Method for Sulfide S-Benzylation or S-Allylation Using Trimethylsilyl Triflate Activated Benzyl or Allyl Ethers

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Attempts in our laboratory to prepare benzyl triflate from benzyl alcohol and trifluoromethanesulfonic anhydride–pyridine have been unsuccessful. Although small amounts of the triflate apparently do survive long enough in solution to be trapped by subsequent addition of sulfides (<10% salt formation), a practical synthetic procedure has so far proved elusive.

We now report that the combination of benzyl trimethylsilyl ether with trimethylsilyl triflate is synthetically useful as a substitute for benzyl triflate. When these reagents are combined in the presence of a sulfide, good yields of S-benzylsulfonium triflates can be isolated (Table I). A similar procedure allows preparation of S-allylsulfonium triflates from a variety of allyl ethers. Although yields of crystalline S-allyl salts are modest, the procedure may prove advantageous in situations where the high reactivity of allyl triflate[1] is an intimidating factor.

The exact identity of the reactive alkylating agent formed from benzyl or allyl ethers and $(CH_3)_3SiOTf$ is not known. In methylene chloride, either the oxonium salt 1 or the derived triflate 2 may be involved. With acetonitrile as solvent, the nitrilium salt 3 must also be considered since allyl triflate attacks acetonitrile rapidly.[1] In general, acetonitrile has proved to be the best solvent for alkylation of relatively unreactive sulfides which are inductively deactivated by carbonyl substituents. In one case (Table I, entry 4), the alkylation of a deactivated sulfide is sufficiently fast in methylene chloride.

$$RCH_2OR' + Me_3SiOSO_2CF_3 + R''SR''' \longrightarrow$$

1   2   3
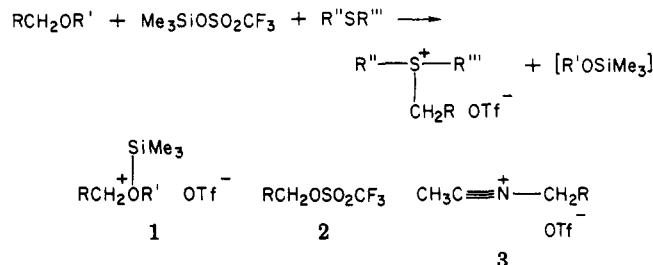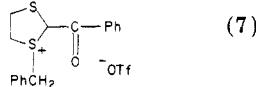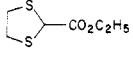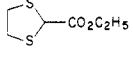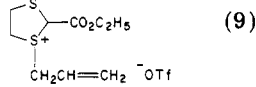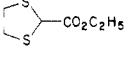
More reactive sulfides such as 1,3-dithiane can also be alkylated in less polar solvents (4:1 toluene–CH_3CN), using $CH_2{=}CHCH_2OSi(CH_3)_3/(CH_3)_3SiOSO_2CF_3$. The initial salt 4 has not been obtained in crystalline form, but the reaction is quite efficient as evidenced by conversion of 4 into 5 (2,3-shift) upon treatment with $KOC(CH_3)_3$ (68% yield over two steps).

4   5

Similar treatment of *n*-propyl trimethylsilyl ether with $(CH_3)_3SiOSO_2CF_3$ in the presence of sulfides gives no isolable sulfonium salts at temperatures up to 80 °C. Evidently, the solvolytic reactivity of the benzyl or allyl
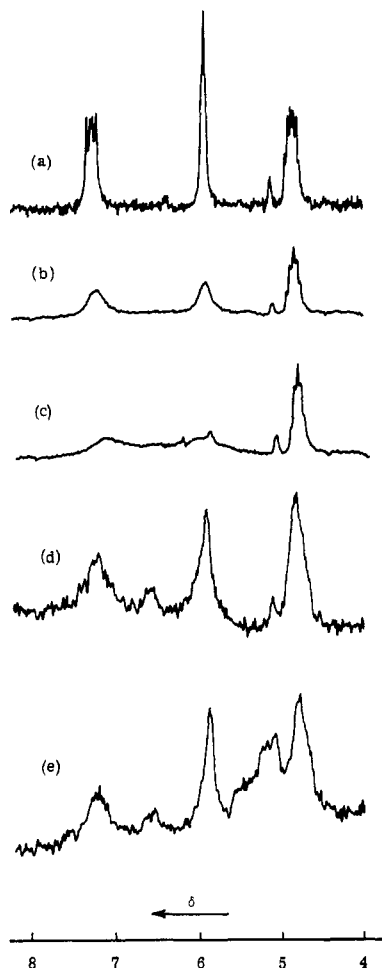
Figure 1. Temperature and pressure dependence of 7-methyl-7-nornornadienyl cation; the bound vinyl, unbound vinyl, and bridgehead ^1H NMR signals occur at δ 7.3, 5.9 and 4.9, respectively. (a) At −45.7 °C; (b) at −25.8 °C; (c) at −15.6 °C; a, b, and c were recorded at atmospheric pressure with a 5-mm spinning sample tube. (d) At atmospheric pressure and −23 °C; (e) at 195 MPa and −23 °C; d and e were recorded with the sample in the high-pressure vessel.

in 1 and 2 both are in excellent agreement with expectations based on the Drude–Nernst correlation between volume and charge distribution.

Experimental Section

The solution of 7-methyl-7-norbornadienyl cation was prepared from quadricyclanone in three steps. 7-Methylquadricyclanol was prepared in a reaction of methylmagnesium bromide with quadricyclanone. The isomerization to 7-methylnorbornadienol was carried out with a catalytic amount of bis(chlorodicarbonylrhodium) in CCl_4 solution under an argon atmosphere; this is a modification of the procedure described by Lustgarten et al.[12] The reaction was complete in 30 h. The 7-methylnorbornadienol was dissolved in CD_2Cl_2, degassed with a freeze–thaw cycle, and dissolved in triply distilled FSO_3H under high vacuum at −80 °C. This solution was placed in the capillary cell, and spectra were obtained by means of a Brucker WP-60 at −23 °C as previously described.[4]
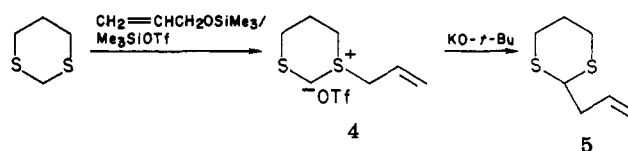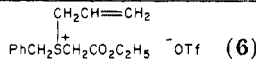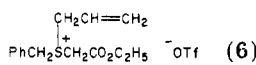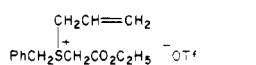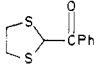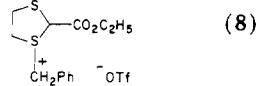
(1) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* 1977, *42*, 3109.

Table I. Alkylation of Sulfides Using Trimethylsilyl Triflate and Allyl or Benzyl Ethers

entry	sulfide	ether	product	% yield[c]
1[a]	PhCH$_2$SCH$_2$CO$_2$C$_2$H$_5$	(CH$_2$=CHCH$_2$)$_2$O	(6)	34
2[a]	PhCH$_2$SCH$_2$CO$_2$C$_2$H$_5$	CH$_2$=CHCH$_2$OSiMe$_3$	(6)	43
3[a]	CH$_2$=CHCH$_2$SCH$_2$CO$_2$C$_2$H$_5$	PhCH$_2$OSiMe$_3$		48
4[b]		PhCH$_2$OSiMe$_3$	(7)	89
5[a]		PhCH$_2$OSiMe$_3$	(8)	70
6[a]		(CH$_2$=CHCH$_2$)$_2$O	(9)	55
7[a]		CH$_2$=CHCH$_2$OSiMe$_3$		56

[a] Alkylation performed in acetonitrile, 24 h, 20 °C.   [b] Alkylation in CH$_2$Cl$_2$, 24 h, 20 °C.   [c] Yields refer to isolated crystalline salts.

groups is essential, either in the ether activation step or in the alkylation step. Previous applications of trimethylsilyl triflate as an activating agent for replacement of an oxygen substituent in acetals or ketals by various nucleophiles are no doubt related mechanistically.[2]

Experimental Section

General Procedures. **(1) Alkylation with (CH$_2$= CHCH$_2$)O/Me$_3$SiOTf.** A solution of trimethylsilyl triflate (Petrarch, 0.68 g, 3.1 mmol) in CH$_3$CN (4 mL, distilled from P$_2$O$_5$) was combined with allyl ether (0.17 g, 1.7 mmol) and the sulfide substrate (2.9 mmol). After 24 h, the solvents were removed and the dark residue was triturated with ether (3 × 15 mL). The residue was crystallized from CHCl$_3$–ether. The following products were made by this method for characterization: C$_6$H$_5$CH$_2$S$^+$-(CH$_2$CH=CH$_2$)CH$_2$CO$_2$C$_2$H$_5$ $^-$O$_3$SCCF$_3$[3] (6), mp 62.5 °C; 1-allyl-2-(carboethoxy)-1,3-dithiolanium triflate[3] (9), mp 83–83.5 °C.

(2) Alkylation with CH$_2$=CHCH$_2$OSiMe$_3$/Me$_3$SiOTf. A solution of the sulfide (2 mmol) and allyl trimethylsilyl ether (2.2 mmol) in CH$_3$CN (1.5 mL, distilled from P$_2$O$_5$) was combined with Me$_3$SiOTf (0.49 g, 2.2 mmol). After 24 h at ambient temperature, the salts were isolated as above.

(3) Alkylation with PhCH$_2$OSiMe$_3$/Me$_3$SiOTf. The sulfide (2.2 mmol) and benzyl trimethylsilyl ether (0.4 g, 2.2 mmol) were dissolved in acetonitrile (2 mL). Trimethylsilyl triflate (0.47 g, 2.1 mmol) was added and the reaction was allowed to proceed for 24 h at room temperature. After removal of solvent and trituration with ether, the salts were isolated by crystallization from ether–CHCl$_3$ as before.

The following salts were prepared by this method for characterization: 1-benzyl-2-benzoyl-1,3-dithiolanium triflate[3] (7), mp 135.5 °C;[3] 1-benzyl-2-(carboethoxy)-1,3-dithiolanium triflate (8), mp 85.5–87 °C.[3]

Conversion of 1,3-Dithiane into 5. A solution of 1,3-dithiane (0.24 g, 2 mmol, Aldrich) and allyl trimethylsilyl ether (0.29 g, 2.2 mmol) in toluene (3 mL) and acetonitrile (0.5 mL, distilled from P$_2$O$_5$) was stirred with Me$_3$SiOTf. After 48 h, a brown oil had precipitated. The solvents were evaporated and dry THF (3 mL, distilled from Na–Ph$_2$CO) was added, followed by KOC-(CH$_3$)$_3$ (0.25 g)(magnetic stirring). After the exothermic reaction

had subsided (ca. 5 min), the mixture was diluted with ether (10 mL) and extracted once with water (5 mL), and the organic phase dried over MgSO$_4$. After solvent removal (aspirator) the residual oil was purified by preparative layer chromatography over silica gel, 30% ether–hexane, to give 5 (R_f 0.5): 0.22 g; 69%. Spectral comparisons with literature data established the identity of 5.[4]

(4) Harding, K. E.; Nash, W. D. Synth. Commun. 1977, 7, 19.
(5) Note added in proof: the generation of benzyl triflate in situ from PhCH$_2$Br + CF$_3$SO$_3$Ag has recently been reported: Booth, B. L.; Haszeldine, R. N.; Laali, K. J. Chem. Soc., Perkin Trans. 1 1980, 2287.

Folate Analogues. 19. Construction of Some 6-Substituted 7,8-Dihydro-8-thiopterins[1]

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As part of our continuing interest in developing synthetic substrates of dihydrofolate reductase[2] (EC 1.5.1.3) whose enzymatic reduction products are potentially capable of interfering with tetrahydrofolate utilization,[2,3] we have

(1) For the previous papers in this series see: Nair, M. G.; Bridges, T. W.; Henkel, T. J.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. J. Med. Chem., in press; Nair, M. G.; Adapa, S. R.; Bridges, T. W. J. Org. Chem., in press. The pterins are 6-substituted derivatives of the 2-amino-4-hydroxy-pyrimido[4,5-b](1,4)thiazine ring system.
(2) Nair, M. G.; Colleen, S.; Chen, S. Y.; Kisliuk, R. L.; Gaumont, Y. J. Med. Chem. 1980, 23, 59.
(3) Misra, D. K.; Humphreys, S. R.; Friedkin, M.; Goldin, A.; Crawford, E. J. Nature (London) 1961, 189, 39.

(2) Murata, S.; Suzuki, M.; Noyori, R. J. Am. Chem. Soc. 1980, 102, 3248; Tetrahedron Lett. 1980, 2527. Murata, S.; Noyori, R. Ibid. 1980, 767. Tsunoda, T.; Suzuki, M.; Noyori, R. Ibid. 1980, 71; Ibid. 1979, 4679.
(3) Satisfactory C, H analysis was obtained.