The Utility of *t*-Butyldimethylsilane as an Effective Silylation Reagent for the Protection of Functional Groups

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Synopsis. Treatment of compounds containing functional groups, such as alcohols, amines, and carboxylic acids, with *t*-butyldimethylsilane in the presence of a catalytic amount of palladium on carbon is described to provide a new, convenient method for the introduction of a *t*-butyldimethylsilyl (TBDMS) group.

Protection of functional groups via chlorosilanes occupies a prominent place in a variety of protection techniques which are often indispensable for organic syntheses.[1] Corey and Venkateswarlu[2] have invented the use of *t*-butyldimethylsilyl chloride (TBDMSCl) to protect alcohols effectively in *N,N*-dimethylformamide (DMF) solution under the catalytic influence of imidazole (Im). The protection with this reagent is most widely used, mainly because of the stability of the corresponding silyl ethers towards certain oxidation, reduction, and mild solvolytic conditions and, moreover, an easy removal of the silyl group from silyl ethers by fluoride ions. Since TBDMSCl/Im/DMF method does not apply well to amines and carboxylic acids, many variations therefrom have been reported.[3]

Hazardous preparation of TBDMSCl using *t*-butyllithium[4] can be avoided on an industrial scale by a sequence of reactions of dimethoxymethylsilane with *t*-butylmagnesium chloride and with methylmagnesium chloride, followed by chlorination of the resulting *t*-butyldimethylsilane.[5] We became aware of the possibility of the selective protection of functional groups with use of the latter compound. Described herein is a convenient method for the protection of certain alcohols, amines, and carboxylic acids, which involves a simple treatment of these compounds with *t*-butyldimethylsilane in the presence of 10% palladium on carbon as a catalyst.

It has previously been documented by Sommer and Lions[6] that the group VIII metal-catalyzed solvolysis of an optically active methyl-1-naphthylphenylsilane with a wide variety of nucleophilic solvents such as alcohols and amines takes place to proceed with inversion of configuration at the silicon center.

Results and Discussion

The group VIII metals and their salts catalyze the cleavage of the silicon-hydrogen bond by certain nucleophiles containing OH and NH functions (Eq. 1). Besides the mechanistic implications of the nucleo-

$$\text{Nu-H} + \text{R}_3\text{SiH} \xrightarrow{\text{metal cat.}} \text{Nu-SiR}_3 + \text{H}_2 \qquad (1)$$

Nu-H=alcohols, amines, and carboxylic acids

philic substitution on the silicon center which is activated by the catalyst, the reaction is experimentally ideal for the selective protection of alcohols, for example, in that only hydrogen is formed as a by-product and the catalyst is easily removed by filtration.

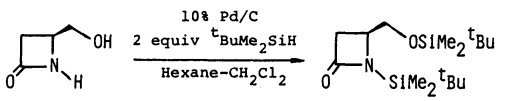
Alcohols: Thus, when *t*-butyldimethylsilane in hexane was treated with 3-phenyl-1-propanol and 10% Pd/C (5 mol% equiv) at room temperature, hydrogen slowly evolved and the silyl ether was obtained in 96% conversion (by GLC) in 2 h. Simple filtration of the reaction mixture through a Celite plug and, if necessary, flash chromatography, provided 3-phenylpropyl *t*-butyldimethylsilyl (TBDMS) ether with satisfactory purity in 72% yield. In the protection of alcohols, rhodium on carbon (10%) worked even better than 10% Pd/C and Ru/C, although it is more expensive. More polar solvents, such as, CH_2Cl_2, THF, and benzene, retarded significantly the rate of reaction, although they are often desirable for solubility purposes.

Several alcohols were examined in this protection procedure under the same conditions (0.3 mol dm^{-3} of the substrate in hexane at 70 °C), and we have found the relative reactivity (percent conversion and reaction time in parentheses) in the order $PhCH_2OH$ (99%, 1 h) > $PhCH_2CH_2CH_2OH$ (96%, 2 h) > $C_6H_{11}OH$ (92%, 7 h) PhCHMeOH (76%, 7 h) ≫ *t*-BuOH (trace, 9 h). The reactivity pattern clearly indicates that a primary alcohol, especially benzyl alcohol, undergoes protection faster than a secondary alcohol, whereas *t*-butyl alcohol hardly reacted under the conditions employed.[4b] Selective protection of primary hydroxyl group in 1,2-propanediol and 1-phenyl-1,2-ethanediol was easily achieved with >96% selectivity. It should be mentioned that no hydrogenolysis at the benzylic position of 1-phenyl-1,2-ethanediol was observed at all under the present conditions. Taking higher reactivity of benzylic alcohols into account, we examined by GLC analysis any competitive formation of $PhCH(OSiMe_2Bu^t)CH_2OH$, an authentic sample of which was prepared separately (see, Experimental). The ratio of primary silylation to secondary silylation was efficiently 96 : 4. The reagent combination of TBDMSCl, 4-(dimethylamino)pyridine, and triethylamine can be employed as well with a pronounced kinetic preference for primary against secondary alcohols.[7]

Protection of allylic alcohols (e.g., cinnamyl alcohol and geraniol) always accompanied partial hydrogenation of the olefin moiety due to the hydrogen which formed as the protection proceeded. Attempted quenching of the by-product hydrogen with excess 1-hexene instead of hexane as a solvent resulted in little improvement. It is worthy of mention that the stoichiometric hydrogenation of certain olefins has previously been reported by employing either ethanol/hydrosilane/Pd-C[8] or methanol/$NaBH_4$/H_2PtCl_6 catalyst[9] system under ambient conditions.

Amines: In the protection of amines, palladium

on carbon was the only choice as a catalyst. Benzene was a better solvent than hexane and CH_2Cl_2. Again benzyl amine reacted faster than morpholine in benzene at 70 °C: $PhCH_2NH_2$ (100%, 1.5 h) > $PhCHMeNH_2$ (82%, 12 h); morpholine (93%, 5 h). In order to exhibit a synthetic usefulness of the procedure, optically active 4-hydroxymethyl-2-azetidinone was subjected to the present protection to provide easily an *N,O*-disilylated derivative (Eq. 2).[10]



(2)

Carboxylic Acids: An expeditious synthesis of *t*-butyldimethylsilyl triflate has been reported by a direct reaction of *t*-butyldimethylsilane with a strong acid.[11] There is another precedent[12] in which $RhCl(PPh_3)_3$-catalyzed reaction of carboxylic acids with $EtMe_2SiH$ or $PhMe_2SiH$ gives the corresponding silyl esters. Hydrocinnamic acid and 2-methylbutanoic acid were reacted with *t*-butyldimethylsilane under the same conditions as those for alcohols described above to afford the silyl esters, respectively, in almost quantitative yields. Since the latter compounds are sensitive to hydrolysis, the present protection procedure is of special advantage due to its easy isolation.

Finally, (1,1,2-trimethylpropyl)dimethylsilane was prepared in a reasonable yield by the reaction of tetramethylethylene and dimethylsilane in the presence of a catalytic amount of $AlCl_3$.[13] All protection procedures presented here are equally applicable to the use of (1,1,2-trimethyl)dimethylsilane. The results will be discussed separately along with the novel mechanistic aspects of the $AlCl_3$-catalyzed hydrosilylation.

In conclusion, we propose the utility of *t*-butyldimethylsilane as an effective silylation reagent for alcohols, amines, and carboxylic acids, the method suffering from a drawback of incompatibility with olefinic functionality.

Experimental

Materials. *t*-$BuMe_2SiH$[4b] is a stable colorless liquid with a low boiling point (80 °C), being provided by Shin-Etsu Chemical Industry, Co., Ltd. and used as received. Group VIII metal catalysts (10% Pd/C, Rh/C, and Ru/C dry type) were obtained from Kawaken Fine Chemicals Co., Ltd. All substrates examined are commercial samples except a 2-azetidinone and mostly purified by distillation before use. Solvents were dried according to the standard procedure. (*S*)-4-Hydroxymethyl-2-azetidinone was prepared starting from pure L-aspartic acid in four steps.[10]

Protection Procedures. Alcohols: In a 20 mL two-necked flask, equipped with a reflux condenser topped with a nitrogen balloon, a rubber septum, and a magnetic stirring bar, were placed an alcohol (1.0 mmol), *t*-$BuMe_2SiH$ (140—174 mg, 1.2—1.5 mmol), 10% Pd/C (53.2 mg, 5 mol%), and dry hexane (3 mL) under a nitrogen atmosphere. The whole mixture was heated at 70 °C for a given time (0.5—9 h). The extent of the reaction was monitored by either GLC or TLC analysis. After the protection was completed (mostly at the conversion > 96% except for *t*-butyl alcohol), the catalyst was filtered through a short Celite plug, and the solvent and excess *t*-$BuMe_2SiH$ were evaporated under reduced pressure. The residue was purified by either column chromatography or by distillation (Kugelrohr), being practically pure for further use.[14] Selective protection of 1,2-propanediol and 1-phenyl-1,2-ethanediol was also carried out using 1.2 equiv amount of *t*-$BuMe_2SiH$ in hexane-CH_2Cl_2 (1 : 1 v/v). In the case of 1-phenyl-1,2-ethanediol, a little phenacyl alcohol was detected as a by-product during the protection. An authentic sample of the secondary silylated product, $PhCH(OSiMe_2Bu^t)CH_2OH$:[15] ^1H NMR (90 MHz, TMS, $CDCl_3$) δ=−0.10 (s, 3H), 0.06 (s, 3H), 0.91 (s, 9H), 3.58 (d, 2H, J=6.1 Hz), 4.76 (brt, 1H, J=5.9 Hz), and 7.31 (brs, 5H). GLC (Silicone DC-550, 3 m, at 200 °C, H_2 40 mL min^{-1}): T_R=2.4 min. For the primary silylated product, T_R=3.1 min. Table 1 lists ^1H NMR data

Table 1. ^1H NMR (90 MHz, $CDCl_3$, TMS) of TBDMS Derivatives of Alcohols, Amines, and Carboxylic Acids

TBDMS derivative	Chemical shifts (δ)
$PhCH_2OSiMe_2Bu^t$	0.11 (s, 6H), 0.95 (s, 9H), 4.75 (s, 2H), 7.31 (s, 5H)
$PhCH_2CH_2CH_2OSiMe_2Bu^t$	0.05 (s, 6H), 0.91 (s, 9H), 1.7—2.0 (m, 2H), 2.5—2.8 (m, 2H), 3.63 (t, 2H, J=6.3 Hz), 7.2—7.3 (m, 5H)
$PhCHMeOSiMe_2Bu^t$	0.03 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.40 (d, 3H, J=6.4 Hz) 4.86 (q, 1H, J=6.4 Hz), 7.29 (s, 5H)
c-$C_6H_{11}OSiMe_2Bu^t$	0.05(s, 6H), 0.89 (s, 9H), 1.1—1.9 (m, 10H), 3.4—3.8 (m, 1H)
$MeCH(OH)CH_2OSiMe_2Bu^t$	0.08 (s, 6H), 0.91 (s, 9H), 1.12 (d, 3H, J=6.2 Hz),3.33 (dd, 1H, J=9.7, 7.7 Hz), 3.60 (dd, 1H, J=9.7, 3.3 Hz), 3.80 (ddq, 1H, J=7.7, 6.2, 3.3 Hz)
$PhCH(OH)CH_2OSiMe_2Bu^t$	0.06 (s, 6H), 0.91 (s, 9H), 3.53 (dd, 1H, J=10.0, 8.6 Hz), 3.77 (dd, 1H, J=10.0, 3.7 Hz), 4.75 (dd, 1H, J=8.6, 3.7 Hz), 7.34 (brs, 5H)
$PhCH_2NHSiMe_2Bu^t$	0.07 (s, 6H), 0.94 (s, 9H), 3.99 (d, 2H, J=7.5 Hz), 7.31 (s, 5H)
$PhCHMeNHSiMe_2Bu^t$	−0.06 (s, 3H), −0.04 (s, 3H), 0.87 (s, 9H), 1.38 (d, 3H, J=6.6 Hz), 3.8—4.3 (m, 1H), 7.23 (s, 5H)
$CH_2CH_2OCH_2CH_2N$-$SiMe_2Bu^t$	0.03 (s, 6H), 0.86 (s, 9H), 2.8—3.0 (m, 4H), 3.4—3.6 (m, 4H)
$PhCH_2CH_2COOSiMe_2Bu^t$	0.26 (s, 6H), 0.93 (s, 9H), 2.5—2.8 (m, 2H), 2.8—3.1 (m, 2H), 7.25 (s, 5H)
$EtCHMeCOOSiMe_2Bu^t$	0.17 (s, 6H), 0.84 (s, 9H), 0.7—0.9 (m, 3H), 1.04 (d, 3H, J=7.0 Hz), 1.1—1.8 (m, 2H), 2.0—2.5 (m, 1H)

for all silyl ethers thus obtained here.

Amines and carboxylic acids were also treated in a similar manner to that for alcohols except for the use of benzene as solvent in the protection of amines. Table 1 is also for ^{1}H NMR data of the protected amines and acids examined in this paper.

a 2-Azetidinone: (*S*)-4-Hydroxymethyl-2-azetidinone (33.8 mg, 0.33 mmol) was dissolved in hexane-CH_2Cl_2 (1:1 v/v, 3.0 mL). To the solution were added *t*-$BuMe_2SiH$ (116 mg, 1.0 mmol) and 10% Pd/C (35.5 mg, 5 mol%) and the whole mixture was stirred at room temperature for 2 h. Usual workup gave an *N,O*-disilylated 2-azetidinone as a colorless oil (87 mg, 80% isolated yield): ^{1}H NMR δ=0.06 (s, 6H), 0.22 (s, 3H), 0.24 (s, 3H), 0.90 (s, 9H), 0.96 (s, 9H), 2.5—3.2 (m, 2H), and 3.4—3.8 (m, 3H).

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14) It should be mentioned that Corey and his coworker[2] observed a slow hydrogenolysis of certain silyl ethers including dimethylisopropylsilyl ones using 10% Pd/C, 1 atm H_2, and ethanol solvent. However, this was not the case of TBDMS ethers under present conditions.

15) The following sequence of reactions applied: $PhCH(OH)CH_2OH \rightarrow PhCH(OH)CH_2OBz \rightarrow PhCH(OSiMe_2Bu^t)CH_2OBz \rightarrow PhCH(OSiMe_2Bu^t)CH_2OH$.