

NEW SYNTHETIC APPROACH FOR AZOLOPURINES AND ANALOGS

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Abstract - A new synthetic approach has been developed for the synthesis of some azolopurines, i.e. derivatives of 1,2,4-triazolo(3,4-b)purine (3) and pyrrolo(2,1-b)purine (8), and for some pyrazolo(3,4-d)pyrimidines (12,14).

Recently, several tricyclic heterocycles, structurally derived from purines, have been isolated and identified. From yeast phenylalanine tRNA and other sources the γ -base (Wybutine) ¹ and several related compounds have been isolated. They all contain the imidazo(1,2-a)purine skeleton. ²⁻⁸ The isomeric imidazo-(2,1-i)purine system is formed from N⁶-(Δ^2 -isopentenyl)adenine ^{9,10} and also by reaction of vinyl chloride derived chloroethylene oxide and its rearrangement product, chloroacetaldehyde, with DNAs from various sources. ¹¹

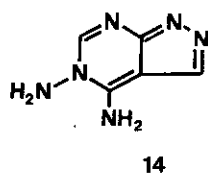
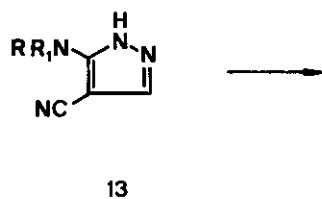
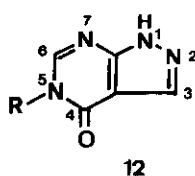
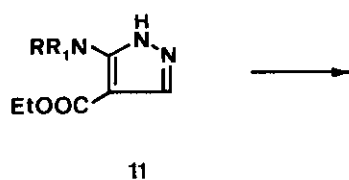
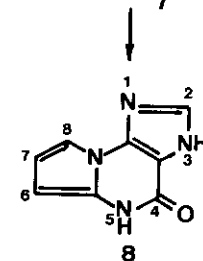
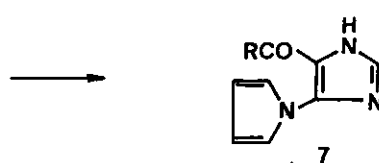
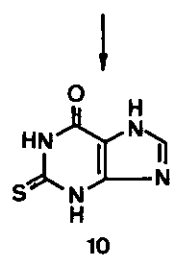
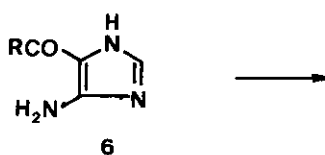
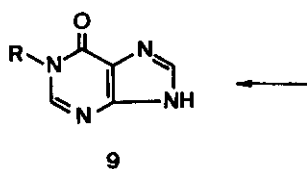
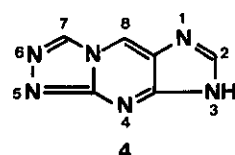
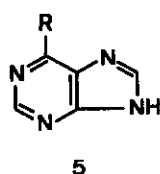
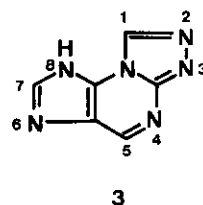
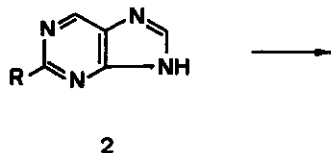
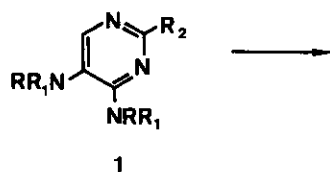
Our recent investigations in heterocyclic amidines as synthons for bi- and polycyclic heterocyclic systems ¹²⁻¹⁹ prompted us to investigate the possibility of synthesizing some azolopurines. In the first approach, the appropriate pyrimidines were used as starting material. From 2,4,5-triaminopyrimidine and N,N-dimethylformamide dimethyl acetal under various reaction conditions only the corresponding triamidine (1, R, R₁ = Me₂NCH=, R₂ = Me₂NCH=N) was obtained. The compound was prepared also with N,N-dimethylformamide dineopentyl acetal in boiling N,N-dimethylformamide in 59% yield or in the absence of solvent in 11% yield (3 h under reflux), mp 192-196 °C (from ethanol); m/e 290 (M⁺). This contrasts the easy imidazole ring formation from the corresponding o-diaminopyridines as described earlier. ²⁰ The above compound, when heated in boiling diethylene glycol underwent ring closure to give the corresponding purine derivative (2, R = Me₂NCH=N) in 75% yield, mp 299-302 °C (from water); m/e 190 (M⁺). The triamidine is also easily hydrolyzed in hot water to the triformylamino compound

(1, R = H, R₁ = HCO, R₂ = NHCHO) in 91% yield, mp > 300 °C (from water); m/e 209 (M⁺). However, 2,4,5-triaminopyrimidine is easily cyclized to 2-aminopurine (2, R = NH₂) with diethoxymethyl acetate (room temperature for 6 h and 30 min under reflux, yield 61%), mp 275-282 °C (lit., ²¹ mp 277-278 °C); m/e 135 (M⁺).

In a similar manner, 2-chloro-4,5-diaminopyrimidine (1, R = R₁ = H, R₂ = Cl) was transformed with N,N-dimethylformamide dimethyl acetal in hot N,N-dimethylformamide to 2-dimethylaminopurine (2, R = Me₂N) in 37% yield, mp about 260 °C (dec) (from toluene); m/e 163 (M⁺). Apparently, ring closure was followed by displacement of the 2-chlorine atom with dimethylamine, formed during the reaction. On the other hand, 2-chloro-4,5-diaminopyrimidine reacted with diethoxymethyl acetate in hot triethyl orthoformate to give after 1 h 2-chloropurine (2, R = Cl) in 64% yield, mp 263-264 °C (dec) (from triethyl orthoformate) (lit., ^{22,23} mp 231-234 °C and the product was identical with an authentic specimen); m/e 154 (M⁺).

From 2-chloropurine the 2-hydrazino derivative (2, R = NNNH₂) was prepared.²⁴ When treated either with diethoxymethyl acetate or, preferentially, with N,N-dimethylformamide dineopentyl acetal in boiling toluene (6 h) it afforded a tricyclic product (3) in 56% yield, mp > 280 °C (from water; m/e 160 (M⁺). The compound is highly fluorescent in uv light. To the product the structure of a 1,2,4-triazolo(3,4-b)purine (3) or 1,2,4-triazolo(4,3-a)purine (4) could be assigned. The nmr spectrum (in DMSO-d₆ at 120 °C) revealed three singlets at δ 9.23 (H₁), 8.86 (H₅) and 8.09 (H₇) and is compatible with the angular structure (3). In the alternative case one would expect a very significant downfield shift for H₈ in 4 as observed in the case of the linear tetrazolo(1,5-a)purine.²⁵

We have further attempted to prepare a fused tricycle based on adenine by ring closure at N₁. Adenine could be transformed with N,N-dimethylformamide dineopentyl acetal in boiling N,N-dimethylformamide (1 h) to the corresponding 6-N,N-dimethylaminomethyleneaminopurine (5, R = Me₂NCH=N) in 88% yield, mp 268-270 °C (from N,N-dimethylformamide and ethyl acetate); m/e 190 (M⁺) and δ nmr (DMSO-d₆, 80 °C) three singlets at 8.81, 8.15 and 8.36, corresponding to H₂, H₈ and CH-group. The use of N,N-dimethylformamide dineopentyl acetal is advantageous since the big neopentyl group prevents during the reaction further alkylation at the imidazole nitrogen as experienced with other sterically not hindered acetals.²⁶ Further transformation with methanolic hydroxylamine hydrochloride



at room temperature afforded immediately the corresponding 6-hydroxyiminomethyleneamino derivative (5, R = HON=CHNH) in 94% yield, mp > 290°C; m/e 178 (M⁺) and δ nmr (DMSO-d₆, 145 °C) 8.29 (s, H₂), 8.13 and 8.11 (s, H₈ and CH). Several attempts to cyclize this side chain into a fused triazolo ring by the method which we have successfully applied for other heterocycles ¹⁶⁻¹⁸ failed. With acetic anhydride at room temperature, for example, the corresponding 6-acetylaminopurine (5, R = MeCONH) was obtained, mp > 290 °C (lit., ²⁷ mp > 260 °C); m/e 177 (M⁺) and δ nmr (DMSO-d₆) 8.52 (s, H₂), 8.26 (s, H₈), 2.24 (s, Me).

In the other synthetic approach we used appropriate imidazoles as starting material. Ethyl 4-aminoimidazole-5-carboxylate (6, R = OEt) when heated with 2,5-diethoxytetrahydrofuran in glacial acetic acid for 1 h afforded the pyrrolo derivative (7, R = OEt) in 21% yield, mp 188-191 °C (from n-heptane); m/e 205 (M⁺) and δ nmr (CDCl₃, 50 °C) 7.19 (s, H₂), 7.47 (m, H₂- and H₅-), 6.23 (m, H₃- and H₄-), 4.80 (q, CH₂), 1.33 (t, Me). The compound was transformed with ethanolic hydrazine hydrate (30 min reflux) into the corresponding hydrazide (7, R = NHNH₂) in 26% yield, mp 215 °C; m/e 191 (M⁺). The hydrazide was dissolved in glacial acetic acid and treated at room temperature with isoamyl nitrite. The initially formed acyl azide was not isolated, but it decomposed into pyrrolo-(2,1-b)purin-4-one (8) in low yield (9%), mp > 280 °C; m/e 174 (M⁺).

On the other hand, the ester (6, R = OEt) when treated with 100% hydrazine hydrate at room temperature for 3 days yielded upon evaporation of the solvent and treatment of the residue with hot ethyl acetate the hydrazide (6, R = NHNH₂) (insoluble in ethyl acetate) in 36% yield, mp 209-213 °C; m/e 141 (M⁺). The hydrazide was thereafter heated in the presence of triethyl orthoformate in diethylene glycol dimethyl ether (2 h) to give 1-aminohypoxanthine (9, R = NH₂) in 39% yield, mp > 310 °C (from N,N-dimethylformamide and toluene); m/e 151 (M⁺). A solution of this compound in acetic acid was treated with isoamyl nitrite at room temperature (12 h) and hypoxanthine (9, R = H) was obtained in 69% yield, mp > 310 °C (from EtOH) (lit., ²¹, 28-30 mp > 350 °C); m/e 136 (M⁺). The compound was identical in all respects with an authentic specimen. This method represents a simple and short synthesis of hypoxanthine.

The 2-thioxo analog of hypoxanthine (10) could be prepared in a relative simple manner by heating 4-aminoimidazole-5-carboxamide (6, R = NH₂) hydrochloride in pyridine and in the presence of phenyl isothiocyanate for 2 h. The

separated product was crystallized from *N,N'*-dimethylformamide and toluene and had mp > 280 °C (yield 76%) (lit., ²¹ mp 325-340 °C). The product was identical with an authentic specimen prepared according to ref. ³¹. *M/e* 168 (*M*⁺) and δ nmr (DMSO-*d*₆) 8.01 (s, *H*₈). From the filtrate *N,N'*-diphenylthiourea was isolated. The above method represents a simple way for the preparation of the above thioxo analog of hypoxanthine since the difficulties in introduction of a thioxo group by ring closure of aminoimidazolecarboxamides are well known.³²

In a similar manner as described above, ethyl 3-aminopyrazole-4-carboxylate (11, *R* = *R*₁ = H) was transformed with *N,N*-dimethylformamide dimethyl acetal into the corresponding amidine (11, *RR*₁ = =CHNMe₂) in 55% yield, mp 106 °C (from *n*-heptane); *m/e* 210 (*M*⁺) and δ nmr (CDCl₃) 7.87 (s, *H*₅), 8.06 (s, CH), 3.96 (q, CH₂), 1.22 (t, CH₂Me), 2.9 (s, NMe₂). Upon treatment with hydrazine hydrate at room temperature (3 days) 5-aminopyrazolo(3,4-*d*)pyrimidin-4-one (12, *R* = NH₂) was obtained in 73% yield, mp 299-303 °C (from water); *m/e* 151 (*M*⁺). Deamination with isoamyl nitrite or nitrous acid at room temperature afforded in 76% yield allopurinol (12, *R* = H), mp > 315 °C (from water) (lit., ³³ mp 383-384 °C), identical with an authentic specimen; ³⁴ *m/e* 136 (*M*⁺) and δ nmr (DMSO-*d*₆) 7.66 and 7.54 (s, *H*₃ and *H*₆).

Also 3-amino-4-cyanopyrazole (13, *R* = *R*₁ = H) was easily transformed into the corresponding amidine (13, *RR*₁ = =CHNMe₂) in 86% yield. The product was first sublimed at 160-170 °C/10 mm and then crystallized from a mixture of benzene and *n*-hexane, or from 1,2-dimethoxyethane, mp 168-170 °C; *m/e* 163 (*M*⁺) and δ nmr (DMSO-*d*₆) 7.71 and 7.68 (s, *H*₅ and CH), 2.84 (s, Me₂N). Treatment of this compound with ethanolic hydrazine hydrate at room temperature (3 days) afforded 4,5-diaminopyrazolo(3,4-*d*)pyrimidine (14) in 60% yield, mp 242-246 °C; ir no CO or CN absorption, *m/e* 150 (*M*⁺) and δ nmr (DMSO-*d*₆) 7.61 and 7.06 (s, *H*₃ and *H*₆). Satisfactory analyses (C, H, N) were obtained for all compounds.

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