Enaminones as Building Blocks in Heterocyclic Synthesis: New Syntheses of Nicotinic Acid and Thienopyridine Derivatives

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Received December 15, 2003

Reacting 1,3-diphenyl-propan-2-one with equimolecular amount of dimethylformamide dimethylacetal afforded the enaminone **4**. This when reacted with another equimolecular amount of dimethylformamide dimethylacetal afforded the dienaminone **5**. Compound **4** condenses with cyanothioacetamide and with cyanoacetamide to yield 2-thioxo- and 2-oxo-pyridine-3-carbonitrile derivatives **6a,b** respectively. Compound **6a** reacted with α-chloroacetone **8** to yield the thieno[2,3-*b*]pyridine derivative **10** that cyclized further into 4,7,8-trisubstituted pyrido[2',3':2,3] thieno[4,5-d]pyrimidine **12**. Compound **4** also afforded 2,5,6-trisubstituted nicotinic acid ethyl ester **13** by reaction with ethyl acetoacetate in acetic acid in the presence of ammonium acetate. The dienaminone **5** reacted with acetic acid, ammonium acetate/acetic acid, phenylhydrazine and 5-amino-3-methylpyrazole yielding 3,5-diphenyl-pyran-4-one **15a**, 3,5-diphenyl-1*H*-pyridin-4-one **15b** and 1,3,5-trisubstituted pyridin-4-ones **16a-b**.

J. Heterocyclic Chem., **41**, 431 (2004).

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 evolution 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] (Figure 1).

In conjunction to previous interest in developing syntheses of polyfuctionally substituted heteroaromatics utilizing readily obtainable and inexpensive starting materials [6-8], we report here on syntheses of 7-benzyl-4-methyl-8-phenyl-pyrido[2',3':2,3]thieno[4,5-*d*]pyrimidine **12**, 4-unsubstituted 2,5,6-trisubstituted nicotinic acid ethyl ester **13**, 3,5-diphenyl-pyran-4-one **15a**, 3,5-diphenyl-1*H*-pyridin-4-one **15b** and of 1,3,5-trisubstituted pyridin-4-ones **16(I)a,b** using compounds **4** and **5** as key intermediates.

Enaminone **4** was readily obtained from the reaction of an equimolecular amount of 1,3-diphenyl-propan-2-one with dimethylformamide dimethylacetal for four hours at 120 °C in absence of solvent (Figure 1). This product **4** reacted with another equimolecular molecule of dimethylformamide dimethylacetal (DMFDMA) for ten hours to yield the dienaminone **5**. Compound **5** has been prepared earlier [9] *via* reacting dibenzylketone with excess of DMFDMA at 110° C. In our hands a higher yield was obtained on refluxing **4** with an equivalent amount of DMFDMA in toluene solution for 10 hours.

Compound **4** condensed with cyanothioacetamide *via* dimethylamine elimination to yield the thioxo-pyridine-carbonitrile derivative that may be formulated as **6a** or isomeric **7a**. The cyclization reaction may proceed by two possible mechanisms, which differ in their sequential nucleophilic attack/amine exchange reaction. The ^{1}H NMR spectra for the reaction product showed the pyridine ring CH as singlet at δ = 7.76 ppm. This may suggest a favorable reaction product **6a** formed *via* initial addition of the active methylene moiety in cyanothioacetamide across the activated double bond in **4** and subsequent cyclization

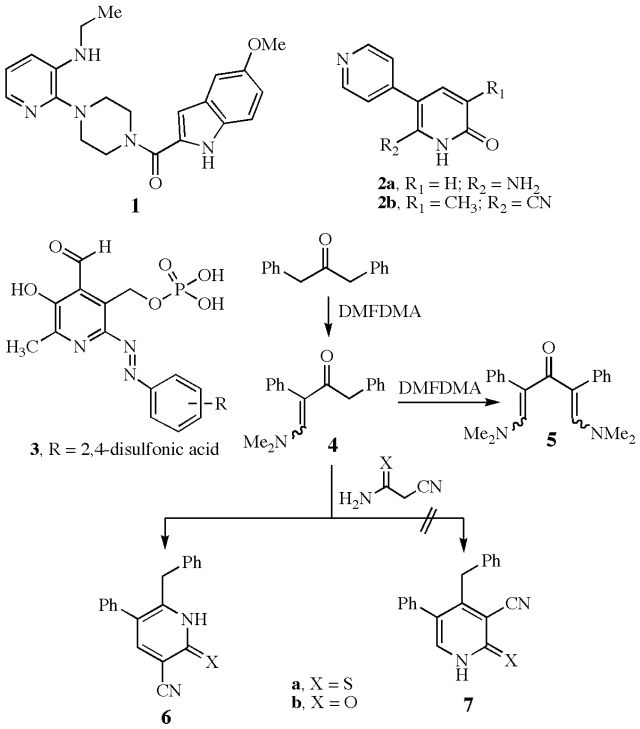

Figure 1

and aromatization *via* dimethylamine elimination (Figure 1). The alternative structure **7** which could have resulted *via* initial condensation of the active methylene with the carbonyl function, should display a doublet for the pyridine ring CH.

Similarly reaction of **4** with cyanoacetamide afforded the 5,6-disubstituted 2-oxo-pyridine-3-carbonitrile **6b** in good yield.

Reacting **6a** with α-chloroacetone **8** afforded the 3-amino-thieno[2,3-*b*]pyridine derivative **10** most likely *via* intermediacy of **9**. This when condensed with DMFDMA afforded the *N*,*N*-dimethyl-formamidine derivative **11**, which is subsequently reacted with acetic acid in the presence of ammonium acetate to yield 4,7,8-trisubstituted pyrido[2',3':2,3]thieno-[4,5-*d*]pyrimidine derivative **12** (Figure 2).

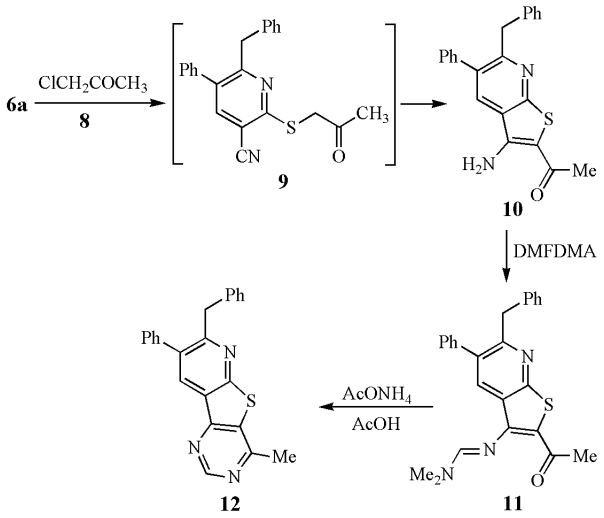

Figure 2

Compound **4** reacted with ethyl acetoacetate in acetic acid in the presence of ammonium acetate affording 2,5,6-trisubstituted nicotinic acid ethyl ester that was confirmed to be **13** rather than **14** as the NOE difference experiments indicated proximity of the carboethoxy methyl protons and nicotine ring CH.

Compound **5** cyclized directly to the pyran-4-one **15** on boiling in acetic acid. This pyranone has been obtained earlier [10] *via* reaction of dibenzyl ketone **4** with ethyl formate in sodium ethoxide and subsequent cyclization of the formed formylated product (lit mp 186 °C). A mixture of products **15a,b** was obtained when the reaction of **5** was conducted in acetic acid in the presence of ammonium acetate. Product **15b** has been found to be identical with an authentic specimen [10] as obtained from the reaction of pyranone **15a** in acetic acid in the presence of ammonium acetate (lit mp. 376 °C), or *via* reaction of 1,5-dihydroxy-2,4-diphenyl-penta-1,4-dien-3-one di-sodium salt with ammonium ion in aqueous solution [11] in 40-50% yield (lit mp. 396 °C) (Figure 3).

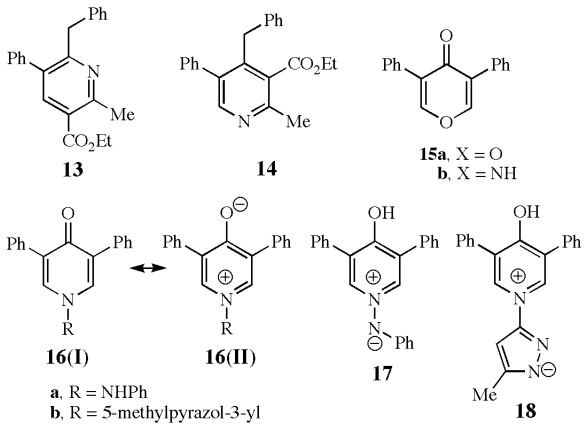

Figure 3

Compound **5** was similarly treated with phenylhydrazine and 3-amino-5-methyl-pyrazole to furnish the reasonance stabilized product **16(I)a,b** and **16(II)a,b** or their potential tautomers *e.g* **17** and **18**, which are difficult to establish with certainty. Possible initial condensation of the hydrazine and/or amine with the carbonyl group in an intermediately formed pyranone was excluded based on the stability of the reaction product at reflux in acetic acid in the presence of ammonium acetate, a condition that would lead to conversion of this pyranhydrazone into pyridine. It is thus believed that initially hydrazine and/or aminopyrazole add to the enaminone double bond and this addition reaction is then followed by dimethylamine elimination and subsequent cyclization (Figure 3).

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

4-Dimethylamino-1,3-diphenyl-but-3-en-2-one (**4**).

A mixture of 1,3-diphenyl-propan-2-one (2.10 g, 10 mmol) and dimethyl-formamide dimethylacetal (1.19 g, 10 mmol) was heated under reflux for 6 hrs. The solvent was reduced *in vacuo* and the oil obtained was purified by flash chromatography on silica gel using chloroform/*n*-hexane (3:1) as eluent.

This compound was obtained in yield 2.0 g (76%); ir (KBr): ν max/cm^{-1}: 1640 CO); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 3.02 (s, 3H, NMe), 3.08 (s, 3H, NMe), 4.18 (s, 2H, CH_2), 6.95-

7.00 (m, 2H, arom. H), 7.10-7.18 (m, 5H, arom. H), 7.40-7.43 (m, 3H, arom. H), 8.20 (s, 1H, H-4).

1,5-Bis(dimethylamino)-2,4-diphenylpenta-1,4-dien-3-one (**5**).

A mixture of compound **4** (2.65 g, 10 mmol) and dimethylformamide dimethylacetal (1.19 g, 10 mmol) was heated under reflux for 12 hrs in toluene solution (10 ml). The solvent was reduced *in vacuo* and left to cool at room temperature to deposit a solid after 3 days. The solid product so obtained was crystallized from dilute ethanol. This compound was obtained in yield 2.36 g (74%). mp 136-138 °C (EtOH); ir (KBr): ν max/cm^{-1}: 1645 (CO); MS: *m/z* = 320 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 3.00 (s, 6H, 2NMe), 3.12 (s, 6H, 2NMe), 7.01-7.12 (m, 2H, arom. H), 7.22-7.28 (m, 5H, arom. H), 7.42-7.49 (m, 3H, arom. H), 8.24 (s, 2H, vinyl H).

Anal. Calcd. for $C_{21}H_{24}N_2O$ (320.42): C, 78.71; H, 7.55; N, 8.74%. Found: C, 78.70; H, 7.50; N, 8.62.

Preparation of Compounds (**6a,b**).

General Procedure.

Each of cyanothioacetamide or cyanoacetamide (10 mmol) was added to a stirred suspension of the enaminone **4** (2.56 g, 10 mmol) in ethanol (20 ml) in the presence of a few drops of triethyl amine. The reaction mixture was heated under reflux for 2 hrs. The solvent was reduced *in vacuo*, then the mixture was pour onto water and neutralized with dil. HCl to deposit a solid, which was crystallized from the proper solvent.

6-Benzyl-5-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**6a**).

This compound was obtained in yield 2.6 g (86%); mp 190-191 °C (dioxan); ir (KBr): ν max/cm^{-1}: 2835 (NH), 2227 (CN); MS: *m/z* = 302 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 4.15 (s, 2H, CH_2), 6.99-7.01 (m, 2H, arom. H), 7.22-7.28 (m, 4H, arom. H), 7.46-7.47 (m, 4H, arom. H), 7.76 (s, 1H, pyridyl H-4), 12.65 (br s, 1H, NH).

Anal. Calcd. for $C_{19}H_{14}N_2S$ (302.32): C, 75.48; H, 4.67; N, 9.27; S, 10.58 %. Found: C, 75.22; H, 4.78; N, 9.33, S, 10.71.

6-Benzyl-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**6b**).

This compound was obtained in yield 2.4 g (84%); mp 235-237 °C (EtOH); IR ν = 2830 (NH), 2226 (CN), 1658 (CO); MS: *m/z* = 285 [M$^+$-1]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 4.02 (s, 2H, CH_2), 7.09-7.11 (m, 2H, arom. H), 7.28-7.33 (m, 4H, arom. H), 7.45-7.50 (m, 4H, arom. H), 7.87 (s, 1H, pyridyl H-4), 12.96 (br s, 1H, NH).

Anal. Calcd. for $C_{19}H_{14}N_2O$ (286.32): C, 79.70; H, 4.93; N, 9.78%. Found: C, 79.72; H, 4.90; N, 9.71.

1(3-Amino-6-benzyl-5-phenyl)thieno[2,3-*b*]pyridin-2yl)-ethanone (**10**).

To a stirred suspension of compound **6a** (3.02 g, 10 mmol) and chloroacetone (1 g, 11 mmol) in DMF (20 ml), potassium hydroxide (0.06 g) is added. The reaction mixture was heated under reflux for 2 hrs. The solvent was reduced *in vacuo*, then the mixture was pour onto water and neutralized with dil. HCl to deposit a solid, which was crystallized from ethanol. This compound was obtained in yield 2.85 g (80%); mp 176-178 °C; ir (KBr): ν max/cm^{-1}: 3284 and 3179 (NH_2), 1620 (CO); MS: *m/z* = 357 [M$^+$-1]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 2.51 (s, 3H, $COCH_3$), 4.27 (s, 2H, CH_2), 6.81-6.98 (m, 2H, arom. H), 7.16-7.23 (m, 5H, arom. H), 7.28-7.32 (m, 2H, NH_2, D_2O exchangeable) 7.42-7.43 (m, 3H, arom. H), 7.78 (s, 1H, H-4).

Anal. Calcd. for $C_{22}H_{18}N_2OS$ (358.38): C, 73.73; H, 5.06; N, 7.82; S, 8.92 %. Found: C, 73.59; H, 5.06; N, 7.75, S, 8.75.

N-(2-Acetyl-6-benzyl-5-phenyl)thieno[2,3-*b*]pyridine-3-yl-*N*,*N*-dimethylformamidine (**11**).

A mixture of compound **10** (3.58 g, 10 mmol) and dimethylformamide dimethylacetal (1.19 g, 10 mmol) was heated under reflux in dioxane (20 ml) for 4 hrs. The solvent was reduced *in vacuo* and left to cool at room temperature to deposit a solid that was crystallized from dioxane. This compound was obtained yield 3.4 g (82%); mp 188-190 °C; ir (KBr): ν max/cm^{-1}: 1628 (CO); MS: *m/z* = 413 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 2.58 (s, 3H, $COCH_3$), 3.08 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 4.24 (s, 2H, CH_2), 6.95-6.97 (m, 2H, arom. H), 7.12-7.21 (m, 5H, arom. H), 7.39-7.41 (m, 3H, arom. H), 7.62 (s, 1H, H-4), 7.80 (s, 1H, amidine H).

Anal. Calcd. for $C_{25}H_{23}N_3OS$ (413.46): C, 72.62; H, 5.61; N, 10.16; S, 7.74 %. Found: C, 72.57; H, 5.67; N, 10.15, S, 7.54.

7-Benzyl-4-methyl-8-phenylpyrido[2',3':2,3]thieno[4,5-*d*]pyrimidine (**12**).

Compound **11** (4.13 g, 10 mmol) was heated under reflux in a mixture of ammonium acetate (1 g) acetic acetic acid (10 ml) for 1 hr. The reaction mixture was left to cool at room temperature to deposit a solid that was crystallized from dioxane.

This compound was obtained in yield 3.3 g (90%); mp 103-105 °C; MS: *m/z* = 367 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 2.60 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 6.96-7.00 (m, 2H, arom. H), 7.10-7.23 (m, 5H, arom. H), 7.39-7.42 (m, 3H, arom. H), 7.64 (s, 1H, H-9), 9.26 (s, 1H, H-2).

Anal. Calcd. for $C_{23}H_{17}N_3S$ (367.39): C, 75.19; H, 4.66; N, 11.44; S, 8.71 %. Found: C, 75.10; H, 4.71; N, 11.43, S, 8.65.

6-Benzyl-2-methyl-5-phenylnicotinic Acid Ethyl Ester (**13**).

To a solution of compound **4** (2.65 g, 10 mmol) and ethyl acetoacetate (1.30 g, 10 mmol), ammonium acetate (1 g) in acetic acid (10 ml) was added. The reaction mixture was heated under reflux for 3 hr. The solvent was evaporated *in vacuo*, and the residual solid was crystallized from dioxane. This compound was obtained in yield 2.45 g (74%); mp 66-67 °C (EtOH); ir (KBr): ν max/cm^{-1}: 1724 (CO); MS: *m/z* = 331 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ (ppm) = 1.39 (t, 3H, J = 8 Hz, OCH_2CH_3), 2.91 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 4.38 (q, 2H, J = 8 Hz, OCH_2), 7.00-7.02 (m, 2H, arom. H), 7.14-7.22 (m, 5H, arom. H), 7.40-7.45 (m, 3H, arom. H), 8.07 (s, 1H, H-4).

Anal. Calcd. for $C_{22}H_{21}NO_2$ (331.40): C, 79.73; H, 6.39; N, 4.23 %. Found: C, 79.66; H, 6.32; N, 4.10.

Preparation of Compounds (**15a,b**).

General Procedure.

Compound **5** (3.20 g, 10 mmol) was treated with acetic acid (5ml) in the presence of ammonium acetate (1 g). The reaction mixture was heated under reflux for 1 hr and left to cool at room temperature then triturated with ethanol to deposit a mixture of compound **15a,b** that was separated by flash chromatography on silica gel using chloroform/*n*-hexane (3:1) as eluent (19% for compound **15a** and 60% for compound **15b**).

3,5-Diphenyl-pyran-4-one (**15a**).

Compound **5** (3.2 0g, 10 mmol) was treated with acetic acid (5 ml) The reaction mixture was heated under reflux for 1 hr and left to cool at room temperature to deposit a solid that was collected by filtration and crystallized from ethanol (lit. mp 187 C). This compound was obtained in yield 1.70 g (69%); mp 180-181 °C; ir (KBr): ν max/cm^{-1}: 1645 (CO) MS: *m/z* = 248 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 7.30-7.42 (m, 6H, arom. H), 7.62-7.69 (m, 4H, arom. H), 7.96 (s, 2H, pyranyl 2-H and 6-H).

Anal. Calcd for $C_{17}H_{12}O_2$ (248.27): C, 82.24; H, 4.87 %. Found: C, 82.22; H, 4.88.

3,5-Diphenyl-1*H*-pyridin-4-one (**15b**).

This compound was obtained in yield 1.48 g (60%); mp > 300 °C (EtOH); ir (KBr): ν max/cm^{-1}: 3190 (NH), 1635 (CO); MS: *m/z* = 248 [M$^+$+1]; ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 7.30-7.43 (m, 6H, arom. H), 7.60-7.65 (m, 4H, arom. H), 7.84 (s, 2H, pyridyl 2-H and 6-H), 12.42 (br s, 1H, NH).

Anal. Calcd. for $C_{17}H_{13}NO$ (247.28): C, 82.57; H, 5.30; N, 5.66 %. Found: C, 82.56; H, 5.42; N, 5.69.

Preparation of Compounds (**16a,b**).

General Procedure.

Compound **5** (3.20 g, 10 mmol) was treated with each of phenylhydrazine and 3-amino-5-methyl-pyrazole (10 mmol) in acetic acid (5 ml) in the presence of ammonium acetate (1 g). The reaction mixture was heated under reflux for 1 hr and left to cool at room temperature to deposit a solid that was collected by filtration and crystallized from ethanol.

3,5-Diphenyl-1-phenylamino-1*H*-pyridin-4-one (**16a**).

This compound was obtained in yield 2.45 g (73%); mp 232-233 °C; ir (KBr): ν max/cm^{-1}: 3185 (NH), 1635 (CO); MS: *m/z* = 338 [M$^+$]; ^{1}H nmr (dimethyl s.ulfoxide-d_6): δ (ppm) = 6.72-6.75 (m, 2H, arom. H), 6,91-6.96 (m, 1H, arom. H), 7.27-7.41 (m, 8H, arom. H), 7.63-7.67 (m, 4H, arom. H), 7.91 (s, 2H, pyridyl 2-H and 6-H), 9.65 (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{18}N_2O$ (338.39): C, 81.63; H, 5.36; N, 8.28 %. Found: C, 81.60; H, 5.40; N, 8.27.

1-(5-Methyl-1*H*-pyrazol-3-yl)-3,5-diphenyl-1*H*-pyridin-4-one (**16b**).

This compound was obtained in yield 2.45 g (75%); mp 298-300 °C; ir (KBr): ν max/cm^{-1}: 3180 (NH), 1640 (CO); MS: *m/z* = 327 [M$^+$]; ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 2.29 (s, 3H, CH_3), 6.62 (s, 1H, pyrazolyl 4-H), 7.31-7.41 (m, 6H, arom.H), 7.65-7.70 (m, 4H, arom.H), 8.27 (s, 2H, pyridyl 2-H and 6-H), 12.74 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{17}N_3O$ (327.37): C, 77.04; H, 5.23; N, 12.84 %. Found: C, 77.01; H, 5.17; N, 12.85.

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