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A Novel Synthesis of Purine and Deazapurine Derivatives from 5-Aminoimidazoles

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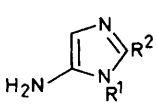
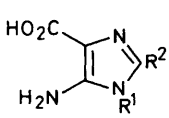
Catalytic reduction of 4-unsubstituted-5-nitroimidazoles (**3**) in 1,4-dioxane solution is an excellent route to the 5-aminoimidazoles (**1**) which can be isolated or used *in situ* to generate good yields of purine or deazapurine derivatives.

An important C–C bond forming step in the *de novo* biosynthesis of purine ribonucleotides is carboxylation of 5-aminoimidazole ribonucleotide (AIR) (**1a**) giving 5-amino-4-imidazolecarboxylic acid ribonucleotide (carboxy AIR) (**2a**).[1] In spite of the importance of this biological process, the chemical properties of 4-unsubstituted-5-aminoimidazoles (**1**) have received little attention.[2] Several synthetic approaches to the 5-aminoimidazoles (**1**),[3—7] including catalytic reduction of 4-unsubstituted-5-nitroimidazoles (**3**).[3,8—11] have been described but simple derivatives have never been fully characterised, except by conversion to salts. Furthermore, the physical, chemical, and biological properties of the free bases (**1**), including their potential use as synthetic intermediates, are virtually unexplored. It has been demonstrated by Shaw and co-workers,[12—13] that carboxylation of 5-aminoimidazoles (**1**) using aqueous potassium hydrogen carbonate (70 °C) can be achieved *in vitro* without enzymic assistance, but this has not been developed into a preparative procedure. We now describe the full characterisation of simple 5-aminoimidazoles (**1**) and demonstrate novel transformations into purine and deazapurine derivatives.

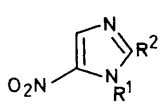
A number of 5-nitroimidazoles (**3**) are important therapeutic agents[14] and their commercial availability makes them attractive precursors to the amines (**1**). In contrast to the use of ethanol as solvent,[10,11] we have found the catalytic hydrogenation of 5-nitroimidazoles (**3**) in 1,4-dioxane solution to be a superior method of generating the amines (**1**), which are conveniently used *in situ* or can be isolated in good yield and characterised. Thus, compound (**3b**) (0.05 mol) in 1,4-dioxane (120 ml) was hydrogenated (1 atm) using 40% w/w of 5% Pd/C: over-reduction was never observed. Filtration and concentration using standard procedures gave 5-amino-1,2-dimethylimidazole (**1b**) (74%), m.p. 120—140 °C [$\delta_H(CD_3SOCD_3)$ 2.10 (s, 2-Me), 3.20 (s, 1-Me), 4.15 (br. s, NH_2), 5.8 (s, 4-H)]. Similar procedures gave (**1c**) (53%), m.p. 107—109 °C (lit.[5] 101 °C; no analytical data) and (**1d**) (58%), m.p. 118—122 °C.† Compound (**1d**) has previously been described[10,11] but only fully characterised as its hydro-



(**1**)



(**2**)



(**3**)

† Satisfactory elemental analyses and n.m.r. spectra have been obtained for all compounds.

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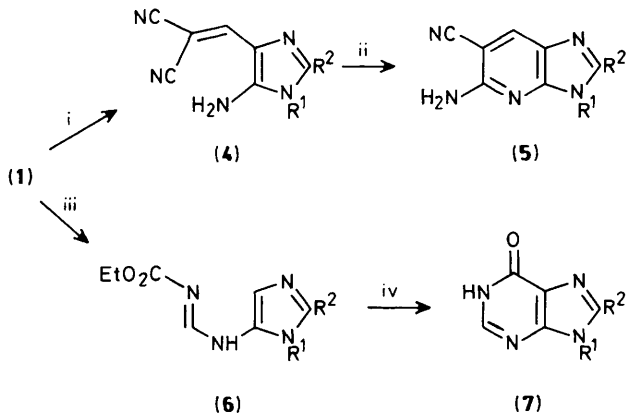

Scheme 1. *Reagents and conditions*: i, $EtOCH{=}C(CN)_2$; ii, aq. MeOH, NaOH, 80 °C; iii, $EtOCH{=}NCO_2Et$; iv, Thermex, 260 °C.

In compounds (**1**—**7**), **a**; R^1 = 1-ribofuranosyl-5-phosphate, R^2 = H
b; $R^1 = R^2$ = Me
c; R^1 = Me, R^2 = H
d; $R^1 = CH_2CH_2OH$, R^2 = Me
e; R^1 = Me, $R^2 = Pr^i$

chloride.[11] At ambient temperatures and upon exposure to air for periods of more than an hour, the crystalline amines (**1**) or their solutions in dioxane are unstable and slowly decompose, but if thoroughly dried in a desiccator (silica gel) can be stored under vacuum (0 °C) for months. As intermediates, the amines are best used *in situ* in 1,4-dioxane solution and in the following transformations, (Scheme 1) yields refer to the overall yield from the corresponding 5-nitroimidazoles (**3**).

Reaction of amine (**1b**) with ethoxymethylenemalononitrile (EMMN) [$EtOCH{=}C(CN)_2$][15] gave (5 min) the 5-amino-4-(2,2-dicyanovinyl)imidazole (**4b**) (84%), m.p. indistinct (cyclisation). Similarly the derivatives (**4d**) (72%), m.p. 198—200 °C, and (**4e**) (57%), m.p. 216—218 °C, were obtained. Reaction was exclusively at the 4-position of the imidazole ring; no *N*-condensation products were detected. In the reaction (**1**)→(**4**), the formation of the C–C bond is comparable to the biological transformation (**1a**)→(**2a**), and the derivatives (**4**) are useful intermediates. Treatment of compound (**4b**) with hot aqueous/methanolic NaOH gave the 1-deazapurine derivative (**5b**) (64%), m.p. 315—317 °C, and compounds (**5d**) (65%), m.p. 245—247 °C, and (**5e**) (77%), m.p. 254—255 °C, were obtained in a similar manner.

In contrast to reaction with EMMN, reaction of the amines (**1**) with ethoxymethyleneurethane ($EtOCH{=}NCO_2Et$)[16] occurred exclusively on the amino group. Typically, compound (**1b**) gave the *N*-ethoxycarbonyl-*N'*-(imidazol-5-yl)-formamidine (**6b**) (49%), m.p. indistinct (cyclisation), and the derivatives (**6c**) (52%), m.p. 161—163 °C, and (**6d**) (33%), m.p. 172—173 °C, were similarly obtained. The formation of the derivatives (**6**) provides a new synthetic approach to hypoxanthines: thermal cyclisation of compounds (**6b**) and (**6d**) rapidly occurred giving 8,9-dimethylhypoxanthine (**7b**) (91%), m.p. >360 °C, and (**7d**) (65%), m.p. >360 °C, respectively.

We have investigated the reactions of 5-aminoimidazoles (**1**) with a number of other reagents and find that often mixtures of *C*- and *N*-condensation products are formed. Amine (**1c**) and ethyl *N*-cyanoformimidate ($EtOCH{=}NCN$)[17] gave the isomers (**8**) (42%), m.p. 178—180 °C, and (**9**) (4%), m.p. 184—186 °C. The major product (**8**) was transformed into 9-methyladenine (**10**) (10%), m.p. 302—304 °C (lit.[18] 301—302 °C), by heating at 190 °C (1 min). A similar treatment of the minor product (**9**) gave the isomeric 2-amino-9-methylpurine (**11**) (59%), m.p. 244—246 °C (lit.[19] 242—243 °C).

The examples described above illustrate the value of the 5-aminoimidazoles (**1**) as synthetic intermediates and further examples will be reported.

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