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4-DIMETHYLAMINOPYRIDINE: AN EFFICIENT AND SELECTIVE CATALYST FOR THE SILYLATION OF ALCOHOLS

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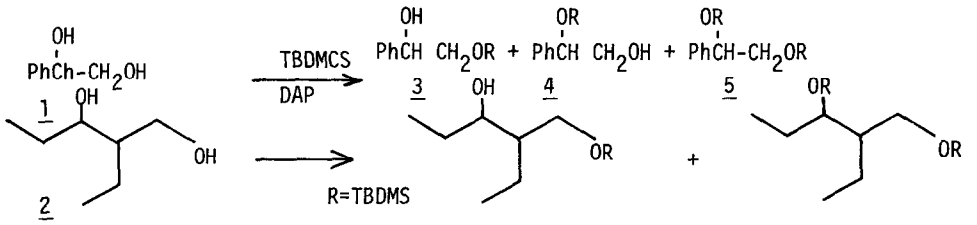
The importance of the hydroxyl group functionality in synthetic organic chemistry is reflected by the continuous appearance in the literature of methods for developing complex structures based on the chemical interconversion of oxygenated functionalities. A limiting factor in some cases is the presence of more than one oxygen function of comparable reactivity in the molecule to be transformed. This difficulty is circumvented by the use of protective groups, a practice which in theory allows free manipulation of the desired functionality.[1] However, it is only in a few cases that this practice reaches a practical level, mostly due to the difficulties involved in selectively protecting and regenerating specific hydroxyl groups.

One of the most widely used protective groups for alcohols since its introduction by Corey and Venkateswarlu is the tert-butyldimethylsilyl (TBDMS) group.[2] The chemical properties of these hindered silyl ethers make them desirable intermediates for a large number of synthetic transformations involving multifunctional compounds. The established procedure for the preparation of TBDMS ethers involves reaction of an alcohol with t-butyldimethylchlorosilane (TBDCS, 1.1 eq) in the presence of imidazole (Im, 2.2 eq) in N,N-dimethylformamide (DMF) at room temperature. Other amines, including pyridine,[3] catalyze the reaction although not as efficiently, and even with imidazole present the silylation reaction with TBDCS is sluggish if carried out in a solvent other than DMF.[2]

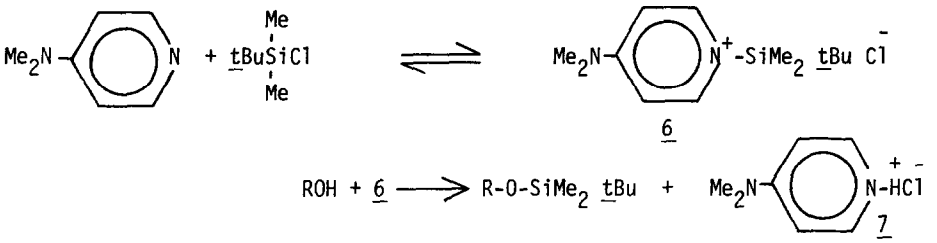
We recently reported on the effectiveness of 4-dimethylaminopyridine (DAP) as a group transfer agent in the triphenylmethylation of alcohols.[4] As an extension of that work, we decided to explore the effect of DAP on the silylation of alcohols particularly on the preparation of TBDMS ethers. The two characteristics of the DAP-triphenylmethylation reaction which could be of particular value if extended to the synthesis of TBDMS ethers are, (a) larger choice of reaction solvents, (b) kinetic preference for primary over secondary alcohols.[5]

Examination of Table 1 shows that preparation of TBDMS ethers of primary alcohols is exceptionally simple even in solvents other than DMF. The reaction is carried out in the presence of DAP and triethylamine, the latter used to regenerate the catalyst.[6] Reaction of secondary alcohols is slower and requires higher concentrations of DAP but the yields are comparable to those obtained by the classical imidazole procedure. We have also examined the reaction of two diols, phenylethanediol (1) and 2-ethyl-1,3-hexanediol (2) in the presence of catalytic amounts of DAP.



Reaction of diol 1 proceeds with predominant formation of the monosilylether 3 accompanied by small amounts of the bis-silylether 5 (see Table 2).[7] The imidazole procedure yields a mixture of all three isomers with slight preference for formation of 3. Similarly, reaction of diol 2 produces almost exclusively the primary silylether 3, while imidazole gives again a mixture of all the possible isomers. The most significant differences between the two methods are the absence of the secondary silyl ether 4 in the DAP reaction, and that reaction of diol 1 with triethylamine and catalytic amounts of imidazole does not produce significant amounts of products (see Table 2, entry 3).

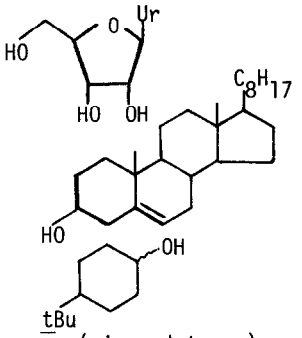
On attempting to explain the mechanism of action of DAP one has to consider the mechanisms postulated for the silylation of alcohols catalyzed by amines.[8] The two most commonly accepted proposals are (1) the amine functions as a proton acceptor, and (2) the amine forms a complex with the silyl chloride such as 6 which subsequently reacts with the alcohol to form the silyl-ether.



The first proposal can be easily ruled out since DAP is used in catalytic amounts and triethylamine does not catalyze the reaction as demonstrated by experiment 3 on Table 2. The second proposal is more attractive since it implies formation of an intermediate (6) which can be expected to have large steric requirements as in the related triphenylmethylation reaction.[4] This mechanism also finds support in the fact that TBDMCS reactions catalyzed by pyridine are comparatively sluggish and proceed with difficulty while in the case of DAP the p-dimethylamino substituent , a powerful electron donating group, facilitates formation of a charged intermediate (6) and in this way reaction with alcohols is accelerated.

In summary, we feel that the present procedure will compliment the classical method in those cases in which selectivity is desired, or it is not practical to use DMF solvent. Similar results would be expected with the recently introduced t-butyldiphenylchlorosilane.[9]

Table 1. Formation of TBDMS Ethers from Primary and Secondary Alcohols by the TBDMCS-DAP Procedure.

Alcohol	DAP (eq)[a]	Reaction Conditions	TBDMS ether Yield (%)[b]
$PhCH_2OH$	0.04	CH_2Cl_2, 25°	89
 (cis and trans)	0.24	DMF, 25°	60[c]
	0.33	CH_2Cl_2, 25°	68
	0.33	DMF, 25°	85[d]

[a]TBDMCS (1.1 eq) and triethylamine (1.2 eq) used.[6] [b]Yields are for purified samples.[6] [c]5-O'-TBDMS-uridine. [d]74% equatorial and 26% axial isomer by GC analysis.[7]

Table 2. Reaction of Selected Diols with TBDMS in the Presence of DAP and Imidazole.

Run No.	Diol	Solvent	Amine/eq[a]	Products (% yield)[b] 3	4	5
1	1	CH_2Cl_2	DAP/0.04	95	0	5
2		DMF	Im/2.2	59	11	30
3		DMF	Im/0.04	-	-	-[c]
4		DMF	DAP/0.04	-	-	96[d]
5	2	CH_2Cl_2	DAP/0.04	98	-	trace
6		DMF	Im/2.2	60	15	24

[a]Triethylamine (1.1 eq) used for DAP and Im (Run No. 3) reactions. [b]Related yields by GC.[7] [c]Negligible reaction after 18 hr at 25°. [d]TBDMCS (2.2 eq).

References and Notes

1. J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, 1973.
2. E.J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1972).
3. K.K. Ogilvie, Can. J. Chem., 51, 3799 (1973).
4. S.K. Chaudhary and O. Hernandez, see accompanying communication.
5. For examples of preferential silylation of primary alcohols in nucleoside chemistry see: K.K. Ogilvie, E.A. Thompson, M.A. Quilliam, and J.B. Westmore, Tetrahedron Lett., 2865 (1974).
6. Typically reactions were allowed to proceed overnight under nitrogen. Work-up involved washing the organic solution with water, saturated ammonium chloride, and drying with sodium sulfate. Crude products were purified by silica gel chromatography using a Waters Associates Prep-500 liquid chromatograph and dichloromethane-hexane eluent mixtures. Isomers 3 and 4 from diols 1 and 2 were cleanly separated by this procedure.
7. Samples were analyzed by gas chromatography (GC) in a 3% OV-1 column on 100/120 Supelcoport at 1 50°. Structures were verified by mass spectrometry and by proton and carbon magnetic resonance spectra of individual isomers isolated as described on ref. 6.
8. A.E. Pierce, "Silylation of Organic Compounds", Pierce Chemical Co., Rockford, Ill., 1968.
9. S. Hanessian and P. Lavalee, Can. J. Chem., 53, 2975 (1975).

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