$P(MeNCH_2CH_2)_3N$: An Efficient Silylation Catalyst

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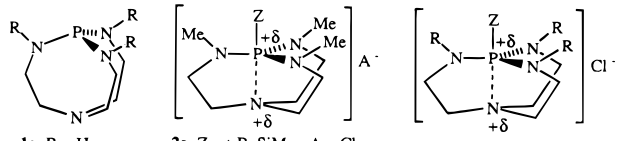
In our continuing quest[1] for new synthetic applications of our recently synthesized and commercially available proazaphosphatrane **1b**, we have discovered that **1b** is an efficient and mild catalyst for the silylation of tertiary alcohols and hindered phenols that are difficult to silylate using the reagent *tert*-butyldimethylsilyl chloride (TBDMSCl). The influence of solvent on the yield of silylated benzyl alcohol is discussed, and evidence for the first example of a P-silylating intermediate, namely **2a**, is given that stems from the detection of its analogue **3a**. Of the functional groups amenable to silylation (e.g., -SH,



1a, R = H
1b, R = Me
1c, R = i-Pr

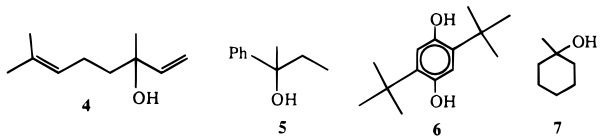
2a, Z = t-BuSiMe$_2$, A = Cl
2b, Z = C(O)Ph, A = PhCOO
2c, Z = C(O)OEt, A = Cl

3a, R = H, Z = t-Bu SiPh$_2$
3b, R = H, Z = H
3c, R = Me, Z = H

-COOH, -NH_2, and -OH), the hydroxy group has thus far received the most attention because of its presence in many natural products. Among the many trialkylsilyl derivatives used to protect hydroxyl groups, the TBDMS (*tert*-butyldimethylsilyl) group has proven to be invaluable in synthetic organic chemistry, ever since its introduction in 1972 by Corey and Venkateswarlu.[2] This is primarily due to the comparative ease with which TBDMSCl transforms an alcohol to the corresponding TBDMS ether, the facile specific removal of the TBDMS group by either fluoride ion or aqueous acid, and its stability to hydrogenation, saponification, and to Jones, Grignard, and Wittig reagents. Moreover, TBDMS ethers are approximately 10^4 times more stable to solvolysis than the corresponding trimethylsilyl ether,[3] thus facilitating hydroxy group protection during the synthesis of a variety of structures including prostaglandins,[4] paclitaxels,[5] and vitamin D_3.[6]

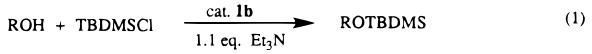
Conventional methods[7] for the preparation of TBDMS ethers include the reaction of an alcohol with TBDMSCl in the presence of bases such as imidazole,[2] Et_3N/1,1,3,3-tetramethylguanidine (TMG),[7a] Et_3N/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene),[7b,c] 18-crown-6/K_2CO_3,[7d] *i*-Pr_2NEt,[7e] Et_3N/DMAP (4-(dimethylamino)pyridine),[7f] and Li_2S[7g] in solvents such as DMF, CH_3CN, and CH_2Cl_2. TBDMS derivatives, such as its ketene methyl acetyl,[7h] enol ether of pentane 2,4-dione (with catalytic PTSA (*p*-toluenesulfonic acid)),[7i] allyl silane (with catalytic PTSA),[7j] *N*-methyl-*N*-*tert*-butyldimethylsilyl amides,[7k] *N*,*O*-bis-(*tert*-butyldimethylsilyl)acetamide,[7l] perchlorate (with pyridine),[7m] and triflate (with 2,6-lutidine),[7n] have also been employed. The foregoing methods have two general disadvantages, however. Thus, *p*-toluenesulfonic acid (PTSA) and potassium carbonate cannot be used for acid and base sensitive alcohols, respectively. Secondly, the use of DMF as a solvent, the relatively high base concentrations, long reaction times, and high reaction temperatures required for obtaining high yields of secondary silyl ethers when TBDMSCl is used as a silylating reagent incur procedural inconveniences. A particular problem with TBDMS protection has been the difficulty of silylating tertiary or hindered secondary alcohols and hindered phenols. This problem became acute during the total synthesis of maytansine[8] and of 1,4-bis (*tert*-butyldimethylsiloxy)-2,5-di-*tert*-butylbenzene for electrochemical oxidation studies.[9] Hence, more reactive silylating agents, namely TBDMS perchlorate[7m] and TBDMS triflate,[7n] were developed, which were found to be capable of silylating tertiary and hindered secondary alcohols in high yield.[7m,n] The perchlorate derivative, however, is explosive, must be handled with great care, and is not commercially available.

We report here a very effective and mild procedure for the preparation of TBDMS ethers of tertiary alcohols and hindered phenols. To this end, the commercially available and relatively inexpensive TBDMSCl is employed in the presence of the commercially available nonionic superbase **1b**, first reported from our laboratories,[10] as a catalyst under a nitrogen atmosphere in CH_3CN or in DMF. The analogue **3a** of the proposed P-silylating intermediate **2a** was detected by NMR spectroscopy. Table 1 outlines the efficacy and the scope of this procedure using alcohols **4**−**7**. The silylated products were purified by silica gel chromatography using hexanes as the eluent.



4 **5** **6** **7**

When 0.2 equiv of **1b**, one equiv of benzyl alcohol, and 1.1 equiv each of Et_3N and TBDMSCl in CH_3CN at 24 °C were mixed, the corresponding silyl ether was produced in quantitative yield in 0.2 h (eq 1). A similar yield was obtained in 2.5 h



(1)

employing only 0.04 equiv of **1b**. The influences of different solvents on the yield of the silyl benzyl ether at 24 °C using 0.04 equiv of **1b** are pentane, 43%; ether, 46%; benzene, 78%; THF, 92%; CH_3CN, ∼100%; and DMF, ∼100%.

The favorable effect of polar solvents on the silylation of alcohols under our conditions may be rationalized on the basis of an ionic species such as **2a** being formed as an active intermediate in the reaction of **1b** and TBDMSCl, even though such an intermediate was not detectable by variable temperature

(1) (a) D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963. (b) Tang, J. S.; Verkade, J. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 896. (c) Tang, J. S.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931. (d) Tang, J. S.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793. (e) Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233. (f) Laramay, M. A. H.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163. (g) Tang, J. S.; Verkade, J. G. *J. Org. Chem.* **1996**. In press.

(2) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(3) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed.; John Wiley and Sons, Inc.: New York, 1991; pp 77−80, 414.

(4) Hwang, S. W.; Adiyaman, M.; Khanapure, S.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829.

(5) Wong, T.; Romero, M. A.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 5527.

(6) Huang, P.; Sabbe, K.; Pottie, M.; Vandewalle, M. *Tetrahedron Lett.* **1995**, *36*, 829.

(7) (a) Kim, S.; Chang, H. *Synth. Commun.* **1984**, *14* (10), 899. (b) Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669. (c) Aizpuraua, J. M.; Palono, C. *Tetrahedron Lett.* **1985**, *26*, 475. (d) Lissel, M.; Weiffer, J. *Synth. Commun.* **1981**, *11* (7), 545. (e) Lombardo, L. *Tetrahedron Lett.* **1984**, *25*, 227. (f) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *2*, 99. (g) Olah, G. A.; Gupta, B. G.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272. (h) Kita, Y.; Haruta, J.; Fuji, T.; Segawa, J.; Tamura, Y. *Synthesis* **1981**, 451. (i) Verysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, *22*, 1299. (j) Morita, T.; Okamoto, Y.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 835. (k) Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, *47*, 3336. (l) Johnson, D. A.; Taubner, L. M. *Tetrahedron Lett.* **1996**, *37*, 605. (m) Barton, T. J.; Tully, C. R. *J. Org. Chem.* **1978**, *43*, 3649. (n) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(8) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.

(9) Stewart, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999.

(10) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *75*, 578.

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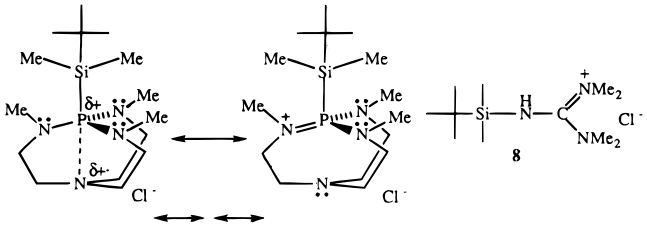
Table 1. Conditions for Alcohol Silylation with TBDMSCl Using **1b** as a Catalyst[a]

alcohol[b]	equiv of **1b**	solvent[c]	time (h)	*T* (°C)	yield (%)
4	0.2	A	24	24	4
	0.2	D	24	24	12
	0.2	D	24	80	80
	1.1	N	24	80	90
5	0.2	D	24	80	12
	0.4	D	48	80	77
	1.1	N	24	80	80
6	0.4	A	18	24	50
	0.4	A	18	60	86
7	0.2	D	24	80	86

[a] No attempt was made to maximize yields by optimizing reaction time and temperature and the concentration of **1b**. [b] All the alcohols are commercially available and were used as received. [c] A = acetonitrile, D = dimethylformamide, N = no solvent.

^{31}P NMR spectroscopy in an equimolar mixture of **1b** and TBDMSCl, TBDMS triflate, *tert*-butyldiphenylsilyl chloride (TBDPSCl), or triphenylsilyl chloride (TPSCl) in CD_3CN (−10 to +40 °C) or C_6D_6 (+10 to +40 °C). It may be noted in this respect, however, that the P-acylated intermediate **2b** in our benzoylation of alcohols was found by NMR spectroscopy to be in equilibrium with **1b** at room temperature.[1a] We also have substantial NMR spectroscopic evidence that the active catalytic site in compounds of type **1** for the synthesis of isocyanurates and carbodiimides is the phosphorus atom.[1c] Molecular structures determined by X-ray analysis for **1c**[11] as well as **3b**[12] and **3c**[12] show that the three R groups are attached to planar nitrogens, thus orienting the R groups like a picket fence around the phosphorus. Proceeding from the assumption that intermediate **2a** is too sterically encumbered to form in concentrations detectable by NMR spectroscopy, we sought to make the less hindered **3a** in which the **1a** moiety is more basic than **1b**.[1e] Thus, we generated **1a** (δ^{31}P = 89.0 ppm) in deuterated DMSO at 20 °C under nitrogen[1f] and then added a 10% molar excess of TBDPSCl at room temperature. The ^{31}P NMR spectrum of this solution then displayed a single peak at −0.4 ppm, with or without proton decoupling, which we assign to **3a**. The ^{1}H NMR spectrum revealed the presence of unreacted TBDPSCl and a doublet centered at 1.07 ppm with J_{HP} = 24 Hz, which we assign to a two-bond PNH spin−spin interaction in **3a** on the basis of a 28 Hz value for this coupling in **3b**.[1f] This substantiates the assignment of the −0.4 ppm ^{31}P NMR peak to the cation of **3a** rather than that of **3b** (δ^{31}P = −42.0 ppm), since the latter exhibits a 453 Hz doublet due to one-bond P−H coupling without proton decoupling.[1f] Evidence for considerable transannulation in **3a** is its high-field ^{31}P NMR chemical shift (−0.4 ppm) which is indicative of phosphorus five-coordination. This shift is consistent with the high-field ^{31}P chemical shifts observed for cations **2b**, **2c**, **3b**, and **3c**.[1a,1f,13] Attempted isolation of **3a** from DMSO resulted in its decomposition. This is not suprising, since **1a** is stable only in solution.[1f] Apparently, the augmented basicity and nucleophilicity of the phosphorus in **1** stemming from transannular bond formation play important roles in the rate of formation and stability, respectively, of the cations of type **2** and **3.** Under the present reaction conditions, we believe that **1b** forms the adduct **2a** with TBDMSCl, which subsequently reacts with alcohols to afford TBDMS ethers. That triethylamine does not catalyze reaction 1 is well-known from earlier alcohol silylation experiments.[7f]

We believe that the extensive positive charge delocalization in cation **2a** is facilitated by transannular bond formation, permitting substantial separation of the ion pair, thereby making the cation more reactive. The resonance structures for cation **2a** shown and implied below indicate the possibility of positive charge delocalization to all four nitrogens, whereas in **8** only three nitrogens can be involved in such delocalization. This reasoning finds support in the fact that the electron-donating dimethylamino group in TMG facilitates formation of the proposed charged intermediate **8**.[7b]



Kim et al.[7a] reported that the silylation of **5** using 0.2 equiv of TMG in the presence of 1 equiv of TBDMSCl and Et_3N resulted in only 11% of the silylated product at room temperature in DMF. Prolonged heating and the use of 1 equiv of TMG did not significantly improve the yield. Alcohol **5** could not be silylated using 1.1 equiv of DBU in DMF at room temperature.[7b] However, silylation of **5** using only 0.4 equiv of **1b** as a catalyst at 80 °C gave a 77% yield of the silylated product in 48 h. TBDMS perchlorate, although not commercially available, rapidly silylates **7** in quantitative yield at room temperature in acetonitrile, whereas the TBDMSCl/DMF/imidazole cocktail produced only 10% of silylated product in 3 days.[7m] From Table 1 it is seen that this alcohol was silylated in 86% yield using our method. Sterically hindered 1,4-bis-(*tert*-butyldimethylsiloxy)-2,5-di-*tert*-butylbenzene was difficult to prepare in reactions of TBDMSCl with **6**, and hence, the more reactive TBDMS triflate was employed.[9] However only a 53% yield of the pure disilylated product was reported, whereas our method gave 86% of the disilylated product of **6** (Table 1). Recently, an efficient and mild palladium(II)-catalyzed desilylation of phenolic TBDMS ethers was reported[14] which should enhance the use of the TBDMS moiety as a protecting group for phenols. Investigations of functional group compatibilities, sterically hindered alcohol silylations using solvents other than DMF, and catalyst recycling are underway.

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Supporting Information Available: Compound characterizational data, NMR peak assignments, and copies of ^{1}H NMR spectra (3 pages). See any current masthead page for ordering and Internet access instructions.

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(11) Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69.

(12) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483.

(13) P-Ethyl carboxylation of **1b** to give the intermediate **2c** is supported by NMR spectroscopy. A ^{1}H NMR spectrum of an equimolar mixture of **1b** and ethyl chloroformate in CD_3CN at 24 °C under N_2 revealed a doublet centered at 2.68 ppm with a P−H coupling constant J_{HP} of 14.1 Hz which we assign to a three-bond spin−spin interaction involving the methyl protons in **2c** on the basis of a 17.4 Hz value for this coupling in **3c**.[1f] The ^{13}C NMR spectrum of this mixture shows a doublet for the carbonyl carbon peak centered at 172.4 ppm with a coupling constant of 201.8 Hz, consistent with a one-bond C−P interaction.[1a] The ^{31}P NMR spectrum displays a single peak at −1.5 ppm with or without proton decoupling which we assign to **2c** rather than **3c** (−9.9 ppm), since the latter resonance without proton decoupling is a doublet owing to one-bond P−H coupling.[1a,c]

(14) Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 153.