Dimethyl-pyridin-4-yl-amine (DMAP) catalysed alcoholysis reactions of 2-amino-N,N,N-trimethyl-9H-purine-6-ylammonium chloride: An effective route to obtain O^6-substituted Guanine derivatives from alcohols with poor nucleophilicity

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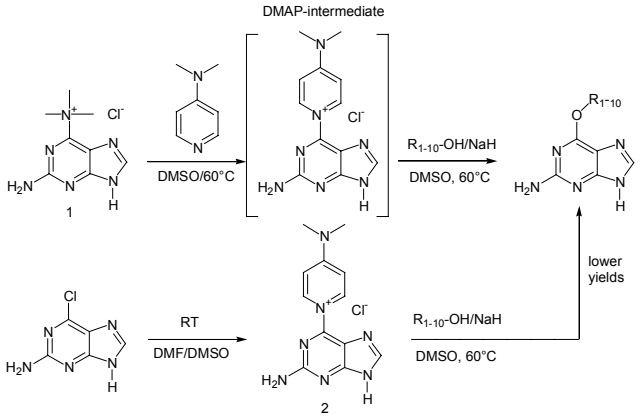
Introduction: The development of new efficient methods for the synthesis of O^6-substituted guanines continues to receive much attention, in part due to the fact that O^6-substituted guanines containing a benzyl or hetarylmethyl moiety are of great medical interest. O^6-substituted guanines were shown to be important synthetic targets as they effectively inactivate O^6-alkylguanine-DNA alkyltransferase (MGMT)[1]. Some synthetic methods have been described in the literature to obtain these compounds. However, the O^6-substituted guanines so far described have usually been synthesized rather inefficiently.

Experimental results: The reaction of 2-amino-N,N,N-trimethyl-1H-purine-6-ammonium chloride 1 with the respective benzyl- and hetarylmethyl alcohols was proved to be the most suitable method by McElhinney et al.[2]

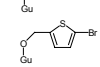


scheme 1
*DMAP (0.3 equiv.) catalyzed reaction of alcohols (5.6 equiv.) and **1** (1 equiv.) and synthesis of **2** and its direct alcoholysis*

We applied this method to the reaction of several fluoro-pyridine methanols, which have a decreased nucleophilicity due to their electron withdrawing N- and F-atoms. The coupling of these fluorine bearing alcohols with the appropriate guanine precursor **1** did not give any product even under modified conditions like increased temperature and extended reaction time. In addition, some other alcoholates gave only low yields, even when applying the method of McElhinney et al. (scheme 1)[3]. Therefore, we modified this procedure and investigated DMAP as a nucleophilic catalyst in DMSO at temperatures of 60°C.
The reaction between **1** and several alcohols and the mechanism of DMAP-catalysis we suggest are shown in scheme 1. Under DMAP-catalysis, the desired compounds could be obtained in chemical yields ranging from 20-87% within 72 h in DMSO at 60°C. Different hetaryl methanols were synthesized.

Table 1 summarizes the results of the coupling reaction between **1** and the hetaryl methanolates under DMAP-catalysis and by using **2** directly in comparison to known procedures which we also applied.

Table 1 Chemical yields of O^6-(hetarylmethyl) guanine derivatives via different methods (DMAP catalysis only, direct use of **2**, literature procedure)
[a] All alcoholysis reactions were carried out in DMSO at 60°C; [b] Yields are referring to the method of McElhinney et al.[2]; [c] Elemental analyses of the fluorinated compounds were in the appropriate range; [d] All compounds displayed satisfactory spectroscopic data in accordance to literature data (^{1}H-, ^{13}C-NMR, FD MS)

Entry	coupling products Gu = Guanine	chemical yields via *in situ* generation of **2** [%][a]	chemical yields via direct use of **2** [%][a]	chemical yields via literature procedures [%][b]	^{1}H NMR (d_6-DMSO); ^{13}C NMR (d_6-DMSO); ^{19}F NMR (d_6-DMSO); FD MS m/z (%), R_f-data (benzene/methanol 4:1) [c]
1		80	40	0	12.5 (s, 1H), 8.25 (m, 1H), 7.8 (s, 1H), 7.4 (m, 1H), 7.2 (s, 1H), 6.3 (s, 2H), 5.5 (s, 2H); 164.7, 162.3, 159.8, 148.0, 141.0, 138.0, 120.6, 108.0, 107.6, 64.7; -69.18 (d); 260. 7 (100); (R_f=0.31)
2		66	34	0	12.5 (s, 1H), 8.4 (m, 1H), 8.1 (m, 1H), 7.75 (s, 1H), 7.1 (dd, 1H), 6.25 (s, 2H), 5.4 (s, 2H); 164.7, 162.3, 159.8, 154.8, 153.7, 148.4, 143.3, 134.7, 109.8, 109.4, 63.7; -69.5 (d); 260.7 (100); (R_f=0.35)
3		60	15	0	12.5 (s, 1H), 7.9 (m, 1H), 7.8 (s, 1H), 7.4 (d, 1H), 7.1 (d, 1H), 6.3 (s, 2H), 5.4 (s, 2H); 161.5, 159.8, 159.7, 154.8, 153.7, 143.2, 134.7, 113.6, 109.9, 108.6, 66.4; -68.5 (d); 260.7 (100); (R_f=0.39)
4		20	10	0	12.5 (s, 1H), 8.2 (d, 1H), 8.17 (m, 1H), 7.8 (s, 1H), 7.4 (m, 1H), 6.35 (s, 2H), 5.45 (s, 2H); 162.5, 159.8, 159.6, 155.65, 147.5, 142.3, 122.5, 119.2, 118.9, 60.8; -69.3 (s); 260.7 (100); (R_f=0.33)
5		85	60	10	d R_f=0.41
6		85	62	58	d R_f=0.4
7		72	42	32	d R_f=0.3
8		83	40	40	d R_f=0.3
9		68	35	28	d R_f=0.34
10		87	39	14	d R_f=0.39

Summary: In summary we have demonstrated the catalytic effect of DMAP on the synthesis of some O^6-(hetarylmethyl) guanine derivatives in DMSO.
Dimethyl-pyridin-4-yl-amine (DMAP) catalysed reactions of 2-amino-N,N,N-trimethyl-9H-purine-6-ylammonium chloride with fluoro-pyridine methanolates and various other alcoholates in DMSO at temperatures of 60°C gave the corresponding coupling products in good yields between 20-87%[3]. Under these reaction conditions, fluorinated O^6-substituted Guanine derivatives could be synthesized which could not be obtained via known analogous literature procedures. The respective yields of other known O^6-substituted guanine derivatives could be significantly improved.

References:

[1] Dolan, M. E.; Pegg, A. E. *Clin. Cancer Res*. 1997, 3, 8837
[2] McElhinney, R. S.; Donnelly, D. J.; McCormick, J. E.; Kelly, J.; Watson, A. J.; Rafferty, J. A.; Elder, R. H.; Middleton, M. R.; Willington, M. A.; McMurry, B. H.; Margison, G. P. *J. Med. Chem*. 1998, 41, 5265
[3] Schirrmacher R., Wängler B., Schirrmacher E., August T., Rösch F. *Synthesis* 2002 (in press)