COMMUNICATIONS

The Preparation and Synthetic Utility of *tert*-Butyldiphenylsilyl Ethers[1]

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The utility of *tert*-butyldiphenylsilyl chloride as a reagent for the protection of hydroxyl groups was explored. The corresponding *tert*-BDPSi ethers have much greater stability to acids, and under conditions of hydrogenolysis, than related silyl and trityl ethers. Preferential removal of trityl, tetrahydropyranyl, benzyl, and other silyl ethers and acetals can be effected in presence of *tert*-BDPSi ethers. Treatment with fluoride ion causes smooth cleavage of the latter.

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L'utilité synthétique du chlorure de *tert*-butyldiphenylsilyle pour la protection temporaire des fonctions hydroxyles a été explorée. Les éthers *tert*-BDPSi démontrent une stabilité supérieure dans des conditions acides et d'hydrogénolyse, par rapport à d'autres éthers silylés analogues, et aux éthers de triphenylméthyle, tétrahydropyrannyle, et benzyle. Plusieurs fonctions y inclus des acétals, peuvent être préférentiellement hydrolysés en présence de la fonction *O*-*tert*-BDPSi.

The availability of appropriate protecting groups for hydroxyl, and related functions (1, 2) is oftentimes a crucial problem in the planning and execution of a synthetic stratagem involving polyfunctional molecules. Silyl ethers, and in particular, *tert*-butyldimethylsilyl ethers, have been extensively used in recent synthetic work related to the prostaglandins (3), and also in the deoxynucleoside series (4).

We wish to report on the protection of hydroxyl groups as *tert*-butyldiphenylsilyl ethers (*tert*-BDPSi). In addition to retaining all the known features that are associated with silyl ethers, such as their ease and selectivity of formation, their adaptability to various analytical techniques, and their compatibility with a variety of conditions or synthetic transformations in organic chemistry (3), the *tert*-BDPSi group offers some unique and novel features that constitute a significant improvement over the existing related groups, and warrants their communication at this time.

Selectivity—Primary hydroxyl groups are silylated preferentially to secondary, as indicated by the following examples. Treatment of methyl α-D-glucopyranoside with 1.1 equiv. of *tert*-butyldiphenylsilyl chloride[3] in DMF containing 2.2 equiv. of imidazole (3) (25 °C, 4 h[4]), afforded the corresponding 6-*O*-*tert*-DBPSi derivative as an amorphous solid, (75–80%); m.p. 119–121 °C; $[\alpha]_D^{23}$ +61.6° (*c* 1.15, $CHCl_3$).[5] Similar silylation of methyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (25 °C, 4 h) gave the corresponding crystalline 6-*O*-*tert*-DBPSi derivative (84%); m.p. 90.5–91.5 °C (ether–hexane); $[\alpha]_D^{23}$ +34.4° (*c* 1.16, $CHCl_3$).[6]

Silylation was equally effective in the case of secondary hydroxyl groups, including axially

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[3] Prepared from dichlorodiphenylsilane and *tert*-butyl lithium in refluxing pentane; b.p. 90 °C/0.015 Torr; 95%.

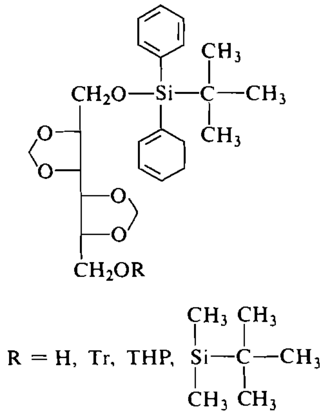
[4] Silylation could also be accomplished in pyridine, in the absence of imidazole, but the reaction times were longer.

[5] The presence of the phenyl chromophore in the *tert*-BDPSi group greatly facilitates the detection of products on chromatograms by spectrophotometric methods, a feature which is not shared by the related *O*-*tert*-butyldimethylsilyl group. Also in many instances there was no need for chromatographic separations.

[6] Satisfactory spectroscopic (i.r., n.m.r., mass) data were obtained for the compounds described herein. Crystalline compounds gave correct microanalyses.

disposed groups, utilizing the same combination of reagents and at temperatures ranging from 25–60 °C.

Stability and Compatibility—The *O*-*tert*-BDPSi group offers unique acid stability properties relative to related analogs. Thus, it is virtually unaffected under conditions that cause complete cleavage of *O*-trityl, *O*-*tert*-butyldimethylsilyl, and *O*-tetrahydropyranyl groups. In such a study, 2,3:4,5-di-*O*-methylene-D-mannitol was monosilylated as usual, and the resulting syrupy *O*-*tert*-BDPSi ether, $[\alpha]_D^{23}$ +32.3° (*c* 1.34, $CHCl_3$), was converted into the corresponding 6-*O*-trityl, 6-*O*-tetrahydropyranyl, and 6-*O*-*tert*-butyldimethylsilyl ethers. Treatment of these derivatives individually with 80% acetic acid caused selective cleavage of the 6-ether groups, and the 6-*O*-*tert*-BDPSi derivative was recovered in each case in over 96% yield.



A distinctive feature of the *O*-*tert*-BDPSi group is its compatibility under conditions required for the acid-catalyzed formation, and cleavage of acetals. The following synthetic transformation will illustrate this point. Silylation of cytidine (1.1 equiv. *tert*-BDPSiCl, 2.2 equiv. imidazole, 25 °C, 3 h) gave the 5′-*O*-*tert*-BDPSi derivative (87%); m.p. 223–226 °C ($CHCl_3$); $[\alpha]_D^{23}$ +56.5° (*c* 1.14, MeOH). Treatment of the former with 2,2-dimethoxypropane and concentrated hydrochloric acid (25 °C, 24 h), followed by conventional workup, gave the corresponding 5′-*O*-*tert*-BDPSi-2′,3′-*O*-isopropylidene derivative (95.5%); m.p. 138–143 °C ($CHCl_3$–ether–hexane); $[\alpha]_D^{23}$ +30.3° (*c* 1.08, $CHCl_3$); $M^{+\cdot}$ 521; 506 (M − 15); 464 (M − 57), etc. Treatment with 50% aqueous trifluoroacetic acid – dioxane (25 °C, 15 min) gave the starting crystalline silyl ether derivative (64%). Benzylidene acetals of the 2-phenyl-1,3-dioxane type could also be preferentially hydrolyzed in the presence of secondary *O*-*tert*-BDPSi groups.[7]

The *tert*-BDPSi group is unaffected under conditions of hydrogenolysis.[8] Thus, benzylation of methyl 6-*O*-*tert*-butyldiphenylsilyl-α-D-glucopyranoside ($PhCH_2Br$, NaH, DMF) gave the corresponding crystalline tribenzyl ether; m.p. 115.5–116 °C; $[\alpha]_D^{23}$ +18.7° (*c* 1.04, $CHCl_3$). Catalytic hydrogenolysis in the presence of 20% palladium hydroxide-on-charcoal (6) gave the starting silyl ether, m.p. 117–118 °C, in 93% yield. The *O*-*tert*-BDPSi group was also found to be stable under the following conditions: 25–75% aqueous formic acid – dioxane, 25 °C, 2–6 h (90% recovery); 50% aqueous trifluoroacetic acid – dioxane, 25 °C, 15 min; hydrogen bromide in glacial acetic acid (2 equiv.), 12 °C, 2 min; catalytic amounts of sodium methoxide in methanol, 25 °C, 24 h (95% recovery); 9 *M* ammonium hydroxide – dioxane, 60 °C 2 h (96% recovery).

Upon treatment with a *M* solution of tetra-*n*-butyl-ammonium fluoride in THF (2 equiv.) (3), smooth cleavage occurred within 1–5 h at 25 °C to regenerate the parent alcohol in over 90% yield in all cases studied.[9] Hydrolysis could also be brought about in 3% methanolic hydrogen chloride (25 °C, 3 h, 71%), and in 2 *N* sodium hydroxide containing 50% ethanol (25 °C, 7 h, 93%).

Thus, the novel *tert*-BDPSi group becomes an important complement to the trityl and other silyl groups, for the selective protection of primary hydroxyl groups, with the added advantage of much greater stability under acidic and hydrogenolytic conditions. It is also a convenient and versatile protecting group for secondary hydroxyl groups, and as

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[7] Little, if any migration of silyl groups was observed under these conditions. When kept in solution (CH_2Cl_2, etc.) for prolonged periods of time, some change (t.l.c.) was observed presumably due to a migration to suitably disposed primary hydroxyl groups. This possibility is presently under study.

[8] Some silyl ethers are susceptible to hydrogenolysis (3); see also ref. 5.

[9] Partial migration of ester (acetate, benzoate) groups occurs during the desilylation reaction in compounds where the esters functions are suitably disposed. This observation has been recently recorded by others also (5).

such, complements the tetrahydropyranyl and benzyl groups in a variety of synthetic transformations. Other applications are presently under study.

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