

Selective Deprotection of Methanesulfonamides to Amines

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ABSTRACT

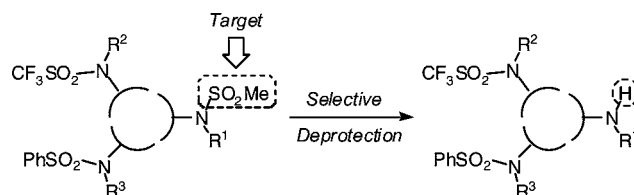


Methanesulfonamides were deprotected to their parent amines via deprotonation and oxygenation with O₂ (g), even in the presence of other traditional sulfonamides.

Sulfonamides are a stable derivative of amines, and they are frequently used as versatile intermediates and for the protection of amines in organic synthesis. However, their stability is not without its drawbacks, because once their deprotection giving back to the parent amines is desired, available methods are limited and often require harsh conditions.¹ To circumvent this problem, new sulfonamides carrying an extra functional group that facilitates the release of the amine portion have been devised.² On the other hand, searching for a new method that serves the selective and efficient deprotection of traditional sulfonamides should not be overlooked.³ In this paper, we report a new entry to the latter approach, which, for the first time, enables the

selective removal of a methanesulfonyl (Ms) group in the presence of other representative sulfonamides as illustrated in Scheme 1.

Scheme 1. Deprotection of a Ms Group



Lithiated methanesulfonamide **2**, generated from **1** with (*n*-)BuLi in a standard manner,⁴ is fairly stable under an inert atmosphere (Scheme 2, path a). However, its exposure to oxygen gas and an aqueous workup afforded the parent amine **3** in a moderated yield (path b).⁵ The yield of **3** was improved to a satisfactory level (70–71%) when excess BuLi (2–3

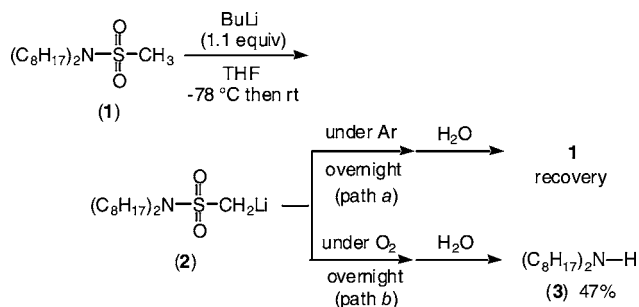
(1) For protection of amines as sulfonamides, see: Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, NJ, 2007; pp 851–868.

(2) Examples of these sulfonamides (and reagents necessary for their deprotection) are as follows. *o*-Anisylsulfonamide (*i*-PrMgCl under Ni catalysis): (a) Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 892–8942-(Trimethylsilyl)ethanesulfonamide (F⁻): (b) Ribiere, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249–2269. (c) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099–2102 *o*-Nitrobenzenesulfonamide (RS⁻): (d) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.

(3) For the latest reports along this line, see: (a) Nandi, P.; Redko, M. Y.; Petersen, K.; Dye, J. L.; Lefenfeld, M.; Vogt, P. F.; Jackson, J. E. *Org. Lett.* **2008**, *10*, 5441–5444. (b) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503–506. In certain cases, our present method and the method of the latter reference could be used complementarily.

(4) (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, UK, 1993. (b) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951–6984. (c) Krief, A. *Tetrahedron* **1980**, *36*, 2531–2640.

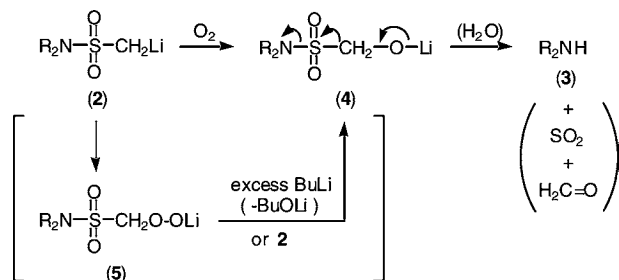
Scheme 2. Lithiation and Oxygenation of Sulfonamide 1



equiv) was used under the conditions described in Table 1 (entries 1 and 2).

Scheme 3 shows the proposed mechanism of this reaction. The oxygenation of lithiated methanesulfonamide **2** with

Scheme 3. Proposed Reaction Course (R = C₈H₁₇)



oxygen generates intermediate **4**, which then collapses to amine **3**.⁶ The presence of excess BuLi as described above might cleave the peroxide bond in the primary intermediate **5**,⁷ which remains unchanged or oxidizes the resulting amine to decrease the yield of **3**. Other reagents for oxidation of carbanions such as MoO₅·py·HMPA (MoOPH)^{8a,b} and the Davis oxaziridine^{8c,d} were far less effective than oxygen gas, probably because of the concomitant oxidation of the released amine.

(5) Deprotection of aryl mesylates to phenols with LDA *under argon* was reported, but its reaction course has not been proposed; Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513–1514. This report also mentions one example for deprotection of methanesulfonamide derived from a reactive amine.

(6) To the contrary, this mechanism is utilized for conversion of α -sulfonylcarbanions to ketones. Reference, 4a pp 338–340. Doye, S.; Hotopp, T.; Wartchow, R.; Winterfeldt, E. *Chem.—Eur. J.* **1998**, *4*, 1480–1488.

(7) For a synthetic application of aerial oxidation of carbanions reported from our laboratory, see: (a) Nobe, Y.; Arayama, K.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 18006–18007. Excess organometallic reagent was necessary also in this reaction to cleave the resulting peroxide bond. For favorable effect of co-oxidation with extra organometallic reagent, see: (b) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, UK, 1995; p 198.

(8) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196. (b) Vedejs, E. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 6, pp 3825–3826. (c) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774–1775. (d) Chen, B.-C. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 6, pp 4054–4057.

Table 1 lists more examples of this deprotection.⁹ During the deprotection of **6–11** and **15**, several functional groups

Table 1. Deprotection of Various Sulfonamides to Their Parent Amines

entry	sulfonamide	BuLi (equiv)	LDA ^a (equiv)	ox. ^b	yield of amine (%) ^c
1		(1)	2		71
2		(1)	3		70
3		(1)	3	air	72
4		(1)		3	71
5		(6)	2		73
6		(6)	3		83
7		(6)		3	76
8		(7)	3		79
9		(8)	3		68
10		(9)	3		72
11		(10)	3		73
12		(11)	3		60 ^d
13		(12)	3		72
14		(13)	2		68 ^d
15		(13)	3		75 ^d
16		(13)	3	air	72 ^d
17		(14)	3		69 ^d
18		(15)	3		72
19		(15)		3	73

^a LDA was used instead of BuLi. ^b Method of oxidation. Unless otherwise stated, O₂ gas was used. Air refers to dry air in place of O₂. ^c Unless otherwise stated, the amines were isolated by flash column chromatography. ^d These amines were isolated by acid–base extraction according to ref 10.

such as olefins, an ether, chlorides, and aromatic rings, the latter two of which are prone to reduction by conventional methods with dissolving metals, remained untouched (entries 5–12, 18 and 19). Sulfonamides derived from sterically hindered amines often resist deprotection particularly in alkaline or acidic hydrolysis, as their amide group is hardly

accessible by external reagents. However, as the present deprotection is initiated at the remote position from the amine moiety (see Scheme 3), followed by the cascade steps ending with the intramolecular scission of an S–N bond, sterically hindered sulfonamides such as **12–15** were readily deprotected as illustrated in entries 13–19. As for the equivalents of BuLi, 3 equiv of this base generally gave better results (cf. entries 5 and 6, or 14 and 15), and most experiments were performed accordingly. A couple of modifications making this method more flexible are also shown in Table 1 and should be emphasized. First, the use of LDA in place of BuLi resulted in a similar outcome as shown in entries 4, 7, and 19.¹¹ Second, a more practical alternative to oxygen gas is dry air, which did not lower the yield of the amines (entries 3 and 16).

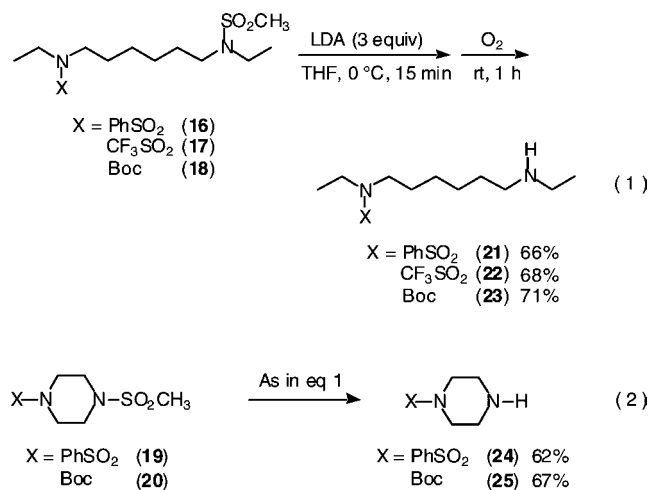
A more important aspect of this reaction is its application to selective deprotection of a methanesulfonyl group in the

(9) **Typical procedures for the demesylation of *N,N*-diocylmethanesulfonamide (1) to diocylamine (3): With BuLi (2 equiv) and O₂ (entry 1, Table 1):** To a stirred solution of *N,N*-diocylmethanesulfonamide (**1**) (63.9 mg, 0.200 mmol) in THF (3 mL) was added BuLi (1.58 M in hexane, 0.253 mL, 0.400 mmol) at 0 °C under argon. After being stirred for 15 min at that temperature, the argon inlet tube was replaced by a balloon filled with oxygen gas. After being stirred for 1 h at room temperature under an O₂ atmosphere, the reaction was terminated by the addition of water (0.15 mL). The resulting heterogeneous mixture was filtered through Celite with the aid of CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated in vacuo to give a crude product, which was chromatographed on Chromatorex “NH” (DM1020, 100–200 mesh, Fuji Silysia Chemical Ltd., Japan) with ca. 0.5% *t*-BuNH₂ in hexane to afford the title compound (34.3 mg, 71%) as an oil. **With BuLi (3 equiv) and O₂ (entry 2):** Sulfonamide **1** (63.9 mg, 0.200 mmol) and BuLi (1.57 M in hexane, 0.382 mL, 0.600 mmol) under the same operations as above afforded the title compound (33.6 mg, 70%) as an oil. **With BuLi (3 equiv) and air (entry 3):** To a stirred solution of **1** (32.0 mg, 0.100 mmol) in THF (2 mL) was added BuLi (1.63 M in hexane, 0.184 mL, 0.300 mmol) at 0 °C under argon. After being stirred for 15 min at that temperature, the argon inlet tube was replaced by a balloon filled with air dried through drying agent, Sicapent (Merck). After being stirred for 1 h at room temperature under dry air, the reaction was terminated by the addition of water (0.15 mL). The same workup and purification as above afforded the title compound (17.4 mg, 72%) as an oil. **With LDA (3 equiv) and O₂ (entry 4):** To a stirred solution of **1** (32.0 mg, 0.100 mmol) in THF (1 mL) was added LDA (prepared from BuLi (1.63 M in hexane, 0.184 mL, 0.300 mmol) and diisopropylamine (30.4 mg, 0.300 mmol) in THF (1 mL)) at 0 °C under argon. After being stirred for 15 min at that temperature, the argon inlet tube was replaced by a balloon filled with oxygen gas. After being stirred for 1 h at room temperature under an O₂ atmosphere, the reaction was terminated by the addition of water (0.15 mL). The same workup and purification as above afforded the title compound (17.2 mg, 71%) as an oil. ¹H NMR δ 0.86 (t, *J* = 6.9 Hz, 6H), 0.88 (br s, 1H, NH), 1.16–1.40 (m, 20H), 1.46 (quintet, *J* = 6.9 Hz, 4H), 2.56 (t, *J* = 7.2 Hz, 4H). ¹³C NMR δ 14.07, 22.64, 27.41, 29.25, 29.53, 30.19, 31.81, 50.16. IR (neat) 3276 (NH), 2925, 2854, 2809, 1467, 1378, 1131, 722 cm⁻¹. These spectral properties and TLC mobility were in agreement with those of a commercially available authentic sample. **Caution:** Although hydroperoxides were not detected in our hands, care must be taken particularly in a large-scale deprotection. For safe operation, see the Supporting Information of ref. 7a. Attempted deprotection of methanesulfonamides derived from primary amines was unsuccessful, due probably to oxygenation of the nitrogen atom of the resulting *C,N*-dilithiated amide.

(10) Escoubet, S.; Gastaldi, S.; Timokhin, V. I.; Bertrand, M. P.; Siri, D. *J. Am. Chem. Soc.* **2004**, *126*, 12343–12352.

(11) Excess LDA proved necessary to perform the deprotection in good yields. It would play the same role as the excess BuLi does.

presence of another sulfonyl group such as a benzene- or trifluoromethanesulfonyl group lacking an α-sulfonyl hydrogen. Thus, when doubly protected diamines **16–20** were subjected to the above deprotection (eqs 1 and 2), mono-protected diamines **21–25** were obtained in comparable yields to those of Table 1. Compatibility with the *tert*-butyloxycarbonyl (Boc) group, a typical *N*-protecting group of a different type, is also shown. In these reactions, a less nucleophilic LDA, rather than BuLi, proved to be more suitable.¹² To the best of our knowledge, the differentiation between sulfonyl groups on the basis of the presence or absence of their α-hydrogen(s) has not been established.



In conclusion, we reported here an efficient deprotection of methanesulfonamides to their parent amines even when they are sterically hindered. Its reaction mechanism enables the deprotection of methanesulfonamide in the presence of other sulfonamides lacking α hydrogens, which provides a new criterion of selection.

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Supporting Information Available: Physical properties of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) It is known that triflamides are susceptible to the attack of BuLi. For example, see: Bozcec-Ogor, S.; Salou-Guiziu, V.; Yaouanc, J. J.; Handel, H. *Tetrahedron Lett.* **1995**, *36*, 6063–6066.