Enaminones as Building Blocks In Heterocyclic Synthesis: A New One Pot Synthesis of Polyfunctional Substituted Pyridines

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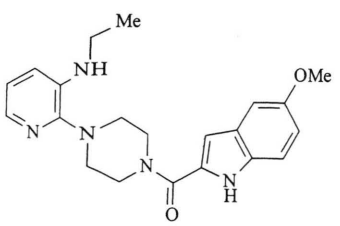
Michael Addition, Acyl- and Aroylpyridines, Dihydropyridines

Enaminones react with a variety of active methyl and methylene reagents in presence of ammonium acetate to yield functionally substituted pyridines in good yields. The reaction proceeded *via* initial Michael addition across the double bond followed by cyclization. The reaction of enaminone with aromatic aldehyde in acetic acid/ammonium acetate afforded the dihydropyridine that was oxidized to the corresponding pyridine.

Certain functionally substituted pyridines are potent inhibitors of the human immunodeficiency virus type **1** (HIV-1) reverse transcriptase. For example atevirdine **1** has been selected for further clinical evaluation as *anti*-HIV agent [1], the dihydropyridines, *e.g.* adalate, are still the most widely used calcium channel blockers [2]. Certain functionally substituted pyridones, *e.g.* amrinone **2a** [3] and milrinone *2b* [4], are used for treatment of congestive heart failure. Compounds **3** have been proved to be selective antagonists of P2 receptors for neurotransmitters [5] (Scheme 1).

In view of our interest in developing efficient syntheses of polyfunctionally substituted heteroaromatics utilizing the readily obtainable enaminones as starting materials [6–11], it is worthwhile to explore their potential utility for the synthesis of polyfunctionally substituted pyridines. In previous studies, we reported syntheses of polyfunctionally substituted pyridines from enaminones using active methylene reagents in sodium ethoxide [9]. It has been observed that the reaction proceeds *via* initial addition across the double bond. In contrast with this behavior, the reaction



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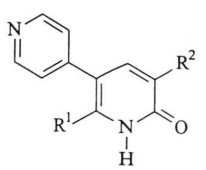
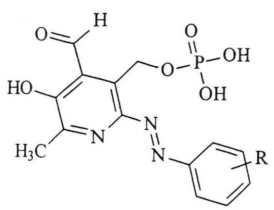
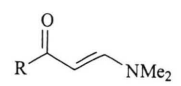


2a, $R^1 = H$, $R^2 = NH_2$
2b, $R^1 = CH_3$, $R^2 = CN$



3, R = 2,4-disulfonic acid



4a, R = phenyl
b, R = 3-coumarinyl
c, R = 2-pyridyl

Scheme 1.

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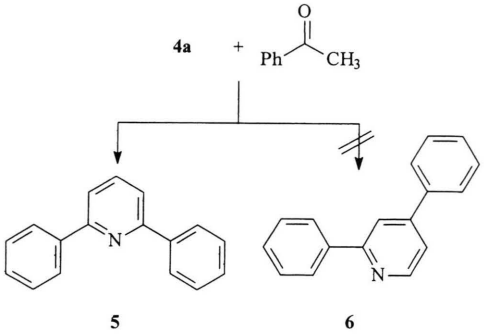
of enaminones with malononitrile and with ethyl cyanoacetate in ethanolic piperidine occurred *via* initial attack of the active methylene moiety at the enone carbonyl function [10–11]. It occurred to us thus of value to investigate further the reactivity of enones toward active methylene compounds.

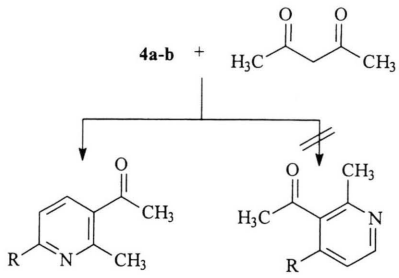
The reaction of **4a** with acetophenone in refluxing acetic acid in the presence of ammonium acetate yields a product that may be formulated as **5** or isomeric **6**. While initial Michael addition of the methyl ketone across the activated double bond in **4a** and subsequent cyclization could lead to structure **5**, initial condensation of the methyl function with the carbonyl function of the enaminone and subsequent cyclization might afford compound **6**. In previous work [9–11], it could be shown that both reaction modes are occurring, and reaction conditions significantly affect the nature of the final products. Structure **5** is established as the sole reaction product based on ^{1}H NMR spectra which revealed a doublet for four protons at δ = 8.23 ppm that are assumed to be the four 2-H and 6-H phenyl protons deshielded under the influence of the anisotropy effect of the pyridine ring nitrogen. For isomeric product **6**, a multiplet for three protons in the same region should be observed. Compound **5** has been reported [12] earlier to result from pyrolysis of acetophenone *N,N,N*-trimethylhydrazonium fluoroborate (lit. m.p. 83 °C; 55% yield) (Scheme 2).



5 **6**

Scheme 2.

Similar to the behaviour of **4a** toward acetophenone, compounds **4a–b** also reacted with acetylacetone to yield **7a–b** as the sole isolable products. The possible isomeric structure **8** was excluded based on the observation of the low field doublet for two protons at δ = 8.16 ppm assigned to the deshielded phenyl protons 2-H and 6-H in **7a**. In structure **7b**, the ^{1}H NMR spectra revealed a low field singlet at δ = 8.87 ppm assigned to coumarin 4-H, two doublets at δ = 7.66 and 7.93 ppm assigned to pyridyl 5-H and 4-H and two multiplet signals for two protons at δ = 7.37–7.44 and 8.21–8.30 ppm assigned to coumarin 6-H, 7-H and 5-H, 8-H respectively. The appearance of coumarin 5-H and 8-H at such a low field is a consequence of van der Waals deshielding (Scheme 3).



7a, R = phenyl
b, R = 3-coumarinyl

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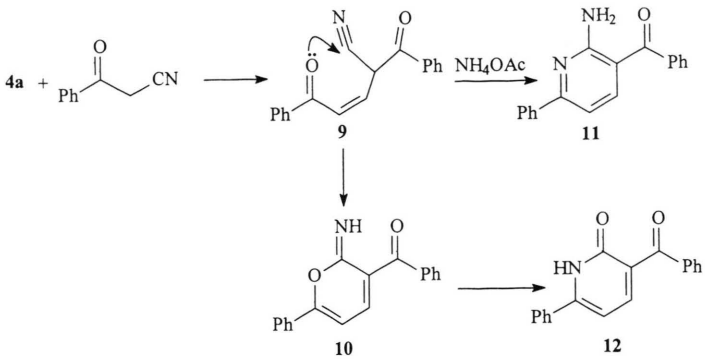
Scheme 3.

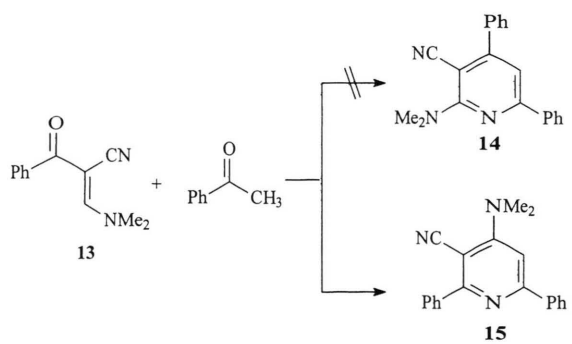
Compound **4a** reacted with benzoylacetonitrile to yield a mixture of two products, which could be successfully separated *via* column chromatography into a colorless product of molecular formula $C_{18}H_{14}N_2O$ and a yellow product of molecular formula $C_{18}H_{13}NO_2$. Several structures seemed for us thus possible, depending on the reaction route. The colorless product was assigned structure **11** and is assumed to be formed *via* initial addition of the active methylene moiety in benzoylacetonitrile to the enaminone C-3 and subsequent elimination of the dimethylamine yielding the acyclic Michael adduct **9**. This may cyclize into the pyrane imine **10** or react with ammonia to yield the compound **11.** Several isomeric structures seemed possible for the yellow product, namely, the pyridone structure resulting from initial condensation of the active methylene moiety with the enaminone carbonyl function followed by hydrolysis and subsequent cyclization, or an isomeric pyridone structure resulting from initial condensation of the benzoylacetonitrile carbonyl function with the enaminone C-2 and subsequent cyclization. Both structures were ruled out based on the absence of a low field (δ > 8.5 ppm) pyridine 2-H signal. Consequently, structure **10** or isomeric **12** were considered. Structure **12** was assigned to the yellow reaction pro-



Scheme 4.

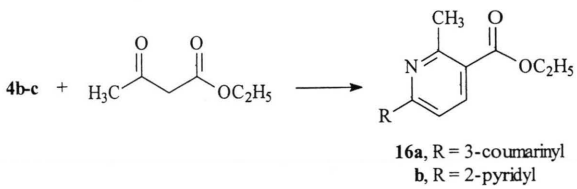
duct based on its stability on reflux in acetic acid or mineral acid, a condition that could lead to hydrolysis of imine function of **10** or at least its rearrangement into **12**. In addition, **12** proved to be identical with an authentic specimen prepared after the procedure reported [13] recently for its synthesis as sole product from **4a** and benzoylacetonitrile in refluxing toluene (lit. m.p. 228 °C) (Scheme 4).

In an attempt to prepare samples of **10** and **11** by an alternative route, benzoylacetonitrile was initially condensed with dimethylformamide dimethylacetal following a recently reported procedure [14], and the formed enaminonitrile **13** was then reacted with acetophenone. However, unexpectedly a product of molecular formula $C_{20}H_{17}N_3$ was the sole isolable reaction product. This product was assigned structure **15** rather than isomeric **14** based on NOE difference NMR experiments where irradiation of pyridine 3-H at δ = 7.37 ppm enhanced the dimethylamino signal (Scheme 5).



Scheme 5.

Trials to react **4a** with ethyl acetoacetate failed to produce an isolable reaction product. However, when **4b, c** were treated with ethyl acetoacetate, a product of addition across the double bond and subsequent cyclization was formed, to which structure **16a, b** was assigned (Scheme 6).



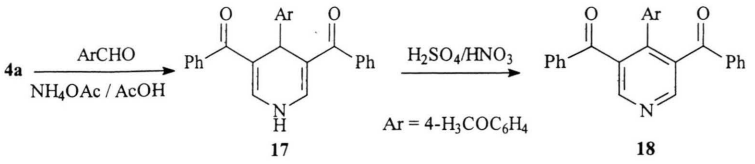
16a, R = 3-coumarinyl
b, R = 2-pyridyl

Scheme 6.

The reaction of aldehydes with 3-oxopropanals in the presence of ammonia has been reported to yield 3,5-dibenzoyl-1,4-dihydropyridines [15]. However to our knowledge, usefulness of the readily obtainable enaminones **4** as start for syntheses of pyridines in a similar reaction has never been investigated. We have found that **4a** reacts with p-methoxybenzaldehyde in refluxing acetic acid and in the presence of ammonium acetate, to yield the dihydropyridine **17** that was oxidized with nitric acid / sulfuric acid to afford **18** (Scheme 7).

Experimental

All melting points are uncorrected. IR spectra were recorded in KBr with a Pye Unicam SP 1100 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer in [$^2H_6$] DMSO as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on MS 30 and MS 9 (AEI),



Scheme 7.

70 eV. Microanalyses were performed on LECO CHNS-932. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

General procedure for the preparation of the pyridine derivatives

To a stirred suspension of the enaminone (10 mmol) and ammonium acetate (1 g) in acetic acid (10 ml), the active methyl or methylene derivatives (10 mmol) were added. The reaction mixture was heated under reflux for 20–60 min. The solvent was evaporated in vacuum, the residual syrup was triturated with alcohol to deposit a solid, which was crystallized from the proper solvent. In some cases, the products were purified by flash chromatography on silica gel using chloroform/*n*-hexane (3:1) as eluent.

2,6-Diphenylpyridine (**5**)

M.p. 85° C (EtOH); yield 1.70 g (74%). – ^{1}H NMR (d_6-DMSO): δ = 7.45–7.55 (m, 6H, arom. H), 7.90–7.93 (m, 3H, arom. H), 8.23 (d, 4H, J = 8 Hz, *ortho*-phenyl H). – MS: m/z = 231 [M$^+$]. – $C_{17}H_{13}N$ (231.28): calcd. C 88.28, H 5.67, N 6.06; found C 88.34, H 5.80, N 6.02.

3-Acetyl-2-methyl-6-phenylpyridine (**7a**)

M.p. 82° C (EtOH); yield 1.54 g (73%). – IR ν = 1690 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 2.59 (s, 3H, CH_3), 2.70 (s, 3H, $COCH_3$), 7.48–7.52 (m, 3H, phenyl H), 7.94 (d, 1H, J = 8 Hz, pyridyl 5-H), 8.16 (d, 2H, J = 8 Hz, *ortho*-phenyl H), 8.30 (d, 1H, J = 8 Hz, pyridyl 4-H). – MS: m/z = 211 [M$^+$]. – $C_{14}H_{13}NO$ (211.25): calcd. C 79.59, H 6.20, N 6.63; found C 79.40, H 6.36, N 6.45.

3-Acetyl-2-methyl-6-(3-coumarinyl)pyridine (**7b**)

M.p. 207° C (EtOH/dioxane 3:1); yield 2.03 g (73%). – IR ν = 1727, 1681 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 2.50 (s, 3H, CH_3), 2.73 (s, 3H, $COCH_3$), 7.37–7.44 (m, 2H, comarin 6-H, 7-H), 7.66 (d, 1H, J = 8 Hz, pyridyl 5-H), 7.93 (d, 1H, J = 8 Hz, pyridyl 4-H), 8.21–8.30 (m, 2H, coumarinyl 5-H, 8-H), 8.87 (s, 1H, coumarin 4-H). – MS: m/z = 279 [M$^+$]. – $C_{17}H_{13}NO_3$ (279.28): calcd. C 73.11, H 4.69, N 5.02; found C 73.31, H 4.71, N 4.72.

2-Amino-3-benzoyl-6-phenylpyridine (**11**)

M.p. 218° C (chloroform/*n*-hexane (3:1) as eluent); yield 1.12 g (41%). – IR: ν = 3386, 3166 (NH_2), 1645 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 7.46–7.57 (m, 7H, arom. H, NH_2), 7.80–8.00 (m, 4H, arom. H, pyridyl 5-H), 8.18 (d, 2H, J = 8 Hz, *ortho*-phenyl H). 8.32 (d, 1H, J = 8 Hz, pyridyl 4-H). – MS: m/z = 274 [M$^+$]. – $C_{18}H_{14}N_2O$ (274.31): calcd. C 78.81, H 5.14, N 10.21; found C 78.89, H 5.32, N 10.00.

3-Benzoyl-1,2-dihydro-6-phenylpyridin-2-one (**12**)

M.p. 230 °C (chloroform/*n*-hexane (3:1) as eluent); yield 1.0 g (37%). – IR: ν = 3249 (NH), 1647 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 6.78 (br s, 1H, NH), 7.49–7.54 (m, 5H, arom. H), 7.62–7.65 (m, 1H, pyridyl 5-H), 7.78–7.83 (m, 5H, arom. H), 8.12 (d, 1H, J = 8 Hz, pyridyl 4-H). – MS: m/z = 275 [M$^+$]. – $C_{18}H_{13}NO_2$ (275.29): calcd. C 78.53, H 4.76, N 5.09; found C 78.57, H 4.80, N 5.19.

4-(Dimethylamino)-2,6-diphenylpyridine-3-carbonitrile (**15**)

M.p. 135° C (AcOH); yield 2.39 g (80%). – IR: ν = 2220 cm^{-1} (CN). – ^{1}H NMR (d_6-DMSO): δ = 3.26 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 7.37 (s, 1H, pyridyl 3-H), 7.51–7.61 (m, 6H, arom. H), 8.24 (d, J = 8 Hz, 4H, *ortho*-phenyl H). – MS: m/z = 299 [M$^+$]. – $C_{20}H_{17}N_3$ (299.27): calcd. C 80.24, H 5.72, N 14.04; found C 80.38, H 5.03, N 14.18.

Ethyl 2-methyl-6-(3-coumarinyl)pyridine-3-carboxylate (**16a**)

M.p. 165° C (EtOH/dioxane); yield 2.10 g (86%). – IR: ν = 1715, 1677 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 1.33 (t, 3H, J = 8 Hz, CH_3), 2.80 (s, 3H, CH_3), 4.32 (q, 2H, J = 8 Hz, OCH_2), 7.38–7.50 (m, 2H, comarin 6-H, 7-H), 7.69 (d, 1H, J = 8 Hz, pyridyl 5-H), 7.94 (d, 1H, J = 8 Hz, pyridyl 4-H), 8.15–8.24 (m, 2H, coumarin 5-H, 8-H),

9.11 (s, 1H, coumarin 4-H). – MS: *m/z* = 309 [M$^+$]. – $C_{18}H_{15}NO_4$ (309.31): calcd. C 69.89, H 4.89, N 4.53; found C 69.91, H 4.82, N 4.34.

Ethyl 2-methyl-6-(2-pyridyl)pyridine-3-carboxylate (**16b**)

M.p. 80° C (EtOH); yield 2.10 g (86%). – IR: ν = 1718 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 1.41 (t, 3H, *J* = 8 Hz, CH_3), 2.91 (s, 3H, CH_3), 4.38 (q, 2H, *J* = 8 Hz, OCH_2), 7.30–7.33 (m, 1H, pyridyl 5′-H), 7.49 (m, 1H, pyridyl 4′-H), 8.27–8.32 (m, 2H, pyridyl 3′-H, 5-H), 8.48 (d, 1H, *J* = 8 Hz, 4-H), 8.67 (d, 1H, *J* = 8 Hz, pyridyl 6′-H). – MS: *m/z* = 242 [M$^+$]. – $C_{14}H_{14}N_2O_2$ (242.27): calcd. C 69.40, H 5.83, N 11.56; found C 69.29, H 5.76, N 11.61.

3,5-Dibenzoyl-4-(4-methoxyphenyl)-1,4-dihydropyridine (**17**)

To a stirred suspension of compound **2a** (1.75 g, 10 mmol) and ammonium acetate (1 g), acetic acid (10 ml), anisaldehyde (1.36 g, 10 mmol) was added. The reaction mixture was heated under reflux for 5h, then allowed to cool to room temperature. The solid product so obtained was filtered off, and crystallized from ethanol.

M.p. 210° C (EtOH); yield 2.96 g (75%). – IR: ν = 3423 (NH), 1658 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 3.68 (s, 3H, OCH_3), 5.34 (s, 1H, 4-H), 6.82 (d, 2H, *J* = 8 Hz, arom. H), 7.09 (s, 2H, 2-H, 6-H), 7.24 (d, 2H, *J* = 8 Hz, arom. H), 7.43–7.51 (m, 10H, arom. H), 9.23 (s, 1H, NH). – MS: *m/z* = 395 [M$^+$]. – $C_{26}H_{21}NO_3$ (395.44): calcd. C 78.96, H 5.35, N 3.54; found C 78.73, H 5.31, N 3.57.

3,5-Dibenzoyl-4-(4-methoxyphenyl)pyridine (**18**)

Compound **15** (3.95 g, 10 mmol) was heated under reflux for 1 h, in a mixture of water (10 ml) conc. HNO_3 (d = 1.42, 3 ml) and conc. H_2SO_4 (2.5 ml) following the procedure described for oxidation of diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate [16] The reaction mixture was allowed to assume room temperature. The solid product, so obtained was filtered off and crystallized from ethanol.

M.p. 92° C (EtOH); yield 3.37 g (86%). – IR: ν = 1664 cm^{-1} (C=O). – ^{1}H NMR (d_6-DMSO): δ = 3.52 (s, 3H, OCH_3), 6.60–6.62 (m, 2H, arom. H), 6.93–6.95 (m, 2H, arom. H), 7.38–7.41 (m, 4H, arom. H), 7.53–7.57 (m, 2H, arom. H), 7.65–7.67 (m, 4H, arom. H), 8.83 (s, 2H, 2-H, 6-H). – MS: *m/z* = 393 [M$^+$]. – $C_{26}H_{19}NO_3$ (395.46): calcd. C 79.37, H 4.87, N 3.56; found C 79.45, H 4.86, N 3.56.

[1] R. Troschütz, A. Karger, J. Heterocycl. Chem. **34**, 1147 (1997)
[2] R. M. Robertson, D. Robertson, The pharmacological basis of therapeutics, Goodman and Gillman's, p. 759, 9th ed. A. G. Gilman, consulting ed., McGraw-Hill Health Professions Divisions, New York (1996).
[3] A. E. Farah, A. A. Alousi, Life Sci. **22**, 1139 (1978).
[4] A. A. Alousi, J. M. Canter, M. J. Montenaro, D. J. Fort, R. A. J. Ferrari, Cardiovasc. Pharmacol. **5**, 792 (1983).
[5] J. Lambrecht, U. Ardanuy, H. G. Baumert, X. Bo, C. H. V. Hoyle, P. Nickel, O. Pfaff, V. Ralevic, U. Windschief, A. U. Ziganshin, R. Ziyal, E. Mutschler, G. Burnstock, in D. Giardina, S. Piergentili, M. Pigini (Eds): Perspectives in Receptor Research, p. 33, Elsevier, Amsterdam (1996).
[6] K. M. Al-Zaydi, E. A. Hafez, M. H. Elnagdi, J. Chem. Res. (S) 154 (2000); (M) 510 (2000).
[7] B. Al-Saleh, N. Al-Awadi, H. Al-Kandari, M. M. Abdel-Khalik, M. H. Elnagdi, J. Chem. Res. (S) 16 (2000); (M) 201 (2000).
[8] A. Al-Enezi, B. Al-Saleh, M. H. Elnagdi, J. Chem. Res. (S) 4 (1997); (M) 116 (1997).
[9] F. Al-Omran, N. Al-Awadi, A. A. El-Khair, M. H. Elnagdi, Org. Prep. Proc. Int. **29**, 285 (1997).
[10] S. M. Al-Mousawi, K. S. George, M. H. Elnagdi, Pharmazie **8**, 571 (1999).
[11] F. Al-Omran, N. Al-Awadi, M. M. Abdel-Khalik, K. Kaul, A. A. El-Khair, M. H. Elnagdi, J. Chem. Res. (S) 84 (1997); (M) 601 (1997).
[12] G. R. Newkome, D. L. Fishel, J. Org. Chem. **37**, 1329 (1972).
[13] F. Bondavalli, O. Bruno, E. Lo Presti, G. Menozzi, L. Mosti, Synthesis 1169 (1999).
[14] B. Al-Saleh, M. M. Abdel-Khalik, A. Al-Enzy, M. H. Elnagdi, J. Chem. Res. (S) 654 (1999); (M) 2848 (1999).
[15] F. Michael, H. Dralle, Liebigs Ann. Chem. **57**, 670 (1963).
[16] B. S. Furniss, A. J. Harmaford, P. W. G. Smith, A. R. Tatchell, Vogel's Text Book of Practical Organic Chemistry, 5th ed., p. 1168, Longman Scientific & Technical Harlow, Essex (1989).