2.47 (s, 6 H, Ar CH_3), 2.07 (s, 6 H, pyridinium CH_3).

Anal. Calcd for $C_{36}H_{42}NO_5 \cdot BF_4$: C, 65.96; H, 6.46; N, 2.14. Found: C, 65.67; H, 6.44; N, 1.93.

X-ray Crystallography. X-ray diffraction measurements were performed on a Philips PW1100 or an Enraf-Nonius CAD4 diffractometer, both using graphite-monochromated Mo Kα radiation. Crystal data and data collection parameters are in Table III. Lattice parameters were determined by a least-squares method from 19–25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of 3 control reflections, measured every hour, and for Lorentz polarization, but not for absorption.

The structures were solved by direct methods[27] and refined with full-matrix least-squares. Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered observed and included in the refinement (on F); weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, $\sigma(I)$ based on counting statistics and p an instability factor obtained from plots of F_o vs weighted error. Due to disorder of methyl groups not all hydrogens were located on difference Fourier maps. Depending on data/parameter ratio and data quality the hydrogens were included in the refinement (**2b**·NaPic and **4c**·NaPic) or put in calculated positions (C–H distance 0.96 Å) and treated as riding on their parent C atoms ($B_{iso}(H) = 1.2B_{eqv}(C)$).

Parameters refined were the overall scale factor, isotropic extinction parameter g (correction of F_c with $(1 + gI_c)^{-1}$), positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms (if included), and occupancy factors for a positionally disordered nitro oxygen (**2b**·NaPic). Refinement converged with a shift/error ratio less than unity, except for the disordered atom in **2b**·NaPic. Final difference Fourier maps showed no significant features. All calculations were done using SDP.[28]

Acknowledgment. We thank the Dutch Kidney Fund and the Netherlands Foundation for Technical Research (STW), Future Technical Science Branch/Division of the Netherlands Organization for the Advancement of Pure Research (ZWO), for support of these investigations.

Registry No. 1·NaPic, 112021-14-4; **2a**, 106942-89-6; **2b**, 106942-96-5; **2b**·NaPic, 111999-83-8; **3a**, 111999-71-4; **3b**, 111999-73-6; **3c**, 111999-77-0; **3d**, 112021-13-3; **4a**, 112021-11-1; **4b**, 111999-74-7; **4c**·NaPic, 111999-84-9; **4d**, 111999-78-1; **5a**, 111999-80-5; **5b**, 111999-82-7; **6**, 111999-75-8; **7**, 938-45-4; **8b**, 2892-30-0; **8c**, 106942-90-9; **9a**, 106942-86-3; **9b**, 106942-92-1; **10a**, 106942-87-4; **10b**, 106942-93-2; **11a**, 106960-71-8; **11b**, 106942-94-3; **12a**, 106942-88-5; **12b**, 106942-95-4; diethylene glycol ditosylate, 7460-82-4.

Supplementary Material Available: Positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms, and bond distances and angles and selected torsion angles for the X-ray crystal structures of the NaPic complexes of **1**, **2b**, and **4c** (24 pages). Ordering information is given on any current masthead page.

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Rearrangements in Heterocyclic Synthesis: A Novel Translocation of an (*N*-Amino-*N*-methylamino)methylene Group from a Heterocyclic *N*-Amino-*N*-methylformamidine Side Chain to the Vinylogous Nitrile Function[1]

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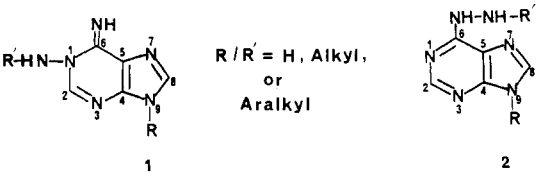
Reaction of the imidate 1-benzyl-4-cyano-5-[(methoxymethylene)amino]imidazole (**5**) with an equivalent of hydrazine provided 1-amino-9-benzyl-6-iminopurine (**6**), which, upon treatment with excess hydrazine, rearranged to 9-benzyl-6-hydrazinopurine (**7**). Reaction of **5** with methylhydrazine gave *N*-amino-*N*-methyl-*N'*-(1-benzyl-4-cyanoimidazol-5-yl)formamidine (**8b**). Thermolysis of **8b** in refluxing toluene–methanol, catalyzed by trifluoroacetic acid, provided an equimolar mixture of 5-amino-1-benzyl-4-cyanoimidazole (**9**) and 3-(5-amino-1-benzylimidazol-4-yl)-1-methyl-1,2,4-triazole (**10**). Compound **9** was recycled to **8b** via **5**. The structure of **10** was established by spectral data coupled with an unequivocal synthesis. The conversion **8b** to **10** represents a novel "translocative" rearrangement involving the transfer of an $NH_2N(Me)CH=$ group from the imidazole 5-position to the nitrile function at position 4. Successful application of the rearrangement to the analogous pyrazole system is demonstrated. The rearrangement carries useful practical implications in the synthesis of the otherwise not easily accessible heterocycles of potential biological and medicinal significance.

1-Amino-6-iminopurines (**1**) and 6-hydrazinopurines (**2**) are potential chemotherapeutic agents[2] which have been little explored. As part of a program to study structure–activity relationships of such compounds, we set out to synthesize various derivatives of **1** and **2**. To this end, the Taylor–Loeffler transformation[3] (**3** → **4**; Scheme I) offered



1 **2**

a convenient route to the synthesis of both **1** and **2**. The course of this endeavor has, however, led us to discover a new "translocative" rearrangement[4] which carries useful

(1) This paper is dedicated to Professor Nelson J. Leonard of the University of Illinois, Urbana, on the occasion of his 70th birthday.

(2) See the introductory paragraphs and the references contained therein of: (a) Wiemer, D. F.; Leonard, N. J. *J. Org. Chem.* **1974**, *39*, 3438. (b) Maeda, M.; Kawazoe, Y. *Chem. Pharm. Bull.* **1975**, *23*, 844.

(3) Taylor, E. C.; Loeffler, P. K. *J. Am. Chem. Soc.* **1960**, *82*, 3147.

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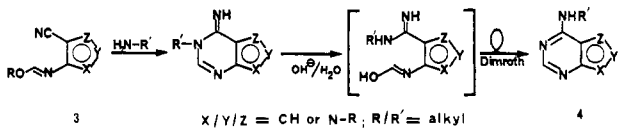
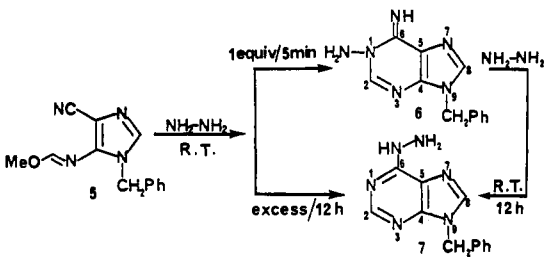
Scheme I



Scheme II



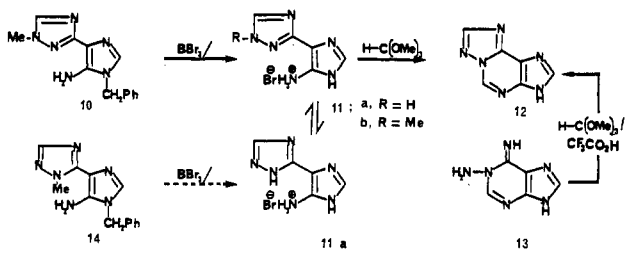
implications in the synthesis of the otherwise not easily accessible heterocycles of potential biological and medicinal significance.

Our studies began with the reagent methyl *N*-(dicyanomethyl)methanimidate [$(CN)_2CHN{=}CHOMe$] which was prepared by an improvement of the literature procedure previously reported for the analogous ethyl ester.[5,6] The above reagent, upon treatment with benzylamine, afforded 5-amino-1-benzyl-4-cyanoimidazole in nearly quantitative yield. Further reaction of the latter with trimethyl orthoformate, catalyzed by trifluoroacetic acid, provided the required 1-benzyl-4-cyano-5-[(methoxymethylene)amino]imidazole (**5**) for our studies.

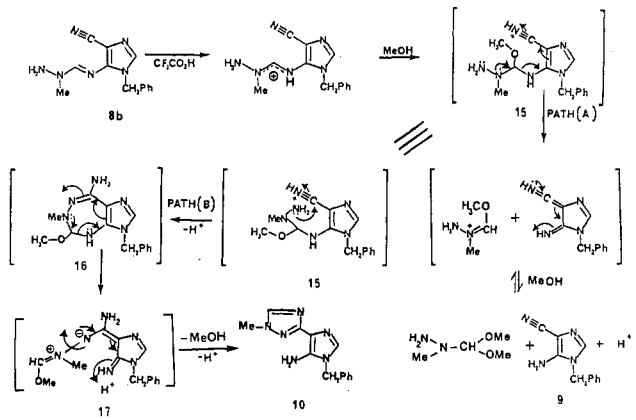
The reaction of the imidate 5 (Scheme II) with an equivalent of hydrazine for 5 min provided **6**, while the same reaction with excess hydrazine for 12 h gave **7**. Compound **6** rearranged to **7** upon prolonged reaction with hydrazine. The structure of **7** was confirmed by its independent synthesis from 9-benzyl-6-chloropurine[7] and that of **6** by (a) the reduction with Raney Ni/H_2 which afforded 9-benzyladenine[7] and (b) the UV spectrum (λ_{max} (EtOH) 258 nm) unchanged either in acid or base, which closely paralleled that of 1,9-disubstituted adenine.[8]

When hydrazine was replaced with methylhydrazine in the above reaction, the product obtained had the ring-open structure **8b**, as evidenced by its IR spectrum which revealed a distinct C≡N function at 2200 cm^{-1}. The structure **8b** was distinguished from the alternative **8a** by the ^1H NMR spectrum which exhibited singlets for both NMe and NH_2. This structural assignment was also consistent with the known reactivity of methylhydrazine which is reported to react with electrophiles from its *N*-methyl end.[9,10] While the thermolysis of **8b** in refluxing toluene/methanol yielded only the starting material, catalysis of the same reaction by trifluoroacetic acid provided a mixture of **9**[11] and a second product, in nearly equimolar amounts (total yield ≥90%), whose molecular formula,

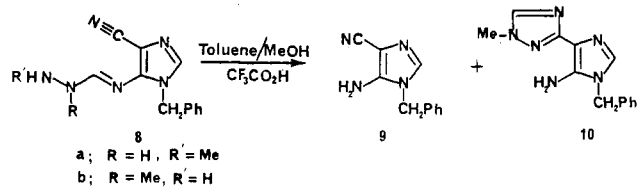
Scheme III



Scheme IV



$C_{13}H_{14}N_6$, was the same as the starting material. The two compounds were readily separated by differential solubility or by flash chromatography on silica gel. Structure **10** was assigned for the $C_{13}H_{14}N_6$ product based on the following synthesis coupled with Nuclear Overhauser Enhancement (NOE) analysis. The product was dealkylated (Scheme



III) with boron tribromide in xylene (to obtain **11a**), followed by treatment with trimethyl orthoformate. This operation gave rise to a new product (**12**) which was identical with that[2a,12] obtained by the orthoformate ring closure of 1-aminoadenine (**13**)[2a] prepared from the imidate 4-cyano-5-[(methoxymethylene)amino]imidazole with an equivalent of hydrazine, thus pointing to **10** or **14** as the structure of the $C_{13}H_{14}N_6$ product. Further distinction between **10** and **14** was achieved by evaluation of the NOE effect by the methyl protons on the triazole methine protons. The observed large NOE (14.9%) was consistent with only structure **10**, thus confirming 3-(5-amino-1-benzylimidazol-4-yl)-1-methyl-1,2,4-triazole (**10**) as the second product of thermolysis of **8b** in toluene/methanol/TFA.

There are documented precedents for transformations of compounds of type **1**[13] and **2**[12] to the products of type **10**, under basic and acidic conditions, respectively. However, in spite of carefully monitoring the reaction at frequent intervals, we were unable to detect or isolate either **1** or **2** (R = CH_2Ph, R′ = Me)[14] in the conversion **8b** → **9**

(4) See, for example: (a) Hosmane, R. S.; Bakthavachalam, V.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 235. (b) Balicki, R.; Hosmane, R. S.; Leonard, N. J. *J. Org. Chem.* **1983**, *48*, 3.

(5) Rayner, B.; Tapiero, C.; Imbach, J.-L. *J. Carbohydr. Nucleosides, Nucleotides* **1976**, *3*, 1.

(6) Greenhalgh, M.; Shaw, G.; Wilson, D. V.; Cusack, N. J. *J. Chem. Soc. C* **1969**, 2198.

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(9) Leiby, R. W.; Heindel, N. D. *J. Org. Chem.* **1976**, *41*, 2736.

(10) Sunder, S.; Peet, N. P.; Trepanier, D. L. *J. Org. Chem.* **1976**, *41*, 2732.

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(12) Temple, C., Jr.; Kussner, C. L.; Montgomery, J. A. *J. Org. Chem.* **1965**, *30*, 3601.

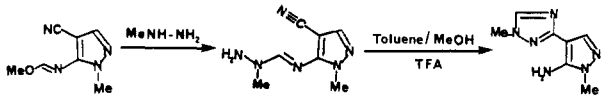
(13) (a) Huang, G.-F.; Okamoto, T.; Maeda, M.; Kawazoe, Y. *Chem. Pharm. Bull.* **1974**, *22*, 1938. (b) Huang, G.-F.; Maeda, M.; Okamoto, T.; Kawazoe, Y. *Tetrahedron* **1975**, *31*, 1363.

+ 10. In this regard, it is noteworthy that the conversion of 1 (R = Me or β-D-ribofuranosyl, R′ = H) into the corresponding imidazolyl-1,2,4-triazole derivatives of type 10 is reported *not* to proceed through the intermediate Dimroth product 2 (R = Me or β-D-ribofuranosyl, R′ = H), and instead, a seven-membered ring intermediate analogous to the one proroposed in Scheme IV (vide infra) has been proposed.[13]

In speculating about a mechanism for the transformation 8b → 9 + 10, it was noted that the reaction failed in the absence of methanol in spite of acid catalysis. A tentative mechanism (Scheme IV) for the conversion involves the initial formation of the intermediate 15, which decomposes to 9 via path A or rearranges to 10 via path B upon sequential ring closure (15 → 16), ring opening (16 → 17), and ring closure again, followed by elimination of methanol (17 → 10).

Another plausible pathway for the formation of 10 would involve recombination of 9 with the byproduct of path A (Scheme IV), namely, 1-formyl-1-methylhydrazine dimethyl acetal. However, this latter possibility was ruled out by the observed failure of 9 to react with either formylhydrazine or methylhydrazine in a mixture of toluene–methanol at reflux for 3 days with or without the TFA catalysis.

The conversion 8b → 10 represents a novel "translocative" rearrangement wherein an (*N*-amino-N-methylamino)methylene group attached to the imidazole amino side chain at position 5 has been translocated to the vinylogous nitrile function at position 4. Since the byproduct 9 can be easily separated from the reaction mixture (vide supra) and recycled back to 8b via 5, the rearrangement carries useful practical implications in the synthesis of rare heterocycles of potential biological and pharmaceutical significance.[15] Therefore, in an attempt to explore its generality, the rearrangement was extended to one other heterocyclic system. Thus, when the analogous imidate 18 of pyrazole was treated with methyl-



18 19 20

hydrazine, the corresponding intermediate 19 was obtained in 89% yield. The latter underwent facile rearrangement in toluene/MeOH/TFA to the corresponding triazole derivative 20 in 43% yield, along with the byproduct 5-amino-4-cyano-1-methylpyrazole[16] (48%). As before, the latter byproduct was recycled to 19 via the imidate 18.

The study of the described translocative rearrangement to other heterocyclic as well as carbocyclic systems is currently in progress.

Experimental Section

Proton nuclear magnetic resonance spectra were reported on an IBM NR/80 spectrometer. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet) integration. The electron impact (EI) and chemical ionization (CI) 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. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording instrument. Elemental microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Methyl *N*-(Dicyanomethyl)methanimidate. Aminomalononitrile *p*-toluenesulfonate[17] (33.6 g, 0.124 mol) was neutralized with a saturated solution of aqueous $NaHCO_3$ (40 mL). The aqueous mixture was extracted with ether (6 × 100 mL), the combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was evaporated to dryness on a rotary evaporator at a temperature not exceeding 30 °C, to obtain the free aminomalononitrole as an oil (8.0 g, 0.1 mol, 79.6%).

A portion of the above oil (1 g, 12 mmol) was suspended in dry acetonitrile (20 mL), and the resulting solution was introduced dropwise with an hypodermic syringe needle into the refluxing mixture of trimethyl orthoformate (10 mL, 91.4 mmol) containing a drop of concentrated sulfuric acid. The reaction mixture was heated at reflux, under N_2, for 3.5 h, cooled, and rotary evaporated to obtain an oil, which was distilled in a Kugelrohr apparatus [92–100 °C (oven temperature) (0.5 mmHg)] to obtain the title reagent as a colorless oil (1.1 g, 8.94 mmol, 75%): ^{1}H NMR (Me_2SO-d_6) δ 3.61 (s, 3, CH_3), 5.38 (s, 1, malononitrile CH), 7.92 (s, 1, imidate CH); IR (neat) 3000 (=CH), 2225 (C≡N) cm^{-1}; mass spectrum (70 eV), *m/e* 123 (M^+).

Anal. Calcd for $C_5H_5N_3O$: C, 48.78; H, 4.09; N, 34.13. Found: C, 48.75; H, 4.12; N, 33.97.

5-Amino-1-benzyl-4-cyanoimidazole. To a stirring solution of methyl *N*-(dicyanomethyl)methanimidate (1.5 g, 12 mmol) in dry acetonitrile (30 mL) was added, dropwise, benzylamine (1.3 g, 12 mmol). The reaction mixture was stirred at room temperature, under N_2, for 12 h, and the precipitated solid was filtered in vacuo, and recrystallized from acetonitrile to give colorless crystals of the title compound (2.1 g, 10.6 mmol, 88%), mp 197–199 °C (lit.[11] mp 199–200 °C): ^{1}H NMR (Me_2SO-d_6) δ 5.07 (s, 2, CH_2), 6.21 (br s, 2, NH_2, exchangeable with D_2O), 7.26 (s, 1, imidazole CH), 7.25–7.33 (br, m, 5, C_6H_5); IR (KBr) 3450–3100 (NH), 2220 (C≡N) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 198 (M^+, 100%).

1-Benzyl-4-cyano-5-[(methoxymethylene)amino]imidazole (5). A mixture of 5-amino-1-benzyl-4-cyanoimidazole (1.4g, 7.07 mmol), trimethyl orthoformate (50 mL, 0.46 mol), and trifluoroacetic acid (0.125 mL, 1.62 mmol) was 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 was evaporated to dryness on a rotary evaporator to obtain a yellow liquid, which solidified upon refrigeration for several hours. The solid was recrystallized from benzene–petroleum ether (30–60 °C) into colorless crystals of 5 (1.33 g, 5.93 mmol, 84%), mp 69–71 °C: ^{1}H NMR (Me_2SO-d_6) δ 8.43 (s, 1, imidate CH), 7.87 (s, 1, imidazole CH), 7.31 (s, 5, C_6H_5), 5.14 (s, 2, CH_2), 3.89 (s, 3, OCH_3); IR (neat) 2250 (C≡N) cm^{-1}; mass spectrum (70 eV), *m/e* 240 (M^+).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.04; N, 23.32. Found: C, 65.05; H, 5.04; N, 23.30.

1-Amino-9-benzyl-6-iminopurine (6). To a stirring solution of 5 (1.5 g, 6.25 mmol) in absolute MeOH (30 mL), under N_2, was added hydrazine monohydrate (0.3 mL, 6.25 mmol). After 5 min, the separated precipitate was filtered in vacuo, dried, and recrystallized from benzene into colorless needles of 6 (1.38 g, 5.75 mmol, 92%), mp 170–173 °C: ^{1}H NMR (Me_2SO-d_6) δ 8.06 (s, 1, CH), 8.03 (s, 1, CH), 7.30 (s, 5, C_6H_5), 5.64 (s, 2, NH_2, exchangeable with D_2O), 5.30 (s, 2, CH_2); mass spectrum (70 eV), *m/e* 240 (M^+), 224 ($M^+ - NH_2$), 149 ($M^+ - CH_2Ph$), 91 ($PhCH_2^+$); UV λ_{max} (EtOH) 250 nm (sh), 258, 266 (sh), (pH 13) 250 (sh), 258, 266 (sh), (pH 1) 257.

Anal. Calcd for $C_{12}H_{12}N_6$: C, 59.98; H, 5.04; N, 34.98. Found: C, 59.77; H, 5.10; N, 34.89.

9-Benzyl-6-hydrazinopurine (7). Method A. Reaction of 5 with Excess Hydrazine. A mixture of 5 (1.5 g, 6.25 mmol), absolute MeOH (30 mL), and hydrazine monohydrate (4 mL, 82.5 mmol) was stirred at room temperature under N_2 for 12 h. The initial precipitate (of 6) formed after 5 min went back into solution, and after several hours a second solid started separating out. The

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(15) See, for example: (a) U.S. Secretary of Army. U.S. Patent 2432642, 1946. (b) U.S. Secretary of Army. U.S. Patent 2555330, 1951. (c) Richardson, C. H.; Shepard, H. H. *J. Agric. Res.* **1930**, *40*, 1007.
(16) Cheng, C. C.; Robins, R. K. *J. Am. Chem. Soc.* **1956**, *21*, 1240.
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solid was filtered in vacuo, dried, and recrystallized from a large volume of aqueous EtOH to obtain **7** (1.22 g, 5.08 mmol, 81%), mp 205–208 °C (lit.[7] mp 209–210 °C): ^{1}H NMR (Me_2SO-d_6) δ 4.72 (br s, 2, NH_2, exchangeable with D_2O), 5.40 (s, 2, CH_2), 7.31 (s, 5, C_6H_5), 8.26 (s, 1, CH), 8.28 (s, 1, CH), 9.0 (br s, 1, NH, exchangeable with D_2O); mass spectrum (70 eV), *m/e* 240 (M^+), 209 ($M^+ - NHNH_2$), 149 ($M^+ - CH_2Ph$), 120 ($M^+ - CH_2Ph\text{-}N_2H$), 91 ($PhCH_2^+$); UV λ_{max} (EtOH) 266 nm, (pH 1) 263, (pH 13) 294, 320.

Anal. Calcd for $C_{12}H_{12}N_6$: C, 59.98; H, 5.04; N, 34.98. Found: C, 59.84; H, 5.07; N, 34.95.

Method B. Treatment of 6 with Excess Hydrazine. A mixture of **6** (1.0 g, 4.17 mmol), absolute MeOH (30 mL), and hydrazine monohydrate (4 mL, 82.5 mmol) was stirred under N_2 at room temperature for 12 h. The precipitated solid was filtered in vacuo, dried, and recrystallized as mentioned in method A to obtain **7** (0.8 g, 3.33 mmol, 79.9%), 207–209 °C (lit.[7] mp 209–210 °C). The spectral data of this compound were identical with those of **7** obtained from either method A (see above) or method C (see below).

Method C. Reaction of 9-Benzyl-6-chloropurine with Hydrazine. A mixture of 9-benzyl-6-chloropurine[7,18] (0.14 g, 0.57 mmol), dry acetonitrile (10 mL), and hydrazine monohydrate (0.03 g, 0.6 mmol), was stirred under N_2 at room temperature for 3 h. The separated solid was purified as mentioned in method A above to obtain **7** (0.12 g, 0.5 mmol, 87.7%), mp 208–209 °C (lit.[7] mp 209–210 °C). The ^{1}H NMR, UV, and mass spectrum of this compound were superimposable with those of **7** obtained from either method A or method B as described above.

Reduction of 1-Amino-9-benzyl-6-iminopurine (6) with Raney Ni/H_2. Raney Ni (50% slurry in H_2O) was washed twice with EtOH and was suspended in a solution of **6** (100 mg, 0.42 mmol) in 25 mL of warm EtOH. The mixture was hydrogenated at 44 psi in a Parr apparatus for 18 h and filtered in vacuo, and the filtrate was evaporated to dryness. The residual solid was recrystallized from EtOH–H_2O to obtain colorless crystals of 9-benzyladenine, mp 229–230 °C (lit.[7] mp 235 °C): ^{1}H NMR (Me_2SO-d_6) δ 5.38 (s, 2, CH_2), 7.28 (s, 5, Ph), 8.17 (s, 1, CH), 8.26 (s, 1, CH).

***N*-Amino-*N*-methyl-*N'*-(1-benzyl-4-cyanoimidazol-5-yl)-formamidine (8b).** To a solution of **5** (0.5 g, 2.1 mmol) in absolute MeOH (20 mL), cooled in an ice-water bath, was added methylhydrazine (0.12 mL, 2.2 mmol) in one portion. The resulting solution was stirred at that temperature, under N_2, for 3 h. The reaction mixture was rotary evaporated to dryness at 23 °C to obtain a dense oil. The traces of solvent and methylhydrazine were removed by using a vacuum pump, and the residual oil was refrigerated overnight and triturated with ether to obtain a solid, which was recrystallized from benzene–petroleum ether (30–60 °C) into colorless needles of **8b** (0.48 g, 1.89 mmol, 90%), mp 96–97 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.18 (s, 3, Me), 5.07 (s, 2, CH_2), 5.30 (br s, 2, NH_2 exchangeable with D_2O), 7.30 (s, 5, Ph), 7.62 (s, 1, imidazole CH), 8.26 (s, 1, amidine CH); mass spectrum (70 eV), *m/e* 254 (M^+), 224, ($M^+ - NHCH_3$), 163 ($M^+ - CH_2Ph$); IR (KBr) 2200 cm^{-1} (C≡N).

Anal. Calcd for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.44; H, 5.55; N, 33.00.

5-Amino-1-benzyl-4-cyanoimidazole (9) and 3-(5-Amino-1-benzylimidazol-4-yl)-1-methyl-1,2,4-triazole (10). A mixture of **8b** (540 mg, 2.13 mmol), dry toluene (15 mL), dry MeOH (15 mL), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for 3 days. The reaction mixture was cooled and rotary evaporated to dryness. The solid was dissolved in MeOH (15 mL) and mixed with 2 g of silica gel (40–63 μm), and the mixture was evaporated to dryness. The residue was suspended in 10 mL of $CHCl_3$ and the resulting slurry loaded onto a flash chromatography column, packed with a slurry of silica gel (40–63 μm, 20 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (29:1), and appropriate UV-absorbing fractions were pooled and evaporated to obtain **9** (200 mg, 1.0 mmol, 47%), mp 199 °C (lit.[11] mp 199–200 °C), and a second crystalline product which formed a characteristic blue spot on a TLC plate of silica gel upon brief exposure to atmosphere. The latter compound was recrystallized from MeOH into colorless needles of **10** (245 mg, 0.96 mmol, 45%), mp 254–255 °C (dec: ^{1}H NMR (Me_2SO-d_6) δ 3.82 (s, 3, CH_3), 5.09 (s, 2, CH_2), 5.41 (s, 2, NH_2, exchangeable with D_2O), 7.28 (s, 6, Ph + imidazole CH), 8.35 (s, 1, triazole CH); mass spectrum (70 eV), *m/e* 254 (M^+), 177 (M^+ – Ph), 163 ($M^+ - CH_2Ph$); UV λ_{max} (EtOH) 258 nm, (pH 13) 258, (pH 1) 246, 276.

Anal. Calcd for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.28; H, 5.58; N, 33.03.

3-(5-Aminoimidazol-4-yl)-1,2,4-triazole Hydrobromide (11a) and 3-(5-Aminoimidazol-4-yl)-1-methyl-1,2,4-triazole Hydrobromide (11b). To a suspension of compound **10** (300 mg, 1.18 mmol) in dry xylene (25 mL) was added BBr_3 (0.8 mL, 8.5 mmol) dropwise with a syringe needle during a period of 2 min while the reaction mixture was stirred under N_2. Soon after the addition was complete, the reaction mixture turned yellow and clear. The solution was heated at reflux under N_2 for 43 h, cooled, mixed with 20 mL of MeOH, and refluxed again for 30 min. The reaction mixture was cooled, mixed with 5 g of silica gel (40–63 μm), and evaporated to dryness on a rotary evaporator. The residue was suspended in 10 mL of $CHCl_3$, and the suspension was loaded onto a flash chromatography column packed with silica gel (40–63 μm, 25 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (8:1), and appropriate UV-absorbing fractions were pooled and evaporated.

Compound **11b**, which eluted first, was recrystallized from a mixture of MeOH–$CHCl_3$–petroleum ether (30–60 °C) into colorless needles (150 mg, 0.61 mmol, 52%), mp >250 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.95 (s, 3, CH_3), 8.66 (s, 2, 2 CH); mass spectrum (70 eV), *m/e* 164 (M^+ – HBr), 147, 136, 109.

Anal. Calcd for $C_6H_9N_6Br$: C, 29.40; H, 3.70; N, 34.29. Found: C, 29.45; H, 3.70; N, 34.27.

Compound **11a** was recrystallized from MeOH–$CHCl_3$ into colorless crystals (95 mg, 0.41 mmol, 35%), mp >250 °C: ^{1}H NMR (Me_2SO-d_6) δ 8.64 (s, 1, CH), 8.72 (s, 1, CH); mass spectrum (70 eV), *m/e* 150 (M^+ – HBr).

Anal. Calcd for $C_5H_7N_6Br$: C, 25.99; H, 3.05; N, 36.38. Found: C, 26.13; H, 3.03; N, 36.48.

1,2,4-Triazolo[5,1-*i*]purine (12). Method A. Ring Closure of 11a. A mixture of **11a** (25 mg, 0.108 mmol) and trimethyl orthoformate (10 mL) was heated at reflux under N_2 for 4 h, cooled, and evaporated to dryness on a rotary evaporator. The residue was triturated with AcOEt, and the resulting solid was recrystallized from a mixture of CH_3CN–MeOH–H_2O into colorless crystals of **12** (17 mg, 0.106 mmol, 98%), mp >250 °C (lit.[12] mp >264 °C): ^{1}H NMR (Me_2SO-d_6) δ 8.51 (s, 1, CH), 8.63 (s, 1, CH), 9.61 (s, 1, CH), 14 (br s, 1, NH, exchangeable with D_2O); mass spectrum (70 eV), *m/e* (relative intensity) 160 (M^+, 100). These spectral data were identical with those of **12** prepared from method B, described below.

Method B. Ring Closure of 1-Aminoadenine (13). 1. 5-(4)-Amino-4(5)-cyanoimidazole. A stream of NH_3 gas was passed into the dry ice cooled solution of the reagent methyl *N*-(dicyanomethyl)methanimidate, described above (1.8 g, 14.6 mmol), in dry MeOH (30 mL) for 5 min. The dark red solution was evaporated to dryness, and the residue was dissolved in MeOH and mixed with 6 g of silica gel (40–63 μm), and the mixture was rotary evaporated to dryness. The residue was suspended in $CHCl_3$ (15 mL), and the suspension was loaded onto a column of flash chromatography packed with a slurry of silica gel (40–63 μm, 40 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (8:1), and the appropriate UV-absorbing fractions were pooled and evaporated to obtain colorless crystals (0.8 g, 7.4 mmol, 51%), mp 126–128 °C (lit.[19] mp 124–128 °C): ^{1}H NMR (Me_2SO-d_6) δ 5.93 (br s, 2, NH_2, exchangeable with D_2O), 7.17 (s, 1, CH), 11.69 (br s, 1, NH, exchangeable with D_2O).

2. 4(5)-Cyano-5(4)-[(methoxymethylene)amino]imidazole. To the boiling mixture of trimethyl orthoformate (20 mL, 0.18 mol) and trifluoroacetic acid (0.05 mL, 0.65 mmol), under N_2, was added 5(4)-amino-4(5)-cyanoimidazole (0.80 g, 7.4 mmol) in several small portions. The reaction mixture was heated at reflux for 1 h, cooled, and filtered through a dry sintered-glass funnel in vacuo. The precipitate was washed with 2 × 10 mL of boiling dry acetonitrole, and the filtrate and the washings were combined

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and rotary evaporated to obtain the title product, which was directly employed in the next step: ^{1}H NMR (Me_2SO-d_6) δ 3.86 (s, 3, OMe), 7.71 (s, 1, imidazole CH), 8.46 (s, 1, imidate CH).

3. 1-Aminoadenine (13). The above 4(5)-cyano-5(4)-[(methoxymethylene)amino]imidazole was dissolved in dry acetonitrole (60 mL). To the resulting solution was added hydrazine hydrate (0.34 mL, 6.9 mmol) dropwise with a syringe needle. After the addition, the mixture was stirred under N_2 at room temperature for 30 min. The precipitated solid was filtered in vacuo and recrystallized from a mixture of CH_3CN–MeOH into colorless crystals of **13** (0.87 g, 5.83 mmol, 79%), mp 210 °C: ^{1}H NMR (Me_2SO-d_6) δ 6.33 (br s, 2, NH_2, exchangeable with D_2O), 7.89 (s, 1, CH), 8.13 (s, 1, CH).

Anal. Calcd for $C_5H_6N_6 \cdot {}^1/_8H_2O$: H_2O: C, 39.40; H, 4.10; N, 55.17. Found: C, 39.36; H, 4.09; N, 55.05.

The HCl salt of the above compound, prepared by passing dry HCl gas in methanolic solution of the compound for 30 min, had spectral data identical with those reported for **13**·HCl.[2a]

4. 1,2,4-Triazolo[5,1-*i*]purine (12). A mixture of compound **13** (300 mg, 2 mmol), trimethyl orthoformate (15 mL, 0.14 mol), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for 2 h. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was triturated with CH_3CN to obtain a solid, which was recrystallized from a mixture of CH_3CH–MeOH–H_2O into colorless crystals of **12** (278 mg, 1.74 mmol, 87%), mp >250 °C. The ^{1}H NMR,[2a] UV,[12] and mass spectral data[2a] of this compound were identical with the reported values.

4-Cyano-5-[(methoxymethylene)amino]-1-methylpyrazole (18). A mixture of 5-amino-4-cyano-1-methylpyrazole,[16] (2 g, 16.4 mmol) trimethyl orthoformate (50 mL, 0.46 mol), and trifluoroacetic acid (0.1 mL, 1.3 mmol) was heated at reflux under N_2 for 1 h. The reaction mixture was cooled and rotary evaporated to dryness. The residual oil was 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 mmHg)] to obtain **18** as a colorless oil, which solidifies upon cooling in a refrigerator overnight (2.3 g, 14.0 mmol, 86%): ^{1}H NMR (Me_2SO-d_6) δ 3.68 (s, 3, N-Me), 3.95 (s, 3, OMe), 7.87 (s, 1, imidazole CH), 8.49 (s, 1, imidate CH); IR (KBr) 2230 cm^{-1}.

***N*-Amino-*N*-methyl-*N'*-(1-methyl-4-cyanopyrazol-5-yl)formamidine (19).** To an ice-cooled solution of methylhydrazine (0.53 mL, 10 mmol) in dry acetonitrile (10 mL) was added dropwise a solution of the imidate **18** (1.15 g, 7.0 mmol) in 10 mL of dry acetonitrile over a period of 10–15 min. After the addition was complete, the ice–water bath was removed, and the reaction mixture was stirred at room temperature overnight. The mixture was evaporated to dryness on a rotary evaporator, and the solid residue was recrystallized from ether or benzene into colorless needles (1.11 g, 6.23 mmol, 89%), mp 103–105 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.21 (s, 3, side chain CH_3), 3.59 (s, 3, ring CH_3), 5.28 (s, 2, NH_2, exchangeable with D_2O), 7.67 (s, 1, pyrazole CH), 8.33 (s, 1, side chain CH); mass spectrum (70 eV), *m/e* 178 (M^+), 163 ($M^+ - CH_3$); IR (KBr) 2200 cm^{-1} (C≡N).

Anal. Calcd for $C_7H_{10}N_6$: C, 47.18; H, 5.66; N, 47.16. Found: C, 47.20; H, 5.68; N, 47.12.

3-(5-Amino-1-methylpyrazol-4-yl)-1-methyl-1,2,4-triazole (20) and 5-Amino-4-cyano-1-methylpyrazole. A mixture of **19** (500 mg, 2.8 mmol), dry toluene (10 mL), dry MeOH (10 mL), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for 3 days. The reaction mixture was cooled and worked up by employing the procedure described above for the rearrangement of **8b** to **9** and **10** except that the eluting solvent system for flash chromatography was $CHCl_3$–MeOH (50:1). The first product to elute from the column was **5-amino-4-cyano-1-methylpyrazole** (165 mg, 1.35 mmol, 48%), mp 222 °C (lit.[16] mp 222–223 °C): ^{1}H NMR (Me_2SO-d_6)δ 3.52 (s, 3, Me), 6.48 (br s, 2, NH_2, exchangeable with D_2O), 7.49 (s, 1, CH). The physical data and chemical yield for compound **20**, which followed, are as follows: colorless needles from benzene; 214 mg, 1.2 mmol, 43%; mp 177–179 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.58 (s, 3, pyrazole CH_3), 3.84 (s, 3, triazole CH_3), 5.75 (br s, 2, NH_2, exchangeable with D_2O), 7.47 (s, 1, pyrazole CH), 8.36 (s, 1, triazole CH); mass spectrum (70 eV), *m/e* 178 (M^+), 163 ($M^+ - CH_3$); UV λ_{max} (EtOH) 239 nm (ϵ 12 260), (pH 0.1) 262 (11 000), 231 (9600), (pH 13) 237 (12 000).

Anal. Calcd for $C_7H_{10}N_6$: C, 47.18; H, 5.66; N, 47.16. Found: C, 47.09; H, 5.71; N, 47.07.

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Registry No. **3** (R = Me, X = Z = N, Y = CH), 23142-09-8; **5**, 111267-84-6; **6**, 111267-85-7; **7**, 6268-73-1; **8b**, 111267-86-8; **9**, 60598-48-3; **10**, 111267-87-9; **11a**, 111267-88-0; **11b**, 111267-89-1; **12**, 4022-94-0; **13**, 72621-40-0; **13**·HCl, 111267-90-4; **18**, 111267-91-5; **19**, 111267-92-6; **20**, 111267-93-7; $(CN)_2CHNH_2 \cdot TsOH$, 5098-14-6; $(CN)_2CHNH_2$, 5181-05-5; $MeOCH{=}NCH(CN)_2$, 111267-83-5; $PhCH_2NH_2$, 100-46-9; 9-benzyl-6-chloropurine, 1928-76-3; 9-benzyladenine, 4261-14-7; 5(4)-amino-4(5)-cyanoimidazole, 5098-11-3; 5-amino-4-cyano-1-methylpyrazole, 5334-41-8.

A Convenient Palladium-Catalyzed Coupling Approach to 2,5-Disubstituted Pyridines

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2,5-Dibromopyridine has been found to undergo a regioselective palladium-catalyzed coupling reaction with terminal acetylenes and arylzinc halides to give the corresponding 2-alkynyl-5-bromo- and 2-aryl-5-bromopyridines, respectively, in 70%–90% isolated yields. To complement this chemistry, the triflate derived from 2-methyl-5-pyridinol was found to participate in a palladium-catalyzed reaction with terminal acetylenes leading to the corresponding 5-alkynyl-2-methylpyridines. These intermediates can be further manipulated to afford a broad range of 2,5-disubstituted pyridines.

In recent years, there has been considerable interest in the regioselective preparation of disubstituted pyridines, but no convenient, practical approach to 2,5-dialkyl- and 2-aryl-5-alkylpyridines has yet been described. Existing routes to such compounds involve attack of an electrophile on a 1-lithio-2-substituted-1,2-dihydropyridine formed from addition of an alkyllithium to pyridine followed by oxidation of the resulting dihydropyridine,[1-4] by reaction

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