An Expeditious Procedure for the Synthesis of Purines from Aminoimidazolecarbaldehydes

Francisco Perandones and José L. Soto*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

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Reactions of 4-amino-1,2-dimethylimidazole-5-carbaldehyde (**1**) and 5-amino-1-methylimidazole-4-carbaldehydes **3** with nitriles, in the presence of dry hydrogen chloride afforded to the formation of purine derivatives. This constitutes a facile and versatile one-pot synthesis of purines. The use of formamide instead of nitriles leads to the respective purines without substituents on the pyrimidine ring, **2d** and **4e,f**.

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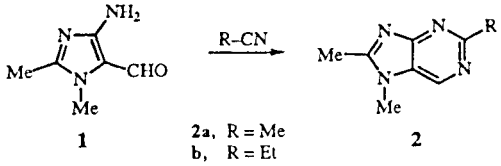
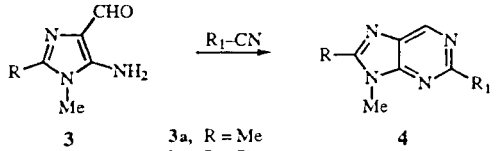
In a recent previous paper, we have reported that aminoimidazolecarbaldehydes **1** and **3**, which can be readily prepared by catalytic reduction of the corresponding aminoimidazolecarbonitriles, react with active methylene compounds in the presence of sodium ethoxide to give imidazo[4,5-*b*]pyridines [1]. This reaction is practical for the synthesis of imidazopyridines because of the simplicity of the procedure. Considering the substitution pattern on the imidazole ring in compounds **1** and **3**, they are interesting precursors for the preparation of other imidazole containing heterocyclic fused systems. Thus, in the present paper we report the reaction of **1** and **3** with formamide and a wide variety of different nitriles under the influence of hydrogen chloride to give differently substituted purines (Scheme 1).

Scheme 1



1 **2a**, R = Me; **b**, R = Et; **c**, R = Ph; **2**



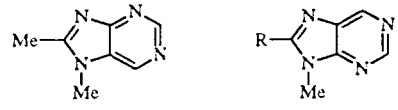
3 **3a**, R = Me; **b**, R = Ph; **4a**, R = Me, R_1 = Me; **b**, R = Ph, R_1 = Me; **c**, R = Ph, R_1 = Et; **d**, R = Ph, R_1 = Ph; **4**

The hydrogen chloride catalysed reaction of nitriles with *o*-aminocarbonyl compounds is an useful route to synthesize fused pyrimidines [2-4]. This pyrimidine cyclization from *ortho*-aminocarbonyl compounds and nitriles under acidic conditions, could be accounted for by formation of the amidine intermediate, which undergoes intramolecular cyclization by nucleophilic attack on the carbonyl group to yield the pyrimidine ring. The protonation of the carbonyl compound also seems to facilite the cyclization.

Compounds **2** and **4** were obtained in moderate to good yields as stable crystalline solids. The structure of the purines **2** and **4** were fully supported by their elemental analyses and spectroscopic properties. In particular, the ir spectra of the aminoimidazolecarbaldehydes show a strong absorption band in the carbonyl stretching region (ν_{max} 1640-1650 cm^{-1}) which disappears upon cyclisation. Furthermore, the ^1H nmr spectra [5,6] of the purines showed the presence of pyrimidine 6-H (δ 8.65-9.20) thus demonstrating that cyclocondensation occurs.

Treatment of **1** and **3a,b** with formamide proceeds similarly to give the corresponding purine derivatives **2d**, **4e** and **4f** with no substituents on the pyrimidine moiety. In place of formamide, formamidine acetate could be used in the condensation reaction. However, less reactive amidines, such as acetamidine and benzamidine, failed to react (Scheme 2). These compounds were obtained in good yields as stable crystalline solids and their structures are in full agreement with the analytical and spectroscopic data (see experimental section).

Scheme 2



2d **4e**, R = Me; **f**, R = Ph

In summary, we report a new application of the readily available aminoimidazolecarbaldehydes **1** and **3** as precursors for the preparation of bicyclic fused heterocycles. Thus, a wide variety of purines with different substitution patterns were obtained by reaction of **1** and **3** with nitriles or formamide under acidic catalysis.

EXPERIMENTAL

Melting points were determined on a Büchi 530 or on a Gallenkamp open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer

781 instrument as potassium bromide pellets. The nmr spectra were recorded at 300 MHz on a Varian VXR 300S or at 250 MHz on a Bruker AC-250 F spectrometer in deuteriochloroform solution. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane as internal standard. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by tlc on silica gel plates (Merck 60-F) using chloroform-ethanol or toluene-ethyl acetate as the eluants.

General Procedure for the Cyclization Reactions of Compounds **1** and **3a,b** with Nitriles.

A stream of dry hydrogen chloride gas was passed through a mixture of the *ortho*-aminocarbaldehyde compound (1.8 mmoles) and the corresponding nitrile (2 ml) in dioxane (5 ml) for about 8 hours. The solvent was removed under reduced pressure, and the resulting residue was poured into 20 ml of ice-water and neutralized with 10% ammonium hydroxide solution. The aqueous mixture was extracted with chloroform, dried with magnesium sulfate and evaporated to give the crude product, which was purified as specified for each compound.

2,7,8-Trimethylpurine (**2a**).

The crude product obtained from aminoimidazolecarbaldehyde **1** by cyclocondensation with acetonitrile was subjected to silica gel column chromatography. Elution of the column with ethyl acetate:ethanol (1:1, v/v) gave a crystalline substance which was recrystallized from ethanol to yield 0.12 g (43%) of **2a**; ir (potassium bromide): 1610, 1570 (C=N), 1500, 1460 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.65 (s, 1H, 6-H), 3.82 (s, 3H, CH_3N), 2.82 (s, 3H, 2-CH_3), 2.67 (s, 3H, 8-CH_3); ^{13}C nmr (deuteriochloroform): δ 162.3 (C2), 158.9 (C4), 148.0 (C8), 137.7 (C6), 125.0 (C5), 30.5 (CH_3N), 26.0, 14.1 (2 CH_3).

Anal. Calcd. for $C_8H_{10}N_4$ (162.19): C, 59.23; H, 6.23; N, 34.55. Found: C, 59.52; H, 6.59; N, 34.54.

7,8-Dimethyl-2-ethylpurine (**2b**).

This compound was obtained from aminoimidazolecarbaldehyde **1** and propionitrile by following the above general procedure in 64% yield, mp 174-175° (from ethyl acetate-hexane); ir (potassium bromide): 1590 (C=N), 1480, 1410, 1390 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.69 (s, 1H, 6-H), 3.83 (s, 3H, CH_3N), 3.09 (c, 2H, CCH_2), 2.68 (s, 3H, CH_3), 1.42 (t, 3H, CH_3C); ^{13}C nmr (deuteriochloroform): δ 166.8 (C2), 161.1 (C4), 158.0 (C8), 137.8 (C6), 125.1 (C5), 32.7 (CH_2), 30.5 (CH_3N), 14.2, 13.4 (2 CH_3).

Anal. Calcd. for $C_9H_{12}N_4$ (176.22): C, 61.33; H, 6.88; N, 31.79. Found: C, 60.51; H, 6.81;N, 31.57.

7,8-Dimethyl-2-phenylpurine (**2c**).

The crude product obtained from aminoimidazolecarbaldehyde **1** by cyclocondensation with benzonitrile was subjected to silica gel column chromatography. Elution of the column with chloroform:ethanol (10:1, v/v) gave a crystalline substance which was recrystallized from ethanol:hexane (2:1, v/v) to yield 0.11 g (28%) of **2c**, mp 190-192°; ir (potassium bromide): 1610, 1500 (C=N), 1460 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.80 (s, 1H, 6-H), 7.80-7.46 (m, 5H, phenyl protons), 3.82 (s, 3H, CH_3N), 2.68 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 162.1 (C4), 159.0 (C2), 158.0 (C8), 137.7 (C6), 125.6 (C5), 30.6 (CH_3N), 14.2 (CH_3).

Anal. Calcd. for $C_{13}H_{12}N_4$ (224.27): C, 69.62; H, 5.40; N, 24.98. Found: C, 70.03; H, 5.33; N, 24.90.

2,8,9-Trimethylpurine (**4a**).

This compound was prepared in 44% yield from compound **3a** and acetonitrile by a procedure analogous to that described for the preparation of **2c**. The product was recrystallized from ethanol, as white needles, mp 194-196°; ir (potassium bromide): 1600, 1580 (C=N), 1460, 1320 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.86 (s, 1H, 6-H), 3.78 (s, 3H, CH_3N), 2.81 (s, 3H, CH_3), 2.65 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 162.5 (C2), 154.9 (C4, C8), 146.2 (C6), 133.4 (C5), 28.4 (CH_3N), 25.8, 14.3 (2 CH_3).

Anal. Calcd. for $C_8H_{10}N_4$ (162.19): C, 59.23; H, 6.23; N, 34.55. Found: C, 59.15; H, 6.34; N, 34.28.

2,9-Dimethyl-8-phenylpurine (**4b**).

The crude product obtained from aminoimidazolecarbaldehyde **3b** by cyclocondensation with acetonitrile was subjected to silica gel column chromatography. Elution of the column with ethyl acetate gave a crystalline substance which was recrystallized from ethyl acetate to yield 0.19 g (46%) of **4b**, mp 175-178°; ir (potassium bromide): 1600, 1590 (C=N), 1420 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.03 (s, 1H, 6-H), 7.82-7.57 (m, 5H, phenyl protons), 3.95 (s, 3H, CH_3N), 2.86 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 162.5 (C2), 157.2 (C8), 154.2 (C4), 147.5 (C6), 132.1 (C5), 130.7, 129.2, 129.0 (phenyl), 30.5 (CH_3N), 26.0 (CH_3).

Anal. Calcd. for $C_{13}H_{12}N_4$ (224.27): C, 69.61; H, 5.39; N, 24.98. Found: C, 69.26; H, 5.49; N, 24.44.

2-Ethyl-9-methyl-8-phenylpurine (**4c**).

This compound was similarly prepared from aminoimidazolecarbaldehyde **3b** by cyclocondensation reaction with propionitrile in 22% yield, mp 128-130°; ir (potassium bromide): 1590 (C=N), 1490, 1410 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.02 (s, 1H, 6-H), 8.35-7.53 (m, 5H, phenyl protons), 3.96 (s, 3H, CH_3N) 3.10 (q, 2H, CCH_2), 1.45 (t, 3H, CH_3C); ^{13}C nmr (deuteriochloroform): δ 164.7 (C2), 157.3 (C8), 153.7 (C4), 148.2 (C6), 132.2 (C5), 130.8, 129.3, 129.0 (phenyl), 33.0 (CH_2), 30.6 (CH_3N), 13.2 (CH_3).

Anal. Calcd. for $C_{14}H_{14}N_4$ (238.29): C, 70.55; H, 5.93; N, 23.51. Found: C, 70.03, H, 6.01; N, 23.34.

2,8-Diphenyl-9-methylpurine (**4d**).

This compound was prepared in 33% yield from compound **3b** and benzonitrile by a procedure analogous to that described for the preparation of **4b**. The product was recrystallized from ethanol, mp 172-174°; ir (potassium bromide): 1600, 1580 (C=N), 1490, 1400 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.19 (s, 1H, 6-H), 8.56-7.55 (m, 10H, phenyl protons), 4.03 (s, 3H, CH_3N); ^{13}C nmr (deuteriochloroform): δ 158.9 (C2), 156.0 (C8), 154.5 (C4), 147.8 (C6), 138.3 (C5), 30.7 (CH_3N).

Anal. Calcd. for $C_{18}H_{14}N_4$ (286.34): C, 75.50; H, 4.93; N, 19.57. Found: C, 75.33; H, 5.08; N, 19.64.

General Procedure for the Cyclization Reactions of Compounds **1** and **3a,b** with Formamide.

A mixture of the corresponding aminoimidazolecarbaldehyde (1.8 mmoles) and formamide (1 ml) was refluxed for 10 hours. After cooling, the reaction mixture was poured into 20 ml of ice-water and neutralized with 10% ammonium hydroxide solution. The aqueous mixture was extracted with chloroform, dried with magnesium sulfate and evaporated to give the crude product, which was purified as specified for each compound.

7,8-Dimethylpurine (**2d**).

The crude product obtained from aminoimidazolecarbaldehyde **1** by cyclocondensation with formamide was subjected to silica gel column chromatography. Elution of the column with ethyl acetate:ethanol (1:1, v/v) gave a crystalline substance which was recrystallized from ethanol to yield 0.15 g (56%) of **2d**, mp 194-196° [lit [7] 196-197°].

8,9-Dimethylpurine (**4e**).

This compound was obtained from aminoimidazolecarbaldehyde **3a** and formamide by following the above general procedure in 52% yield, mp 122-124° (from ethanol) [lit [8]].

8-Phenyl-9-methylpurine (**4f**).

The crude product obtained from aminoimidazolecarbaldehyde **3b** by cyclocondensation with formamide was subjected to silica gel column chromatography. Elution of the column with ethyl acetate:ethanol (15:1, v/v) gave a crystalline substance which was recrystallized from ethyl acetate to yield 0.30 g (79%) of **4f**, mp 157-159° [lit [9]].

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