An Improved Route to Guanines Substituted at N-9

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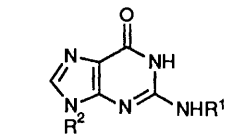
2-Amino-6-chloropurines (**2b**)—(**2e**) react with trimethylamine/3-hydroxypropionitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene to afford the corresponding *N*-9-substituted guanines (**1b**)—(**1e**) in near-quantitative yield.

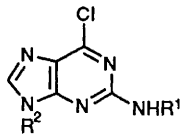
Synthetic procedures leading to *N*-9 substituted guanines in a simple, direct manner are of considerable interest,[1] primarily because of the potential antiviral activity of such derivatives [*e.g.* acyclovir,[2] (**1a**)]. In connection with our studies[3] of a polymer-linked guanine for the *in vivo* trapping and detection of carcinogens we required a synthesis of the guanine derivative (**1b**). We describe an efficient route to the guanine (**1b**) and related compounds (**1c**)—(**1e**), that exhibits the following important features: (i) Conversion of a 2-amino-6-chloropurine into an *N*-9 substituted guanine using trimethylamine/3-hydroxypropionitrile/1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dichloromethane. (ii) Protection of the 2-amino group during procedure (i) using 4,4'-dimethoxytrityl (DMT) tetrafluoroborate. (iii) Conversion of a methyl ester into the corresponding carboxylate under the reaction conditions.

Previous methods for the conversion of 2-amino-6-chloropurines into guanines have mostly utilised vigorous acidic[4] or basic[5] conditions that are not compatible with sensitive functional groups within an *N*-9 substituent. Our method for the conversion of *N*-9 substituted 2-amino-6-chloropurines into *N*-9 substituted guanines preserves acetal and silyl protecting groups in the *N*-9 substituent. The method exploits the well established propensity[6] of 2-cyanoethoxy groups to undergo base-induced elimination of the oxygen function when this is attached to a suitable carrier (*e.g.* P in phosphates). Thus, it is known[7] that 6-chloropurines react with trimethylamine to afford 6-trimethylammonium derivatives, that are susceptible to nucleophilic displacement of the trimethylammonium group.[8] We have found that treatment of 6-chloropurines (**2b**)—(**2e**) with trimethylamine in the presence of 3-hydroxypropionitrile and DBU leads efficiently to the corresponding guanine (**1b**)—(**1e**) (95—98% yield)† *via* intermediate 6-trimethylammonium [*e.g.* (**3a**)] and 6-(2-cyanoethoxy) [*e.g.* (**3b**)] derivatives. The trimethylammonium compound can be isolated in low yield (~50%) from treatment of the 2-amino-6-chloropurine with an excess of trimethylamine. The low yield is presumed to be due to further reaction of the trimethylammonium compound with trimethylamine leading to the observed 6-dimethylamino by-product [*e.g.* (**3c**)].[9] In our system the trimethylammonium compound is trapped by reaction with 3-hydroxypropionitrile faster than its reaction with trimethylamine. The trimethylammonium compound was shown to react with 3-hydroxypropionitrile in the presence of DBU to produce initially the 6-(2-cyanoethoxy) derivative and then the guanine. The conversion of the ester group of (**2b**) into the carboxylic acid of (**1b**) presumably occurs *via* base-catalysed transesterification of the methyl ester to a 2-cyanoethoxy ester, which undergoes DBU-catalysed elimination.[10]

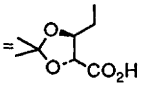
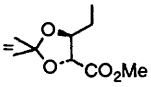
† To the *N*-9 alkylated 2-amino-6-chloropurine (**2b**)—(**2e**) (1 mmol) in dichloromethane (3 ml) containing 3-hydroxypropionitrile (5 mmol) at 0 °C, was added trimethylamine (1 ml) and DBU (1.5 mmol). The mixture was set aside at 4 °C (16 h). The solvent and excess of trimethylamine were removed *in vacuo* at 30 °C. The resulting oil was dissolved in dichloromethane (10 ml), and silica gel added. Removal of the solvent to give a free-flowing solid was followed by chromatography on silica gel to give the guanines (**1b**)—(**1e**) (elution with dichloromethane–methanol, proportion dependent on substrate).

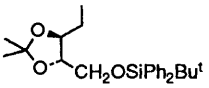
New compounds were chromatographically homogeneous and gave analytical/spectroscopic data in accord with the assigned structures.





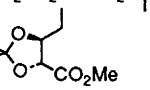
(1a) R^1 = H, R^2 = $CH_2OCH_2CH_2OH$ (2a) R^1 = R^2 = H

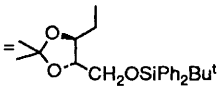
(1b) R^1 = DMT, R^2 =  (2b) R^1 = DMT, R^2 = 

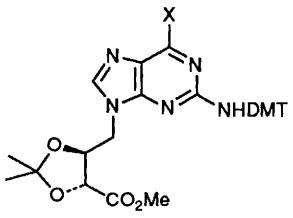
c; R^1 = DMT, R^2 = 

d; R^1 = H, R^2 = Et

e; R^1 = H, R^2 = $CH_2CH_2OSiMe_2$ 

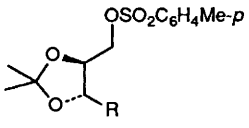
f; R^1 = H, R^2 = 

g; R^1 = H, R^2 = 



(3)

a; X = N^+Me_3
b; X = $O(CH_2)_2CN$
c; X = NMe_2



(4)

a; R = CO_2Me
b; R = $CH_2OSiPh_2Bu^t$

The 2-amino-6-chloropurines (**2d**) and (**2e**) were prepared by the reaction of 2-amino-6-chloropurine (**2a**) with the appropriate alkylating agent [ethyl toluene-4-sulphonate for (**2d**), 2-bromoethyl dimethylthexylsilyl ether for (**2e**); thexyl = 1,1,2-trimethylpropyl] in dimethylformamide in the presence of potassium carbonate.[4a,11] A similar procedure was used to obtain purines (**2f**) and (**2g**) from (**4a**) and (**4b**), respectively. Purines (**2f**) and (**2g**) were readily converted into (**2b**) and (**2c**), respectively by treatment with 4,4′-dimethoxytrityl tetrafluoroborate/2,6-di-t-butyl-4-methylpyridine in acetonitrile.[12] The use of dimethoxytrityl protection here facilitated chromatographic isolation and purification of guanines (**1b**) and (**1c**) and enables spectroscopic assay of the extent of reaction of (**1b**) with a polymer, by acidic cleavage of the dimethoxytrityl group.

The methods described should be of general utility for the preparation of *N*-9 substituted guanines.

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