# A Novel Method for the Synthesis of 9-Benzyl-6-(2-methylhydrazino)purine and 1-Methyl-4-(2-methylhydrazino)-1*H*-pyrazolo[3,4-*d*]pyrimidine

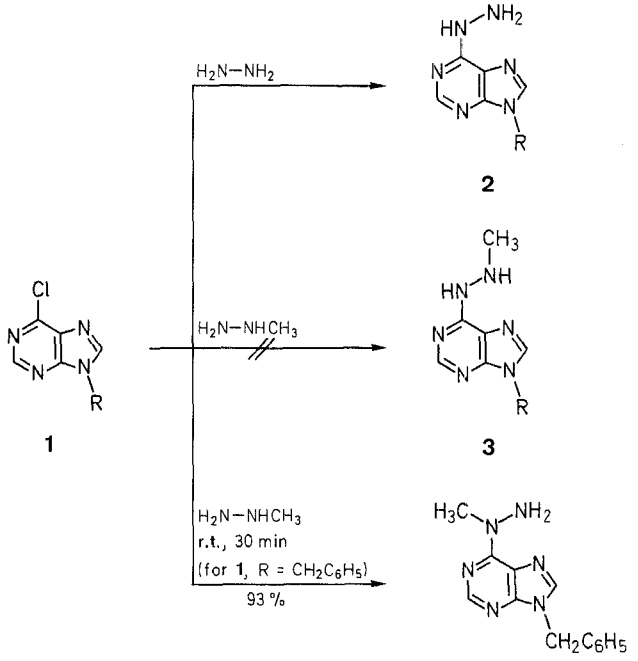
Ramachandra S. Hosmane,* Benjamin B. Lim

Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Catonsville, MD 21228, USA

A novel method for the synthesis of 9-benzyl-6-(2-methylhydrazino)purine (**8a**) and 1-methyl-4-(2-methylhydrazino)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8b**) is reported. The method consists of reacting the formimidates of the corresponding 5-amino-4-cyanoimidazole and -pyrazole (i.e. **6a** and **6b**, respectively) with excess methylhydrazine catalyzed by trifluoroacetic acid. A tentative mechanism for the reaction is proposed.

6-Hydrazinopurines and its analogues are of interest in view of their little explored chemical, biological and chemotherapeutic properties.[1] While the parent or the 9-substituted 6-hydrazinopurines **2** (Scheme **A**) can be prepared by reaction of the corresponding 6-chloropurines **1** with hydrazine, the analogous 6-(2-methylhydrazino)purines **3** cannot be accessed by this route, since methylhydrazine is known to react with electrophiles from its *N*-methyl end.[2,3]

Indeed, when **1** (R = benzyl) was reacted with methylhydrazine, the product obtained was 9-benzyl-6-(1-methylhydrazino) pourine (**4**), as evidenced by its $^1$H-NMR spectrum, which exhibited singlets for both the methyl ($\delta$ = 3.59) and amine ($\delta$ = 5.55) functions, and by UV data (see experimental), which were significantly different, especially in basic medium, from those of the corresponding 9-benzyl-6-hydrazinopurine (**2**; R = benzyl)[4] [UV $\lambda_{max}$ (EtOH) 266 nm; (pH 1) 263 nm; (pH 13) 294, 320 nm).



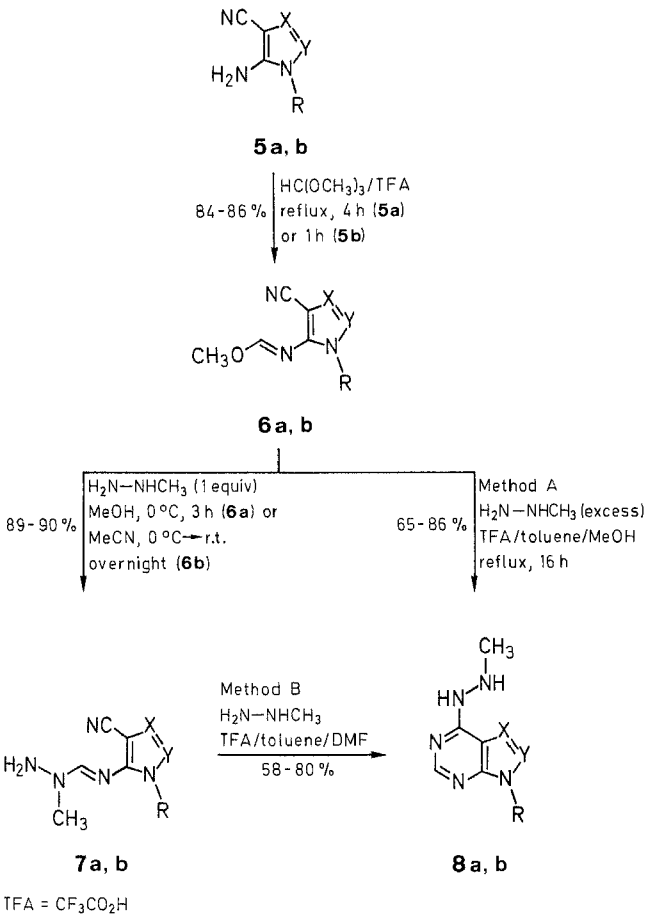

Scheme A

We report here a simple and efficient method for the synthesis of the hitherto unknown 9-benzyl-6-(2-methylhydrazino)purine (**8a**) and of 1-methyl-4-(2-methylhydrazino)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8b**). The method is also potentially applicable to the synthesis of other 2-alkylhydrazino derivatives and for heterocyclic systems other than the ones reported here.

Our method (Scheme **B**) consists of reacting the formimidates **6a, b** prepared from 5-amino-1-benzyl-4-cyanoimidazole (**5a**)[5] and 5-amino-4-cyano-1-methylpyrazole (**5b**),[6] respectively, with excess methylhydrazine catalyzed by trifluoroacetic acid (TFA). Spectral data for the products obtained agreed with structures **8a, b**. The UV spectrum of **8a** (see experimental) was very similar to that of **2** (R = benzyl) (*vide supra*), and the methyl absorption of the methylhydrazino group in the $^1$H-NMR of both **8a** and **8b** appeared in the expected $\delta$ = 2.6 range, as opposed to $\delta$ = 3.59 (*vide supra*) for the methyl of **4**. Finally, the structure **8b** was confirmed by a single crystal X-ray analysis.[7]

In considering a mechanism for the conversion of **6** into **8**, the following observations were taken into consideration: (a) when the imidates **6a, b** were treated with one equivalent each of methylhydrazine at room temperature, the ring-open formohydrazide imides **7a** and **7b**, respectively, were isolated. Compounds **7a** and **7b** both exhibited a C≡N absorption in IR at ca. 2200 cm$^{-1}$ and singlets in $^1$H-NMR spectrum for the sidechain methyl ($\delta$ = ca. 3.20) and $NH_2$ ($\delta$ = ca. 5.30); (b) the isolated formohydrazide imide intermediates, **7a** and **7b**, upon further reaction with excess methylhydrazine catalyzed by trifluoroacetic acid yielded **8a** and **8b**, respectively; (c) the conversion **7** → **8** failed in the absence of acid catalysis, in spite of the presence of excess methylhydrazine; (d) the above conversion also failed in the absence of methylhydrazine despite acid catalysis; and (e) the amount of methylhydrazine for the conversion **7** → **8** needed

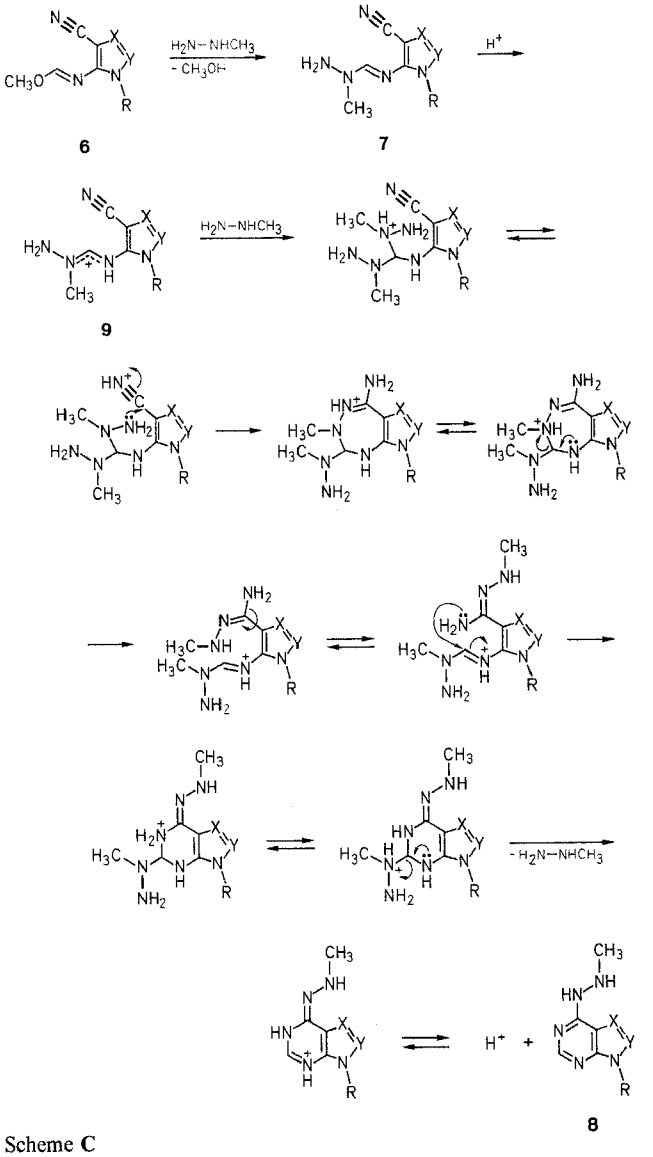
only be catalytic, although an excess aided in faster conversion. Based upon these experimental observations, we tentatively propose the mechanism in Scheme **C** for the conversion **6** → **8**.




TFA = $CF_3CO_2H$

| 5–8 | X | Y | R |
|---|---|---|---|
| **a** | N | CH | $CH_2C_6H_5$ |
| **b** | CH | N | $CH_3$ |

Scheme **B**




Scheme **C**

$^1$H-NMR spectra were recorded on an IBM NR/80 spectrometer. EI mass spectra were performed at the School of Pharmacy, University of Maryland at Baltimore, on a Du Pont 21-490 mass spectrometer with a 21-094 data system and an Extranuclear Simulscan GC/MS instrument. IR spectra were obtained on a Perkin-Elmer 1420 Ratio Recording Instrument. Elemental microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

**9-Benzyl-6-(1-methylhydrazino)purine (4):**
A mixture of 9-benzyl-6-chloropurine[4] (300 mg, 1.23 mmol) and methylhydrazine (1 mL, 18.8 mmol) is stirred under $N_2$ for 30 min. To the reaction mixture is added a mixture of ligroin/ether (1:1) until the precipitation of white solid is complete. The solid is filtered by suction, washed with cold water and recrystallized from water to give **4** as colorless crystals; yield: 290 mg (93%); mp 123–125 °C.

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{14}N_6$ | calc. | C 61.40 | H 5.55 | N 33.05 |
| (254.3) | found | 61.38 | 5.58 | 33.00 |

MS (70 eV): $m/z$ = 254 ($M^+$), 238 ($M^+$-$NH_2$).

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 3.59 (s, 3 H, $CH_3$); 5.40 (s, 2 H, $CH_2$); 5.55 (s, 2 H, $NH_2$, exchangeable with $D_2O$); 7.31 (s, 5 H, $C_6H_5$); 8.22 (s, 1 H, CH); 8.29 (s, 1 H, CH).

UV (EtOH): $\lambda_{max}$ = 276 nm; (pH 1) 266 nm; (pH 13) 276 nm.

**1-Benzyl-4-cyano-5-(methoxymethyleneamino)imidazole (6a):**
A mixture of 5-amino-1-benzyl-4-cyanoimidazole[5] (1.4 g, 7.07 mmol), trimethyl orthoformate (50 mL, 0.46 mol), and TFA (0.125 mL, 1.62 mmol) is heated at reflux under $N_2$ for 4 h. A TLC of the reaction mixture (silica gel, $CHCl_3$/MeOH, 4:1) indicated the formation of a less polar (faster moving), intense UV absorbing compound. The reaction mixture is evaporated to dryness on a rotary evaporator to obtain a yellow liquid, which solidified upon refrigeration for several hours.

The solid is recrystallized from benzene/petroleum ether (30–60 °C) to give **6a** as colorless crystals; yield: 1.33 g (84%); mp 69–71 °C.

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{12}N_4O$ | calc. | C 64.98 | H 5.04 | N 23.32 |
| (240.3) | found | 65.05 | 5.04 | 23.30 |

MS (70 eV): $m/z$ = 240 ($m^+$).

IR (neat): $\nu$ = 2250 (C≡N) $cm^{-1}$.

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 3.89 (s, 3 H, $CH_3$); 5.14 (s, 2 H, $CH_2$); 7.31 (s, 5 H, $C_6H_5$); 7.87 (s, 1 H, imidazole CH); 8.43 (s, 1 H, OCH=N).

**4-Cyano-5-(methoxymethyleneamino)-1-methylpyrazole (6b):**
A mixture of 5-amino-4-cyano-1-methylpyrazole[6] (2 g, 16.4 mmol), trimethyl orthoformate (50 mL, 0.46 mol) and TFA (0.1 mL, 1.3 mmol) is heated at reflux under $N_2$ for 1 h. The reaction mixture is cooled and evaporated on a rotary evaporator to dryness. The residual oil is directly employed in the next step. Further purification of the oil, if desired, can be effected by distillation in a Kugelrohr apparatus (oven temperature: 94–106 °C/0.25 Torr) to obtain **6b** as a colorless oil which solidifies upon cooling in a refrigerator overnight; yield: 2.3 g (86%).

MS (70 eV): $m/z = 164$ ($M^+$).

IR (KBr): $\nu = 2230\ cm^{-1}$.

$^1H$-NMR (DMSO-$d_6$/TMS): $\delta = 3.68$ (s, 3H, $NCH_3$); 3.95 (s, 3H, $OCH_3$); 7.87 (s, 1H, imidazole CH); 8.49 (s, 1H, OCH=N).

**9-Benzyl-6-(2-methylhydrazino)purine (8a); Typical Procedures:**

Method A: (Reaction of Formimidate **6a** with Methylhydrazine): Compound **6a** (1.2 g, 4.16 mmol) is dissolved in a mixture of dry toluene (15 mL) and dry MeOH (5 mL). To the stirring solution, under $N_2$, is added TFA (0.1 mL, 1.3 mmol), followed by methylhydrazine (0.75 mL, 14.1 mmol) dropwise during a period of 5 min. The reaction mixture is heated at reflux for 16 h, cooled and evaporated on a rotary evaporator to dryness. The residue is triturated with MeCN, and the separated solid is filtered by suction, dried *in vacuo* and recrystallized from MeCN to give **8a** as colorless crystals; yield: 1.1 g (86%), mp 117–118 °C.

Spectral data of this solid are identical with those of **8a** obtained by Method B described below.

Method B: (Reaction of Formohydrazide Imide **7a** with Methylhydrazine): To a solution of compound **7a** (see below) (500 mg, 1.96 mmol) in a mixture of dry MeOH (9 mL) and dry toluene (5 mL) is added methylhydrazine (0.5 mL, 9.4 mmol), followed by TFA (0.01 mL, 0.13 mmol). This reaction mixture is heated at reflux under $N_2$ for 15 h, cooled and evaporated on a rotary evaporator to dryness. The residue is dissolved in MeOH (20 mL), and the solution is mixed with silica gel (40–63 μm, 2 g). The mixture is evaporated to dryness, and the residue is suspended in $CHCl_3$ (10 mL). The resulting slurry is loaded onto a flash chromatography column, packed with a slurry of silica gel (40–63 μm, 20 g) in $CHCl_3$. The column is eluted with a mixture of $CHCl_3$/MeOH (39:1). The appropriate UV absorbing fractions are combined and rotary evaporated to give a solid, which is recrystallized from MeCN to give **8a** as colorless crystals; yield: 400 mg (80%); mp 119–120 °C.

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{14}N_6$ | calc. | C 61.40 | H 5.55 | N 33.05 |
| (254.3) | found | 61.43 | 5.56 | 32.96 |

MS (70 eV): $m/z = 254$ ($M^+$); 225 ($M^+$-$NCH_3$); 163 ($M^+$-$CH_2C_6H_5$).

$^1H$-NMR (DMSO-$d_6$/TMS): $\delta = 2.62$ (s, 3H, $CH_3$); 5.22 (s, 1H, NH, exchangeable with $D_2O$); 5.41 (s, 2H, $CH_2$); 7.32 (s, 5H, $C_6H_5$); 8.27 (s, 1H, CH); 8.30 (s, 1H, CH); 9.30 (s, 1H, NH, exchangeable with $D_2O$).

UV (EtOH): $\lambda_{max} = 269$ nm.

**1-Methyl-4-(2-methylhydrazino)-1*H*-pyrazolo[3,4-*d*]pyrimidine (8b):** compound **8b** is prepared in a manner analogous to that described above for compound **8a**, by employing **6b** (Method A) or **7b** (Method B): colorless crystals; yield: 65% (Method A); 58% (Method B); mp 205–207 °C.

| | | | | |
|---|---|---|---|---|
| $C_7H_{10}N_6$ | calc. | C 47.18 | H 5.66 | N 47.16 |
| (178.2) | found | 47.08 | 5.67 | 47.04 |

MS (70 eV): $m/z = 178$ ($M^+$), 163 ($M^+$-$CH_3$); 149 ($M^+$-$NCH_3$).

$^1H$-NMR (DMSO-$d_6$/TMS): $\delta = 2.58$ (s, 3H, $CH_3$); 3.88 (s, 3H, $CH_3$); 8.13 (s, 1H, CH); 8.14 (s, 1H, CH).

UV (EtOH): $\lambda_{max} = 281$ nm ($\log\varepsilon$ 4.0); (pH 0.2) 264 ($\log\varepsilon$ 4.21).

**1-Benzyl-4-cyano-5-(1-methylhydrazinomethyleneamino)imidazole (7a):** To a solution of **6a** (0.5 g, 2.1 mmol) in absolute MeOH (20 mL), cooled in an ice-water bath, is added methylhydrazine (0.12 mL, 2.2 mmol) in one portion. The resulting solution is stirred with further cooling, unter $N_2$, for 3 h. The reaction mixture is evaporated on a rotary evaporator to dryness at 23 °C to obtain a dense oil. The traces of solvent and methylhydrazine are removed using a vacuum pump. The residual oil is refrigerated overnight, and then triturated with ether to obtain a solid, which is recrystallized from benzene/petroleum ether (30–60 °C) to give **7a** as, colorless needles; yield: 0.48 g (90%); mp 96–97 °C.

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{14}N_6$ | calc. | C 61.40 | H 5.55 | N 33.05 |
| (254.3) | found | 61.44 | 5.55 | 33.00 |

MS (70 eV): $m/z = 254$ ($M^+$); 224 ($M^+$-$NHCH_3$), 163 ($M^+$-$CH_2C_6H_5$).

IR (KBr): $\nu = 2200$ (C≡N) $cm^{-1}$.

$^1H$-NMR (DMSO-$d_6$/TMS): $\delta = 3.18$ (s, 3H, $CH_3$); 5.07 (s, 2H, $CH_2$); 5.30 (br s, 2H, $NH_2$, exchangeable with $D_2O$); 7.30 (s, 5H, $C_6H_5$); 7.62 (s, 1H, imidazole CH); 8.26 (s, 1H, NCH=N).

**4-Cyano-1-methyl-5-(1-methylhydrazinomethyleneamino)pyrazole (7b):** To an ice-cooled solution of methylhydrazine (0.53 mL, 10 mmol) in dry MeCN (10 mL) is added dropwise a solution of **6b** (1.15 g, 7.0 mmol) in dry MeCN (10 mL) over a period of 10–15 min. After the addition is complete, the ice-water bath is removed, and the reaction mixture is stirred at room temperature overnight. The mixture is evaporated to dryness on a rotary evaporator, and the solid residue is recrystallized from ether or benzene to give **7b** as colorless needles; yield: 1.11 g (89%); mp 103–105 °C.

| | | | | |
|---|---|---|---|---|
| $C_7H_{10}N_6$: | calc. | C 47.18 | H 5.66 | N 47.16 |
| (178.2) | found | 47.20 | 5.68 | 47.12 |

MS (70 eV): $m/z = 178$ ($M^+$); 163 ($M^+$-$CH_3$).

IR (KBr): $\nu = 2200$ (C≡N) $cm^{-1}$.

$^1H$-NMR (DMSO-$d_6$/TMS): $\delta = 3.21$ (s, 3H, side-chain $CH_3$); 3.59 (s, 3H, ring $CH_3$); 5.28 (s, 2H, $NH_2$, exchangeable with $D_2O$); 7.67 (s, 1H, pyrazole CH); 8.33 (s, 1H, NCH=N):

*This research was supported by a grant (# CA 36154) from the National Institutes of Health. We also thank Professor Patrick Callery of the School of Pharmacy University of Maryland at Baltimore for the mass spectral data.*

*Dedicated to Professor Nelson J. Leonard of the University of Illinois, Urbana, on the occasion of his 70th birthday.*

Received: 6 May 1987

(1) See the introductory paragraphs and the references contained in: Wiemer, D.F., Leonard, N.J. *J. Org. Chem.* **1974**, *39*, 3438. Maeda, M., Kawazoe, Y. *Chem. Pharm. Bull.* **1975**, *23*, 844.
(2) Leiby, R.W., Heindel, N.D. *J. Org. Chem.* **1976**, *41*, 2736.
(3) Sunder, S., Peet, N.P., Trepanier, D.L. *J. Org. Chem.* **1976**, *41*, 2732.
(4) Montgomery, J.A., Temple, Jr.C. *J. Am. Chem. Soc.* **1961**, *83*, 630.
(5) Sen, A.K., Ray, S. *Indian J. Chem.* **1976**, *14B*, 346.
(6) Cheng, C.C., Robins, R.K. *J. Am. Chem. Soc.* **1956**, *21*, 1240.
(7) X-ray analysis of compound **8b** was performed by Professor N.S. Hosmane and co-workers at the Department of Chemistry, Southern Methodist University, Dallas, Texas. Detailed X-ray analysis will be published elsewhere.