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β-TRIMETHYLSILYLETHANESULFONYL CHLORIDE (SES-Cl): A NEW REAGENT FOR PROTECTION OF AMINES

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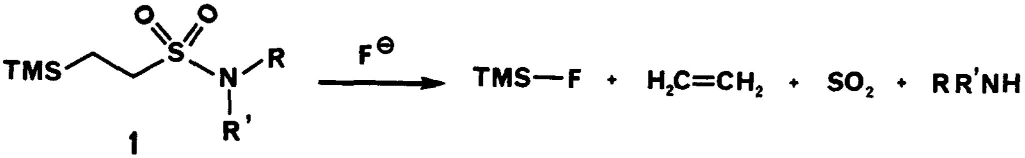
ABSTRACT: The title compound, easily prepared in two steps from vinyltrimethylsilane, is a useful reagent for the protection of primary and secondary amines as their sulfonamides, which are cleaved by fluoride ion.

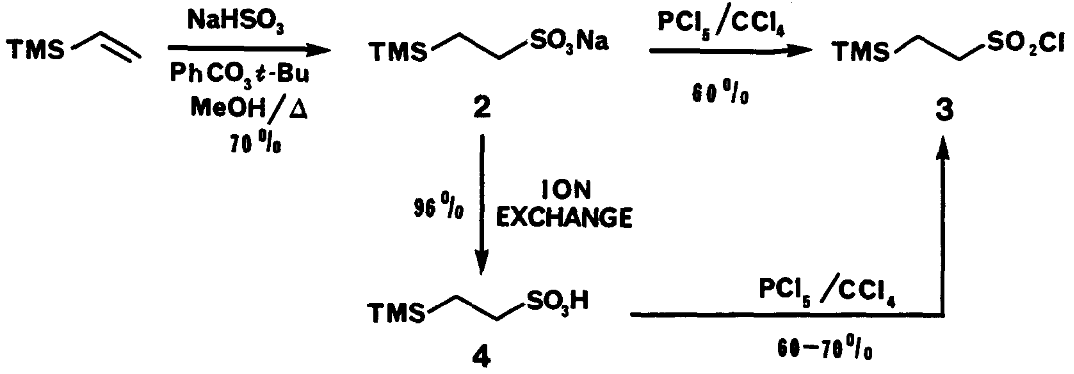
Sulfonamides are among the most stable of amine protecting groups.[1] However, it is this stability that detracts from their utility, since rather extreme conditions are usually needed for removal.[2] We now report the synthesis of a sulfonamide protecting group 1 which is readily cleaved by fluoride ion to regenerate the parent amine [eq. (1)].[3]

These sulfonamides can be readily prepared from a primary or secondary amine and the previously unknown β-trimethylsilylethanesulfonyl chloride (3), which we give the acronym SES-Cl. An efficient synthesis of 3 has been developed from vinyltrimethylsilane as shown in the Scheme. Free radical addition[4] of sodium bisulfite to the vinyl group catalyzed by t-butyl perbenzoate yields sulfonate salt 2, which could be directly converted to 3 with phosphorous pentachloride.[5] Similar overall yields of SES-Cl could be obtained via the free sulfonic acid 4,

eq. (1)



Scheme



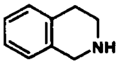
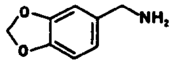
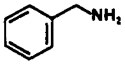
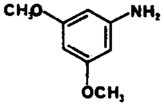
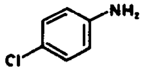
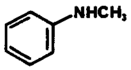
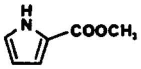
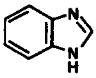
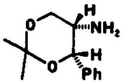
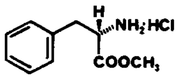
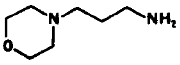
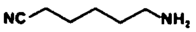
prepared from salt 2 via ion exchange chromatography. SES-Cl is a stable, distillable liquid which can be stored at room temperature for weeks. It can even be purified by chromatography on silica gel.

Sulfonamides 1 can be prepared from a wide variety of primary and secondary amines using sulfonyl chloride 3 in DMF containing triethyl amine. For aromatic and heterocyclic amines, NaH was found to be preferable as the base. These sulfonamides are generally quite stable and are untouched by: refluxing TFA; 6M HCl in refluxing THF; 1M TBAF in refluxing THF; $LiBF_4$ in refluxing MeCN; BF_3•etherate; 40% HF in ethanol. However, they could be cleaved in good yields with cesium fluoride (2-3 equiv) in DMF at 95°C for 9-40 h, or by TBAF•$3H_2O$ (3 equiv) in refluxing acetonitrile. The main disadvantage of the latter cleavage procedure is an occasional difficulty in separating tetrabutylammonium salts from some amines. Some examples of various amines which have been converted to SES derivatives and subsequently deprotected are shown in the Table. Interestingly, the pyrrole-SES derivative could be cleaved with commerical 1M TBAF in THF at room temperature, conditions somewhat milder than removal of the SEM group from pyrrole.[3b]

In summary, SES-Cl allows high yield formation of sulfonamides which are quite stable to a number of reagents and can be removed with fluoride ion under conditions compatible with a variety of functional groups.

Sodium β-Trimethylsilylethanesulfonate (2). Vinyltrimethylsilane (25.96 g, 0.259 mol) and t-butyl perbenzoate (1.02 g; 0.005 mol) were combined in 100 mL of methanol at room temperature, and sodium bisulfite (52.60 g; 0.505 mol) in 100 mL of H_2O was slowly added. After addition was complete, the mixture was heated at reflux for 48 h. The reaction mixture was concentrated (caution: peroxides!) and water was removed by azeotroping the mixture three times with methanol on a rotary evaporator. The resulting solid was extracted three times with 250 mL of methanol, which was concentrated to afford a white solid. This material was dried in a vacuum oven at 150°C for 16 h to afford 37.0 g (70%) of 2 of >95% purity.

Table **Synthesis and Cleavage of Sulfonamides 1**

Amine	Sulfonamide 1 (% Yield)	Cleavage (% Yield, time)
	92	82 (29h)
	95	80 (22h)
	92	86 (16h)
	85	93 (40h)
	83	93 (40h)
	86*	85 (9h)
	93*	98 (1.5h)**
	93	91 (9h)
	88	89 (24h)
	93	87 (10h)
	95	90 (40h)
	94	83 (40h)

*NaH used as base
**Tetrabutylammonium fluoride (1M in THF) used for cleavage

β-Trimethylsilylethanesulfonyl Chloride (3). Sodium salt 2 (16.8 g, 0.08 mol) was suspended in 50 mL of carbon tetrachloride and phosphorous pentachloride (51.3 g, 0.247 mol) was added in portions over 15 min, during which time an exothermic reaction occurred. The mixture was stirred at room temperature for 1.5 h, was carefully poured into 30 mL of ice water, and was extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ (100 mL), dried (Na_2SO_4), and concentrated to afford a yellow oil which was distilled (60°C/0.1 mm) to afford 10 g (60%) of SES-Cl (3).

General Procedure for Preparation of Amine SES Derivatives. A primary or secondary amine (1.93 mmol) and triethyl amine (1.5 mL) in 2 mL of dry DMF at 0°C was treated dropwise with SES-Cl (3, 0.58 g, 2.89 mmol) in 1.5 mL of DMF over 15 min. The reaction mixture was stirred at 0°C for 1.5 h, poured into water and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Crude sulfonamide 1 was purified by chromatography on silica gel. Yields of purified products are listed in the *Table*.

General Procedure for Sulfonamide Cleavage. CsF (0.30 g, 1.96 mmol)[6] and a sulfonamide 1 (0.61 mmol) were diluted with 1.0 mL of dry DMF, and the mixture was heated at 95°C until TLC indicated the disappearance of starting material (9-40 h). Methanol (0.5 mL) was added, and the mixture was concentrated *in vacuo*. The residue was diluted with 5 mL of ether, filtered, and evaporated. The crude amine was usually purified by chromatography on silica gel (see *Table* for yields).

Acknowledgment. This research was supported by NIH grant CA-36023.

References and Notes

1. Greene, T. W. "Protective Groups in Organic Synthesis," Wiley-Interscience: New York, NY, 1981.
2. The p-methylbenzylsulfonamide group (PMS) was recently developed and is removable with liquid HF: Fukuda, T.; Kitada, C.; Fujino, M. *J. Chem. Soc., Chem. Commun.* 1978, 220.
3. For other N-protecting groups which are removed by a related type of fragmentation see: a) (TEOC) Carpino, L. A.; Tsao, J.-H. *J. Chem. Soc., Chem. Commun.* 1978, 358. b) (SEM) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* 1984, 49, 203.
4. Sulfonate salt 2 has previously been prepared from sodium bisulfite and vinyltrimethylsilane using $NaNO_2/NaNO_3$ as the radical initiator (Tiers, G. V. D., US patent 3,141,898 (1964) [*CA*, 61, P9527c]). In our hands less than 15% of 2 could be obtained by this method. The use of t-butyl perbenzoate is based upon: Harman, D., US patent 2,504,411 (1950) [*CA*, 44, P5897f].
5. We have also prepared 3 from β-trimethylsilylethylmagnesium chloride and sulfuryl chloride in 50% yield, although this procedure is more expensive.
6. Cesium fluoride is very hygroscopic and appropriate precautions should be taken to exclude water.

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