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Synthesis of isoquinoline and quinoline derivatives using multicomponent reactions of ammonium acetate

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Abstract: In this research, isoquinoline or quinolinethat reacts smoothly with activated acetylenic compounds in the presence of ammonium acetate to produce isoquinoline or quinoline 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: Three-component reactions, Ammonium acetate, Isoquinoline, Quinoline.

Introduction

Bridgehead *N*-heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity [1, 2]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [3]. 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 [4].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.

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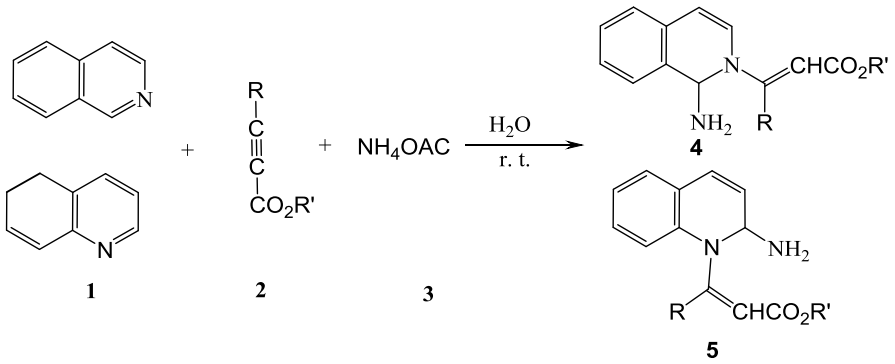
The fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. Usually the addition of nucleophiles devoid of acidic hydrogen atoms leads to a 1:1 zwitterionic intermediate that can undergo further transformations culminating in a stabilized product [5]. It has been known from the studies of various groups that triphenylphosphine [6], pyridine [7], amines [8], and isocyanides [9] 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 [10].

In this research the reaction of isoquinoline or quinoline **1** and activated acetylenic compounds **2** in the presence of ammonium acetate **3** proceeds smoothly in H_2O at room temperature to produce 2-butenedioate **4** and **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 isoquinoline or quinoline. The reaction of isoquinoline

or quinoline **1** and activated acetylenic compounds **2** in the presence of ammonium acetate **3** proceeds smoothly in H_2O at ambient temperature to produce N-heterocycle derivatives **4** and **5** in good yields (Scheme 1).



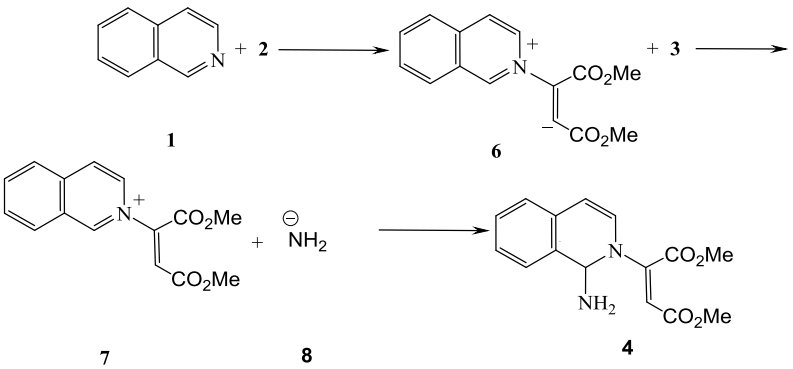
4	R	R'	Yield (%) of **4**	Yield (%) of **5**
a	H	Me	90	85
b	CO_2Me	Me	92	87
c	CO_2Et	Et	95	80
d	H	Et	98	83

Scheme 1: Synthesis of N-heterocyclic compounds **4** and **5**

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 **4a** 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 **4a** 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 **4a** showed sixteen distinct resonances in agreement with the proposed structure.

Mechanistically, it is conceivable that the reaction started by formation of a 1:1 zwitterionic intermediate [11] **6** between isoquinoline and activated acetylenic compounds **2**, which is protonated by **3** to produce **7** and **8**. Intermediate **8** is attacked to **7** to produce **4** (Scheme **2**).



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

Conclusion

In conclusion, we report a novel transformation involving activated acetylenic compounds and isoquinoline in the presence of ammonium acetate 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.

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*, ^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 $C_{22}H_{20}N_2O_5$ (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 5a:

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

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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**.**

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