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Synthesis of Structurally Related Purines: Benzimidazo[1,2-*a*]pyridines, Benzimidazo-[1,2-*c*]pyrimidines, and Pyrazolo-[1,5-*a*]pyrimidines

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Summary. Reactions of sodium salts of 3-hydroxymethylene-2-alkanones with 2-cyanomethylbenzimidazole afforded benzimidazo[1,2-*a*]pyridines. Analogues reactions with 2-aminobenzimidazole and 5-aminopyrazoles afforded benzimidazo[1,2-*c*]pyrimidines and pyrazolo[1,5-*a*]pyrimidines.

Keywords. 3-Hydroxymethylene-2-alkanone salts; Benzimidazole derivatives; 5-Aminopyrazoles; Benzimidazo pyridines; Pyrazolo pyrimidines.

Introduction

Synthetic analogs of purines are widely used in the medical sciences and in clinical medicine. Typically, most applications exploit the role of their nucleotides as components of the nucleic acids essential for cellular growth and division. For a cell to divide, its *DNA* must be replicated, and therefore all its precursors must be available. The pharmacologic approach uses an analog in which the heterocyclic ring structure has been altered in a way to induce toxic effects when the analog is incorporated into specific cellular constituents. As a part of our program directed to the development of new simple and efficient procedures for the synthesis of antimetabolites [1–3], we have recently reported different successful approaches for the synthesis of purine, pyrimidine nucleoside, and 5-deazafolic analogues [4, 5]. Derivatives of these ring system are interesting because they have useful properties as antimetabolites in biochemical reactions. We now report a one-step synthesis of interesting purine analogues by reactions of substituted methyldiazoles and aminodiazole derivatives with sodium salts of 3-hydroxymethylene-2-alkanones.

Results and Discussion

It was found that 2-cyanomethylbenzimidazole (**1**) reacts with sodium salts of 3-hydroxymethylene-2-alkanones (**2**) to yield a 1:1 adduct. Two isomeric structures

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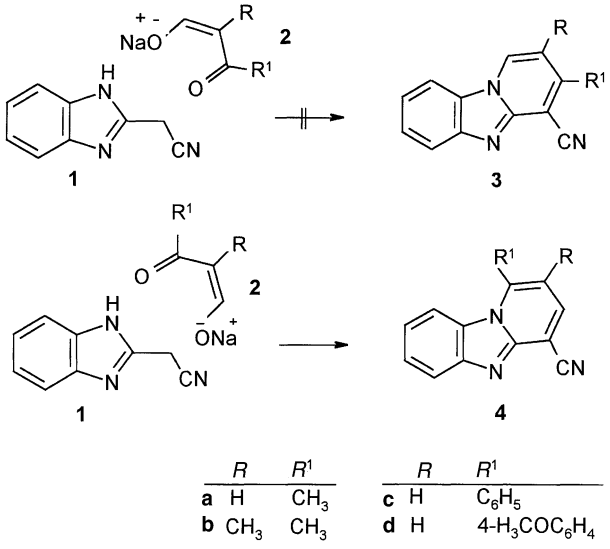


Scheme 1

are possible in principle (**3** and **4**, Scheme 1). The spectroscopic data were of little help in discriminating between these structures. In order to establish unambiguously the structure of the products, their crystal structure was determined. The X-ray analysis confirmed the exclusive presence of **4** in the solid state (Fig. 1). This implies that the active methylene group of **1** will initially attack the unhindered formyl group of **2** to yield the substituted imidazo[1,2-*a*]pyridine-4-carbonitriles **4** rather than attacking the hindered and electronically disfavoured keto group leading to **3**. The X-ray analysis for compound **4b** revealed that molecules of type **4** are planar (mean deviation of non-H atoms from least-squares plane: 0.030 Å). The bond lengths and angles are closely similar to those of a benzimidazo[1,2-*a*]pyridine derivative with a further annelated seven-membered ring [6]. In

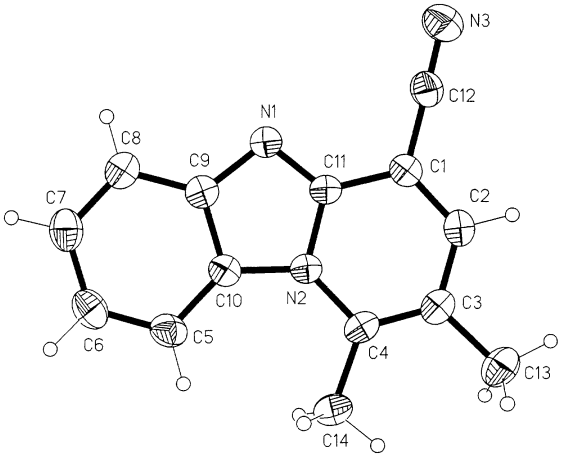
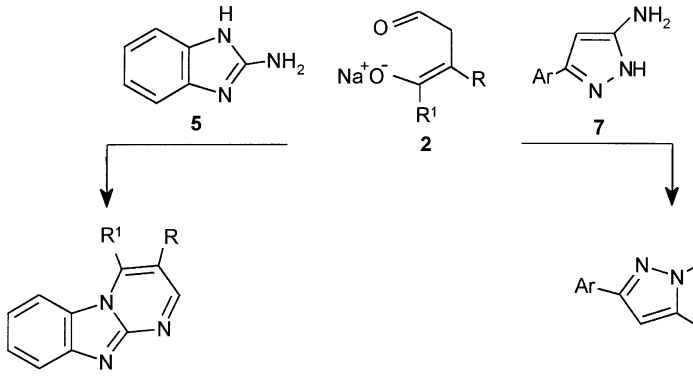


Fig. 1. Crystal structure of **4b**; ellipsoids represent 50% probability levels; H atom radii are arbitrary



6	R	R^1
a	H	CH_3
b	CH_3	CH_3
c	H	C_6H_5

8	R	R^1	Ar
a	H	CH_3	C_6H_5
b	H	CH_3	4-$H_3CC_6H_4$
c	CH_3	CH_3	C_6H_5
d	CH_3	CH_3	4-$H_3CC_6H_4$

8	R	R^1	Ar
e	H	C_6H_5	C_6H_5
f	H	C_6H_5	4-$H_3CC_6H_4$
g	H	4-$H_3COC_6H_4$	C_6H_5
h	H	4-$H_3COC_6H_4$	4-$H_3CC_6H_4$

Scheme 2

particular, wide angles are observed exocyclic to the five-membered ring (*e.g.* C1-N1-C9: 132.41(18), C8-C9-N1: 134.2(2)°).

We became interested to see if these reactions can be extended to aminodiazoles. Thus, the behaviour of 2-aminobenzimidazole (**5**) towards salts **2** was also investigated. Products resulting from condensation at the active sites of benzimidazole were obtained. Accordingly, substituted imidazo[1,2-*a*]pyrimidines **6** were obtained (Scheme 2). The structure of compounds **6** could be established and confirmed on the basis of their elemental analyses and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and MS; see Experimental).

Similarly, 5-aminopyrazoles (**7**) reacted with **2** under the same conditions to yield the pyrazolo[1,5-*a*]pyrimidines **8**. The structure of compounds **8** was established on the basis of their elemental analyses and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and MS; see Experimental).

In conclusion, we have developed an excellent route for the synthesis of several otherwise difficult accessible purine analogues by the reaction of sodium salts of 3-hydroxymethylene-2-alkanones with substituted methylazoyl and aminodiazole derivatives. The obtained products are promising for biological evaluation studies.

Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra (KBr): Pye Unicam; ^{1}H NMR and ^{13}C NMR spectra (*DMSO*-d_6): Wilmad 270 MHz, *TMS* as internal standard, chemical shift in δ (ppm); mass spectra: Shimadzu GCMS-QP 100 EX (70 eV); microanalytical data: Microanalytical Data Center at Cairo University.

1,2-Disubstituted Benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitriles (**4a–d**; general method)

A solution of 2-cyanomethylbenzimidazole (**1**, 0.01 mol), sodium salt of 3-hydroxymethylene-2-alkanones **2** (0.01 mol), and 1 cm^3 piperidine acetate in 50 cm^3 H_2O and 30 cm^3 EtOH was refluxed

for 10 min. 1.5 cm^3 acetic acid were added to the hot solution. The precipitated solid was collected by filtration and crystallized from the appropriate solvent.

1-Methyl-benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**4a**; $C_{13}H_9N_3$)

Yield: 1.2 g (60%); m.p.: 210°C (EtOH); IR (KBr): 2229 (CN) cm^{-1}; ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.32 (s, 3H, CH_3), 6.50 (d, 1H, H-5), 7.81–8.10 (m, 4H, C_6H_4), 8.20 (d, 1H, H-4) ppm; MS: *m/z* = 207(M^+, 72.6%).

1,2-Dimethyl-benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**4b**; $C_{14}H_{11}N_3$)

Yield: 1.1 g (50%); m.p.: 254°C (EtOH/dioxane); IR (KBr): 2229 (CN) cm^{-1}; ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.40 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 7.90–8.42 (m, 4H, C_6H_4), 8.18 (s, 1H, H-4) ppm; MS: *m/z* = 221 (M^+, 85.3%).

1-Phenyl-benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**4c**; $C_{18}H_{11}N_3$)

Yield: 1.7 g (67%); m.p.: >300°C (AcOH); IR (KBr): 2229 (CN) cm^{-1}; ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 6.51 (d, 1H, H-5), 6.90–8.0 (m, 4H, C_6H_4), 7.18–7.70 (m, 5H, C_6H_5), 8.32 (s, 1H, H-4) ppm; MS: *m/z* = 269 (M^+, 78.3%).

1-(4-Methoxyphenyl)-benzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (**4d**; $C_{19}H_{13}N_3O$)

Yield: 2 g (67%); m.p:. >300°C (AcOH); IR (KBr): 2228 (CN) cm^{-1}; ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 6.61 (d, 1H, H-5), 6.90–7.80 (m, 4H, C_6H_4), 7.21–8.20 (m, 4H, C_6H_4), 8.35 (d, 1H, H-4) ppm; MS: *m/z* = 299 (M^+, 80.0%).

3,4-Disubstituted Benzo[4,5]imidazo[1,2-a]pyrimidines (**6a–c**; general method)

A solution of 2-aminobenzimidazole (**5**, 0.01 mol), sodium salt of 3-hydroxymethylene-2-alkanones **2** (0.01 mol), and 1 cm^3 piperidine acetate in 50 cm^3 H_2O and 30 cm^3 EtOH was refluxed for 10 min. 1.5 cm^3 acetic acid were added to the hot solution. The precipitated solid was collected by filtration and crystallized from the appropriate solvent.

4-Methyl-benzo[4,5]imidazo[1,2-a]pyrimidine (**6a**; $C_{11}H_9N_3$)

Yield: 0.8 g (45%); m.p.: 225°C (EtOH); MS: *m/z* = 183 (M^+, 82.3%).

3,4-Dimethyl-benzo[4,5]imidazo[1,2-a]pyrimidine (**6b**: $C_{12}H_{11}N_3$)

Yield: 0.7 g (40%); m.p.: 267°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.31 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.32–7.50 (m, 4H, C_6H_4), 8.20 (s, 1H, H-4) ppm; MS: *m/z* = 197 (M^+, 78.5%).

4-Methyl-3-phenyl-benzo[4,5]imidazo[1,2-a]pyrimidine (**6c**; $C_{16}H_{11}N_3$)

Yield: 1.4 g (60%); m.p.: 285°C (EtOH); MS: *m/z* = 245 (M^+, 84.3%).

6,7-Disubstituted Pyrazolo[1,5-a]pyrimidines (**8a–h**; general method)

A solution of 5-aminopyrazoles (**7**, 0.01 mol), sodium salt of 3-hydroxymethylene-2-alkanones **2** (0.01 mol), and 1 cm^3 piperidine acetate in 50 cm^3 H_2O and 30 cm^3 EtOH was refluxed for 10 min.

1.5 cm^3 acetic acid were added to the hot solution. The precipitated solid was collected by filtration and cystallized from the appropriate solvent.

7-Methyl-2-phenyl-pyrazolo[1,5-a]pyrimidine (**8a**; $C_{13}H_{11}N_3$)

Yield: 0.4 g (78%); m.p.: 200°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.40 (s, 3H, CH_3), 6.92 (d, 1H, H-6), 7.07 (s, 1H, H-3), 7.46–8.04 (m, 5H, C_6H_5), 8.97 (d, 1H, H-5) ppm; MS: *m/z* = 209 (M^+, 76.5%).

7-Methyl-2-(4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (**8b**; $C_{14}H_{13}N_3$)

Yield: 1.3 g (60%); m.p.: 220°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.90 (d, 1H, H-6), 7.10 (s, 1H, H-3), 7.50–8.20 (m, 4H, C_6H_4), 8.95 (d, 1H, H-5) ppm; MS: *m/z* = 223 (M^+, 76.5%).

6,7-Dimethyl-2-phenyl-pyrazolo[1,5-a]pyrimidine (**8c**; $C_{14}H_{13}N_3$)

Yield: 1.7 g (78%); m.p.: 165°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.24 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.98 (s, 1H, H-3), 7.46–8.0 (m, 5H, C_6H_5), 8.81 (s, 1H, H-5) ppm; MS: *m/z* = 223.

6,7-Dimethyl-2-(4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (**8d**; $C_{15}H_{15}N_3$

Yield: 2 g (84%); m.p.: 215°C (AcOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.24 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.92 (s, 1H, H-3), 7.27–7.85 (m, 4H, C_6H_4), 8.79 (s, 1H, H-5) ppm; ^{13}C NMR (67.5 MHz, δ, *DMSO*-d_6): 15.4 (CH_3), 20.8 (CH_3), 22.7 (CH_3), 91.0 (C-3), 117.4 (C-7), 125.8–132.4 (aromatic carbons), 138.0 (C-6), 147.7 (C-5), 154.0 (C-2) and 159.6 (C-3a) ppm; MS: *m/z* = 237 (M^+, 81.4%).

2,7-Diphenyl-pyrazolo[1,5-a]pyrimidine (**8e**; $C_{18}H_{13}N_3$)

Yield: 2 g (82%); m.p.: 200°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 6.90 (d, 1H, H-6), 7.12 (s, 1H, H-3), 7.36–8.10 (m, 10H, $2C_6H_5$), 8.92 (d, 1H, H-5) ppm; MS: *m/z* = 271.

2-(4-Methylphenyl)-7-phenyl-pyrazolo[1,5-a]pyrimidine (**8f**; $C_{19}H_{15}N_3$)

Yield: 2.1 g (75%); m.p.: 230°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.34 (s, 3H, CH_3), 6.90 (d, 1H, H-6), 7.06 (d, 1H, H-3), 7.24–8.0 (m, 4H, C_6H_4), 7.46–7.74 (m, 5H, C_6H_5), 8.97 (d, 1H, H-5) ppm; MS: *m/z* = 285 (M^+, 78.5%).

2-Phenyl-7-(4-methoxyphenyl)-pyrazolo[1,5-a]pyrimidine (**8g**; $C_{19}H_{15}N_3O$)

Yield: 2.3 g (75%); m.p.: 140°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 7.19 (d, 1H, H-6), 7.23–8.0 (m, 5H, C_6H_5), 7.30 (s, 1H, H-3), 7.47–8.38 (m, 4H, C_6H_4), 8.55 (d, 1H, H-5) ppm; MS: *m/z* = 301 (M^+, 84.2%).

2-(4-Methylphenyl)-7-(4-methoxyphenyl)-pyrazolo[1,5-a]pyrimidine (**8h**; $C_{20}H_{17}N_3O$)

Yield: 2 g (65%); m.p.: 166°C (EtOH); ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 2.26 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.10 (d, 1H, H-6), 7.20 (s, 1H, H-3), 7.30–8.34 (m, 8H, $2C_6H_4$), 8.53 (d, 1H, H-5) ppm; MS: *m/z* = 315.

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters; $U_{eq} = (1/3)\,\Sigma_i\Sigma_j U^{ij}\alpha^i\alpha^j a_i a_j$

	x	y	z	U_{eq}
N1	0.2307(2)	0.4811(2)	0.52358(9)	0.0266(4)
C2	0.1953(2)	0.3651(3)	0.46758(11)	0.0263(5)
C3	0.2334(3)	0.4113(3)	0.39549(11)	0.0315(5)
C4	0.3030(3)	0.5640(3)	0.38293(11)	0.0324(5)
C5	0.3375(3)	0.6783(3)	0.44046(12)	0.0315(5)
C6	0.2983(2)	0.6374(3)	0.51024(11)	0.0288(5)
N2	0.1294(2)	0.2243(2)	0.49023(9)	0.0296(4)
C7	0.1821(3)	0.4030(3)	0.58794(11)	0.0281(5)
C8	0.1854(3)	0.4491(3)	0.66176(11)	0.0369(6)
C9	0.1233(3)	0.3372(3)	0.71037(12)	0.0432(6)
C10	0.0592(3)	0.1819(3)	0.68801(12)	0.0411(6)
C11	0.0568(3)	0.1342(3)	0.61540(12)	0.0340(5)
C12	0.1195(3)	0.2468(3)	0.56517(11)	0.0287(5)
C13	0.1920(3)	0.2956(3)	0.33753(12)	0.0387(6)
C14	0.4099(3)	0.8459(3)	0.42232(14)	0.0441(6)
C15	0.3195(3)	0.7521(3)	0.57402(12)	0.0387(6)
N3	0.1578(3)	0.2015(3)	0.29170(12)	0.0593(7)

X-Ray analysis

The X-ray structure analysis for **4b** was performed at the Institute of Organic Chemistry at Braunschweig, Germany. H atoms: methyl groups were held rigid, allowed to rotate, however not to tip; starting positions from difference synthesis, others riding. Data collection: Stoe DIF4 [7]. Cell refinement: Stoe DIF4. Data reduction: Stoe REDU4 [8]. Program used to solve structure: SHELXS86 [9]. Program used to refine structure: SHELXL97 [10]. Molecular graphics: Siemens XP [11]. Software used to prepare material for publication: SHELX-97.

The molecule of **4b** (Fig. 1) is planar (mean deviation of non-H atoms from least-squares plane: 0.030Å). Crystal data of **4b**: $C_{14}H_{11}N_3$; $M_r = 221.26$; monoclinic; $P2_1/n$; $a = 7.469(2)$, $b = 8.106(2)$, $c = 18.238(4)$ Å; $\beta = 93.78\ (3)^\circ$; $V = 1101.8\ (5)$ Å^3; $Z = 4$; $D_x = 1.334\,\mathrm{Mg \cdot m^{-3}}$; D_m not measured; MoK_α radiation; $\lambda = 0.71073$ Å. Cell parameters from 46 reflections; $\theta = 10.0$–11.5°; $\mu = 0.082\,\mathrm{mm^{-1}}$; $T = 143(2)$ K; crystal: $0.80\times0.25\times0.10$ mm, pale yellow. Data collection: Stoe Stadi-4 diffractiometer; w/θ scans; absorption correction: none; 2722 measured reflections; 1935 independent reflections; 1448 reflections with $I > 2\sigma(I)$ $R_{int} = 0.0284$; $\theta_{max} = 25.03^\circ$; $h = 0 \rightarrow 8$; $k = -9 \rightarrow 3$; $l = -12 \rightarrow 21$; 3 standard reflections; frequency: $60\,\mathrm{min^{-1}}$; intensity decay: none; refinement on F^2; $R(F^2 > 2\sigma(F^2)) = 0.0490$; $wR\ (F^2) = 0.1316$; $S = 1.043$; 1935 reflections; 156 parameters; mixed; $w = 1/(\sigma^2\ (F_o^2)\ +(0.0631\ P)^2\ +0.2377\ P)$ where $P = (F_o^2 + 2F_o^2)/3$; $(\Delta/\sigma)_{max} < 0.001$; $\Delta\rho_{max} = 0.159\,\mathrm{e \cdot Å^{-3}}$; $\Delta\rho_{min} = -0.18\,\mathrm{e \cdot Å^{-3}}$; extinction correction: none scattering factors: see Ref. [12].

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