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Preparation of Bis(β-trimethylsilylethanesulfonyl)imide and Its Use in the Synthesis of Protected Amine Derivatives

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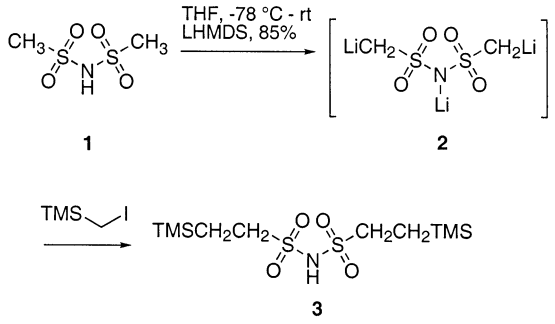
Abstract: Bis(β-trimethylsilylethanesulfonyl)imide (SES_2NH) can be easily prepared in 85% yield by alkylation of the trianion of bismethanesulfonimide with 2 equiv of commerically available (iodomethyl)trimethylsilane. This synthon undergoes effective Mitsunobu alkylation reactions with both primary and secondary alcohols to afford the corresponding bis-SES imides. These imides can be selectively cleaved to the mono-SES-protected amines, and in addition undergo a one-pot cleavage/*N*-alkylation to afford SES derivatives of secondary amines.

In the course of an alkaloid total synthesis involving the use of reactive organometallic reagents, we required a non-carbonyl-containing group to fully protect a primary amine. The choices currently available for such protection are quite limited, and many of the ones that do exist are often hydrolytically and/or oxidatively labile (e.g., imines and silyl derivatives), or require harsh conditions for removal.[1] Imides have been widely used for amine protection, and over the years a number of variations of imide protection, as well as several new Gabriel-type reagents, have been developed.[2] However, bissulfonimides have not previously been utilized for this purpose, probably due in large part to potential problems in installation and cleavage.[3]

Several years ago, we introduced the β-trimethylsilylethanesulfonyl group (SES) for protection of primary and secondary amines.[4] This group can be conveniently introduced using easily prepared β-trimethylsilylethanesulfonyl chloride, and is removed under relatively mild conditions using fluoride ion. It appeared to us that a bis-SES imide might function as a useful protecting group for a primary amine, and in this paper we describe some studies in this area.

SCHEME 1



The plan was to directly introduce this functionality by a Mitsunobu reaction between the parent imide, i.e., bis(β-trimethylsilylethanesulfonyl)imide (SES_2NH), and an alcohol. Numerous examples now exist of Mitsunobu reactions of *N*-acylsulfonamides,[2,5,6] but to our knowledge a simple bissulfonimide has never been used in this process. Our first goal, therefore, was to develop a convenient synthesis of SES_2NH (**3**). The initial approach to this imide was to condense β-trimethylsilylethanesulfonyl chloride[4b] with ammonia or ammonium chloride/base under various conditions, but these experiments gave only poor yields of the desired bissulfonimide. As an alternative, we examined a strategy related to one used by Campbell and Hart to synthesize an SES/Boc mixed imide.[6] Thus, bismethanesulfonimide (**1**), readily prepared by a modification of the literature procedure from mesyl chloride in 79% yield,[7] can be converted to the trianion **2** using 3 equiv of lithium hexamethyldisilazide in THF at −78 °C (Scheme 1). Subsequent addition of 2 equiv of commercially available (iodomethyl)trimethylsilane to the anion, followed by slowly warming to room temperature, afforded the desired sulfonimide **3** in high yield.

We were pleased to find that imide **3** indeed undergoes Mitsunobu reactions with both primary and secondary alcohols to afford bissulfonimides **4** in good yields (Scheme 2). It was found preferable to effect the Mitsunobu reactions with primary alcohols in THF at 50 °C, and those with secondary alcohols in benzene at 80 °C.

This transformation has been effected on a number of substrate alcohols, and the results are summarized in Table 1. We have also examined the stabilty of these bissulfonimides using compound **4c** as a test substrate. The compound was unchanged in 5% aqueous NaOH or 1 N HCl at room temperature overnight. However, upon

(1) For comprehensive reviews of amine protection, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; Chapter 7. Barton, J. W. Protection of N−H Bonds and NR_3. In *Protective Groups in Organic Chemistry*; McOmie, J. F. W., Ed.; Plenum: New York, 1973; pp 43−94.

(2) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285.

(3) The primary application of bissulfonimides to date has been to convert a primary amine nitrogen into a leaving group. See for example: Hendrickson, J. B.; Okano, S.; Bloom, R. K. *J. Org. Chem.* **1969**, *34*, 3434. DeChristopher, P. J.; Adamek, J. P.; Lyon. G. D.; Galante, J. J.; Haffner, H. E.; Boggio, R. J.; Baumgarten, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 2384. DeChristopher, P. J.; Adamek, J. P.; Klein, S. A.; Lyon. G. D.; Baumgarten, R. J. *J. Org. Chem.* **1975**, *40*, 3288. Sorbye, K.; Tauterman, C.; Carlsen, P.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1998**, *9*, 681. Carlsen, P. H. J. *Tetrahedron Lett.* **1998**, *39*, 1799. Rhee, H.; Yoon, D.; Jung, M. E. *Nucleosides Nucleotides* **2000**, *19*, 619.

(4) (a) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099. (b) Weinreb, S. M.; Chase, C. E.; Wipf, P.; Venkatraman, S. *Org. Synth.* **1997**, *75*, 161.

(5) See inter alia: Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172.

(6) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900.

(7) Helferich, B.; Grunert, H. *Chem. Ber.* **1940**, *73*, 1132. Helferich, B.; Flechsig, H. *Chem. Ber.* **1942**, *75*, 532.

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TABLE 1. Conversion of Alcohols to Bis-SES-Protected Amines under Mitsunobu Conditions and Monodeprotection with CsF in Acetonitrile

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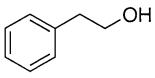
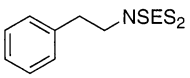
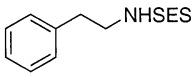
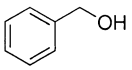
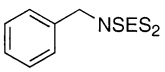
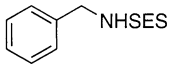
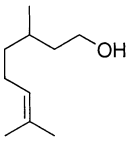
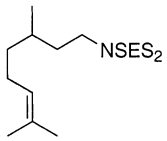
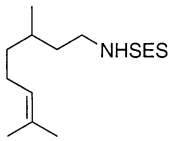
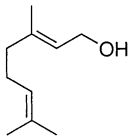
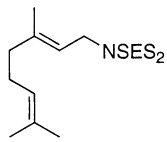
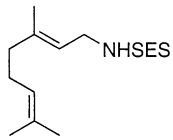
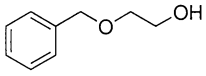
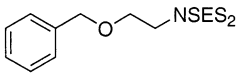
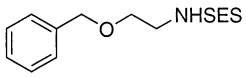
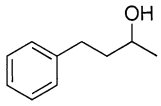
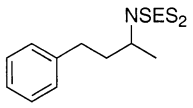
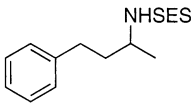
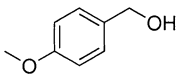
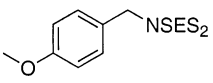
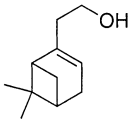
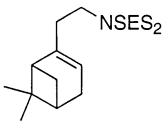
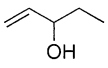
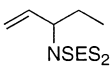
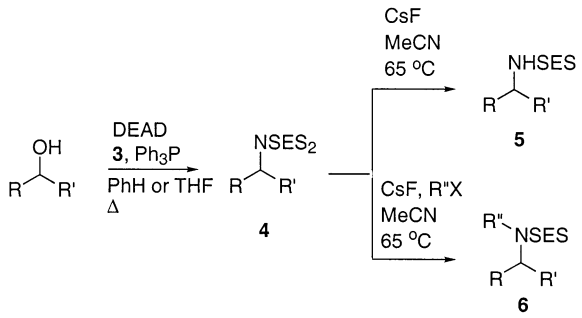
a			84		73
b			59		71
c			83		83
d			76		64
e			85		62
f			68		91
g			74		
h			93		
i			61		

SCHEME 2



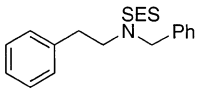
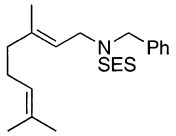
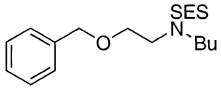
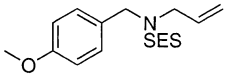
heating **4c** with NaOEt in EtOH, or NaOH in EtOH/H_2O, it was observed that slow cleavage of one of the SES groups occurs.[8] In addition, sulfonimide **4c** is stable to 3 equiv of benzylmagnesium chloride in THF at room temperature overnight.

It is possible to selectively remove one of the SES groups of imides **4** using cesium fluoride in acetonitrile at 65 °C to give the mono-SES derivatives **5** (Scheme 2). Several examples of this monodeprotection reaction have been incorporated into Table 1. It was also found that CsF was more effective for this transformation than is TBAF. However, we have been unable to develop a procedure for fluoride-induced removal of both SES groups of bissulfonimides **4** by a one-pot operation to directly produce the primary amine.

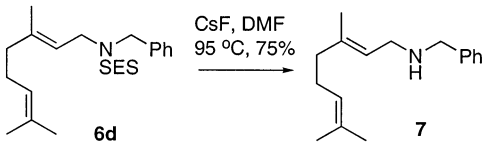
In addition, we have found that bissulfonimides **4** can be used in an efficient one-pot monodeprotection/*N*-alkylation sequence (Scheme 2). Thus, treatment of **4** with CsF in acetonitrile in the presence of an alkyating agent, followed by heating overnight at 65 °C, leads to

(8) We have seen no evidence for nucleophilic displacement of the bissulfonimide moiety under these conditions.[3]

TABLE 2. One-Pot Monodeprotection/*N*-Alkylation of Bis-SES-Protected Amines

bis-SES-protected amine **4**	alkylating agent	SES-protected secondary amine **6**	isolated yield (%)
4a	BnBr		95
4d	BnBr		75
4e	BuI		65
4g	allyl bromide		93

the *N*-alkylated mono-SES derivative **6** in good yield. A few examples of this process are shown in Table 2. If one then exposes the alkylated product **6** to CsF/DMF at a somewhat higher temperature (95 °C), it is then possible to remove the remaining SES group as we have previously reported.[4] For example, alkylated product **6d** can be converted to the secondary amine **7** in 75% yield by this procedure (eq 1).



(1)

In summary, we have developed a short, efficient synthesis of **3** in two steps in 67% overall yield from mesyl chloride. It has been shown that synthon **3** is effective in Mitsunobu reactions with both primary and secondary alcohols to produce non-carbonyl-containing bis-SES-protected amine derivatives **4**. In addition, these bissulfonimides can be selectively converted to the corresponding mono-SES-protected compounds **5** or can be deprotected and *N*-alkylated in situ in a one-pot procedure to give mono-SES derivatives of secondary amines **6**. We believe that the chemistry described here therefore extends the scope and utility of SES protection of amines.[4]

Experimental Section

General Procedures. Reactions were run under an atmosphere of argon. Silica gel 60 (70−230 mesh) was used for flash column chromatography. THF and benzene were distilled from sodium/benzophenone ketyl. Acetonitrile was distilled from calcium hydride.

Bismethanesulfonimide (1).[7] To a solution of ammonium chloride (1.38 g, 25.8 mmol) and water (16 mL) at 0 °C was slowly added a solution of mesyl chloride (5.00 mL, 64.6 mmol) in acetone (6 mL). Aqueous sodium hydroxide (2.6 mL, 10 M) was added slowly, and the mixture was stirred until acidic to litmus paper. Sodium hydroxide (2.6 mL, 10 M in water) was again added slowly, and the mixture was again stirred until acidic to litmus paper. The mixture was allowed to warm to rt, two more portions of sodium hydroxide (2.6 mL, 10 M in water) were added, and the mixture was again stirred until acidic. Additional sodium hydroxide was added until the mixture remained basic. Concentrated hydrochloric acid was then added until the mixture was strongly acidic. The mixture was extracted twice with ethyl acetate (30 mL) and twice with methylene chloride (30 mL). The combined organic layers were dried (Mg_2SO_4) and concentrated to give $HNMs_2$ (3.51 g, 79%) as a pale yellow solid sufficiently pure for use in the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 6H), 7.68 (br, 1H).

Bis(*β*-trimethylsilylethanesulfonyl)imide (3). To a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.89 mL, 8.96 mmol) in dry THF (6 mL) at −78 °C was added *n*-BuLi (3.69 mL, 2.43 M solution in hexane) over 5 min. The resulting mixture was stirred for 15 min, and a solution of **1** (500 mg, 2.89 mmol) in THF (6 mL) was added over 10 min. After the resulting solution was stirred for 5 min, a solution of (iodomethyl)trimethylsilane (855 μL, 5.78 mmol, used as received) in THF (6 mL) was added. The solution was allowed to warm from −78 °C to rt overnight, and was poured into 5% aqueous HCl solution (30 mL). The aqueous layer was extracted four times with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated aqueous sodium bisulfite solution and brine, dried over $MgSO_4$, and concentrated in vacuo to afford **3** as an off-white solid (849 mg, 85%) which was sufficiently pure for use in subsequent reactions: mp 144−145 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.36 (m, 4H), 1.09 (m, 4H), 0.07 (s, 18H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 52.5, 10.4, 1.8; HRMS ($C_{10}H_{27}NO_4S_2Si_2$) *m*/*z* calcd 344.0842 ($M - H^+$), found 344.0812. An analytical sample was prepared by flash silica gel chromatography (hexanes/ethyl acetate/acetic acid, 10/9/1). Anal. Calcd for $C_{10}H_{27}NO_4S_2Si_2$: C, 34.75; H, 7.87; N, 4.05. Found: C, 35.32; H, 8.04; N, 3.98.

General Procedure for Mitsunobu Reactions of 3 with Primary Alcohols. To a solution of **3** (200 mg, 0.579 mmol) and triphenylphosphine (304 mg, 1.157 mmol) in dry THF (6 mL) was added the alcohol (0.526 mmol). After the resulting solution was stirred for 5 min, DEAD (166 μL, 1.052 mmol) was added dropwise. After the solution was stirred overnight at 50 °C, silica gel was added and the mixture was concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 100/0 → 25/1) to afford the desired Mitsunobu products **4**. The results are summarized in Table 1.

General Procedure for Mitsunobu Reactions of 3 with Secondary Alcohols. To a solution of **3** (200 mg, 0.579 mmol) and triphenylphosphine (500 mg, 1.906 mmol) in dry benzene (10 mL) was added the alcohol (0.526 mmol). After the resulting solution was stirred for 5 min, DEAD (273 μL, 1.734 mmol) was added dropwise. After the solution was stirred overnight at 80 °C, silica gel was added and the mixture was concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 100/0 → 25/1) to afford the desired Mitsunobu products **4**. The results are summarized in Table 1.

General Procedure for Monodeprotection of Bis-SES-Protected Amines. To cesium fluoride (186 mg, 1.22 mmol), which had been heated at 100 °C under vacuum for 2 h, was added a solution of bissulfonimide **4** (0.245 mmol) in acetonitrile (3 mL). The suspension was heated and stirred at 65 °C overnight. The mixture was then diluted with ether (6 mL) and filtered through a pad of Celite. After concentration of the solution the residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 9/1) to afford the mono-SES-protected amine **5**. The results are summarized in Table 1.

Typical Procedure for One-Pot Monodeprotection/*N*-Alkylation of Bis-SES-Protected Amines. 2-(Trimethylsilanyl)ethanesulfonic Acid Benzyl(3,7-dimethylocta-2,6-dienyl)amide (6d). To cesium fluoride (327 mg, 0.432 mmol), which had been heated at 100 °C under high vacuum for 2 h, was added a solution of compound **5d** (208 mg, 0.432 mmol) and benzyl bromide (81.0 μL, 0.475 mmol) in acetonitrile (7 mL). The suspension was heated and stirred at 65 °C overnight. The mixture was then diluted with ether and filtered through a pad

of Celite. After concentration of the filtrate, the residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 9/1) to afford amine **6d** as a pale yellow oil (127 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.23 (m, 5H), 5.16 (m, 1H), 5.04 (m, 1H), 4.36 (s, 2H), 3.76 (d, J = 7.1 Hz, 2H), 2.85 (m, 2H), 2.04−1.99 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.48 (s, 3H), 0.99 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 136.9, 132.0, 129.0, 128.7, 127.9, 123.9, 118.9, 50.4, 49.7, 44.2, 39.8, 26.5, 25.9 17.9, 16.3, 10.5, −1.8; HRMS ($C_{22}H_{37}NO_2$-SSi) m/z calcd 430.2212 (M + Na^+), found 430.2220.

Benzyl(3,7-dimethylocta-2,6-dienyl)amine (7). To cesium fluoride (70 mg, 0.460 mmol) was added a solution of compound **6d** (37.5 mg, 0.092 mmol) in DMF (3 mL). The suspension was heated at 95 °C and stirred overnight. The mixture was then diluted with methanol (4 mL), concentrated, extracted with ether (3 × 3 mL), and filtered through a pad of Celite. After concentration of the mixture the residue was purified by flash silica gel chromatography (hexanes/ethyl acetate/triethylamine, 3/16/1) to give secondary amine **7** (16.7 mg, 75%) as a dark yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26−7.18 (m, 5H), 5.23 (m, 1H), 5.03 (m, 1H), 3.72 (s, 2H), 3.19 (d, J = 6.6 Hz, 2H), 2.01−1.81 (m, 5H), 1.61 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 138.6, 131.9, 128.7, 128.4, 127.3, 124.5, 123.2, 53.5, 46.7, 39.9, 26.7, 25.9, 17.9, 16.53; HRMS ($C_{17}H_{25}N$) m/z calcd 244.2065 (M + H^+), found 244.2055.

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Supporting Information Available: Copies of proton and carbon NMR spectra and other spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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