Synthesis of Pyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazoles

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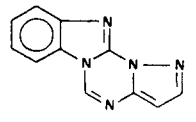
The synthesis of a new class of tetracyclic bridgehead heterocycle pyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazoles is reported. The key intermediate 2-(3-aminopyrazol-2-yl)benzimidazoles were prepared by the reaction of 2-hydrazinobenzimidazole with an appropriate reagent such as ethyl ethoxymethylenecyanoacetate, ethoxymethylenemalononitrile, β-cyanoacetophenone or α-formylphenylacetonitrile. The treatment of these key intermediates with triethylorthoesters afforded the corresponding pyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazoles.

Recently, considerable study has been directed in our laboratory toward the synthesis of pyrazolo[1,5-*a*]-1,3,5-triazines for their pharmacological evaluation (1-4). In conjunction with this program, we wish to report the synthesis of a new class of tetracyclic bridgehead heterocycle which involves a pyrazolo[1,5-*a*]-1,3,5-triazine ring system in the molecule, namely pyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole. In this communication, the basic synthetic approach to the desired heterocycle was established by the following route: (I) preparation of the key intermediates, 2-(3-aminopyrazol-2-yl)-benzimidazoles, from a readily available 2-hydrazinobenzimidazole (**1**) (5); (II) cyclization of the key intermediate to the parent heterocycle. Although the starting material **1** is a relatively well known compound and certain 2-(pyrazol-2-yl)benzimidazoles (6,7) have been synthesized from 2-hydrazinobenzimidazoles, nothing has been reported on pyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole and its derivatives. The only reported tetracyclic bridgehead heterocycle is 2,5-dimethylpyrazolo[1′,5′:3,4]-pyrimido[1,2-*a*]benzimidazole (8) which was obtained by the direct cyclization of **1** with acetylacetone.



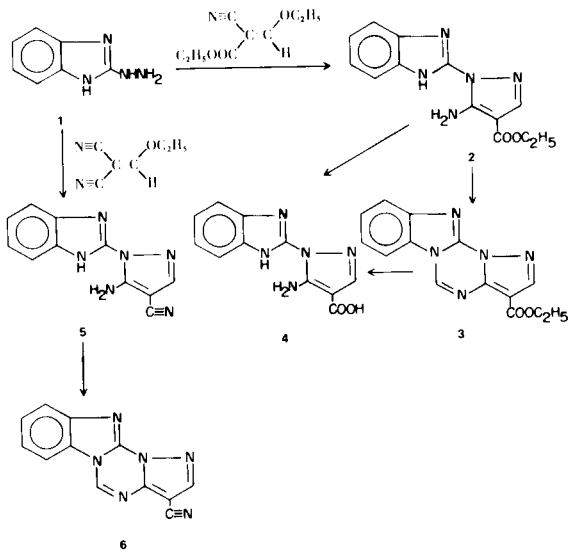
Pyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole

Refluxing of a mixture of **1** and ethyl ethoxymethylenecyanoacetate in ethanol provided 2-(3-amino-4-ethoxycarbonylpyrazol-2-yl)benzimidazole (**2**) as a single product. The structure of **2** was supported by the analytical and spectroscopic (ir, nmr) data, as well as by the known fact that the reaction of hydrazine with ethyl ethoxymethylenecyanoacetate gives 3-amino-4-carbethoxypyrazole (9). The unequivocal structure was confirmed on the basis of successful conversion to the expected 3-ethoxycarbonylpyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**3**) by heating of **2** in triethylorthoformate. Attempted hydrolysis of the carbethoxy function of **3** with hot 2*N* sodium hydroxide resulted in the formation of 2-(3-amino-4-carbohydroxypyrazol-2-yl)benzimidazol (**4**). Alternatively, the compound **4** was obtained by the treatment of **2** with hot 2*N* sodium hydroxide.

Furthermore, the use of ethoxymethylenemalononitrile instead of ethyl ethoxymethylenecyanoacetate gave similar results. As expected from the reaction which gives 3-amino-4-cyanopyrazole (10) by the condensation of hydrazine with ethoxymethylenemalononitrile, the treatment of **1** with ethoxymethylenemalononitrile in ethanol afforded 2-(3-amino-4-cyanopyrazol-2-yl)benzimidazole (**5**). The heating of **5** in triethylorthoformate gave 3-cyanopyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**6**) (Scheme I).

In order to synthesize further derivatives of pyrazolo-[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole, the reaction of **1** with β-ketonitrile or α-cyanoaldehyde was studied. The starting material **1** can be considered as a cyclic *N*-aminoguanidine, as well as a hydrazine derivative. It has been reported that the reaction of hydrazine or *N*-aminoguanidine with β-cyanoacetophenone (11) (β-ketonitrile) gives 3-amino-5-phenylpyrazole (12) or *N*-(3-amino-5-phenylpyrazol-2-yl)guanidine (12), respectively. The latter compound recently has been used as a useful intermediate

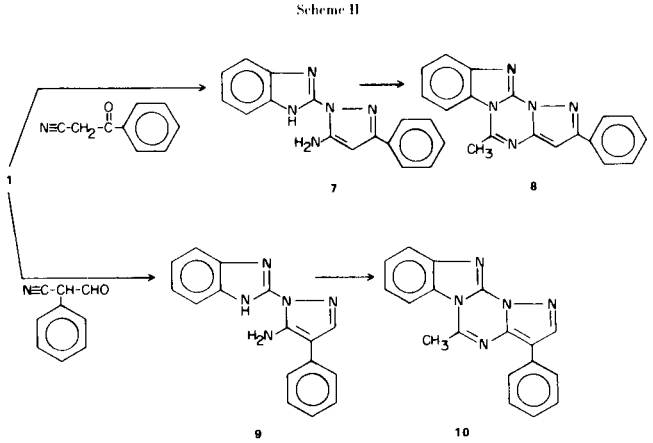
Scheme I



for the synthesis of 2-substituted-4-amino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazines (3). Similarly, it had also been shown that the reaction of hydrazine with α-formylphenylacetonitrile (13) (α-cyanoaldehyde) provides 3-amino-4-phenylpyrazole (14).

Heating of **1** with β-cyanoacetophenone (11) in ethanol containing acetic acid afforded 2-(3-amino-5-phenylpyrazol-2-yl)benzimidazole (**7**). Analogously, the treatment of **1** with α-formylphenylacetonitrile (13) gave an isomer of **7**, 2-(3-amino-4-phenylpyrazol-2-yl)benzimidazole (**9**). The structure of these intermediates **7** and **9** were substantiated by the nmr spectra. The nmr spectra of **7** and **9** in DMSO-d_6 exhibited a singlet at δ 6.00 and δ 8.02 for pyrazole proton, respectively. The reaction of **7** or **9** with triethylorthoacetate provided 5-methyl-2-phenylpyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**8**) and 5-methyl-3-phenylpyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**10**), respectively (Scheme II).

Scheme II



EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R-20A high resolution nuclear magnetic resonance spectrometer. The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 257 infrared spectrophotometer. Elemental analyses were accomplished by the Heterocyclic Chemical Corp., Harrisonville, Missouri.

2-(3-Amino-4-ethoxycarbonylpyrazol-2-yl)benzimidazole (**2**).

A mixture of 2-hydrazinobenzimidazole (**1**) (5) (2.96 g., 20 mmoles) and ethyl ethoxymethylenecyanoacetate (3.38 g., 20 mmoles) in 30 ml. of ethanol was heated at reflux for 2 hours. After cooling the reaction mixture, the precipitated solid was collected by filtration and washed with ethanol. Recrystallization from a mixture of dimethylformamide and ethanol gave 4.6 g. (85%) of pure product, m.p. 203-205°; ir (potassium bromide) cm^{-1}, 1685 (CO); nmr (DMSO-d_6): δ 1.36 (t, 3, CH_3), 4.35 (q, 2, OCH_2), 7.18-7.80 (m, 6, phenyl protons and NH_2), 7.98 (s, 1, pyrazol proton).

Anal. Calcd. for $C_{13}H_{13}N_5O_2$: C, 57.41; H, 4.83; N, 25.81. Found: C, 57.61; H, 5.13; N, 25.78.

3-Ethoxycarbonylpyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**3**).

A mixture of **2** (2.71 g., 10 mmoles) and 20 ml. of triethylorthoformate was heated at reflux for 3 hours. After cooling the reaction mixture, the precipitated solid was collected by filtration and washed with ethanol. Recrystallization from a mixture of dimethylformamide and ethanol gave 2.4 g. (86%) of pure crystals, m.p. 235°; ir (potassium bromide) cm^{-1}, 1680 (CO); nmr (deuteriotrifluoroacetic acid): δ 1.53 (t, 3, CH_3), 4.65 (q, 2, OCH_2), 7.85-8.50 (m, 4, phenyl protons), 8.95 (s, 1), 9.80 (s, 1).

Anal. Calcd. for $C_{14}H_{11}N_5O_2$: C, 59.77; H, 3.94; N, 24.90. Found: C, 59.79; H, 4.23; N, 25.09.

2-(3-Amino-4-carbohydroxypyrazol-2-yl)benzimidazole (**4**).

Method A.

A mixture of **3** (2 g., 7.1 mmoles) and 30 ml. of 5% sodium hydroxide was heated on steam bath for 30 minutes with stirring. The resulting clear solution was acidified (*p*H 5) by the addition of acetic acid. The precipitates were collected by filtration, washed with water and then with ethanol. Recrystallization from a mixture of dimethylformamide and ethanol afforded 1.6 g. (89%) of pure crystals, m.p. 255-256°; nmr (DMSO-d_6): δ 7.20-7.80 (m, 6, phenyl protons and NH_2), 7.99 (s, 1, pyrazole proton), 13.10 (b, 1, NH).

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.31; H, 3.73; N, 28.79. Found: C, 54.38; H, 3.68; N, 28.92.

Method B.

A mixture of **2** (0.54 g., 2 mmoles) and 15 ml. of 5% sodium hydroxide was heated on steam bath for 10 minutes. The resulting clear solution was acidified (*p*H 5) by the addition of acetic acid. The precipitates were collected by filtration and washed with water. Recrystallization from a mixture of dimethylformamide and ethanol provided 0.4 g. (83%) of pure crystals which were identical in all respects to the product prepared by Method A.

2-(3-Amino-4-cyanopyrazol-2-yl)benzimidazole (**5**).

A mixture of **1** (1.49 g., 10 mmoles) and ethoxy methylene malononitrile (1.22 g., 10 mmoles) in 20 ml. of ethanol was heated

at reflux for 2 hours. After cooling the reaction mixture, the precipitated solid was collected by filtration and washed with ethanol. Recrystallization from a mixture of dimethylformamide and ethanol afforded 2.1 g. (94%) of pure product, m.p. 274.5-276°; ir (potassium bromide): cm^{-1}, 2210 (C≡N); nmr (DMSO-d_6): δ 7.19-7.71 (m, 4, phenyl protons), 8.12 (s, 1, pyrazole proton), 8.33 (bs, 2, NH_2), 13.2 (b, 1, NH).

Anal. Calcd. for $C_{11}H_8N_6$: C, 58.91; H, 3.60; N, 37.48. Found: C, 58.71; H, 3.91; N, 37.21.

3-Cyanopyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**6**).

A mixture of **5** (1.12 g., 5 mmoles) and 10 ml. of triethylorthoformamate was heated at reflux for 48 hours. After cooling the reaction mixture, the precipitated solid was collected by filtration. Recrystallization from a mixture of dimethylformamide and ethanol afforded 0.7 g. (59%) of pure crystals, m.p. 346-348° with decomposition; ir (potassium bromide): cm^{-1}, 2230 (C≡N); nmr (deuteriotrifluoroacetic acid): δ 7.85-8.50 (m, 4, phenyl protons), 8.78 (s, 1), 9.71 (s, 1).

Anal. Calcd. for $C_{12}H_6N_6$: C, 61.53; H, 2.58; N, 35.88. Found: C, 61.51; H, 2.77; N, 35.76.

2-(3-Amino-5-phenylpyrazol-2-yl)benzimidazole (**7**).

A mixture of **1** (0.74 g., 5 mmoles), β cyanoacetophenone (11) (0.73 g., 5 mmoles) and 3 ml. of acetic acid in 20 ml. of ethanol was heated at reflux for 3 hours. After cooling, the precipitated solid was collected by filtration, washed with ethanol and dried to give 0.85 g. (62%) of an analytically pure product, m.p. 231-232°; nmr (DMSO-d_6): δ 6.00 (s, 1, pyrazole proton), 7.05 (bs, 2, NH_2), 7.15-8.05 (m, 9, phenyl protons).

Anal. Calcd. for $C_{16}H_{13}N_5$: C, 69.79; H, 4.76; N, 25.44. Found: C, 69.48; H, 4.96; N, 25.22.

5-Methyl-2-phenylpyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**8**).

A mixture of **7** (0.55 g., 2 mmoles) and 5 ml. of triethylorthoacetate was heated at reflux for 2 hours. After cooling the reaction mixture, the precipitated solid was collected by filtration, washed with ethanol and then ether to give 0.5 g. (83%) of an analytically pure product, m.p. 258-259°; nmr (deuteriotrifluoroacetic acid): δ 3.32 (s, 3, CH_3), 7.25 (s, 1, pyrazole proton), 7.35-8.33 (m, 9, phenyl protons).

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.21; H, 4.38; N, 23.39. Found: C, 72.03; H, 4.58; N, 23.14.

2-(3-Amino-4-phenylpyrazol-2-yl)benzimidazole (**9**).

A mixture of **1** (1.48 g., 10 mmoles), α-formylphenylacetonitrile (14) (1.45 g., 10 mmoles) and 3 ml. of acetic acid in 20 ml. of ethanol was heated at reflux for 3 hours. After cooling, the precipitated solid was collected by filtration washed with ethanol and ether. Recrystallization from ethanol afforded 1.7 g. (62%) of pure product, m.p. 194-195°; nmr (DMSO-d_6): δ 7.75 (m, 11, phenyl protons), 8.02 (s, 1, pyrazole proton).

Anal. Calcd. for $C_{16}H_{13}N_5$: C, 69.79; H, 4.76; N, 25.44. Found: C, 69.71; H, 4.77; N, 25.50.

5-Methyl-3-phenylpyrazolo[1′,5′:1,2]-1,3,5-triazino[5,6-*a*]benzimidazole (**10**).

A mixture of **9** (0.83 g., 3 mmoles) and 5 ml. of triethylorthoacetate was heated at reflux for 3 hours. After cooling the reaction mixture, the precipitated solid was collected by filtration, washed with chtanol and then ether. Recrystallization from a mixture of dimethylformamide and ethanol gave 0.6 g. (67%) of pure product, m.p. 206-208°; nmr (deuteriotrifluoroacetic acid): δ 3.41 (s, 3, CH_3), 7.10-8.43 (m, 9, phenyl protons), 8.85 (s, 1, pyrazole proton).

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.21; H, 4.38; N, 23.39. Found: C, 72.01; H, 4.32; N, 23.39.

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