Communications to the Editor

Protection of Hydroxyl Groups as *tert*-Butyldimethylsilyl Derivatives

Sir:

Despite the recent introduction of several useful methods for the protection of hydroxyl groups,[1] there exists a real need for still others, and especially for new protecting groups which combine stability under a wide range of conditions with susceptibility to facile removal by a highly specific reagent. Complementarity with other protecting groups is also highly desirable for synthetic reactions involving multifunctional compounds. For example, a group which can be removed in the presence of *O*-benzyl, *O*-β,β,β-trichloroethyl, and *O*-tetrahydropyranyl and which is stable to organometallic reagents, reducing agents, base, and mildly acidic reagents would be invaluable. This study was performed in order to develop such a blocking group.

Trimethylsilyl ethers are too susceptible to solvolysis in protic media (either in the presence of acid or base) to be broadly useful in synthesis. The dimethylisopropylsilyloxy group which has recently been used in hydroxyl masking,[2] while 10^2–10^3 times less readily solvolyzed than trimethylsilyloxy,[3] is still too labile to survive processes such as Grignard reagent formation, Wittig reaction, or Jones (CrO_3) oxidation.[4] The dimethyl-*tert*-butylsilyloxy group which is *ca.* 10^4 times more stable than trimethylsilyloxy[3] seemed more promising and, consequently, was selected for detailed study. Initial experiments were unpromising, since dimethyl-*tert*-butylchlorosilane (a readily available reagent[5]) was found to react with alcohols very slowly and in unsatisfactory yield using conventional, or even forcing, silylating techniques, for example, with excess silyl chloride, excess dry pyridine in tetrahydrofuran at temperatures from 20 to 60° for many hours.[6] However, the use of *imidazole as catalyst and dimethylformamide as solvent* proved to be exceedingly effective and to result in the conversion of a variety of alcohols to dimethyl-*tert*-butylsilyl ethers in high yield under mild conditions.[7]

Another key discovery was that dimethyl-*tert*-butylsilyl ethers are cleaved rapidly to alcohols by treatment with 2–3 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran at 25°.[8] Further, dimethyl-*tert*-butylsilyl ethers may be converted to alcohols under acidic conditions (*e.g.*, in 2:1 acetic acid–water at 25°) at a rate comparable to that for the cleavage of tetrahydropyranyl ethers.

Dimethyl-*tert*-butylsilyl ethers are stable to aqueous or alcoholic base under the normal conditions for acetate saponification, and are also stable to hydrogenolysis[4] (H_2–Pd) and mild chemical reduction (*e.g.*, Zn–CH_3OH). Consequently, such protection can be used, for instance, in the case of a hexahydroxy compound with hydroxyl groups 1–6 protected as: 1, acetate; 2, β,β,β-trichloroethyl ether; 3, benzyl ether; 4, dimethyl-*tert*-butylsilyl ether; 5, tetrahydropyranyl ether; and 6, methyl ether. For this case the unmasking of hydroxyls can be conducted in a number of ways including the following: (a) groups 1–6 may be unmasked in that order by the reagents K_2CO_3–CH_3OH, Zn–CH_3OH, H_2–Pd, F^-, H_2O–HOAc, BBr_3 or (b) the groups may be exposed in the order 4, 5, 2, 1, 3, 6 with the same reagents.

The dimethyl-*tert*-butylsilyl group may be used as an alternative to the tetrahydropyranyl group,[1c,9] being especially advantageous in that it does not possess a chiral center, and also in that its derivatives frequently are nicely crystalline and suitable for gas chromatography and mass spectral measurements.

The specific reactions which are outlined immediately below provide an illustration of the stability and applicability of the dimethyl-*tert*-butylsilyl group in the protection of alcohols. The substrates involved are all of interest with regard to the synthesis of prostaglandins,[2,10] in which area the dimethyl-*tert*-butylsilyl group is playing an ever increasing role in these laboratories. The hydroxy lactone **1**,[11] upon treatment with dimethyl-*tert*-butylsilyl chloride (1.2 equiv) and imidazole (2.5 equiv) in dimethylformamide (2 ml/g of **1**) at 35° for 10 hr, produced the silyl ether–lactone **2**,[12] mp 34°, $[\alpha]^{25}D$ −26.55° (*c* 1.1, $CHCl_3$) in >96% yield.

(1) For example: (a) β,β,β-trichloroethyl-based groups, R. B. Woodward, K. Heusler, J. Gostelli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorburggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966); (b) pivaloyloxymethyl, M. Rasmussen and N. J. Leonard, *ibid.*, **89**, 5439 (1967); and (c) 4-methoxy-4-tetrahydropyranyl, C. B. Reese, R. Saffhill, and J. E. Sulston, *ibid.*, **89**, 3366 (1967).

(2) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971).

(3) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill, New York, N. Y., 1965, pp 132, 138.

(4) Unpublished work by the authors. We have also made the interesting and useful observation that trimethylsilyl and triphenylsilyl ethers can be hydrogenolized easily to form alcohols (*e.g.*, using 10% Pd/C, 1 atm H_2, ethanol solvent, at 25° for 1–10 hr), and further, that dimethylisopropylsilyl ethers undergo slow but appreciable hydrogenolysis under these conditions.

(5) See L. H. Sommer and L. J. Taylor, *J. Amer. Chem. Soc.*, **76**, 1030 (1954). In our work this substance was prepared in 70% yield by the dropwise addition of commercial *tert*-butyllithium in pentane to a 1 *M* solution of dimethyldichlorosilane (1.15 equiv) in pentane at 0° under nitrogen with stirring, maintenance at 0° for 1.5 hr, and at 25° for 48 hr. Distillation at atmospheric pressure (bp 125°) afforded the pure reagent, mp 92.5°.

(6) See (a) A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, Ill., 1968; (b) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(7) This process seems likely to proceed *via* *N*-dimethyl-*tert*-butylsilylimidazole, the conjugate acid of which can be expected to be a very reactive silylating agent.

(8) Fluoride ion in an aprotic medium is a powerful agent for the cleavage of silyl ethers in general. This technique has been used in a number of instances in these laboratories including the recently described synthesis of (±)-fumagillin; see E. J. Corey and B. B. Snider, *J. Amer. Chem. Soc.*, **94**, 2549 (1972).

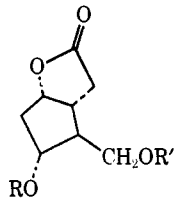
(9) The similarity of hydrolytic reactivities under mildly acidic conditions may be seen from the following results. The hydrolysis of the tetrahydropyranyl and dimethyl-*tert*-butylsilyl derivatives of 2-octanol at 0.1 *M* concentration in acetic acid–water–tetrahydrofuran (3:1:1) at 25° each proceeded to 89 ± 2% of completion in 4 hr and 96 ± 2% of completion in 6 hr (analysis by gas chromatography). The rate of hydrolysis of dimethyl-*tert*-butylsilyl carboxylic esters (*e.g.*, *n*-heptanoate) is *ca.* 20 times faster than for ether derivatives under these conditions.

(10) See E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

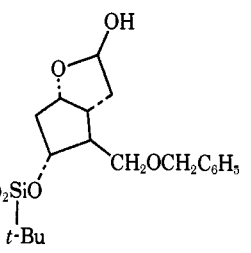
(11) (a) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (b) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971).

(12) Satisfactory (a) infrared and proton magnetic resonance spectra and (b) mass spectra were obtained on a chromatographically homogeneous sample of this substance.

Exposure of **2** to tetra-*n*-butylammonium fluoride[13] (2 equiv) in tetrahydrofuran (10.6 ml/g of **2**) at 0° for 5 min and 25° for 40 min regenerated **1** which was isolated in pure condition in 92% yield. Reaction of **2**



1, R = H; R′ = $C_6H_5CH_2$
2. R = $Si(CH_3)_2$-*t*-Bu; R′ = $C_6H_5CH_2$
7, R = $Si(CH_3)_2$-*t*-Bu; R′ = H



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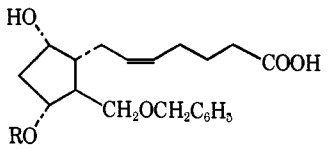
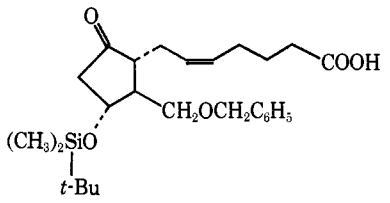


4, R = $Si(CH_3)_2$-*t*-Bu
5, R = H



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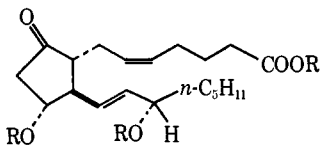

8, R = H
9, R = $Si(CH_3)_2$-*t*-Bu

with diisobutylaluminum hydride (2 equiv) in toluene (26 ml/g of **2**) under nitrogen at −78° for 10 min, quenching in the cold with methanol, and extractive isolation afforded the chromatographically pure, crystalline lactol **3**[12a] in 94% yield. Treatment of **3** under nitrogen with 2.8 equiv of the Wittig ylide derived from 5-triphenylphosphoniovaleric acid[10] in dry dimethyl sulfoxide (7.8 ml/g of **3**) at 25° for 3.5 hr afforded the acid **4**,[12a] $[\alpha]^{25}D$ +24.75° (*c* 0.8, tetrahydrofuran), in 54% yield after chromatographic purification as a colorless, viscous oil. Removal of the silyl protecting group in **4** was accomplished using 3 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran (11 ml/g of **4**) at 25° for 40 min to give the dihydroxy acid **5**[12a] in >99% yield. Oxidation of **4** with Jones reagent in acetone solution at −15° for 25 min produced the oily keto acid **6**,[12a] $[\alpha]^{25}D$ −20.3° (*c* 1.7, tetrahydrofuran), in 87% yield.

Selective removal of the benzyl protecting group from **2** was easily accomplished by hydrogenation at 25° and 1 atm over 10% Pd/C (200 mg/g of **2**) in tetrahydrofuran for 1 hr to give **7**,[12] mp 37°, in 96% yield.

To demonstrate the applicability of the dimethyl-*tert*-butylsilyl blocking group to substances which are sensitive to both acid and base, we have examined the silylation and desilylation of prostaglandin E_2 (**8**). Treatment of **8** with dimethyl-*tert*-butylsilyl chloride (5 equiv) and imidazole (10 equiv) in dimethylformamide (3.5 ml/g of **8**) at 25° for 48 hr afforded (88% yield) the disilyl ether–silyl ester **9**[12] as a chromatographically homogeneous colorless oil which was sufficiently stable thermally to yield a very satisfactory mass spectrum[14] (parent peak at *m/e* 694). The derivative **9** was reconverted to prostaglandin E_2 by exposure to acetic acid–water–tetrahydrofuran (3:1:1) at 25° for 20 hr. It is important to note that an attempted desilylation of **9** to form **8** using tetra-*n*-butylammonium fluoride under the usual conditions was unsuccessful due to the fact that fluoride ion in THF is a sufficiently strong base[15] to affect the highly sensitive β-ketol system in **8** or **9**.

The results of this study lead us to the view that the dimethyl-*tert*-butylsilyl group will find widespread application in the protection of hydroxylic groups.[16,17]

(13) D. L. Fowler, W. V. Loebenstein, D. B. Pall, and C. A. Kraus, *J. Amer. Chem. Soc.*, **62**, 1140 (1940). The reagent employed in this work was prepared by neutralization of a 10% aqueous solution of tetra-*n*-butylammonium hydroxide with 48% hydrofluoric acid, concentration under reduced pressure, drying by azeotropic distillation under reduced pressure using several portions of benzene–acetonitrile (1:1), and final drying at 30° and 0.5 mm for 20 hr.

(14) In contrast to the corresponding tris-THP derivative.

(15) See J. Hayami, N. Ono, and A. Kaji, *Tetrahedron Lett.*, 1385 (1968).

(16) See E. J. Corey and T. Ravindranathan, *J. Amer. Chem. Soc.*, **94**, 4013 (1972).

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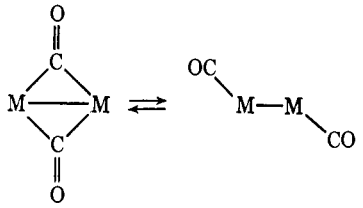
Direct Evidence from Carbon-13 Nuclear Magnetic Resonance for Intramolecular Scrambling of Carbonyl Groups in a Metal Atom Cluster Carbonyl, Tetrarhodium Dodecacarbonyl

Sir:

Several years ago it was shown by Bullitt, Cotton, and Marks[1] that bridge–nonbridge interchange (eq 1)



(1)

occurs rapidly in $[(h^5\text{-}C_5H_5)Fe(CO)_2]_2$. In the reports of this work it was explicitly proposed that processes of this general type (not necessarily in the specific mode of two bridges exchanging with two terminals) should be the basis for a large but generally unrecognized genre of fluxional molecules. Actually, the same essen-

(1) J. G. Bullitt, F. A. Cotton, and T. J. Marks, *J. Amer. Chem. Soc.*, **92**, 2155 (1970). Recently a more extended account of the work has appeared: J. G. Bullitt, F. A. Cotton, and T. J. Marks, *Inorg. Chem.*, **11**, 671 (1972). A recent study of the same molecule using carbon-13 nmr has verified the occurrence of the postulated bridge–terminal exchanges and also supplied a more detailed picture of how they occur in that system.[2]

(2) O. A. Gansow, A. R. Burke, and W. D. Vernon, *J. Amer. Chem. Soc.*, **94**, 2550 (1972).