Synthesis of Certain Imidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidines

Keitaro Senga, Roland K. Robins and Darrell E. O'Brien

ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, 2727 Campus Drive
Irvine, California 92664

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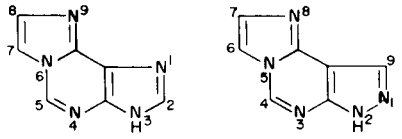
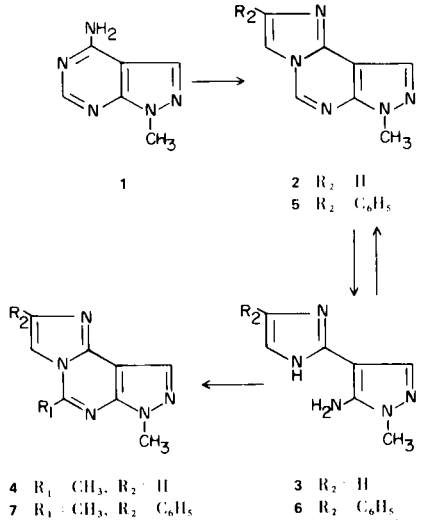
As a new type of chemical modification of base residues in nucleic acids, it has been reported that the reaction of 9-methyladenine with chloroacetaldehyde gave 3-methylimidazo[2,1-*i*]purine (1). In connection with fluorescent modification of nucleic acids, several imidazo[2,1-*i*]purines have been prepared from adenine nucleosides or nucleotides including cyclic nucleotides and their enzymatic activities examined (2-6). More recently, it has also been found that two fluorescent substances isolated from the clinically useful antileukemic agent, N^6-(Δ^2-isopentenyl)adenosine, were imidazo[2,1-*i*]purine derivatives (7). In the present study we were interested in studying a similar but new ring system, the imidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidines.



Imidazo[2,1-*i*]purine Imidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine

Treatment of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (8) (**1**) with chloroacetaldehyde in sodium acetate buffer (*p*H 4.5) at 80° for 30 minutes furnished a good yield of 2-methylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**2**). As expected for this class of compounds, **2** was fluorescent. The structure of **2** was ascertained on the basis of nmr, ir and uv spectra and elemental analysis. The nmr spectrum (DMSO-d_6) of **2** exhibited a pair of doublets at δ 7.55 and δ 8.10 (J = 2 Hz) corresponding to the coupling between 6H and 7H (see Experimental). When **2** was treated with diluted sodium hydroxide solution, ring opening took place at the 4 position and 3-amino-4-(imidazol-2-yl)-2-methylpyrazole (3) was obtained. This reaction was easily monitored on thin-layer chromatography by disappearance of the fluorescence of **2**. In the nmr spectrum (DMSO-d_6) of **3**, the protons at the 4 and 5 positions of the imidazole ring appeared as a sharp singlet at δ 7.00 (see Experimental). Compound **3** was found to be a useful precursor to provide 4-substitutedimidazo[2,1-*f*]pyrazolo-[3,4-*d*]pyrimidines. For example, heating of **3** with triethylorthoformate afforded **2**. Similarly, the reaction of **3** with triethylorthoacetate gave 2,4-dimethylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (4) which was also obtained from **3** and acetic anhydride (Scheme I).

According to the scheme for the preparation of imidazo-[2,1-*f*]pyrazolo[3,4-*d*]pyrimidines, we have also examined the reaction of **1** with α-bromoacetophenone. Heating of **1** with α-bromoacetophenone in dimethylformamide or ethanol for 3 hours afforded 2-methyl-7-phenylimidazo-[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**5**). The structure of **5** was confirmed by its spectrum data and elemental analysis. The location of the phenyl group at 7 position was assigned on the basis of previous studies (2,6). Treatment of **5** with diluted sodium hydroxide solution resulted in the formation of 3-amino-2-methyl-4-(4-phenylimidazol-2-yl)pyrazole (**6**), which was easily converted to **5** by heating with triethylorthoformate. When **6** was treated with triethylorthoacetate, 2,4-dimethyl-7-phenylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**7**) was formed. In these ring closures, the formation of corresponding 8-phenyl derivatives were not detected. The direction of cyclization is attributed to the greater nucleophilicity of nitrogen at the 1 position over that of the nitrogen at 3 position in imidazole ring and the steric effect of phenyl group.



1

2 R_2 = H
5 R_2 = C_6H_5

4 R_1 = CH_3, R_2 = H
7 R_1 = CH_3, R_2 = C_6H_5

3 R_2 = H
6 R_2 = C_6H_5

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer and chemical shifts are reported in parts per million (δ) with DDS or TMS as an internal standard. The uv spectra were undertaken by Cary 15 spectrophotometer. All samples displayed a single spot on thin-layer chromatography (chloroform:methanol = 9:1) and were analyzed by the Heterocyclic Chemical Corporation of Harrisonville, Missouri.

2-Methylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**2**).

Method A.

To a solution of 13.1 g. (40 mmoles) of 30% chloroacetaldehyde in water (30 ml.) was added 7 g. of sodium acetate (*p*H 4.5) and 4.96 g. (20 mmoles) of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (**1**). The mixture was heated on steam bath for 30 minutes with stirring. The solution was extracted with chloroform (100 ml. x 4) and the combined extracts were dried over anhydrous sodium sulfate. The chloroform solution was evaporated to dryness *in vacuo* and the resulting residue was recrystallized from aqueous ethanol to give 3.4 g. (87%) of pure **2** with m.p. 172-173°; uv λ max (ethanol): *p*H 1, 232 nm (ε, 34,502), 262 nm (ε 6,677) sh, 295 nm (ε 2,411) sh; *p*H 11, 231 nm (ε, 35,800), 238 nm (ε, 26,155), 255 nm (ε, 23,745), 280 nm (ε, 21,703) sh, 310 nm (ε, 20,404) sh; nmr (DMSO-d_6): δ 4.11 (s, 3, N-CH_3), 7.55 (d, J = 2 Hz, 1), δ 8.10 (d, J = 2 Hz, 1), δ 8.31 (s, 1), δ 9.31 (s, 1).

Anal. Calcd. for $C_8H_7N_5$: C, 55.47; H, 4.08; N, 40.45. Found: C, 55.49; H, 3.90; N, 40.11.

Method B.

A mixture of 0.82 g. (5 mmoles) of 3-amino-4-(imidazol-2-yl)-2-methylpyrazole (**3**) and triethylorthoformate (10 ml.) was heated at reflux for 16 hours. After cooling the reaction mixture, the precipitate was filtered and recrystallized from aqueous ethanol to afford 0.5 g. (58%) of pure **2**. This product was identical in all respects to the product prepared by Method A.

3-Amino-4-(imidazol-2-yl)-2-methylpyrazole (**3**).

A mixture of 2.6 g. (15 mmoles) of **2**, 2*N* sodium hydroxide (25 ml.) and ethanol (25 ml.) was heated on steam bath for 20 minutes with stirring. The reaction mixture was concentrated to the half volume *in vacuo*. The precipitate was filtered and recrystallized from aqueous ethanol to give 1.1 g. (45%) of pure **3** with m.p. 265-267°; uv λ max (ethanol): *p*H 1, 268 nm (ε, 14,169); *p*H 11, 253 nm (ε, 16,218); nmr (DMSO-d_6): δ 3.62 (s, 3, N-CH_3), δ 6.06 (b, 2, NH_2), δ 7.00 (s, 2, -CH=CH-), δ 7.63 (s, 1), δ 12.00 (b, 1, NH).

Anal. Calcd. for $C_7H_9N_5$: C, 51.51; H, 5.56; N, 42.92. Found: C, 51.49; H, 5.82; N, 42.59.

2,4-Dimethylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**4**).

Method A.

A mixture of 0.82 g. (5 mmoles) of **3** and triethylorthoacetate (15 ml.) was heated at reflux for 16 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from benzene to give 0.7 g. (80%) of pure **4** with m.p. 203-204°; nmr (deuteriochloroform): δ 2.86 (s, 3, CH_3), δ 4.20 (s, 3, N-CH_3), δ 7.52 (s, 3, -CH=CH-), δ 8.25 (s, 1).

Anal. Calcd. for $C_9H_9N_5$: C, 57.73; H, 4.85; N, 37.41. Found: C, 57.64; H, 4.98; N, 37.11.

Method B.

A mixture of 0.82 g. (5 mmoles) of **3** and acetic anhydride (10 ml.) was heated at reflux for 3 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue was triturated with ether. The precipitate was filtered and recrystallized from benzene to give 0.3 g. (32%) of pure **4** which was identical in all respects to product prepared by Method A.

2-Methyl-7-phenylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**5**).

Method A.

A mixture of 1.49 g. (10 mmoles) of **1** and 1.99 g. (10 mmoles) of α-bromoacetophenone in dimethylformamide (30 ml.) was heated at reflux for 3 hours. The reaction mixture was allowed to cool and the precipitate was filtered, washed with ethanol to give 1.25 g. (50%) of pure **5** with m.p. 264-265°; uv λ max (ethanol): *p*H 1, 251 nm (ε, 31,735), 275 nm (ε, 16,341) sh, 285 nm (ε, 13,499) sh; *p*H 11, 245 nm (ε, 34,577), 255 nm (ε, 27,946) sh, 315 nm (ε, 3,789) sh; nmr (deuteriotrifluoroacetic acid): δ 4.43 (s, 3, N-CH_3), δ 7.55 ~ 7.94 (m, 5, C_6H_5), δ 8.42 (s, 1), δ 8.82 (s, 1), δ 9.42 (s, 1).

Anal. Calcd. for $C_{14}H_{11}N_5$: C, 67.44; H, 4.45; N, 28.09. Found: C, 67.44; H, 4.56; N, 28.16.

In an alternative procedure, absolute ehtanol (30 ml.) was used in place of dimethylformamide, yielding 1 g. (40%) of pure **5**.

Method B.

A mixture of 1.19 g. (5 mmoles) of 3-amino-2-methyl-4-(4-phenylimidazol-2-yl) pyrazole (**6**) and triethylorthoformate (10 ml.) was heated on steam bath for 2 hours. The solution was concentrated to half of the volume *in vacuo*. The precipitate was filtered, washed with water and dried. Recrystallization from aqueous ethanol afforded 1.9 g. (79%) of pure **6** with m.p. 225-228°; uv λ max (ethanol): *p*H 1, 288 nm (ε, 20,127); *p*H 11, 285 nm (ε, 18,317), 227 nm (ε, 9,950), 272 nm (ε, 16,734) sh; nmr (DMSO-d_6): δ 3.78 (s, 3, N-CH_3), δ 6.22 (b, 2, NH_2), δ 7.19 ~ 7.94 (m, 7, C_6H_5 and 2 CH), δ 12.19 (b, 1, NH).

Anal. Calcd. for $C_{13}H_{13}N_5$: C, 65.24; H, 5.48; N, 29.27. Found: C, 64.91; H, 5.76; N, 29.36.

2,4-Dimethyl-7-phenylimidazo[2,1-*f*]pyrazolo[3,4-*d*]pyrimidine (**7**).

A mixture of 1.19 g. (5 mmoles) of **6** and triethylorthoacetate (10 ml.) was heated at reflux for 2 hours. The reaction mixture was allowed to cool and then filtered. Recrystallization from ethanol gave 1.14 g. (93%) of pure **7** (as a hemi-hydrate) with m.p. 194.5-196°; uv λ max (ethanol): *p*H 1, 242 nm (ε, 35,229), 275 nm (ε, 18,806) sh; *p*H 11, 243 nm (ε, 35,493), 256 nm (ε, 32,580), 262 nm (ε, 30,990) sh, 320 nm (ε, 4,767) sh; nmr (DMSO-d_6): δ 2.85 (s, 3, CH_3), δ 4.02 (s, 3, N-CH_3), δ 7.35 ~ 8.10 (m, 5, C_6H_5), δ 8.25 (s, 1), δ 8.36 (s, 1).

Anal. Calcd. for $C_{15}H_{13}N_5 \cdot \frac{1}{2}H_2O$: C, 66.15; H, 5.19; N, 25.72. Found: C, 65.93; H, 5.17; N, 25.42.

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