1,4-Diazabicyclo[2.2.2]octane (DABCO)-catalysed Hydrolysis and Alcoholysis Reactions of 2-Amino-9-benzyl-6-chloro-9*H*-purine

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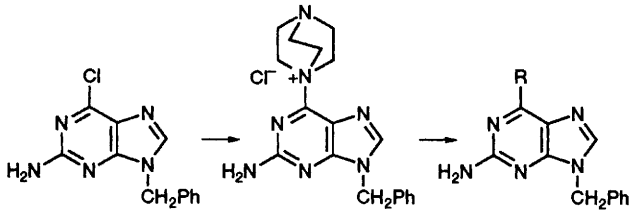
2-Amino-9-benzyl-6-chloro-9*H*-purine **1** is hydrolysed in refluxing water in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to give 2-amino-9-benzyl-1,6-dihydro-6-oxo-9*H*-purine **3**; however, **1** reacts with hydroxide ion at ambient temp., or an alcohol and potassium carbonate at elevated temperatures, in the presence of DABCO to give **3** or 6-alkoxy-2-amino-9-benzyl-9*H*-purines **4–8**, respectively.

The development of efficient methods for the synthesis of *N*(9)-substituted guanines (2-amino-6-oxopurines) continues to receive much attention, in part due to the pivotal role of acyclovir and ganciclovir in the treatment of herpes virus infections.[1] Synthetic routes to *N*(9)-substituted guanines often proceed *via* 9-substituted 2-amino-6-chloropurines. Conversion of the 6-chloro moiety to the 6-oxo function of guanine usually requires treatment with acid or base at elevated temp.[2] Milder conditions for the conversion of 9-substituted 2-amino-6-chloropurines to 9-substituted guanines include the use of alkaline 2-hydroxyethanethiol[3] and 6-pyridinium salts.[4]

Ashwell *et al.*, recently reported a two-stage procedure for the preparation of guanines from 2-amino-6-chloropurines.[5] The 6-chloro group was displaced with trimethylamine at 0 °C to give a 2-amino-6-trimethylammonium purine salt. This salt was treated with 3-hydroxypropionitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give 9-(substituted)guanine derivatives. We applied this method to the preparation of 2-amino-6-oxopurines but the method was problematic owing to the high volatility of trimethylamine. Substitution of the less volatile triethylamine for trimethylamine was not successful; a triethylammonium salt did not form. However, the bicyclic tertiary amine 1,4-diazabicyclo-[2.2.2]octane (DABCO), which has a high melting point, worked very well to form an *in situ* ammonium salt from 2-amino-9-benzyl-6-chloropurine **1** (see Scheme 1). The DABCO moiety was easily hydrolysed in refluxing water or by using aqueous sodium hydroxide in dichloromethane at ambient temp. to provide the 9-substituted guanine. In addition, the DABCO-purine salt could be displaced with alcohols to give 6-alkoxy-2-aminopurines. This method represents a mild and efficient process for the synthesis of 9-substituted guanines or the 6-alkoxy derivatives.



Scheme 1

Table 1[a]

Compound	R	Yield[b] (%)	mp/°C
3[c]	OH (oxo)	40[d], 34[e]	302–304
4	OMe	68[f]	179–181
5	OCH_2Me	65[f]	187–189
6	$OCHMe_2$	40[f]	173–175
7[g]	$O(CH_2)_2OMe$	72[f]	140–142
8	OCH_2Ph	64[f]	144–146

[a] Compounds **3–8** were homogeneous by TLC [silica gel 60 (40–63 μm); ethyl acetate–hexanes]; **2** was an origin spot. All compounds gave combustion C, H and N analyses data to within 0.4% of theoretical values. Mass spectra and ^{1}H NMR spectra were consistent with the assigned structures. [b] The reported yields are for recrystallized material and are non-optimized. [c] See ref. 6. [d] Recrystallized from 80% aq. propan-2-ol; 75% crude yield before recrystallization. See footnote †. [e] Recrystallized from ethanol; 57% crude yield before recrystallization. See footnote §. [f] Recrystallized from ethyl acetate–hexanes. [g] See ref. 8 (lit.[8] mp 95.5–99 °C non-recrystallized; purified by silica gel chromatography).

In our method, **1** was treated with DABCO (1 equiv.) in refluxing water for 15 min to give 9-benzylguanine[6] **3**.† Alternatively, the reaction of 1-(2-amino-9-benzyl-9*H*-purin-6-yl)-4-aza-1-azoniabicyclo[2.2.2]octane chloride **2**‡ with aqueous sodium hydroxide (10 equiv.):dichloromethane (1:1) at ambient temp. gave **3** in 15 min.§ Increasing the number of equivalents of sodium hydroxide from two to ten had an accelerating effect on the reaction. Also, in a control experiment using sodium hydroxide (10 equiv.) and no DABCO, essentially no hydrolysis of **1** occurred after 24 h at ambient temp. The hydrolysis of **2** with 1 mol dm^{-3} hydrochloric acid gave a mixture of products and was not pursued further.

In a modified procedure, **1**¶ was reacted with an appropriate alcohol (with heating) using a catalytic amount of DABCO (0.1 equiv.) and potassium carbonate (1.0 equiv.) to give the 6-alkoxy-2-amino-9-benzyl-9*H*-purines **4–8**.‖ The reaction of **1** in refluxing tertiary butyl alcohol in the presence of DABCO (0.1 equiv.) gave a complex mixture of products. In a control experiment without DABCO, the reaction of **1** with propan-2-ol in the presence of potassium carbonate (1.0 equiv.) gave only 10–20% of the 6-(2-propyloxy) derivative **6** after refluxing for 18 h. Clearly DABCO has an accelerating effect on these displacement reactions since reactions in the presence of DABCO are complete in 2 h or less. In addition, the quaternary DABCO-purine salt **2** was shown to react with primary alcohols at ambient temp. in the presence of potassium carbonate (1 equiv.) in less than 1 h.

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Footnotes

† A mixture of **1**, DABCO (1 equiv.), and water was heated to reflux for 15 min and the solution was cooled to ambient temp. and basified to pH 11 with 1 mol dm^{-3} sodium hydroxide. The aqueous phase was washed twice with a double volume of dichloromethane and then acidified to pH 5 with 12 mol dm^{-3} hydrochloric acid. The precipitated solid was collected by suction filtration (75% crude yield) and recrystallized from 80% aqueous propan-2-ol to give **3** in 40% yield. The product was identical to authentic 9-benzylguanine by UV, mp and ^{1}H NMR spectroscopy.

‡ Compound **2** was prepared directly by the reaction of **1** with DABCO (2.0 equiv.) in anhydrous DMF at ambient temp. The precipitate of **2** was collected by filtration, washed with DMF and dried under high vacuum at 100 °C for 18 h to give analytically pure

material. The FAB$^+$ mass spectrum and ^{1}H NMR spectrum were consistent with the assigned structure. Compound **2** could not be successfully recrystallized because of its poor solubility and reactivity towards hydroxylic solvents. It can be stored in a bottle for several months without significant decomposition when protected from moisture.

§ Compound **2** was treated with 1 mol dm^{-3} sodium hydroxide (10 equiv.) : dichloromethane (1 : 1) at ambient temp. for 15 min, followed by acidification of the aqueous phase to pH 5 with 1 mol dm^{-3} hydrochloric acid and collection of the solids by filtration to give **3** (57% crude yield). Recrystallization of **3** from ethanol provided material which was identical by UV and mp to the literature values.[6,7]

¶ Compound **1** was synthesized by alkylation of 2-amino-6-chloro-9*H*-purine with benzyl bromide (1.1 equiv.) and caesium carbonate (1.1 equiv.) in DMF at ambient temp. for 1 h in 65% yield after chromatography on silica gel; mp 208–210 °C, lit.[6] mp 210–212 °C. Proof that **1** is the 9-substituted purine and not the 7-isomer is based on a comparison of the UV of **1** [^{pH1} λ_{max} 313 nm (ε 7300), λ_{min} 266 (ε 1200); $^{pH7.13}$ λ_{max} 308 (ε 7400), λ_{min} 265 (ε 1100)] with the reported UV[7] of **1** whose structure was unambiguously assigned.[6]

‖ Compound **1** (1 mmol) was heated with DABCO (0.1 equiv.) and potassium carbonate (1.0 equiv.) in the presence of an excess of alcohol (2 ml of methanol, ethanol, propan-2-ol, 2-methoxyethanol, or benzyl alcohol) for 2 h at reflux, or 75–80 °C in the case of 2-methoxyethanol and benzyl alcohol, to give the desired derivatives **4**–**8** in 64–72% recrystallized yield (40% for **6**) without the need for chromatography (see Table 1).

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