COMMUNICATION

# Facilitation of displacements at the 6-position of purines by the use of 1,4-diazabicyclo[2.2.2]octane as leaving group

**Nicola K. Lembicz, Sharon Grant, William Clegg, Roger J. Griffin, Sarah L. Heath and Bernard T. Golding***

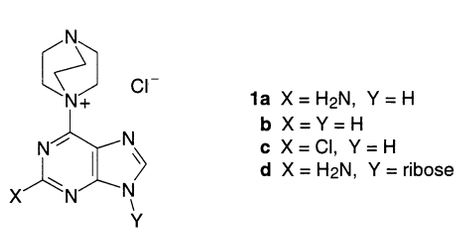
*Department of Chemistry, Bedson Building, The University of Newcastle upon Tyne, Newcastle upon Tyne NE1 7RU, UK*

**Reactions of 6-chloropurines with 1,4-diazabicyclo-[2.2.2]octane (DABCO) give the corresponding 'DABCO-purines' 1a–d, which undergo facile displacement reactions with alkoxides in dimethyl sulfoxide to afford 6-oxy-substituted purines.**

For the development of inhibitors of the DNA repair protein 6-*O*-methylguanine DNA-methyltransferase (MGMT),[1] we required a method for preparing 6-oxy-substituted purines. Such compounds, in which the substituent is *e.g.* benzyloxy or substituted benzyloxy,[2] 2-thienylmethoxy[3] or substituted allyloxy,[4] are known to be potent irreversible inactivators of MGMT. We have found a convenient and efficient method for preparing a variety of 6-oxy-substituted purines by employing 1,4-diazabicyclo[2.2.2]octane (DABCO) as the leaving group in substitution reactions at C-6 of purines.

A standard method to achieve displacements at C-6 of purines utilises a 6-chloropurine as starting material and proceeds *via* an intermediate 6-trimethylammonio species.[5–8] Trimethylammonium is a better leaving group than chloride in the addition–elimination mechanism leading to displacement of the 6-substituent by a nucleophile. However, the production of a 6-trimethylammoniopurine requires reaction of the corresponding 6-chloropurine with trimethylamine, which is problematical, especially on a large scale, because of the volatility, toxicity and unpleasant odour of trimethylamine. Furthermore, the reaction of a 6-trimethylammoniopurine with a nucleophile can display attack of the nucleophile on a methyl of the trimethylammonium group ($S_N2$ displacement) competitive with addition–elimination at C-6.[9]

We have found that trimethylamine can be replaced by either 1-azabicyclo[2.2.2]octane (quinuclidine) or 1,4-diazabicyclo-[2.2.2]octane (DABCO), with the latter being more attractive because of its much lower cost and greater effectiveness (faster rate of displacement compared to chloride or quinuclidine). Thus, reaction of 1 M 2-amino-6-chloropurine in dimethyl sulfoxide with 5.5 equiv. of DABCO for 12 h at room temperature gave a 90% yield of analytically pure 2-amino-6-(1-azonia-4-azabicyclo[2.2.2]oct-1-yl)purine chloride **1a**,† which precipitated directly from the reaction mixture. Similarly, 6-chloro- and 2,6-dichloro-purine gave the corresponding 'DABCO-purines' **1b** and **1c**,† respectively. The purines **1a–c** could also be prepared in ethanol as reaction medium, and indeed this solvent was used to treat 2-amino-6-chloropurine 9-ribofuranoside with 2 equiv. of DABCO (48 h, room temp.) to afford 80–90% of the derivative **1d**,† which again directly precipitated from the reaction.




**1a** X = $H_2N$, Y = H
**b** X = Y = H
**c** X = Cl, Y = H
**d** X = $H_2N$, Y = ribose

† New compounds gave analytical and spectroscopic data in accord with their assigned structures.

The structure of compound **1b** was confirmed by crystal structure analysis (see Fig. 1)‡ and shows the expected system of

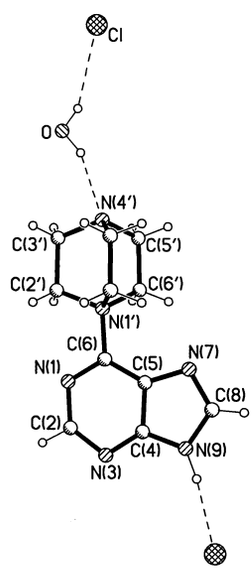


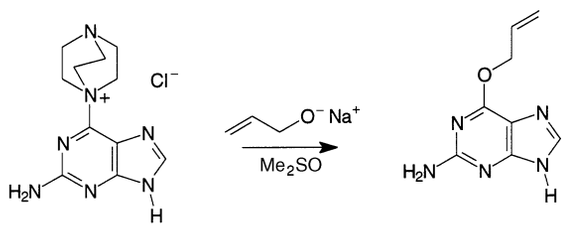

**Fig. 1** The structure of **1b** showing the labelling of the independent non-hydrogen atoms and the hydrogen bonding. All atoms, except for C(5′), C(6′), their symmetry-equivalents and the hydrogen atoms attached to C(2′) and C(3′), lie on crystallographic mirror planes.

‡ Crystal data for **1b**: $[C_{11}H_{15}N_6]Cl{\cdot}H_2O$, $M = 284.76$, orthorhombic, space group *Pnma*, $a = 11.9284(10)$, $b = 6.8762(6)$, $c = 15.5576(13)$ Å, $U = 1276.1(2)$ Å$^3$, $Z = 4$ (all structural fragments lie on mirror planes), $D_c = 1.482$ g cm$^{-3}$, $F(000) = 600$, $T = 160$ K. 7559 reflections were measured on a Siemens SMART CCD area-detector diffractometer (Mo-K$\alpha$ radiation, $\lambda = 0.710\,73$ Å, $\mu = 0.30$ mm$^{-1}$, $2\theta < 57°$). Structure solution was by direct methods, and refinement by full-matrix least-squares on $F^2$ for all 1646 independent reflections ($R_{int} = 0.0284$), with anisotropic displacement parameters and freely refined isotropic H atoms. $R_w = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{\frac{1}{2}} = 0.0827$ for all data, conventional $R = 0.0309$ on $F$ values for 1538 reflections with $F_o^2 > 2\sigma(F_o^2)$, goodness of fit = 1.103 on $F^2$ values for all data and 149 refined parameters. Programs: Siemens SMART and SAINT control and integration software, Siemens SHELXTL and local programs.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/83.

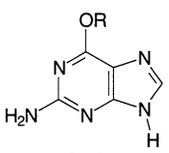
interlocked boat-like 6-membered rings for the DABCO system. The free nitrogen atom of the DABCO is hydrogen-bonded to a water molecule (the presence of which was also indicated by elemental analysis), which acts as a bridge to a chloride anion. The latter is bonded to the hydrogen atom at N-9 of another purine molecule, to give continuous · · · cation · · · anion · · · water · · · hydrogen-bonded chains.

Compounds **1a–d** undergo facile displacement reactions with alkoxides in dimethyl sulfoxide, with a typical example being shown in Scheme 1. Results for **1a** leading to 6-substituted purines **2a–h**† are summarised in Table 1. The order of displacement of groups from the 6-position of purines is $Me_3N$ > DABCO > quinuclidine > Cl (relative rates *ca.* 100 : 10 : 5 : 1). The slower displacement of DABCO *vs.* $Me_3N$ is probably a steric effect (more crowded transition state for DABCO in the addition–elimination pathway). However, we have not observed competing attack of the alkoxide on a DABCO methylene group, and the only disadvantage to the use of DABCO instead of trimethylamine is the slower rate of reaction of the DABCO derivatives. There are several advantages of using DABCO over chloro and trimethylammonio moieties, besides those already mentioned. Reactions with DABCO-purines are easy to monitor by thin layer chromatography (TLC) because they exhibit fluorescent spots at relatively low $R_f$, which disappear as the reaction proceeds. Furthermore, the desired product is very easy to separate from the starting DABCO-purine, because of the latter's greater polarity and solubility in water. In contrast, chloropurines often have a similar $R_f$ (TLC on silica) to the derived 6-substituted purine (*e.g.* with $C_4$ alkoxy groups), which makes separation difficult by normal phase chromatography.

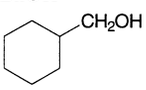
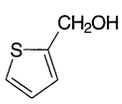
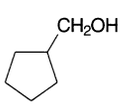
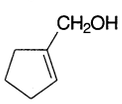



**Scheme 1**

**Table 1** Reactions of DABCO-purine **1a** with alcohols leading to products **2a–h**[a]



**2a–h**

| ROH | Reaction time/h | Product | Yield (%) |
|---|---|---|---|
| MeOH | 12 | **2a** | 88 |
| $H_2C{=}CHCH_2OH$ | 12 | **2b** | 87 |
| $HC{\equiv}CCH_2OH$ | 48 | **2c** | 72 |
| BnOH | 48 | **2d** | 81 |
|  | 72 | **2e** | 51 |
|  | 48 | **2f** | 74 |
|  | 48 | **2g** | 82 |
|  | 48 | **2h** | 70 |

[a]The alcohol (5.5 equiv.) was added to a stirred suspension of sodium hydride (2.0 equiv.) in anhydrous dimethyl sulfoxide under nitrogen at room temperature. After 1 h the DABCO-purine **1a** (1 equiv.; 1 M in DMSO) was added and the mixture was stirred at room temperature until the reaction was complete (an aliquot was assayed by TLC and UV spectroscopy: shift from $\lambda_{max}$ 316 to 280 nm). The base was neutralised by addition of glacial acetic acid and the solvent was removed *in vacuo*. The residue was absorbed onto silica and the product was purified by medium pressure chromatography (elution with 8% v/v MeOH in $CH_2Cl_2$).

In a previously reported preparation of 2,4-dinitrophenyl ethers from carbohydrates with a free hydroxy group, the alcohol (*e.g.* a mixture of the anomers of 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose) was treated with 2,4-dinitrofluorobenzene and an excess of DABCO in dimethylformamide.[10] The mechanism of this reaction was not discussed, but it seems likely that it proceeds *via* 1-(1-azonia-4-azabicyclo[2.2.2]oct-1-yl)-2,4-dinitrobenzene fluoride. Indeed, such adducts have been shown to be intermediates in reactions of DABCO with 2,4-dinitrochlorobenzene[11] and quinuclidine with picryl chloride.[12]

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