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

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Abstract: The reaction of phthalaldehyde and ammonium acetate, DMAD, and amides **4** in the presence of Et_3N at room temperature produce pyrimidine derivatives **5** in excellent yields. High atom economy and yield, mild and clean reaction condition, free catalyst, and short reaction time are some advantages of this procedure for synthesis of pyrimidines.

Keywords: Four-component reactions, Amide, Isoquinoline, Acetylenic ester.

Introduction

Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities such as antimalarial [1], antimicrobial [2], antitumor [3], anticancer [4], antidepressant [5], antiviral [6], antidiabetic [7], anti-inflammatory [8] and anti-HIV [9]. Moreover, they also contribute in the feld of material science, [10] dyes and pigment science [11] as well as agrochemistry [12]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [13, 14]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity.

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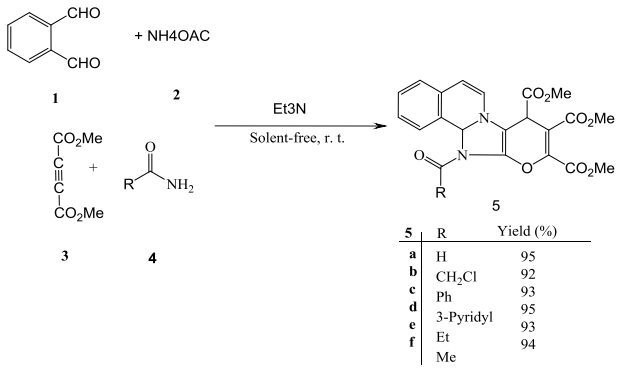
Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [15–17] and could be performed in the presence of nanocatalyst and produce heterocyclic compounds.[18-20]The fascinating chemistry that stems from 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 [15]. It has been known from the studies of various groups that triphenylphosphine [16], pyridine [17], amines [18], and isocyanides [19] can invoke the zwitterions formation. As part of our current studies on the development of new routes in heterocyclic synthesis [20], in this paper, we report on the synthesis of 1,2-disubstituted dihydro-isoquinolines. Thus, the reaction of phthalaldehyde **1** and ammonium acetate **2**, DMAD **3**, amides **4** and DMAD **3** in the presence of Et_3N at room temperature to produce pyrimidine derivatives **5** in excellent yields (Scheme **1**).



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

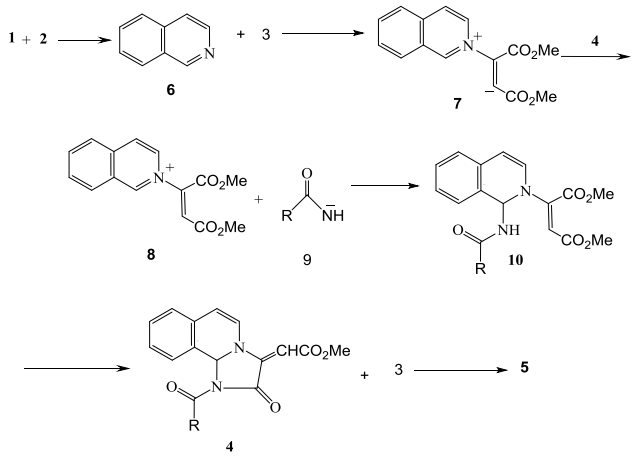
Scheme 1: Synthesis of pyrimidine derivatives.

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 5**a** displayed the 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 5**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 5**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 **6** between phthalaldehyde **1** and ammonium acetate **2** that produced isoquinoline **6** as *in situe*. Intermediate **6** react with DMAD, which is protonated by amide **4** 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**).

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.



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

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.; □ 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* **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.

Trimethyl 12-formyl-12,12a-dihydro-8H-pyrano [2',3':4,5]imidazo[2,1-a]isoquinoline-8,9,10-tricarboxylate (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 = 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.

Trimethyl 12-chloromethyl -12,12a-dihydro-8H-pyrano [2',3':4,5]imidazo[2,1-a]isoquinoline-8,9,10-tricarboxylate (5b):

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.

Trimethyl 12-phenyl -12,12a-dihydro-8H-pyrano [2',3':4,5]imidazo[2,1-a]isoquinoline-8,9,10-tricarboxylate (5c):

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**.**

Trimethyl 12-pyridyl -12,12a-dihydro-8H-pyrano [2',3':4,5]imidazo[2,1-a]isoquinoline-8,9,10-tricarboxylate (5d):

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.

Trimethyl 12-ethyl -12,12a-dihydro-8H-pyrano [2',3':4,5]imidazo[2,1-a]isoquinoline-8,9,10-tricarboxylate (5e):

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.

Trimethyl 12-methyl -12,12a-dihydro-8H-pyrano [2',3':4,5]imidazo[2,1-a]isoquinoline-8,9,10-tricarboxylate (5f):

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.

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