NEW SYNTHETIC APPROACH FOR AZOLOPURINES AND ANALOGS

Miha Tišler*, Branko Stanovnik, and Zdenka Zrimšek
Department of Chemistry, University E. Kardelj,
61000 Ljubljana, Yugoslavia

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 Y-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 N^6-(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]

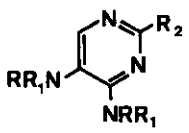
Our recent investigations in heterocyclic amidines as synthons for bi- and polycyclic heterocyclic systems [12-19] prompted us to investigate the possibility of synthesizing some azolopurines. In the first approach, the appropriate pyrimidines were used as starting material. From 2,4,5-triaminopyrimidine and N,N-dimethylformamide dimethyl acetal under various reaction conditions only the corresponding triamidine (1, R, R_1 = Me_2NCH=, R_2 = Me_2NCH=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 tive the corresponding purine derivative (2, R = Me_2NCH=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, R_1 = HCO, R_2 = 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 = NH_2) 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^+).

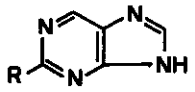
In a similar manner, 2-chloro-4,5-diaminopyrimidine (1, R = R_1 = H, R_2 = Cl) was transformed with N,N-dimethylformamide dimethyl acetal in hot N,N-dimethylformamide to 2-dimethylaminopurine (2, R = Me_2N) in 37% yield, mp about 260 °C (dec) (from toluene); m/e 163 (M^+). Apparently, ring closure was 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 = $NHNH_2$) 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-d_6 at 120 °C) revealed three singlets at δ 9.23 (H_1), 8.86 (H_5) and 8.09 (H_7) and is compatible with the angular structure (3). In the alternative case one would expect a very significant downfield shift for H_8 in 4 as observed in the case of the linear tetrazolo(1,5-a)purine.[25]

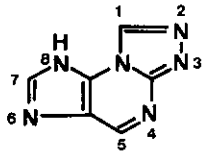
We have further attempted to prepare a fused tricycle based on adenine by ring closure at N_1. Adenine could be transformed with N,N-dimethylformamide dineopentyl acetal in boiling N,N-dimethylformamide (1 h) to the corresponding 6-N,N-dimethylaminomethyleneaminopurine (5, R = $Me_2NCH{=}N$) in 88% yield, mp 268-270 °C (from N,N-dimethylformamide and ethyl acetate); m/e 190 (M^+) and δ nmr (DMSO-d_6, 80 °C) three singlets at 8.81, 8.15 and 8.36, corresponding to H_2, H_8 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



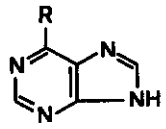
1



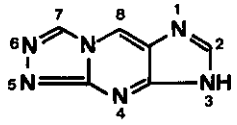
2



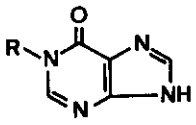
3



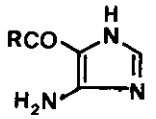
5



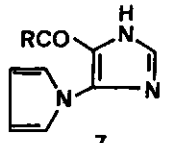
4



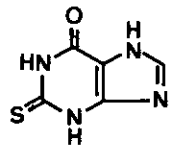
9



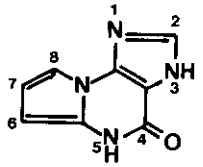
6



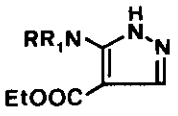
7



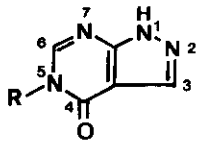
10



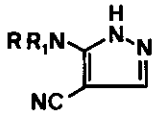
8



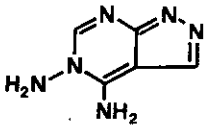
11



12



13



14

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-d_6, 145 °C) 8.29 (s, H_2), 8.13 and 8.11 (s, H_8 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-d_6) 8.52 (s, H_2), 8.26 (s, H_8), 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 ($CDCl_3$, 50 °C) 7.19 (s, H_2), 7.47 (m, H_2- and H_5-), 6.23 (m, H_3- and H_4-), 4.80 (q, CH_2), 1.33 (t, Me). The compound was transformed with ethanolic hydrazine hydrate (30 min reflux) into the corresponding hydrazide (7, R = $NHNH_2$) 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 = $NHNH_2$) (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 = NH_2 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 = NH_2) 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 = =CHNMe_2) in 55% yield, mp 106 °C (from n-heptane); m/e 210 (M^+) and δ nmr ($CDCl_3$) 7.87 (s, H_5), 8.06 (s, CH), 3.96 (q, CH_2), 1.22 (t, CH_2Me), 2.9 (s, NMe_2). Upon treatment with hydrazine hydrate at room temperature (3 days) 5-aminopyrazolo(3,4-d)pyrimidin-4-one (12, R = NH_2) 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 = =CHNMe_2) 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, Me_2N). Treatment of this compound with ethanolic hydrazine hydrate at room temperature (3 says) 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.

ACKNOWLEDGEMENT. We would like to express our thanks to Dr. E. F. Elslager, Parke-Davis & Co., Ann Arbor, Michigan, for the donation of 4-aminoimidazole-5-carboxamide hydrochloride.

REFERENCES

1 K. Nakanishi, N. Furutachi, M. Funamizu, D. Grunberger, and I.B. Weinstein, J. Am. Chem. Soc., 1970, 92, 7617.

2 K. Nakanishi, S. Blobstein, M. Funamizu, N. Furutachi, G. Van Lear, D. Grunberger, K. W. Lanks, and I. B. Weinstein, Nature, 1971, 234, 107.

3 S. Blobstein, D. Grunberger, I.B. Weinstein, and K. Nakanishi, Biochemistry, 1973, 12, 188.

4 A.M. Feinberg, K. Nakanishi, J. Barciszewski, A. J. Rafalski, H. Augustyniak, and M.Wiewiorowski, J. Am. Chem. Soc., 1974, 96, 7797.

5 H. Kasai, Z. Yamaizumi, Y. Kuchino, and S. Nishimura, Nucl. Acid Res., 1973, 6, 993.

6 H.Kasai, M.Goto, S. Takemura, T. Goto, and S. Matsuura, Tetrahedron Letters, 1971, 2725.

7 A. Mochizuki, Y. Omata, and Y. Miyazawa, Bull. Chem. Soc. Japan, 1980, 53, 813.

8 U.L. Raj Bhandary, S. H. Chang, A. Stuart, R. D. Faulkner, R. M. Hoskinson, and H. G. Khorana, Proc. Natl. Acad. Sci., 1967, 57, 751.

9 R. H. Hall, M. J. Robins, L. Stasiuk, and R. Thedford, J. Am. Chem. Soc., 1966, 88, 2614.

10 K. Biemann, S. Tsunakawa, J. Sonnenbichler, H. Feldmann, D. Dütting, and H. G. Zachau, Angew. Chem., 1966, 78, 600.

11 T.Green and D. E. Hathway, Chem. Biol. Interactions, 1978, 22, 211.

12 B. Verček, I. Leban, B. Stanovnik, and M. Tišler, J. Org. Chem., 1979, 44, 1695.

13 M.Zupan, B. Stanovnik, and M. Tišler, J. Org. Chem., 1972, 37, 2960.

14 M. Tišler and B. Stanovnik, J. Chem. Soc., Chem. Commun., 1980, 313.

15 M. Debeljak-Šuštar, B. Stanovnik, M. Tišler, and Z. Zrimšek, J. Org. Chem., 1978, 43, 393.

16 S. Polanc, B. Verček, B. Šek, B. Stanovnik, and M. Tišler, J. Org. Chem., 1974, 39, 2143.

17 B. Jenko, B. Stanovnik, and M. Tišler, Synthesis, 1976, 833.

18 B. Verček, B. Stanovnik, M. Tišler, and Z. Zrimšek, Org. Prep. Proced. Intern., 1978, 10, 293.

19 K. Babič, S. Molan, S. Polanc, B. Stanovnik, J. Stres-Bratoš, M. Tišler, and B. Verček, J. Heterocycl. Chem., 1976, 13, 487.

20 B. Stanovnik and M. Tišler, Synthesis, 1974, 120.

21 R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, J. Am. Chem. Soc., 1953, 75, 263.

22 S. R. Breshears, S. S. Wang, S. G. Bechtolt, and B.E. Christensen, J. Am. Chem. Soc., 1959, 81, 3789.

23 J. A. Montgomery, J. Am. Chem. Soc., 1956, 78, 1928.

24 J. A. Montgomery and L. B. Holum, J. Am. Chem. Soc., 1957, 79, 2185.

25 C. Temple, M. C. Thorpe, W. C. Coburn, and J. A. Montgomery, J. Org. Chem., 1966, 31, 935.

26 B. Stanovnik, M. Tišler, A. Hribar, D. J. Brown, and G. B. Barlin, Austral. J. Chem., 1981, in press.

27 J. Davoll and B. A. Lowy, J. Am. Chem. Soc., 1951, 73, 1650.

28 E. Richter, J. E. Loeffler, and E. C. Taylor, J. Am. Chem. Soc., 1960, 82, 3144.

29 E. C. Taylor and C. C. Cheng, J. Org. Chem., 1960, 25, 148.

30 D. M. Brown and A. Giner-Sorolla, J. Chem. Soc., C, 1971, 128.

31 A. Yamazaki, I. Kumashiro, and T. Takenishi, J. Org. Chem., 1967, 32, 3032.

32 A. Yamazaki and M. Okutsu, J. Heterocycl. Chem., 1978, 15, 353.

33 Kha-Vang-Thang and F. Delbarre, Compt. rend. Acad. Sci., Ser. C, 1969, 268, 525.

34 R. K. Robins, J. Am. Chem. Soc., 1956, 78, 784.

Received, 25th August, 1981