A Versatile Synthetic Approach to Isoguanine Derivatives

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Abstract: 5-Amino-4-(*N*-ethoxycarbonyl)formamidino imidazoles were prepared from 5-amino-4-(*N*-ethoxycarbonyl)cyanoformimidoyl imidazoles and primary alkyl amines, under mild experimental conditions. The product imidazoles were selectively cyclized to N_6-substituted isoguanines by reflux in acetonitrile with one equivalent of sulfuric acid, followed by neutralization. The same imidazoles led to N_1-alkylisoguanines as the major product upon reflux in ethanol.

Key words: heterocycles, rearrangements, ring closure, imidazole, isoguanine

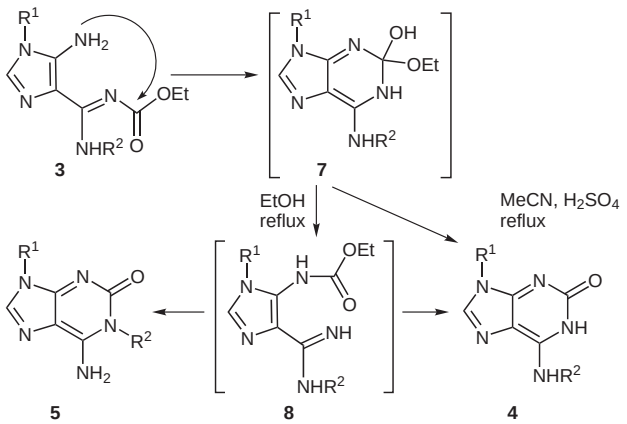
Purine-based compounds display a wide range of biological activities.[1] Their potency and selectivity depends on the position and nature of the substituents on the ring. 6-Alkylamino-2-oxopurines have been isolated both from higher plants and microorganisms, where they stimulate cell division and cell growth and also delay senescence.[2] Analogous structures have been synthesized, usually by varying the side chain of the amino substituent in the 6-position, and some of them are also active as plant growth stimulators.[3] The literature reports several methods for the synthesis of isoguanines or isoguanosines. These compounds were prepared from a substituted imidazole (usually a 5-amino-4-carbamoyl imidazole[4,5] or a 4,5-dicyanoimidazole[5]) or from a substituted purine, in several consecutive steps. 2-Aminoadenosine,[6] adenosine *N*-1-oxide,[7] guanosine,[8] 2-amino-6-chloropurine[9] or 2-oxo-6-chloropurine[10] are some examples of purine compounds that have been used in these synthesis.

1-Methylisoguanosine was isolated from several marine sources,[11] and proved to have potent muscle-relaxant activity, and also cardiovascular and anti-inflammatory properties.[11a,12] The structure of this compound was confirmed by chemical synthesis, from the reaction of 5-amino-4-carbamoylimidazole or 5-amino-4-cyanoimidazole with methyl isocyanate[11c,13] or from direct methylation of isoguanosine.[11b,c]

The synthesis of analogues of this pharmacologically active compound have also been reported, and the substitution pattern was varied on N-1, N-9, and C-8, depending on the substituted imidazole used as starting material and on the isocyanate selected for the reaction.[14]

In our research group, 5-amino-4-cyanoformimidoyl imidazoles **1** have been used as versatile synthons for nitrogen heterocycles fused with the imidazole ring. The synthesis of different 6-substituted purines[15] and imidazopyridines[16] has been reported and usually requires mild reaction conditions. The reaction of imidazoles **1** with ethyl chloroformate led to the formation of compounds **2**, where the acyl group is incorporated in the imine nitrogen[15g] (Table 1). The electron-withdrawing effect of this group facilitates nucleophilic attack to the adjacent carbon atom, and the reaction with methyl and benzylamine occurred after 10 minutes to 18 hours at room temperature. The products **3** were isolated as white solids in 80–89% yield.[17]

A suspension of compound **3** in ethanol was heated under reflux, to induce intramolecular cyclization. A homogeneous solution was initially formed, leading to a different solid suspension. When the starting material was totally consumed (3.5 h to 4 d), the solid was filtered and identified as a mixture of purines **4** and **5**. Variable ratios of these products were obtained, depending mainly on the reaction conditions (solvent, temperature, and time). The experiments described in Table 1, correspond to reaction mixtures with the highest ratio of compound **5**. Compounds **4** and **5** were separated using ethanol or DMF as solvent and one equivalent of DBU (considering the amount of isoguanine **4** present). Upon stirring the mixture at room temperature, the DBU salt of **4** is solubilized, leading to a suspension of isoguanine **5**, quantitatively recovered.[18] The formation of compound **5** can only be rationalized if the acyl substituent migrates from the imine nitrogen to the amino group on C-5 of the imidazole ring (Scheme 1)



Scheme 1

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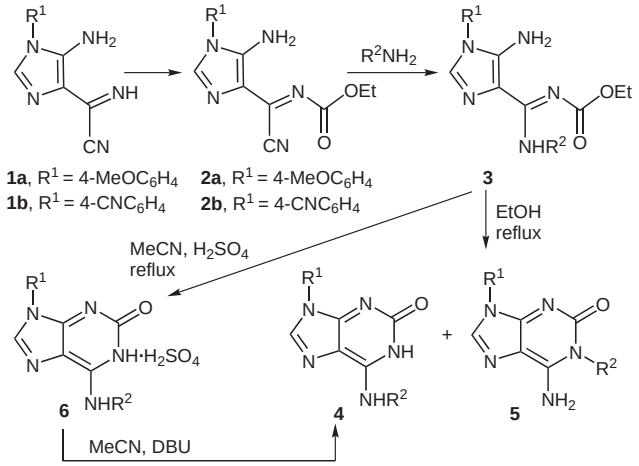
Table 1 Synthesis of Purines **4** and **5**



Compd	R^1	R^2	Reaction conditions	Yield (%)
3a	4-$MeOC_6H_4$	Me	CH_2Cl_2, 10 min, r.t.	80
3b	4-CNC_6H_4	Me	CH_2Cl_2, 30 min, r.t.	85
3c	4-$MeOC_6H_4$	Bn	EtOH, 15 min, r.t.	84
3d	4-CNC_6H_4	Bn	MeCN, 18 h, r.t.	89
4a	4-$MeOC_6H_4$	Me	**6a**, MeCN, DBU (1 equiv), 30 min, r.t.	97
4b	4-CNC_6H_4	Me	**6b**, MeCN, DBU (1 equiv), 3 h, r.t.	90
4c	4-$MeOC_6H_4$	Bn	1. **3c**, MeCN, H_2SO_4 (1 equiv), 2 d, reflux 2. DBU (1 equiv), 1 h, r.t.	80
4d	4-CNC_6H_4	Bn	1. **3d**, MeCN, H_2SO_4 (1 equiv), 11 d, reflux 2. DBU (1 equiv), 3 h, r.t.	43
5a	4-$MeOC_6H_4$	Me	1. **3a**, EtOH, 5 h, reflux 2. KOH (1 N), 45 min, r.t.	53[a]
5b	4-CNC_6H_4	Me	**3b**, EtOH, 9 h, reflux	31[b]
5c	4-$MeOC_6H_4$	Bn	**3c**, EtOH, 3.5 h, reflux	50[c]
5d	4-CNC_6H_4	Bn	**3d**, EtOH, 4 d, reflux	35[d]
6a	4-$MeOC_6H_4$	Me	**3a**, MeCN, H_2SO_4 (1 equiv), 18 h, reflux	97
6b	4-CNC_6H_4	Me	**3b**, MeCN, H_2SO_4 (1 equiv), 3 d, reflux	93

[a] Isolated from a mixture of **4a** and **5a** in a 2:8 ratio.
[b] Isolated from a mixture of **4b** and **5b** in a 3:7 ratio.
[c] Isolated from a mixture of **4c** and **5c** in a 2.5:7.5 ratio.
[d] Isolated from a mixture of **4d** and **5d** in a 2:8 ratio.

The cyclic intermediate **7** can evolve directly to isoguanine **4**, upon elimination of ethanol, or can ring-open, leading to imidazole **8**. This type of migration was previously observed for the acetyl group, and was accelerated when methanol/ethanol were used as solvents.[15g] Compound **8** is postulated as the intermediate in the formation of isoguanine **5**, formed by nucleophilic attack by the alkylamine, in the amidine unit, to the carbonyl carbon atom.

In order to facilitate the elimination of ethanol from the cyclic intermediate **7**, the reflux of imidazole **3** was carried out in acetonitrile, in the presence of one equivalent of sulfuric acid. The solid suspension was filtered when the starting material was completely consumed (18 h to 11 d) leading to the hydrogenosulfate salt of isoguanine (**6a** and **6b**). Direct addition of DBU (1 equiv) to the reaction mixture led to compounds **4c** and **4d** as the only isolated products.[19] Compounds **4a** and **4b** were also isolated upon neutralization of the corresponding salts **6**.

These reactions were carried out from *N*-arylimidazoles with electron-withdrawing (R^1 = 4-CNC_6H_4) and electron-donating (R^1 = 4-$MeOC_6H_4$) substituents. Longer

reaction times were usually required when the 1-(4-cyanophenyl)imidazoles **3b** or **3d** were used as starting material. This may be due to the poor solubility of these compounds in the reaction solvent or to a reduced nucleophilicity of the amino group in the 5-position, as a result of the electron-withdrawing effect of the aromatic substituent. Nevertheless, the yields are usually very good except for the formation of compound **4d**. This reaction was particularly slow (11 d under reflux in acetonitrile and 1 equiv of sulfuric acid) leading to extensive degradation of the reaction mixture and a poor isolated yield of the product (43%).

In conclusion, an easily accessible substituted imidazoles **2** were used as the precursor of imidazoles **3**, formed at room temperature and in the presence of a primary alkyl amine. Compounds **3** were cyclized either to N_1-alkyl-isoguanines **5** or N_6-substituted isoguanines **4**, depending on the reaction conditions used. These compounds, which are not easily prepared by other methods, were isolated in very good yields from this common intermediate.

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(17) **Compounds 3**
Aqueous methylamine (for **3a** and **3b**, 14 equiv), or benzylamine (for **3c** and **3d**, 2–3 equiv) was added to a suspension of imidazole **2** in CH_2Cl_2 (for **3a** and **3b)**, EtOH (for **3c**), or MeCN (for **3d**, 2–12 mL). The mixture was stirred at r.t. for 10 min to 18 h. The product precipitated from the reaction mixture (**3c** and **3d**) or the solvent was removed in the rotary evaporator (**3a** and **3b**) and EtOH was added to the residue. The white solid was filtered and washed with EtOH (**3a**–**c**), or MeCN(**3d)**, and Et_2O. The structure of the products obtained was confirmed by elemental analysis, ^{1}H NMR and ^{13}C NMR spectroscopy.
Characterization of 3a
^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ (mixture of conformers A and B, ratio A/B = 3:2) = 9.90 (br s, 1 H, A), 8.00 (br s, 1 H, B), 7.40 (d, *J* = 9.0 Hz, 2 H), 7.39 (s, 1 H), 7.12 (d, *J* = 9.0 Hz, 2 H), 6.94 (br s, 2 H, A), 5.98 (br s, 2 H, B), 3.97 (q, *J* = 7.2 Hz, 2 H), 3.81 (s, 3 H), 3.41 (s, 3 H, A), 2.74 (s, 3 H, B), 1.17 (t, *J* = 7.2 Hz, 3 H); ^{1}H NMR (300 MHz, DMSO-d_6, 50 °C): δ (only one set of bands is present) = 10.20–9.20 (br s, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.34 (s, 1 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 6.80–6.30 (br s, 2 H), 3.99 (q, *J* = 7.2 Hz, 2 H), 3.82 (s, 3 H), 3.20 (s, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.49 (br, A), 159.20, 156.80 (br, B), 147.08 (br), 142.70, 130.99, 126.91, 126.72, 114.99, 110.00–114.00 (br), 59.47 (br), 55.55, 32.31 (br, A), 23.45 (br, B), 14.68. Anal. Calcd for $C_{15}H_{19}N_5O_3$: C, 56.77; H, 6.04; N, 22.07. Found: C, 56.97; H, 6.06; N, 21.57. IR (mull): 3251 (m), 3116 (m), 1640 (s), 1598 (s).

(18) **Compounds 5**
A suspension of **3a**–**d** in EtOH (20–60 mL) was refluxed for 5 h to 4 d. The resulting suspension was filtered and washed with MeCN (**4** and **5a**), EtOH (**4** and **5b** and **d**) or Et_2O (**4** and **5c**) to give a mixture of compounds **4** and **5** in a ratio of

4.5:5.5 (**4a**:**5a**), 3:7 (**4b**:**5b**), 2.5:7.5 (**4c**:**5c**) and 2:8 (**4d**:**5d**). The mixture **4a**:**5a** (4.5:5.5) was suspended in H_2O and combined with KOH (1 N). The suspension was stirred at r.t. for 45 min to give a 2:8 mixture of **4a**:**5a**. A suspension of these solid mixtures in EtOH (for **a** and **c**) or DMF (for **b** and **d**) was combined with DBU (1 equiv in relation to the amount of compound **4**). The suspension was stirred at 40 °C for 6–18 h (**a** and **b**), or at r.t. for 30 min (**c** and **d**). The white solid was filtered and washed with EtOH and Et_2O to give compound **5a**–**d**. The structure of the products obtained was confirmed by elemental analysis, ^{1}H NMR and ^{13}C NMR spectroscopy.

Characterization of 5a

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.16 (br s, 2 H), 8.07 (s, 1 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 3.80 (s, 3 H), 3.36 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.03, 154.18, 152.39, 151.49, 137.66, 128.13, 124.35, 114.36, 109.00–110.00(br), 55.06, 30.01. Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.60; H, 5.06; N, 25.78. IR (mull): 3385 (m), 3208 (s), 3120 (s), 3052 (s), 1883 (w), 1698 (s), 1640 (s), 1601 (s), 1584 (s).

(19) **Compounds 4**

To a suspension of imidazole **3a**–**d** in MeCN (8–10 mL) was added H_2SO_4 (1 equiv), and the mixture was refluxed for 18 h to 11 d. The resulting suspension was filtered and washed with MeCN (**6a**) or EtOH (**6b**) and Et_2O. Then, DBU (1 equiv) was added to a suspension of compound **6a**,**b** in MeCN (3–20 mL). The mixture was stirred at r.t. for 30 min to 3 h, when the white solid was filtered and washed with MeCN and Et_2O, to give compounds **4a**,**b**. The structure of the products obtained was confirmed by elemental analysis, ^{1}H NMR and ^{13}C NMR spectroscopy.

Characterization of 4a

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.70 (v br s, 1 H), 8.08 (s, 1 H), 8.00 (br s, 1 H), 7.64 (d, *J* = 9.0 Hz, 2 H), 7.08 (d, *J* = 9.0 Hz, 2 H), 3.80 (s, 3 H), 2.93 (br s, 3 H). The compound **4a** was not soluble in DMSO-d_6 and the ^{13}C NMR spectrum was obtained from the salt form. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.16, 151.85, 149.94, 141.98, 139.87, 127.31, 125.55, 115.10, 110.62, 55.86, 29.25. Anal. Calcd for $C_{13}H_{13}N_5O_2 \cdot 0.4H_2O$: C, 56.07; H, 4.99; N, 25.15. Found: C, 55.95; H, 4.92; N, 25.12. IR (mull): 3234 (s), 3126 (m), 3053 (m), 2733 (m), 1681 (s), 1626 (s), 1596 (s).