Chemical Conversion of Thymidine into 5-Methyl-2′-deoxycytidine

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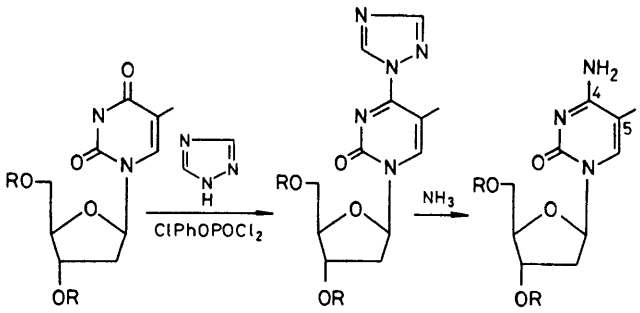
Summary In aqueous ammonia, 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-3,5-di-*O*-acetyl-2-deoxyribofuranosyl)-pyrimidin-2(1*H*)-one, which can be prepared from thymidine, yields 5-methyl-2′-deoxycytidine.

IN eukaryotic DNA, 5-methyl-2′-deoxycytidine (**6**) is the only major modified nucleoside. There is speculation that it is a key element in the control of vertebrate gene function and cell differentiation.[1] This rare nucleoside was first synthesised chemically from thymidine by Fox *et al.*,[2] *via* a thiation–amination approach. Since then, other methods (chlorination–amination[3] and silylation–amination[4]) have also been developed for this transformation. However, the reactions in these three approaches proceed only under very drastic conditions.

In this report, I describe another approach to convert thymidine into 5-methyl-2′-deoxycytidine (**6**) that requires only mild conditions. 3′,5′-Bis(t-butyldimethylsilyl)-thymidine (**1**) was treated with 1,2,4-triazole (3·0 mol. equiv.) and *p*-chlorophenyl phosphodichloridate (1·5 mol. equiv.) in pyridine at room temperature for 3 days to give the intermediate (**3**), m.p. 87 °C (74% yield). An analogous base modification was observed by Reese when uridine was treated with 1-(mesitylene-2-sulphonyl) tetrazolide.[5] Subsequent treatment of (**3**) with aqueous ammonia in dioxan (1:3 v/v) yielded the protected deoxycytidine (**5**) (1 h; room temperature; 89% yield), m.p. 190 °C, identical to a sample prepared by direct silylation of 5-methyl-2′-deoxycytidine[6] (t-butyldimethylchlorosilane, imidazole, pyridine; 3 h).



(1) R = $SiMe_2Bu^t$ (3) R = $SiMe_2Bu^t$ (5) R = $SiMe_2Bu^t$

(2) R = COMe (4) R = COMe (6) R = OH

In order to obtain completely deprotected (**6**), the process was repeated with 3′,5′-diacetyl thymidine (**2**). The triazole–*p*-chlorophenyl phosphodichloridate reaction yielded the triazolylpyrimidinone intermediate (**4**) (72% yield), which in ammonia–dioxan was readily converted into 5-methyl-2′-deoxycytidine (**6**) in 85% yield (m.p. of hydrochloride 150 °C; lit.[2] 154—155 °C). The synthetic material (**6**) was identical (t.l.c., u.v., and ^1H n.m.r. spectra) to an authentic sample.

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[1] A. Razin and A. D. Riggs, *Science*, 1980, **210**, 604.
[2] J. J. Fox, D. Van Pragg, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, 1959, **81**, 178.
[3] J. Žemlička and F. Šorm, *Collect. Czech. Chem. Commun.*, 1965, **30**, 2052.
[4] H. Vobrüggen and K. Krolikiewicz, in 'Nucleic Acid Chemistry,' part 1, eds. L. Townsend and R. Tipson, Wiley–Interscience, 1978, p. 227.
[5] C. B. Reese and A. Ubasawa, *Nucleic Acids Res.*, 1980, Symposium Series 7, 5.
[6] K. K. Ogilvie, A. L. Schefman, and C. L. Penny, *Can. J. Chem.* 1979, **59**, 2230.