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STUDIES WITH TRIALKYLSILYLTRIFLATES: NEW SYNTHESES AND APPLICATIONS

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Summary: Syntheses and applications are described for three useful reagents for silylation of unreactive substrates, tert-butyldimethylsilyl, triisopropylsilyl, and octadecyldimethylsilyl triflate.

The tert-butyldimethylsilyl (TBDMS) group has been much used for hydroxyl protection,[1] partly because of its specific and mild removal by either fluoride ion[1,2,3] or aqueous acid.[1] Protection is normally accomplished using TBDMS chloride as reagent with either imidazole[1] or 4-dimethylaminopyridine[4,5] as catalyst. One problem with TBDMS protection has been the difficulty of silylation in the case of tertiary or hindered secondary alcohols. This problem[6] became urgent during a recent study of the total synthesis of maytansine[7] and prompted a study of TBDMS triflate as a silylating reagent.[8] In this paper we describe the silylation of hindered alcohols by TBDMS triflate, a simple and practical synthesis of this reagent, and similar studies with two other useful silylating agents, triisopropylsilyl triflate and n-octadecyldimethylsilyl triflate.

tert-Butyldimethylsilyl triflate has previously been prepared only by the costly reaction of TBDMS chloride with silver triflate.[9] It can be made much more economically and simply by the following procedure:

TBDMS Triflate: Triflic acid (14 ml, 0.16 mole) was added dropwise to 24 g (0.16 mole) of TBDMS chloride at 23° and the resulting mixture was heated to 60°C for ca. 10 hr at which time no further hydrogen chloride was evolved and the pmr spectrum of an aliquot (in $CDCl_3$) showed peaks corresponding to TBDMS triflate (0.45 and 1.00 δ) but not TBDMS chloride (0.36 and 0.97 δ). The product was directly distilled from the reaction flask to afford 34 g (80%) of TBDMS triflate as a colorless oil bp 60°C at 7 torr.[10] Since TBDMS triflate is much more sensitive to moisture than the crystalline chloride and since this preparation is so simple, we have over the past few years found it preferable to store the chloride and prepare quantities of triflate sufficient for a 1-2 month's supply. To our knowledge this simple metathetical synthesis of silyl triflates has not previously been reported.[11,12]

The use of TBDMS triflate allows the TBDMS protection of tertiary alcohols and unreactive secondary alcohols. Dry 2,6-lutidine (distilled from CaH_2) is an excellent base for these reactions which were generally performed in methylene chloride as solvent (ca. 1 M solution of substrate) at 0 to 25°C with a ratio of alcohol-TBDMS triflate-2,6-lutidine of 1:1.5:2.0 to 2.5. The reaction which is conveniently monitored by thin layer chromatography is usually complete in 10-30 min at

25°C. For example the preparation of the TBDMS ether of tert-butyl alcohol was carried out in 90% yield using 1 equiv of the alcohol, 1.5 equiv of TBDMS triflate, 2 equiv of 2,6-lutidine, in methylene chloride (1 M concentration of the alcohol) at 25° for 10 min followed by extractive isolation and distillation. The following alcohols were silylated in the same way in good yield (70-90%): 2-phenyl-2-propanol, endo-norborneol, 2,2,4,4-tetramethyl-cyclobutan-cis-1,3-diol and 9-O-methylmaytansinol (converted to the 3-TBDMS derivative[7,13]).

The triisopropylsilyl (TIPS) group is an exceedingly useful control element in organic synthesis, as will be demonstrated in forthcoming publications.[14] The three isopropyl substituents provide strong steric screening not only for the silicon to which they are attached, but also for the atom to which silicon is connected (in contrast to trimethylsilyl, triethylsilyl, TBDMS or other commonly used silyl moieties). However, the introduction of the TIPS group has been a problem because of the relative unreactivity of TIPS chloride, for example toward secondary hydroxyl groups or enolates.[15,16] In contrast, TIPS triflate is easily prepared and highly reactive in silylation. Reaction of isopropylmagnesium chloride with commercially available and inexpensive trichlorosilane affords in high yield triisopropylsilane, as previously described.[16] This can be converted to TIPS triflate as follows:

TIPS Triflate: Triflic acid (23.8 ml, 39.9 g, 0.266 mole) was added dropwise to 38.2 g (0.242 mole) of triisopropylsilane,[16] stirred (inert atmosphere) and cooled to 0° in a flask fitted with dropping funnel, gas inlet and exit tubes (H_2 evolution) and thermometer. After completion of the addition, stirring was continued at 22° for 16 hr and the resulting product was distilled through a 30-cm vacuum jacketed Vigreux column to give 71.7 g of TIPS triflate (97%), bp 83-87° at 1.7 torr, d 1.173. The pmr spectrum of TIPS triflate ($CDCl_3$, 80 MHz) consists of a complex multiplet at δ 1.6-1.05 with two major peaks at 1.18 and 1.13 (height ratio 2.2:1).

TIPS triflate in combination with 2,6-lutidine is an excellent silylating agent for primary and secondary alcohols. Benzyl alcohol was silylated quantitatively even at -78° (5 hrs, CH_2Cl_2 solution). 1-Phenylethanol was converted to the TIPS ether in >98% yield at 0° in CH_2Cl_2 in just 2 hr using 1.3 equiv of TIPS triflate and 2.5 equiv of 2,6-lutidine. As might be expected tertiary alcohols are relatively resistant to silylation by this highly electrophilic but exceedingly bulky silylating agent. Cyclopentanone, cyclohexanone, 4-tert-butylcyclohexanone and cycloheptanone were each converted in >98% yield to the corresponding enol TIPS ether with 1.1 equiv of TIPS triflate and 1.5 equiv of triethylamine in benzene at 23° for 1 hr. In a similar way enol TIPS ethers were obtained in high yields from aldehydes, e.g. n-heptanal (→Z-ether), cyclohexanecarboxaldehyde and phenylacetaldehyde. The TIPS enol ethers are sufficiently stable to be chromatographed on silica gel or distilled. TIPS chloride in contrast to the triflate does not yield enol ethers under these conditions.

Another application of silyl triflates is in the silylation of support materials for reversed phase high performance liquid chromatography (RP-HPLC). The most commonly used material for RP-HPLC separations currently is C_{18}-reversed phase silica which is produced by silylation of silica by heating with n-octadecyldimethylsilyl (ODS) chloride-pyridine. Because of incomplete silylation polar sites usually remain which cause problems such as: (1) loss of substrate in preparative RP-HPLC, (2) loss of resolution, (3) limited column life, and (4) batch-to-batch irreproducibility. Our experience with the use of triflates for the silylation of unreactive organic substrates led us to study the application of ODS triflate to this problem which has been of special importance in recent work in these laboratories on the leukotrienes.[17]

ODS triflate was prepared by reaction of ODS chloride with 1 equiv of triflic acid at 60-70° for 30 min with final heating at 6 mm to remove last traces of HCl. Waters Associates μ-Porasil 10 μ silica was dried at 300°/0.1 torr, cooled and treated with 2/3 its weight of ODS triflate and 2 equiv of 2,6-lutidine/triflate in CH_2Cl_2 at 25° for 24 hr. Filtration, washing with (1) methylene chloride, (2) methanol, (3) methanol-water, and (4) methanol, and drying in vacuo afforded C_{18}-silanized silica: porosity, 0.32 cc/g; surface area 177 m^2/g; %C, 17.02; %H, 3.00;[18] μ moles silane/m^2 3.05. This material could be made very reproducibly and columns made from it showed consistent properties. These columns were tested in comparison with commercial columns of C_{18}-silanized 10 μ silica and were found to be superior with respect to resolution of various leukotrienes (see insert below), recovery and durability.[19] Further work along these lines is continuing.

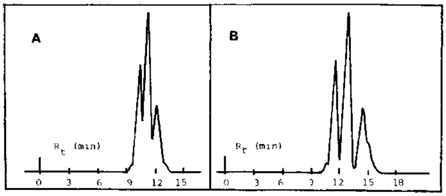

Illustration: RP-HPLC separation of 6-trans-leukotriene B (left peak), 6-trans,10-cis-leukotriene B (center peak), and leukotriene B (right peak) using 3:1 methanol water containing 0.01% acetic acid and 0.39 x 30 cm C_{18} silanized (ODS) columns of 10 μ particle size, flow rate 1 ml/min. Identical method was used for column packing.

Panel A: new commercial column (from ODS chloride).

Panel B: column prepared using ODS triflate made as indicated above.

References and Notes

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3. R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Letters*, 3981 (1979).
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5. S. K. Chaudhary and O. Hernandez, *Tetrahedron Letters*, 99 (1979).
6. See, for example, T. Veysoglu and L. A. Mitscher, *Tetrahedron Letters*, **22**, 1299 (1981).
7. E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho, and D. H. Hua, *J. Am. Chem. Soc.*, **102**, 6613 (1980).
8. For previous work on various silyl triflates as reagents see (a) H. Emde and G. Simchen, *Synthesis*, 867 (1977); (b) M. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Letters*, **22**, 1809 (1981), and (c) H. H. Hergott and G. Simchen, *Ann. Chem.*, 1718 (1980).
9. M. Riediker and W. Graf, *Helv. Chim. Acta*, **62**, 205 (1979).
10. Satisfactory infrared, pmr and mass spectral data have been obtained for all new compounds reported herein.
11. Silyl triflates have been prepared earlier not only by the reaction of chlorides with silver triflate[9] but by the reaction of tetraalkylsilanes with triflic acid (see, U. Finke, H. H. Moretto, H. Niederpruem, and H. Vorbrueggen, German Patent 2,803,125) and by the reaction of hexaalkyldisiloxanes with triflic anhydride (see, *Z. Naturforsch.*, *B*, **25**, 773 (1970).
12. Silyl perchlorates, e.g. di-*tert*-butylmethylsilyl perchlorate, have also been prepared and used as reactive silylating reagents. See, T. J. Barton and C. R. Tully, *J. Org. Chem.*, **43**, 3649 (1978).
13. Although the 3-hydroxyl function of 9-O-methylmaytansinol is secondary, its reactivity toward electrophils is low and quite comparable to tertiary hydroxyl groups. Numerous silylation attempts with TBDMS chloride led to poor yields (range 20-45%).
14. E. J. Corey and Ch. Rücker, in preparation.
15. Unpublished studies by Dr. A. Venkateswarlu in these laboratories in 1970. More recently the TIPS group has been utilized for the selective protection of primary hydroxyl groups in ribo- and deoxyribo nucleosides; see, K. K. Ogilvie, K. L. Sadana, E. A. Thompson, M. A. Quilliam and J. B. Westmore, *Tetrahedron Letters*, 2861, 2865 (1974).
16. R. F. Cunico and L. Bedell, *J. Org. Chem.*, **45**, 4797 (1980).
17. See, for example, E. J. Corey, A. Marfat, K. S. Kim, P. B. Hopkins, and F. Brion, *Tetrahedron Letters*, **22**, 1077 (1981) and references cited therein. In our experience recoveries of previously purified leukotrienes from preparative RP-HPLC (10 to 1000 microgram scale) using commercially available columns varies from 30-70%. Since the weight of column material is large compared to the substrate being chromatographed, only a small percentage of exposed unsilanized silica sites can lead to intolerable losses.
18. Calcd. for ODS, C/H ratio, 5.58; found, 5.67. We are indebted to Dr. Patrick D. McDonald, Waters Associates for the analytical data.
19. This work was assisted by a grant from the National Institutes of Health and a fellowship to Ch. Rücker from the Deutsche Forschungsgemeinschaft. We are grateful to Dr. A. Marfat and Ms. Robyn Easton for the RP-HPLC separations.

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