Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

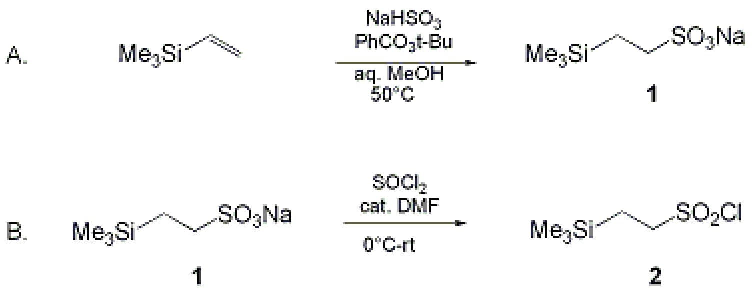
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.075.0161

Organic Syntheses, Coll. Vol. 10, p.707 (2004); Vol. 75, p.161 (1998).

2-TRIMETHYLSILYLETHANESULFONYL CHLORIDE (SES-Cl)

[Ethanesulfonyl chloride, 2-(trimethylsilyl)-]



Submitted by Steven M. Weinreb[1] , Charles E. Chase[1] , Peter Wipf[2] , and Srikanth Venkatraman[2] .
Checked by Geoffrey R. Heintzelman and Robert K. Boeckman, Jr..
Discussion Addendum *Org. Synth.* **2012**, *89*, 34

1. Procedure

Caution! Although tert-butyl perbenzoate is one of the safest peresters/peroxides to handle, one should remain aware of the inherent shock sensitivity and instability of these compounds. Users should exercise appropriate caution during concentration procedures.

A. Sodium β-trimethylsilylethanesulfonate ***(1)*** . To a 500-mL, round-bottomed flask (Note 1) flushed with argon and equipped with a magnetic stirring bar is added vinyltrimethylsilane (28.0 mL, 18.2 g, 181 mmol), methanol (70 mL), and tert-butyl perbenzoate (0.70 mL, 0.70 g, 3.6 mmol) (Note 2),(Note 3),(Note 4). To this solution is added a solution of sodium bisulfite, $NaHSO_3$, (36.1 g, 347 mmol) in 70 mL of water (Note 5),(Note 6),(Note 7). The flask is equipped with a Claisen adapter bearing an immersion thermometer and reflux condenser, and the resulting suspension is heated in an oil bath at 50°C under argon for 48 hr (Note 8). The suspension is concentrated on a rotary evaporator (Note 9) and (Note 10) followed by azeotropic removal of the residual water with methanol (2 × 25 mL). Methanol (200 mL) is added to the resulting white solid, and the resulting suspension is stirred vigorously for 10 min. The mixture is filtered through a pad of Celite into a 500-mL, round-bottomed flask, and the filtrate is concentrated on a rotary evaporator (Note 11). The filter cake is resuspended in 200 mL of methanol and stirred vigorously for 10 min, filtered into the vessel containing the original filtrate, and further concentrated (Note 11). The preceding operations are repeated again on the filter cake. After the final concentration of the combined filtrates (Note 11), the resulting white solid is dried (100°C and 0.1 mm) for 12 hr (Note 12) to give 29.0-31.9 g (∼78-86%) of crude sodium β-trimethylsilylethanesulfonate as white flakes with mp >310°C (Note 13).

B. 2-Trimethylsilylethylsulfonyl chloride ***(2)*** . The 500-mL, round-bottomed flask containing sulfonate salt **1** (29.0 g) is equipped with a magnetic stirring bar and a pressure-equalizing addition funnel fitted at the top with a silicone oil bubbler connected through a rubber septum. The apparatus is purged with argon. The sodium sulfonate is cooled to 0°C in an ice-water bath and the addition funnel is charged with 80 mL (1.10 mol) of thionyl chloride ($SOCl_2$) (Note 14). The slow, dropwise addition of $SOCl_2$ to **1** is accompanied by generation of sulfur dioxide, SO_2 (Note 15). After addition of the $SOCl_2$ is complete, the addition funnel is removed, and the flask is fitted with a rubber septum and bubbler. N,N-Dimethylformamide (DMF) (0.40 mL, 0.38 g, 5.2 mmol) (Note 16) is slowly added via syringe resulting in a substantial increase in the evolution of SO_2 (Note 17). The solution is stirred for an additional 20 min at 0°C during which time evolution of SO_2 ceases. The reaction mixture is warmed to room temperature and stirred overnight, resulting in a white precipitate (Note 18). The reaction flask is fitted with a short path distillation head and excess $SOCl_2$ is distilled off at reduced pressure (Note 19). Twice the resulting white paste is diluted with 50 mL of hexanes and the residual $SOCl_2$ and hexanes are removed under reduced pressure. The resulting pale tan slurry is once again diluted with 50 mL of hexanes and the slurry is filtered through a pad of Celite. The filter cake is washed with an additional 50 mL of hexanes and the combined filtrate and washings are concentrated to afford 23.5 g of a light brown oil (Note 20). Short path distillation of the crude oil using an oil bath as heat source (70-75°C at 0.2 mm) affords 19.3 - 22.0 g (~68-77% yield, or 53-66% overall yield from vinyltrimethylsilane) of the sulfonyl chloride **2** (Note 21) and (Note 22) as a pale tan oil.

2. Notes

1. The submitters employed a 250-mL flask. The checkers found that use of a larger vessel (500 mL) minimized problems associated with bumping during removal of volatile material (see (Note 10) below).
2. Vinyltrimethylsilane was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. Spectrophotometric grade methanol was purchased from Fisher Scientific Company and used without further purification.
4. tert-Butyl perbenzoate (98%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
5. Increasing the concentration of both the methanolic and aqueous solutions results in a 20-30% decrease in the yield of sodium salt **1**.
6. Increasing the ratio of $NaHSO_3$: vinyltrimethylsilane from 1.9:1 to 4:1 results in lower yields of **1**.
7. A fine suspension of $NaHSO_3$ forms immediately. Although the reactants are soluble in 22% (*v/v*) aqueous methanol , no improvement in the yield of **1** is observed.
8. *The reaction should be conducted behind appropriate shielding.* Maintaining the internal temperature of the reaction mixture at 50°C is imperative in order to obtain good yields of **1** [the bp of vinyltrimethylsilane (55°C) should not be exceeded]. Alternatively, the submitters employed a sand bath and the whole assembly was insulated with glass wool. The checkers found that temperature control was more easily achieved with an oil bath and did not employ glass wool insulation.
9. *Caution!* Peroxides may be present. The checkers observed a negative test for peroxides on the filtrate using acidified starch/iodide test paper prior to the final concentration and drying. The checkers recommend testing for peroxides prior to the final concentration and drying.
10. The mixture tends to bump upon concentration.
11. Do not concentrate to dryness. After the third extraction, removing the last 25 mL of methanol on a rotary evaporator at atmospheric pressure and 70°C prevents bumping.
12. The 500-mL flask should be tared in advance, and after breaking up the large chunks of salt **1**, the product can be dried sufficiently in the flask by placing the flask in a vacuum oven, or by applying heat directly to the flask with a sand bath at the same temperature and pressure.
13. NMR spectral data for **1** are as follows: ^{1}H NMR (300 MHz, DMSO-d_6) δ: −0.05 (s, 9 H), 0.76-0.82 (m, 2 H), 2.25-2.31 (m, 2 H) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ: −1.6, 12.1, 46.6 .
14. $SOCl_2$ was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
15. The addition is carried out at a rate that maintains the reaction temperature between 0-10°C (20-30 min). If the temperature is increased beyond this range prior to dissolution of **1**, substantial formation of the sulfonyl anhydride occurs.
16. DMF was purchased from J. T. Baker Inc. and used without further purification.
17. *Caution!* Do not add DMF to the reaction mixture through the pressure equalizing addition funnel.
18. The reaction can be monitored by ^{1}H NMR spectroscopy by removing 0.1-mL aliquots, filtering through glass wool, and diluting with $CDCl_3$. The diagnostic peaks are: δ 3.55-3.63 (m, 2 H) **(2)**; 3.42-3.51 (m, 4 H) (sulfonic anhydride); 2.26-2.35 (m, 2 H) (salt **1**).
19. Using a water aspirator and a warm water bath is sufficient. Recovered $SOCl_2$ can be recycled.
20. ^{1}H NMR spectrum indicates that the crude product is comprised of a mixture of the sulfonyl chloride **2** and the sulfonic anhydride in an 11:1 ratio. Pure sulfonyl chloride **2** is obtained by distillation. Alternatively, the crude sulfonyl chloride can be chromatographed (60 g of silica gel per 1 g of sulfonyl chloride) eluting with hexane to provide pure **2** in equivalent yields.
21. *Caution!* If a sufficiently high vacuum is not maintained, the increased temperature (pot temperatures >100-110°C) required for distillation may cause thermal decomposition of **2** and evolution of hydrogen chloride . The checkers observed that **2** had bp 95-100°C at 0.5 mm. Kugelrohr distillation (85-100°C at 0.3-0.5 mm) of the product in two batches can also be employed.
22. NMR spectral data for **2** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.13 (s, 9 H), 1.30-1.36 (m,

2 H), 3.60-3.66 (m, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: −2.3, 11.7, 63.2 .

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

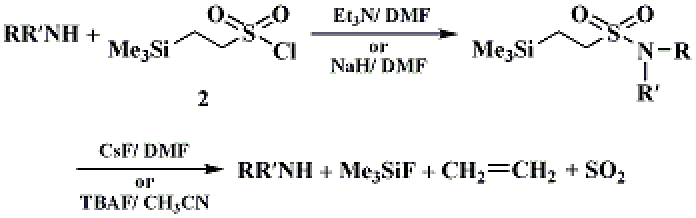
3. Discussion

Sodium sulfonate **1** has previously been prepared from $NaHSO_3$ and vinyltrimethylsilane using sodium nitrite/sodium nitrate as the radical initiator.[3] In the submitters hands this protocol resulted in salt **1** as a pale tan powder in only 15-53% yield if 50% (*v/v*) aqueous methanol is employed as solvent. The yield of **1** could be increased to 63% if 22% (*v/v*) aqueous methanol is employed. An advantage of this method is the elimination of a potentially explosive perester as radical initiator. However, lower yields of **1** and the subsequent lower yield of the sulfonyl chloride **2** (53% for the sulfonylation, 35% overall from vinyltrimethylsilane) make this procedure less desirable than the method presented. The use of tert-butyl perbenzoate as the radical initiator[4] not only provides **1** in a higher yield, but the subsequent conversion to **2** also proceeds in better yield.

Sulfonyl chloride **2** has previously been prepared from salt **1** and phosphorus pentachloride, PCl_5 in carbon tetrachloride, CCl_4 .[5] The disadvantage of this procedure is the difficulty in avoiding sulfonic anhydride formation. Using this method, the ^1H NMR spectrum of the crude reaction mixture prior to distillation indicates a 2-4:1 mixture of **2** and the corresponding sulfonic anhydride. Although the sulfonic anhydride can also serve as an efficient sulfonylating agent (sulfonylation of ammonia resulted in the corresponding sulfonamide in 99% yield), and for most purposes the crude mixture of **2** and the sulfonic anhydride can be used directly, limiting the formation of the sulfonic anhydride is economically desirable. Sulfonyl chloride **2** can be synthesized from β-trimethylsilylethanesulfonic acid (obtained from salt **1** by ion exchange chromatography) and PCl_5 in CCl_4 , although there seems to be no advantage in using the acid.[3] Both sodium salt **1** and the corresponding triethylammonium salt, when treated with triphenylphosphine, PPh_3 , and SO_2Cl_2 , provide **2** in 62% and 79% yields, respectively.[6] Sulfonyl chloride **2** has also been prepared from β-trimethylsilylethylmagnesium chloride and sulfuryl chloride in 50% yield.[3]

The use of a catalytic amount of DMF in $SOCl_2$ here is based on the work of Bosshard.[7] The advantage of this procedure is the ability to minimize the formation of the sulfonic anhydride. At 0°C **1** is reasonably soluble and unreactive in $SOCl_2$, thereby minimizing local high salt concentrations. Upon slow addition of DMF to the mixture, the resulting Vilsmeier-Haack reagent efficiently catalyzes the formation of **2** from **1**. Sulfonyl chloride **2** can be stored in a freezer at −15°C for months without any significant decomposition.

Sulfonyl chloride **2** is used to protect primary and secondary amines as the corresponding sulfonamide.[8] The SES-protected amines are stable compounds that can be readily cleaved by fluoride sources to regenerate the parent amine.



References and Notes

1. Department of Chemistry, The Pennsylvania State University, University Park, PA 16802.
2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

3. Tiers, G. V. **1964**, U.S. Patent 3 141 898; *Chem. Abstr.* **1964**, *61*, P9527c.
4. Harman, D. **1950**, U.S. Patent 2 504 411; *Chem. Abstr.* **1950**, *44*, P5897f.
5. Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099-2102.
6. Huang, J.; Widlanski, T. S. *Tetrahedron Lett.* **1992**, *33*, 2657-2660.
7. Bosshard, H. H; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653-1658.
8. Weinreb, S. M.; Ralbovsky, J. L. "β-Trimethylsilylethanesulfonyl Chloride," in *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., **1995**, Vol. 7, p. 5255-5256.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Trimethylsilylethanesulfonyl chloride:
Ethanesulfonyl chloride, 2-(trimethylsilyl)- (12); (106018-85-3)

tert-Butyl perbenzoate:
Peroxybenzoic acid, tert-butyl ester (8);
Benzenecarboperoxoic acid, 1,1-dimethylethyl ester (9); (614-45-9)

Sodium β-trimethylsilylethanesulfonate:
Ethanesulfonic acid, 2-(trimethylsilyl)-, sodium salt (9); (18143-40-3)

Vinyltrimethylsilane:
Silane, trimethylvinyl- (8);
Silane, ethenyltrimethyl- (9); (754-05-2)

Thionyl chloride: (8, 9); (7719-09-7)

N,N-Dimethylformamide: CANCER SUSPECT AGENT:
Formamide, N,N-dimethyl- (8, 9); (68-12-2)