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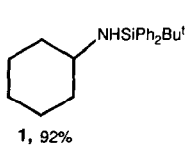
tert-BUTYLDIPHENYLSILYLAMINES: A USEFUL PROTECTING GROUP FOR PRIMARY AMINES

Larry E. Overman*, Mark E. Okazaki, and Pratibha Mishra[1]
Department of Chemistry, University of California
Irvine, California 92717

Summary: The utility of the tert-butyldiphenylsilyl group for protecting primary amines is explored. These derivatives are notably stable to chromatography, basic and hydrolytic reagents, as well as alkylating and acylating reagents. They are smoothly cleaved by mild acid and pyridine-HF.

The selective protection of reactive amine functionality is an important component of contemporary approaches to the synthesis of complex nitrogen-containing organic compounds. Although a variety of options exist for moderating the reactivity of a primary amine by acylation or sulfonation, few generally useful tactics of other types are available.[2] In this communication, we report our recent experience with the preparation and reactions of tert-butyldiphenylsilyl (tert-BDPSi)[3] secondary amines.[4] tert-Butyldiphenylsilyl derivatives of primary amines are stable to hydrolytic and strongly basic reagents and render the amine nitrogen unreactive to common alkylating and acylating reagents. These and other properties make the tert-BDPSi group an important addition to the repertoire of amine protecting groups and warrant their communication at this time.

Primary amines are converted to their mono tert-BDPSi derivatives by reaction with tert-butylchlorodiphenylsilane (1 equiv) and triethylamine (1.5 equiv) in acetonitrile (2-3 mL/mmol) at room temperature for 1-3 h.[5] Secondary amines do not react under these conditions and, thus, selective silylation of N-methyl-1,3-propanediamine was readily achieved. The silylations are easily monitored by silica gel TLC and the silylamine products (e.g. 1 - 5)[6] are conveniently purified by vacuum distillation or chromatography on silica



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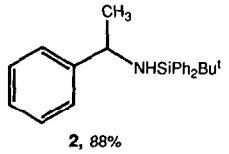

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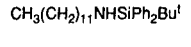

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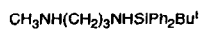

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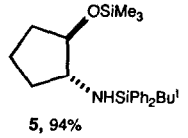


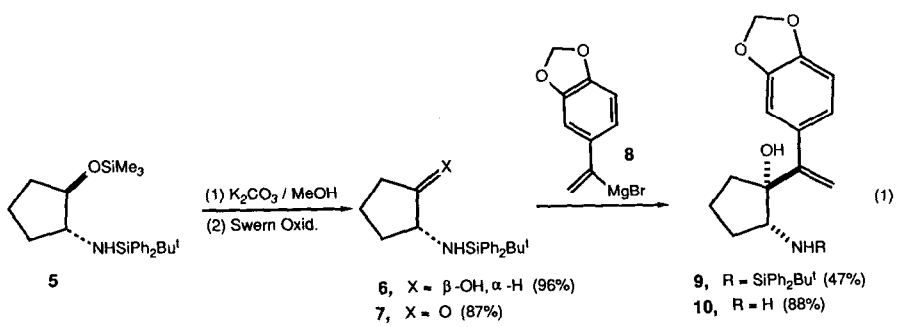
5, 94%

gel using eluent mixtures of $CHCl_3$ and hexane containing 5% Et_3N. The stability of these derivatives to chromatography, which is greater than that of the corresponding triisopropylsilyl secondary amines and apparently much greater than that of the corresponding tert-butyldimethylsilyl[4b] and thexyldimethylsilyl[7] derivatives, was an important factor in choosing tert-BDPSi derivatives for the studies reported herein.

tert-Butyldiphenylsilylamines are stable to a variety of non-acidic reaction conditions. For example, they resist solvolysis in MeOH (6 h, 25°C: 94% recovery of 1) and H_2O (4:1 THF-H_2O, 6 h, 25°C: 75-80% recovery of 1 and 3) and are remarkably stable to strong hot aqueous base (20% KOH/MeOH, 16 h, reflux: 88% recovery of 1).[8] This latter stability should allow the selective removal of acyl protecting groups from alcohols and many amines in the presence of tert-BDPSi secondary amines. Silylamine 1 was also stable to $LiN(CHMe_2)_2$ (2 equiv, THF, 2 h, 0°C: 99% recovery), n-BuLi (1.0 equiv, THF, 1 h, 0°C: 99% recovery) and ethanolic $NaBH_4$ (0.9 equiv, 2 h, 0°C: 93% recovery).[8] A particularly useful feature of these protected primary amines is their stability to reactive alkylating agents such as MeI and allyl bromide (1 equiv of MeI and i-Pr_2NEt, 0.5 M in CH_2Cl_2, 6 h, 25°C: 94% recovery of 3), and acylating agents such as methyl chloroformate (1 equiv, 1.1 equiv of Et_3N, 0.5 M in CH_2Cl_2, 7 h, 25°C: 90% recovery of 3), benzoyl chloride (78% recovery of 2), and acetic anhydride (83% recovery of 2).[8]

Primary amines are readily regenerated from their tert-BDPSi derivatives under mildly acidic conditions (80% HOAc, 25°C, 30 min, or 2:1 THF-0.5 M HCl, 25°C, 6 h: 74% yield of α-methylbenzylamine from 2) or with pyridine-HF (1.0 equiv, THF-H_2O, 2 h, 25°C: 98% cleavage of 1).[8,9] Although tert-BDPSi secondary amines are stable to Swern oxidation[10] (vide infra) they are not stable to other commonly employed oxidizing agents (e.g. m-chloroperoxybenzoic acid, K_2CO_3, CH_2Cl_2, 0°C; pyridinium dichromate, 25°C; $KMnO_4/NaIO_4$, 25°C; $OsO_4/NaIO_4$, 25°C).

The utility of tert-BDPSi amines for the synthesis of polyfunctional basic materials is apparent in the transformations shown in eqs 1 and 2. The greater solvolytic stability of the $NHSiPh_2Bu^t$ group relative to $OSiMe_3$ allows alcohol 6 to be readily generated from 5 (0.2 eq K_2CO_3, MeOH, 3 h, 25°C,

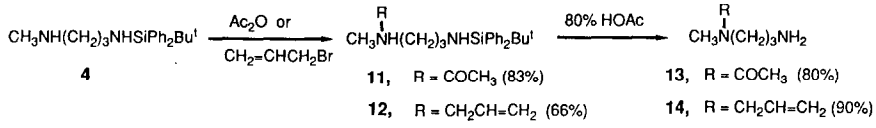


5

6, X = β-OH, α-H (96%)
7, X = O (87%)

9, R = $SiPh_2Bu^t$ (47%)
10, R = H (88%)

97%).[8] Swern oxidation[10] of 6 (DMSO, ClCOCOCl, Et_3N, 87%) gave amino ketone 7,[6] which is remarkably stable at room temperature. Protected acyclic α-amino ketones, e.g. the tert-BDPSi derivative of 1-amino-2-propanone, can be prepared in a similar fashion.[11] Since, secondary α-amino ketones are often inaccessible as a result of rapid dimerization,[12] the marked stabilization provided by the bulky and electron-withdrawing tert-BDPSi substituent should allow access to this relatively unexplored class of amino ketones. One use of intermediates of this type is illustrated in the reaction of ketone 7 with 2.1 equiv of Grignard reagent 8 (Et_2O, -78 to 0°C, 47%) to give 9 as the major product (diastereoselectivity = 6:1).[6,13] Deprotection of 9 (4:1 THF-1.0 M HCl, 25°C, 88%) then provided the primary amino alcohol 10 in reasonable overall yield.[6] The important use of the tert-BDPSi protecting group to allow selective functionalization of a secondary amine in the presence of a primary amine is illustrated in the conversions summarized in eq 2. Diamine 4 was cleanly acetylated (1.0 equiv Ac_2O, 10 equiv i-Pr_2NEt, CH_3CN, 0.5 h, 25°C, 83%) and allylated (1 equiv CH_2=$CHCH_2Br$, 10 equiv i-Pr_2NEt, CH_3CN, 1 h, 66%) to give as the sole products 11 (^1H NMR δ 2.82 and 2.85, CH_3NAc) and 12. Deprotection with 80% HOAc (25°C, 10 min) then liberated the primary amine group to provide 13 and 14[14] in excellent overall yield.



We anticipate that a number of additional applications of the tert-BDPSi group for amine protection will be reported in the future.

Acknowledgment: Support from the National Institutes of Health (PHS Grant No. NS-12389) and the National Science Foundation (Department instrumentation grants) is gratefully acknowledged.

References and Notes

1. NSERC Postdoctoral Fellow of the National Research Council of Canada, 1985-86.
2. Greene, T.W. "Protective Groups in Organic Synthesis"; John Wiley and Sons: New York, 1981; Chapter 7.
3. Hanessian was the first to introduce this functionality as a useful method for protecting hydroxyl groups: Hanessian, S.; Lavallee, P. Can. J. Chem. 1975, 53, 2975.
4. For other important uses of N-silylsecondary amines, see, inter alia, (a) Corriu, R.J.P.; Moreau, J.J.E. in "Selectivity- A Goal for Synthetic

Efficiency"; Bartmann, W., Trost, B.M., Ed. Verlag Chemie: Deerfield Beach, FL.; 1984; p. 21. (b) Calverley, M.J. Synth. Commun. 1983, 13, 601. (c) Bowser, J.R.; Neilson, R.H.; Wells, R.L. Inorg. Chem. 1978, 17, 1882. (d) Ando, W.; Tsumaki, H. Chem Lett. 1981, 693.

5. Product isolation consisted of concentrating the reaction mixture in vacuo, partitioning the residue between 1 M $NaHCO_3$ (or 10% KOH) and an organic solvent (e.g. 4:1 hexane-ethyl acetate), and drying the organic phase over a mixture of K_2CO_3 and Na_2SO_4.
6. (a) Satisfactory spectroscopic data (^1H NMR, ^{13}C NMR, and IR) were obtained for all intermediates. Crystalline compounds gave correct combustion analyses while the molecular composition of liquid samples was established by high resolution MS. (b) Characterization data for 4 are representative: bp (bulb-to-bulb, bath temp) 178-184°C (0.4 mm); IR (film) 3406, 3319, 3070, 1470, 1428, 1107, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4-7.8 (m, 10H, Ph), 2.79 (t, J=6.8 Hz, 2H, CH_2N), 2.53 (t, J=6.9 Hz, 2H, CH_2N), 2.33 (s, 3H, CH_3N), 2.0-2.3 (br m, 1H, NH), 1.61(p, J=6.9Hz, 2H, CH_2CH_2N), 1.04 (s, 9H, Bu^t), 0.9-1.1 (br m, 1H, NH); MS (CI, isobutane) m/e 327 (MH^+, 100); MS (EI, 70 eV) m/e 269.1466 (269.1474 calcd for $C_{16}H_{21}N_2Si$, $M-C_4H_9$).
7. Wetter, H.; Oertle, K. Tetrahedron Lett. 1985, 26, 5515.
8. Yields of recovered starting material or regenerated primary amine refer to pure material isolated after chromatographic purification. Stability studies were conducted in base-washed (NH_4OH) glassware at substrate concentrations of 0.1 - 0.5 M.
9. The stability of tert-BDPSi secondary amines to base and their lability to dilute acid is expected from the extensive mechanistic studies of Eaborn: Bassindale, A.R.; Eaborn, C.; Walton, D.R.M. J. Organomet. Chem. 1970, 25, 57.
10. Mancuso, A.J.; Huang, S.L.; Swern, D. J. Org. Chem. 1978, 43, 2480.
11. The deprotection of (K_2CO_3/MeOH) of acyclic β-trimethylsilyoxy tert-BDPSi amines is somewhat complicated by intramolecular N → O migration of the tert-BDPSi group. Good yields of N-protected amino alcohols can be obtained if the reaction is worked-up rapidly at 0°C. Pure 2-[(tert-butyldiphenylsilyl)amino]-2-propanol undergoes N → O silyl migration only slowly (2-3 days) at room temperature.
12. Bayer, O. in "Houben-Weyl", Mueller, Ed.; Thieme Verlag: Stuttgart; 1977; 4th ed.; Vol. VII/2C, Chapter 5.
13. A study of the diastereoselectivity of the reaction of cyclic and acyclic tert-BDPSi-protected aminoketones with organometallic reagents will be reported in due course.
14. That 14 contains a NH_2 group was indicated by the IR spectra (film, 3364 and 3292 cm^{-1}) and confirmed by benzoylation (^1H NMR δ 8.38, NHCOPh).

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