

## Limitations of t-Butyldimethylsilyl as a Protecting Group for Hydroxy-functions

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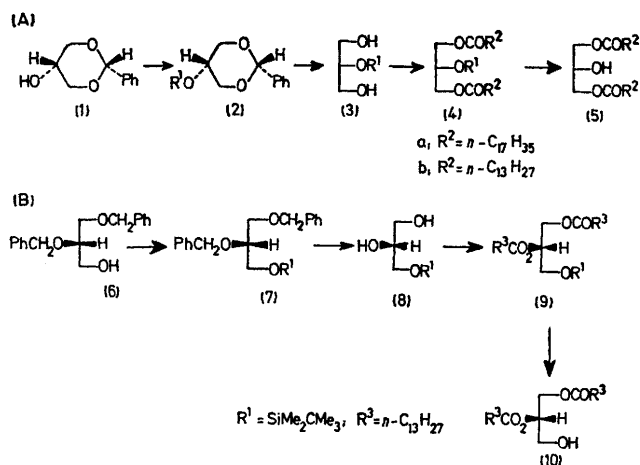
**Summary** t-Butyldimethylsilyl cannot be used for protecting hydroxy-groups in molecules where there is an undesired opportunity for acyl migration.

We have examined the potential of t-butyldimethylsilyl (TBDMS) as a protecting group for hydroxy-functions to aid the synthesis of the 1,2- and 1,3-diacylglycerols (**10**)

and (**5**) respectively. These substances are key intermediates for the synthesis of phospholipids.<sup>1</sup> Since it has been implied<sup>2</sup> that an *O*-TBDMS group is stable to conditions which hydrogenolyse *O*-benzyl groups and that it can be removed by Bu<sup>n</sup><sub>4</sub>NF in anhydrous tetrahydrofuran without affecting *O*-acetyl groups, we tried the sequence of reactions shown in Scheme 1† (routes A and B). We

† Satisfactory combustion analyses were obtained for new compounds and their i.r. and n.m.r. spectra are in accord with the assigned structures. N.m.r. data given in the text refer to solutions in [2H<sub>6</sub>]pyridine with Me<sub>4</sub>Si as internal standard.

suspected, however, that acyl migration might occur during removal of the TBDMS group by  $\text{Bu}^n_4\text{NF}$ . This possibility arises because the mechanism of removal of the TBDMS group presumably involves attack of fluoride anion on silicon with expulsion of an alkoxide anion. If acyl migration in this anion (*cf.* Scheme 2) occurs at a comparable rate to proton-abstraction from the  $\text{Bu}^n_4\text{N}^+$  cation, then 1,2-migration of an acyl group spoils the potential regiospecificity of routes A and B (Scheme 1), whilst two sequential 1,2-migrations or one 1,3-migration destroys the potential stereospecificity of route B. It is also possible that fluoride ion in tetrahydrofuran is sufficiently basic to catalyse equilibration of (5) with (10) as in Scheme 2 (either compound being formed by de-silylation without equilibration). The experiments described below bear out these expectations and also reveal another limitation of *O*-TBDMS as a protecting group.



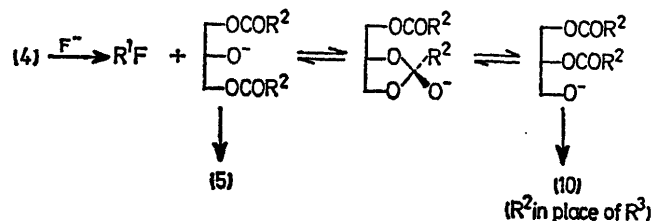
SCHEME 1

*cis*-2-Phenyl-1,3-dioxan-5-ol<sup>1</sup> (1) free of its isomer 2-phenyl-4-hydroxymethyl-1,3-dioxolan<sup>5</sup> was silylated<sup>2</sup> to give compound (2) (84%), b.p. 112–113° at 0.2 mmHg,  $n_D^{20}$  1.4939, which was hydrogenolysed in ethanol (5% Pd-charcoal, 25 lb in<sup>3</sup> H<sub>2</sub>, 2 h) to compound (3) [96%, m.p. 64.5° from ether-light petroleum at room temperature,  $\delta$  0.15 (*MeSi*)]. Acylations of compound (3) gave 1,3-distearoyl-2-*O*-TBDMS glycerol (4a) (60%, m.p. 42–43°) and 1,3-dimyristoyl-2-*O*-TBDMS glycerol (4b) (68%, oil).

Silylation<sup>2</sup> of glycerol (10 molar excess) gave liquid rac. 1-*O*-TBDMS-glycerol [ $\delta$  0.10 (*MeSi*)] containing *ca.* 10% of the 2-isomer (3). Acylation of this mixture gave rac. (9) (containing *ca.* 10% of 1,3-dimyristoyl isomer). In an approach to optically active 3-*O*-TBDMS-*sn*-glycerol (8), 1,2-dibenzyl-*sn*-glycerol<sup>4</sup> (6) was silylated<sup>2</sup> to give com-

pound (7) {70%,  $n_D^{17}$  1.5092,  $[\alpha]_D^{20} + 1.51^\circ$  ( $\text{CHCl}_3$ , *c* 4.3),  $\delta$  0.09 (*MeSi*)}. Debenzylation of compound (7) in ethanol (5% Pd-charcoal, 30 lb in<sup>3</sup> H<sub>2</sub>, 2 h) gave compound (8) (85%) contaminated with (3) (1.5–2.5%, analysis by n.m.r.) and glycerol (identified by t.l.c. comparison with authentic glycerol in five solvent systems). Similar conditions of hydrogenolysis did not affect compound (3). Evidently the benzyl groups in compound (7) transport the silyl group to the vicinity of catalytically active sites, where cleavage to glycerol and *t*-butyldimethylsilane occurs.

Re-examination of the crude product from hydrogenolysis of (2) (see above) showed that glycerol was also produced in that case. However, as (3) is crystalline it can be readily purified.



SCHEME 2

Pure (4a) or rac. (9) (containing *ca.* 10% of 1,3-dimyristoyl-2-*O*-TBDMS glycerol) and  $\text{Bu}^n_4\text{NF}$  in dry tetrahydrofuran<sup>2</sup> (room temp., 10 min) gave close to equilibrium mixtures<sup>5,6</sup> of products [*i.e.* (4a)  $\rightarrow$  (5a) + 1,3-isomer; rac. (9)  $\rightarrow$  (10) + 1,2-isomer: analysis by t.l.c.]. Equilibration also occurs with pure (10;  $\text{R}^3 = n\text{-C}_{17}\text{H}_{35}$ ) under these conditions, whereas 3-benzyl-1,2-distearoyl-*sn*-glycerol was unaffected. The use of 0.5 or 1.0 equiv. of  $\text{Bu}^n_4\text{NF}$  with compound (4b) still effected product equilibration, whilst desilylation was incomplete. Treatment of pure (4a) with either acetic acid-water-tetrahydrofuran (3:1:1)<sup>2</sup> (25° or 100° for 24 h), 80% acetic acid in water (100° for 15 min), or boric acid in trimethylborate (100° for 16 h) did not effect desilylation. HF [1.5 M (300 molar excess) in aqueous ethanol, 25° for 24 h] was partially effective for removing the TBDMS group from compound (4a), giving (4a) (*ca.* 50%), (5a) (*ca.* 50%) contaminated with its 1,2-isomer, free fatty acid, and monoglyceride<sup>7</sup> (t.l.c. analysis). Anhydrous HF-pyridine<sup>8</sup> in tetrahydrofuran gave similar results.

We conclude that unless a satisfactory alternative method for removing the *O*-TBDMS group can be found, then it is of no use for the regio- and stereospecific synthesis of mono- or di-acylglycerols or any molecules where acyl migration is possible and undesirable.<sup>9</sup>

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<sup>1</sup> See *e.g.* V. I. Shvets, *Russ. Chem. Rev.*, 1971, 40, 330.

<sup>2</sup> E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, 94, 6190.

<sup>3</sup> F. H. Mattson and R. A. Volpenhein, *J. Lipid Res.*, 1962, 3, 281.

<sup>4</sup> H. Eibl, O. Westphal, H. Van Den Bosch, and L. L. M. Van Deenen, *Annalen*, 1970, 738, 161; H. F. G. Beving, H. B. Borén, and P. J. Garegg, *Acta Chem. Scand.*, 1967, 21, 2083.

<sup>5</sup> B. Serdarevich, *J. Amer. Oil Chemists' Soc.*, 1967, 44, 381.

<sup>6</sup> I. P. Freeman and I. D. Morton, *J. Chem. Soc. (C)*, 1966, 1710.

<sup>7</sup> *Cf.* N. Shaw and A. Stead, *Biochem. J.*, 1974, 143, 461.

<sup>8</sup> G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 1973, 779.

<sup>9</sup> K. K. Ogilvie (*Canad. J. Chem.*, 1973, 51, 3799) has used the TBDMS group for protecting 3'- and 5'-hydroxy-groups during synthesis of 2'-deoxyribonucleosides, including 3'-*O*-acyldeoxyribonucleosides, without any apparent isomerisation during removal of TBDMS in the latter cases. However, it is likely that isomerisation would occur during removal of TBDMS if it were used to protect the 2'- or 3'-hydroxy-group of 3'- or 2'-*O*-acylribonucleosides.