indolizines. The reaction of pyridine **1** and dialkyl

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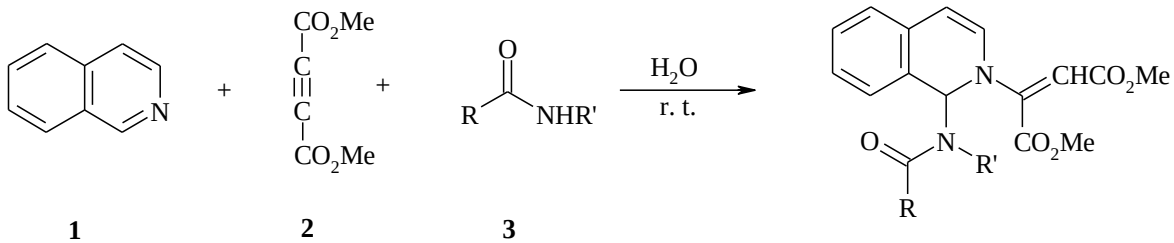
acetylenedicarboxylates **2** in the presence of chloroacetate **3** proceeds smoothly in CH_2Cl_2 at ambient temperature to produce indolizines **4** in 95% yields (Scheme **1**).



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 indolizine **4.**

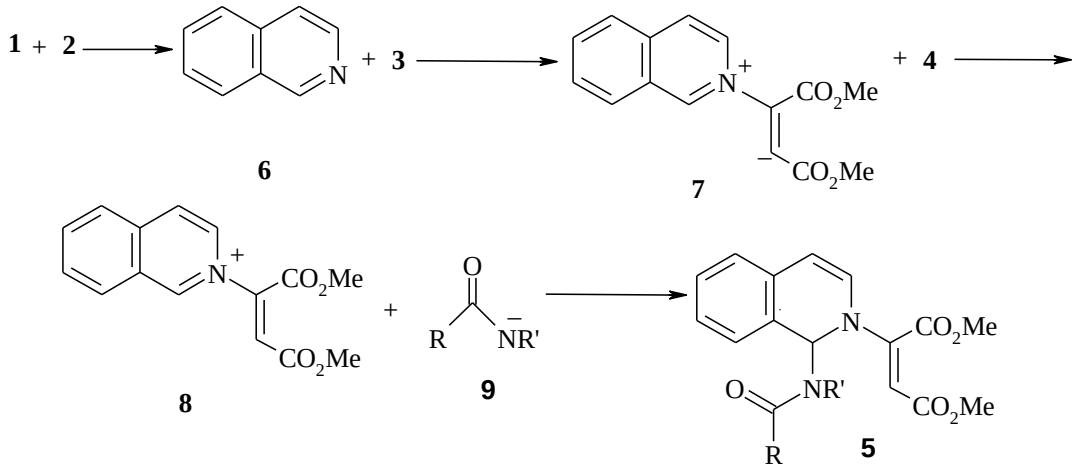
The products were characterized on the basis of their elemental analyses and their IR, ^{1}H-NMR and ^{13}C-NMR spectra. The mass spectrum of 4**a** displayed the molecular ion (M^+) peak at *m*/*z* = 392, which is consistent with the 1:1:1 adduct of isoquinoline, DMAD and formamide.

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 started with insitue preparation of isoquinoline **6** followed by formation of a 1:1 zwitterionic intermediate [11] **6** between isoquinoline and activated acetylenic compounds **3**, which is protonated by **4** to produce **8** and **9**. Intermediate **9** is attacked to **8** to produce **4** (Scheme **2**).

Conclusion

In conclusion, we report a novel transformation involving activated acetylenic compounds and isoquinoline in the presence of amides which affords 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. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.



Scheme 2: Proposed mechanism for the formation of **5.**

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: *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 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 (*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*, ^{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*, ^{3}J = 7.7, CH), 6.48 (*t*, ^{3}J = 7.1, CH), 6.92 (*d*, ^{3}J = 9.6, NH), 7.18 (*d*, ^{3}J = 5.3, CH), 7.21 (*d*, ^{3}J = 2.3, CH), 7.28 (*t*, ^{3}J = 2.3, CH), 7.34 (*t*, ^{3}J = 7.5, CH), 7.40 (*t*, ^{3}J = 7.5, 2 CH), 7.50 (*t*, ^{3}J = 7.8, CH), 7.51 (*t*, ^{3}J = 7.7, CH), 7.72 (*d*, ^{3}J = 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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