

New Synthesis of Substituted
1-Oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles
and Related Derivatives

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The synthesis of some 3-substituted and 2,3-disubstituted-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles **5,6** by fusing 1*H*-benzimidazole-2-acetonitrile **1** with some β -keto esters **2,4** in the presence of ammonium acetate or with ethyl β -aminocrotonate **3** is described. The tricyclic compounds were converted to their N-5 methyl or N-5 ethyl derivatives **8,9**. Vilsmeier-Haack formylation of 3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile **5a** afforded its 2-formyl derivative **10**. Chlorination of **5** and **6** with phosphorus oxychloride yielded the respective 1-chloropyrido[1,2-*a*]benzimidazole-4-carbonitriles **11,12** which were utilized to prepare the 1-azido, 1-amino, 1-piperidino and 1-methoxy derivatives of the ring system. Compound **11a** exhibited strong *in vitro* activity against *S. aureus*. Four compounds were screened against P-388 lymphocytic leukemia in mice but were inactive.

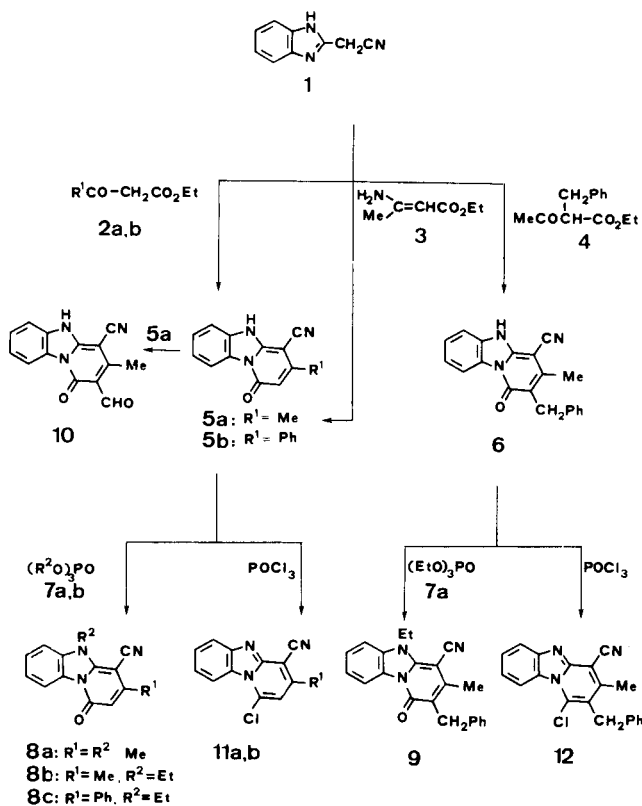
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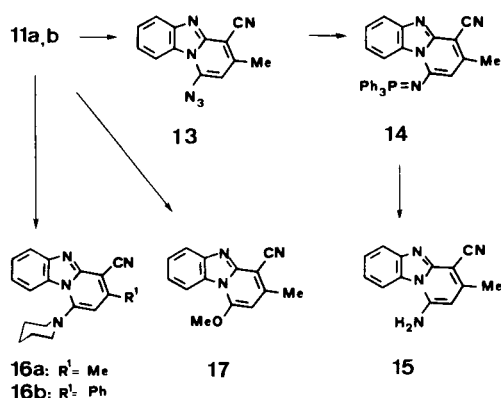
Previously we have described an efficient synthesis of substituted 3-hydroxy-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles by condensing 1*H*-benzimidazole-2-acetonitriles with reactive malonic esters [1,2]. The *in vitro* antibacterial and antifungal activities recorded for some of these compounds [1,2] generated our interest in synthesizing other new derivatives of the basic structure with different substituents at the 3 and 2,3-positions instead of the 3-OH, for chemical and biological studies.

To our knowledge, only two routes leading to such type of compounds have been described in the literature. In one method, 3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile was prepared by the cyclocondensation of 1*H*-benzimidazole-2-acetonitrile **1** with diketene [3]. Whereas, in the other method, 3-methylthio-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile was obtained by cyclizing **1** with methyl di(methylthio)methylene-cyanoacetate [4].

In the present work, it was considered of interest to study the reaction of **1** with some β -keto esters as a possible new route to the designed tricyclic compounds. The use of β -keto esters for the synthesis of fused heterocycles is known. Recently, Kappe and Mayer [5] have reported the use of a mixture of a β -keto ester and excess ammonium acetate, as *in situ* source of β -enamino ester, for the synthesis of coumarins and fused α -pyrono systems from electron rich phenolic compounds. These findings prompted the use of these reagents in the present study. Thus fusing **1** with an equimolar amount of ethyl acetoacetate **2a** in the presence of two equivalents of ammonium

acetate afforded 3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile **5a** (Scheme 1). The latter has been previously prepared from **1** and diketene [3]; however, the yield by the adopted method was much higher





than that obtained using diketene. Mechanistically, this cyclocondensation proceeded through the initial formation of ethyl β -aminocrotonate **3** from **2a** and ammonium acetate followed by interaction with the 1,3-dinucleophilic centers of **1**. Compound **5a** was also obtained by condensing **1** with **3** under the same reaction condition of fusion. In a similar manner, the 3-phenyl and the 2-benzyl-3-methyl derivatives **5b** and **6** were prepared by fusing **1** with ethyl benzoylacetate **2b** and ethyl α -benzylacetoacetate **4**, respectively, in the presence of ammonium acetate. Reacting **5** with trimethyl or triethyl phosphate **7a** or **b** in the presence of potassium carbonate yielded the respective 5-methyl or 5-ethyl derivatives **8a-c**. Analogously, ethylation of **6** yielded **9**. Vilsmeier-Haack formylation of **5a** yielded the 2-carboxaldehyde **10**. Chlorination of **5** and **6** with phosphorus oxychloride yielded the corresponding 1-chloropyrido[1,2-*a*]benzimidazole-4-carbonitriles **11** and **12**, respectively. Taking the advantage of the reactivity of the 1-chloro atom in **11**, the compounds were subjected to nucleophilic substitution reactions in order to prepare other derivatives of the system (Scheme 2). Thus, reacting **11a** with sodium azide at room temperature yielded the 1-azido derivative **13**. The latter was converted to the 1-amino derivative **15** through hydrolysis of the intermediate 1-triphenylphosphoranylideneamino compound **14**, using our reported conditions [1]. The 1-piperidino derivatives **16a** or **b** were obtained in appreciable yields upon treatment of **11a** or **b** with piperidine at room temperature. Reacting **11a** with sodium methoxide afforded the 1-methoxy derivative **17**.

Compounds **8c**, **9**, **11a** and **15** were screened against P-388 lymphocytic leukemia in mice according to a standard protocol [6] and were inactive. Compounds **5a**, **8b** and **8c** were tested for *in vitro* activity against three *Staphylococcus aureus* strains (S 14, S 17 and S 18), two *Escherichia coli* strains (E 21 and E 41) and one *Candida albicans* strain (M 1) using a disc method [7] and were inactive. On the other hand, compounds **6** and **11a** were screened for *in vitro* activity against another *Staphylococ-*

cus aureus and *E. coli* B strain following a standard protocol [8]. Out of these, compound **11a** revealed a prominent activity against *S. aureus* with an MIC value of 16 μ g/ml but was inactive against *E. Coli* B.

EXPERIMENTAL

Melting points were determined in open-glass capillaries on a Callenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide discs. The ^1H nmr spectra were recorded in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) using TMS as an internal standard; the instruments used were the Varian EM 360 at 60 MHz and the XL 200 at 200 MHz.

3-Methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**5a**).

Method A.

1*H*-Benzimidazole-2-acetonitrile **1** (9.43 g, 0.06 mole) and ammonium acetate (10.2 g, 0.132 mole) were mixed with ethyl acetoacetate **2a** (8.3 ml, 0.066 mole) and the mixture was heated in an oil bath at 140-150° for 45 minutes. During this period, ethanol and ammonia were liberated and the reaction mixture was gradually solidified. After cooling, the solid was treated with ethanol-ether mixture, filtered and dried, yield 13.13 g (98%), mp >300° (dimethylformamide-water).

Method B.

The titled compound was obtained in an identical yield from **1** (3.14 g, 0.02 mole) and ethyl β -aminocrotonate **3** (5.1 g, 0.04 mole) following the conditions described under Method A; ir: 3100-2400 cm^{-1} (CN), 1670 s (CO), 1610 w, 1570 m cm^{-1} ; ^1H -nmr: 200 MHz, δ 2.3 (s, CH₃), 5.9 (s, H at C-2), 7.2-7.4 (m, 2 Ar H), 7.5 (d, H at C-6), 8.5 (d, H at C-9).

Anal. Calcd. for C₁₃H₉N₃O: C, 69.94; H, 4.06; N, 18.83. Found: C, 70.0; H, 4.06; N, 18.99.

3-Phenyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**5b**).

This was prepared from **1** (9.43 g, 0.06 mole), ammonium acetate (10.2 g, 0.132 mole) and ethyl benzoylacetate **2b** (11.3 ml, 0.066 mole) as described under method A, yield 11.77 g (69%), mp >300° (dimethylformamide-water); ir: 3200-2500 cm^{-1} (CN), 1670 s (CO), 1630 w, 1610 w, 1590 w, cm^{-1} .

Anal. Calcd. for C₁₈H₁₁N₃O: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.51; H, 4.01; N, 14.93.

2-Benzyl-3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**6**).

This was prepared from **1** (9.43 g, 0.06 mole), ammonium acetate (10.2 g, 0.132 mole) and ethyl α -benzylacetoacetate **4** (13.8 ml, 0.066 mole) as described under method A, yield 17.67 g (94%), mp >300° (dimethylformamide-water); ir: 3400-2600 cm^{-1} (CN), 1670 s (CO), 1630 m, 1550 s, cm^{-1} .

Anal. Calcd. for C₂₀H₁₅N₃O: C, 76.66; H, 4.83; N, 13.41. Found: C, 76.66; H, 4.82; N, 13.49.

3,5-Dimethyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**8a**).

Compound **5a** (2.23 g, 10 mmoles) was refluxed with trimethyl phosphate **7a** (25 ml) for 1 hour in presence of potassium carbonate (0.5 g). After cooling and addition of water, the crystalline product was filtered and dried, yield 2.23 g (94%), mp 270-272° (dimethylformamide); ir: 2210 s (CN), 1670 s (CO), 1610 w, 1590 m cm^{-1} ; ^1H -nmr (trifluoroacetic acid): δ 2.85 (s, CH₃ at C-2), 4.4 (s, N-CH₃), 6.7 (s, H at C-2), 7.5-8.0 (m, 3 Ar H), 8.7 (d, H at C-9).

Anal. Calcd. for C₁₄H₁₁N₃O: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.73; H, 4.61; N, 17.54.

5-Ethyl-3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**8b**).

This was similarly prepared from **5a** (2.23 g, 10 mmoles) and triethyl phosphate **7b** (25 ml), yield 2.46 g (98%), mp $>300^\circ$ (dimethylformamide); ir: 2205 s (CN), 1680 s (CO), 1610 w, 1590 m, cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.83; H, 5.24; N, 16.85.

5-Ethyl-3-phenyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**8c**).

This was similarly prepared from **5b** (2.84 g, 10 mmole) and **7b** (2 ml), yield 2.85 g (91%), mp 210-213° (dimethylformamide-water); ir: 2210 s (CN), 1670 s (CO), 1610 w, 1590 w, cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$: C, 76.66; H, 4.83; N, 13.41. Found: C, 76.59; H, 4.85; N, 13.51.

2-Benzyl-5-ethyl-3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**9**).

This was prepared from **6** (3.13 g, 10 mmole) and **7b** (25 ml) as described for **8a**, yield 2.88 g (92%), mp 224-226° (dimethylformamide); ir: 2200 s (CN), 1650 s (CO), 1610 w, 1600 s, cm^{-1} .

Anal. Calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.24; H, 5.58; N, 12.33.

4-Cyano-3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-2-carboxaldehyde (**10**).

A stirred suspension of **5a** (1.12 g, 5 mmoles) in dimethylformamide (25 ml) was treated with phosphorus oxychloride (1.83 ml, 20 mmoles) keeping the increase in temperature below 80° . After the addition, the reaction mixture was set aside for 15 minutes during which a yellowish product partly crystallized out. After the addition of cold water, the product was filtered, yield 1.16 g (89%), mp $>300^\circ$ (dimethylformamide); ir: 3200-2400 bm, 2210 s (CN), 1680 s (CO), 1640 s, 1600 m, cm^{-1} ; ^1H -nmr: 200 MHz, δ 2.6 (s, CH_3), 7.3-7.4 (m, 3 Ar H), 8.4 (d, H, at C-9), 10.1 (s, aldehyde H).

Anal. Calcd. for $\text{C}_{14}\text{H}_8\text{N}_3\text{O}_2$: C, 66.93; H, 3.61; N, 16.73. Found: C, 66.85; H, 3.77; N, 16.73.

1-Chloro-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**11a**).

Compound **5a** (2.23 g, 10 mmoles) was refluxed with phosphorus oxychloride (30 ml) for 1 hour. The excess phosphorus oxychloride was then distilled under vacuum and the solid was stirred with cold water. After neutralization with saturated sodium hydrogen carbonate solution, the yellowish product was filtered, washed with water and dried, yield 2.23 g (93%), mp 217-220° (dimethylformamide); ir: 2215 s (CN), 1630 s, 1600 m, cm^{-1} ; ^1H -nmr (trifluoroacetic acid): δ 2.9 (s, CH_3), 7.6 (s, H at C-2), 7.7-8.1 (m, 3 Ar H), 8.8 (d, H at C-9).

Anal. Calcd. for $\text{C}_{13}\text{H}_8\text{ClN}_3$: C, 64.60; H, 3.34; N, 17.39. Found: C, 64.30; H, 3.44; N, 17.25.

1-Chloro-3-phenylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**11b**).

This was similarly prepared from **5b** (2.83 g, 10 mmoles), yield 2.97 g (98%), mp 240-243° (dimethylformamide); ir: 2215 s (CN), 1620 m, 1600 s, cm^{-1} ; ^1H -nmr (trifluoroacetic acid): δ 7.7 (s, H at C-2), 7.9-8.3 (m, 3 Ar H), 8.9 (d, H at C-9).

Anal. Calcd. for $\text{C}_{18}\text{H}_{10}\text{ClN}_3$: C, 71.17; H, 3.32; N, 13.83. Found: C, 71.06; H, 3.30; N, 13.89.

2-Benzyl-1-chloro-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**12**).

This was prepared by chlorinating **6** (3.13 g, 10 mmoles) as described for **11a**, yield 3.28 g (99%), mp 220-223° (dimethylformamide-water); ir: 2220 s (CN), 1630 s, 1600 m, cm^{-1} ; ^1H -nmr (trifluoroacetic acid): δ 2.9 (s, CH_3), 4.6 (s, CH_2), 7.0-7.5 (m, 5 Ar H), 7.8-8.1 (m, 3 Ar H), 9.0 (d, H at C-9).

Anal. Calcd. for $\text{C}_{20}\text{H}_{14}\text{ClN}_3$: C, 72.40; H, 4.25; N, 12.67. Found: C, 72.09; H, 4.35; N, 12.68.

1-Azido-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**13**).

A solution of **11a** (2.42 g, 10 mmoles) in dimethylformamide (20 ml) was stirred with sodium azide (0.98 g, 15 mmoles) for 30 minutes at room temperature during which a clear solution was formed followed by sepa-

ration of a bright yellow product. Water was then added and the product was filtered and carefully crystallized from dioxane, yield 2.41 g (97%), mp 183° dec; ir: 2210 s (CN), 2120 s (N_3), 1670 s, 1600 s, cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_8\text{N}_6$: C, 62.90; H, 3.25; N, 33.86. Found: C, 63.17; H, 3.42; N, 34.05.

3-Methyl-1-(triphenylphosphoranylideneamino)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**14**).

To a stirred suspension of **13** (2 g, 8 mmoles) in benzene (20 ml), a solution of triphenylphosphine (2.62 g, 10 mmoles) in benzene (15 ml) was added at room temperature. An immediate orange-red solution was formed with evolution of nitrogen gas followed by precipitation of an orange-red product. After stirring for 45 minutes, the product was filtered, washed with benzene and dried. The yield was almost quantitative, mp 266-268° (dimethylformamide-water); ir: 3050 w, 2205 s (CN), 1620 s, 1580 s, cm^{-1} .

Anal. Calcd. for $\text{C}_{33}\text{H}_{23}\text{N}_4\text{P}$: C, 77.16; H, 4.80; N, 11.61. Found: C, 77.37; H, 4.68; N, 11.58.

1-Amino-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**15**).

Compound **14** (2.41 g, 5 mmoles) was refluxed with a mixture of hydrochloric acid (2*N*) (30 ml) and methanol (25 ml) for 1 hour. After cooling, the reaction mixture was neutralized with ammonium hydroxide and the product was filtered, yield 0.74 g (67%), mp $>300^\circ$ (dimethylformamide-water); ir: 3500-2500 bm, 2210 s (CN), 1650 m, 1630 w, 1600 m, cm^{-1} ; ^1H -nmr: 200 MHz, δ 3.6 (s, CH_3), 6.05 (s, H at C-2), 7.3 (t), 7.5 (t) (2 Ar H at C-7 and C-8), 7.7 (d, H at C-6), 7.85 (s, NH_2), 8.5 (d, H at C-9).

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 69.99; H, 4.66; N, 25.18.

3-Methyl-1-(1-piperidino)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**16a**).

Piperidine (2 ml, 20 mmoles) was added to a stirred suspension of **11a** (1.2 g, 5 mmoles) in dimethylformamide (20 ml). An immediate greenish-yellow solution was formed with the separation of the product within few minutes. Stirring was maintained for 20-30 minutes at room temperature. Water was then added and the product was filtered, yield 1.34 g (92%), mp 269-270° (dimethylformamide); ir: 3000-2800 w, 2215 s (CN), 1630 s, 1600 s cm^{-1} ; ^1H -nmr (trifluoroacetic acid): δ 1.9 (m, 2H at C-4 in piperidino), 2.7 (s, CH_3), 3.2 (m, 4H, at C-3 and C-5 in piperidino), 3.6 (m, 4H, $\text{H}_2\text{C-N-CH}_2$), 7.0 (s, H at C-2), 7.6-8.0 (m, 3 Ar H), 8.5 (d, H at C-9).

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.75; H, 5.95; N, 19.22.

3-Phenyl-1-(1-piperidino)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**16b**).

This was similarly prepared from **11b** (1.51 g, 5 mmoles) and piperidine (2 ml, 20 mmole), yield 1.74 g (99%), mp 216-220° (dimethylformamide); ir: 2215 s (CN), 1620 m, 1600 s, 1510 w, cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_4$: C, 78.38; H, 5.72; N, 15.90. Found: C, 78.19; H, 5.82; N, 15.90.

1-Methoxy-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**17**).

Compound **11a** (0.73 g, 3 mmoles) was refluxed with a solution of sodium (0.1 g, 4 mmoles) in absolute methanol (25 ml) for 2 hours. After concentration and cooling, the product was filtered, yield 0.7 g (99%), mp 274-275° (dimethylformamide-water); ir: 3000 w, 2210 s (CN), 1640 m, 1610 s, 1230 s, 1030 m cm^{-1} ; ^1H -nmr (trifluoroacetic acid): δ 2.8 (s, CH_3 at C-3), 4.3 (s, OCH_3), 6.9 (s, H at C-2), 7.5-7.9 (m, 3 Ar H), 8.6 (d, H at C-9).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.87; H, 4.90; N, 17.84.

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