Pergamon

Tetrahedron Letters 43 (2002) 8479–8483

TETRAHEDRON LETTERS

A mild, convenient synthesis of sulfinic acid salts and sulfonamides from alkyl and aryl halides

Jeremy M. Baskin and Zhaoyin Wang*

Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, PO Box 1005, Pointe-Claire/Dorval, Quebec, Canada H9R 4P8

Received 9 September 2002; accepted 20 September 2002

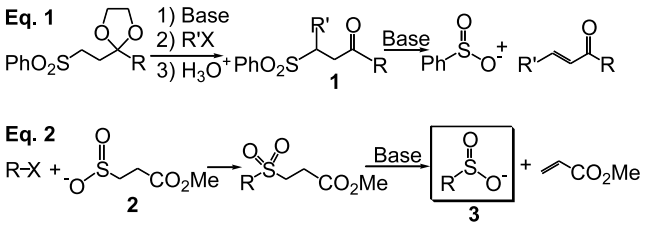
Abstract—A general, mild, and convenient method has been developed for the synthesis of various alkyl and aryl sulfinic acid salts and sulfonamides from the corresponding halides. Key to the success of this methodology is the design and facile synthesis of sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS), a reagent that serves to introduce the protected sulfinate moiety directly to the substrate, thus avoiding the use of oxidizing and other harsh reaction conditions such as organolithium or Grignard reagents. Many functional groups, as well as heterocycles, are tolerated in the sequence. © 2002 Published by Elsevier Science Ltd.

The sulfonamide group is found in many therapeutic agents, including drugs for the treatment of bacterial and viral infections.[1] More recently, it has been found to be a key constituent of a new class of cyclooxygenase inhibitors such as Celecoxib[2] and Valdecoxib.[3] The most commonly used synthetic method to make sulfonamides involves the reaction of ammonia with sulfonyl chlorides.[4] Although the method is sufficient, its utility is limited to the availability of sulfonyl chlorides, which can only be prepared under rather harsh oxidizing or strong Lewis acidic conditions. Alternatively, sulfonamides can be obtained by reacting sulfinic acid salts with an electrophilic nitrogen source such as hydroxylamine-*O*-sulfonic acid[5] or bis(2,2,2-trichloroethyl)-azodicarboxylate.[6] The latter method is particularly attractive due to the mildness of the reaction conditions and the possibility to introduce the sulfonamide group at later stage of a multi-step synthesis. However, the success of the process lies in the availability of the required sulfinic acid salt. The existing synthetic approaches to sulfinic acid salts either involve the use of organolithium or Grignard reagents, which are incompatible with a host of functional groups, or involve tedious, multi-step syntheses.[7] Furthermore, the purity of the sulfinates is not sufficiently high due to an inability to isolate the hygroscopic salt.

Here, we report a novel, convenient strategy for the synthesis of sulfinic acid salts from alkyl and aryl halides under very mild conditions, and for their subsequent conversion to sulfonamides. For the synthesis of alkyl sulfonamides, the entire process can be carried out in a one-pot operation.

β-Phenylsulfonylketones **1** have been used as a template to prepare a variety of β-substituted enones.[8] The key step of the process is the β-elimination of the phenylsulfinate after an appropriate substituent is introduced through an alkylation reaction of the intermediate sulfone anion (Scheme 1, Eq. (1)). Based on the same principle, we envisioned that a sulfinate derivative such as sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS) **2** can serve as a donor for the sulfinate moiety through a simple alkylation and subsequently be removed by a β-elimination (Scheme 1, Eq. (2)). The reaction of the resulting sulfinate **3** with an electrophilic nitrogen source would provide an easy access to various sulfonamides.

We began our study by designing a synthesis of SMOPS, whose only known synthesis is unsuitable for its isolation and characterization, due to contamination

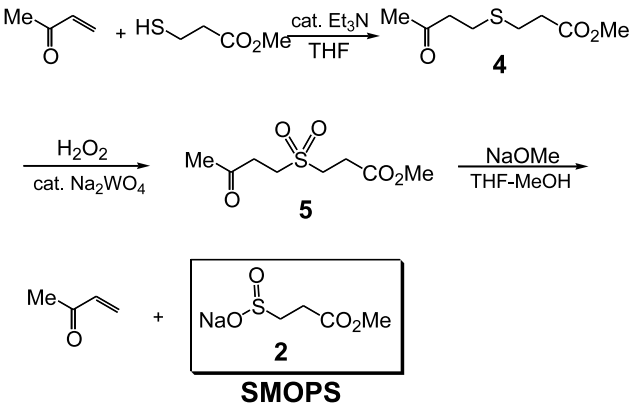


Scheme 1.

* Corresponding author. Tel.: +1-514-428-3235; fax: +1-514-428-4900; e-mail: zhaoyin_wang@merck.com

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02073-7

of the product with borate salts and benzothiazole, though the synthesis is useful for providing SMOPS as an intermediate for further reactions.[7g] A new and practical preparation of SMOPS is shown in Scheme 2. Conjugate addition of methyl 3-mercaptopropionate to methyl vinyl ketone, followed by Na_2WO_4-catalyzed oxidation with H_2O_2, generated sulfone **5**. β-Elimination of **5** was achieved by treatment with 1 equiv. of NaOMe in a mixture of THF and MeOH. Thus, multigram quantities of SMOPS can be isolated in near-quantitative yield from sulfone **5** as a stable white solid simply by evaporation of the solvent under reduced pressure.

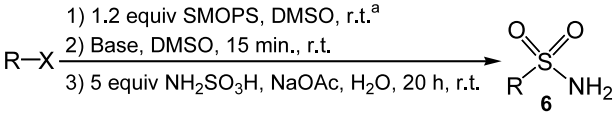


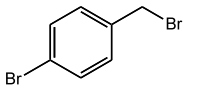
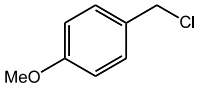
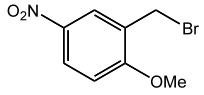
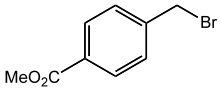
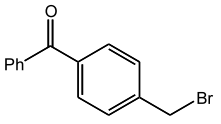
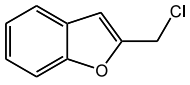
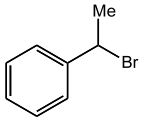
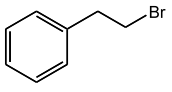
Scheme 2.

With SMOPS in hand, a one-pot synthesis of alkyl sulfonamides from alkyl halides was explored. In particular, the solvent must be compatible with all three steps in the sequence—alkylation, β-elimination, and sulfonamide formation. After screening a number of solvents, DMSO was found to suit the need for the one-pot operation. In addition to promoting the alkylation reaction[9] due to its highly polar, aprotic nature, DMSO also provides a more homogeneous reaction medium for the sulfonamide formation step since many alkyl and aryl sulfinic acid sodium salts have limited solubility in water, which is the solvent in the original procedure involving hydroxylamine-*O*-sulfonic acid as the electrophilic nitrogen source. The second step, the β-elimination of the resulting intermediate sulfone, could be accomplished by treatment either with NaOMe or 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). Thus, a diverse range of alkyl sulfonamides **6a**–**h** was generated, using a one-pot procedure, with satisfactory yields (Table 1). The intermediate sulfones from alkylation of SMOPS with halides in Table 1 can be obtained in >95% yields for all cases after a simple aqueous workup. Additionally, to isolate the intermediate sodium sulfinates, the resulting sulfones can be treated with 1 equiv. NaOMe in a THF/MeOH mixture. The corresponding sodium sulfinates can be isolated quantitatively by evaporation of the solvent under reduced pressure, an identical procedure to the last step in the synthesis of SMOPS.

This new approach to alkyl sulfonamide formation offers several advantages over the traditional methods

Table 1. One-pot formation of alkyl sulfonamides



entry	R—X	base	% yield[b]
a		NaOMe	69
b		NaOMe	85
c		NaOMe	85
d		NaOMe	71
e		DBU	46
f		DBU	45
g		NaOMe	41
h		NaOMe	50

[a] Reaction time ranges from 10 min to 24h depending on the nature of the halides. [b] Isolated yield from alkyl halide.

for the synthesis of alkyl sulfonamides. First, no oxidizing or reducing reagents are involved. The sulfinate moiety is transferred from SMOPS with sulfur at the required oxidation state. Second, many functional groups, such as esters, ketones, and nitro groups are tolerated throughout the entire sequence. It is noteworthy that a secondary bromide can be converted to the corresponding sulfonamide in an acceptable yield, as well as an unactivated primary bromide. (Table 1, entries g–h).

We then investigated the synthesis of aryl sulfonamides using the same strategy. Because the nucleophilic displacement of aryl halides by SMOPS requires an excess both of Cu(I) salts and SMOPS, isolation of the intermediate sulfones **7a**–**f** was necessary in order to minimize the potential complications to the subsequent two steps. The intermediate sulfones **7a**–**f** were prepared in good yields from aryl iodides or bromides by using 3 equiv. SMOPS and CuI in DMSO at 110°C (5 equiv. of

SMOPS and CuI in the case of aryl bromides).[10] Subjecting the sulfones **7a–f** to the same conditions as those for alkyl substrates provided various aryl sulfonamides **8a–f** (Table 2). In general, the formation of sulfonamides proceeded well, with only a couple of exceptions. For 4-acetyl-iodobenzene, none of the desired sulfonamide **8e** was obtained; we speculate that the electron-withdrawing nature of the 4-acetyl substituent reduces the nucleophilicity of the sulfinate intermediate, whose existence was confirmed by ^{1}H NMR, for the following substitution reaction on NH_2OSO_3H. As well, the methylthio group is not compatible with NH_2OSO_3H, as the oxidation of methylthio group to a sulfoxide was observed and none of the sulfonamide **8f** was formed. In this case, the problem may be avoided by using other milder reagents such as bis(2,2,2-trichloroethyl)azodicarboxylate.[6] Nevertheless, the method introduced here has proven to be very useful for molecules with many sensitive groups such as hydroxyls, esters, and halogens. Particularly noteworthy is the success of this methodology in the formation of **8c**, which demonstrates the applicability of this approach toward introduction of a sulfonamide group in a highly functionalized molecule.

Similar to alkyl sulfinates, aryl sulfinates can be isolated by treatment of the intermediate sulfones **7a–f** by 1 equiv. NaOMe in a THF/MeOH mixture followed by evaporation of the solvent under reduced pressure. This method for the synthesis of sodium sulfinates offers obvious advantages over the existing ones[11] and provides an easy access to a variety of sulfinates, which are very useful synthetic intermediates.

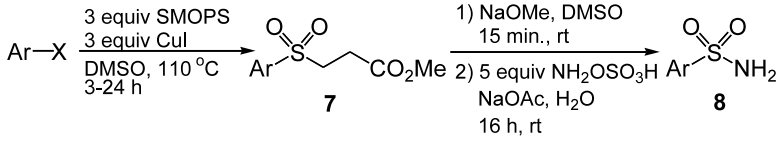
In summary, we have developed a simple, convenient method for synthesis of alkyl and aryl sulfonamides. Additionally, this chemistry also provides a practical route to sodium salts of various alkyl and aryl sulfinic acids, which are otherwise laborious to obtain. The benefits of this novel process include the following: (1) the easy availability of starting materials, (2) a convenient procedure (one-pot for alkyl sulfonamides), and (3) the absence of oxidizing agents, organolithium or Grignard reagents, and strong Lewis acids, rendering the process compatible with many functional groups.

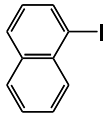
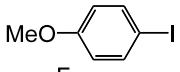
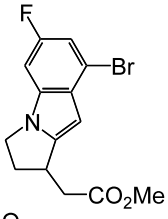
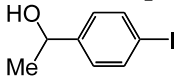
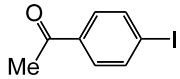
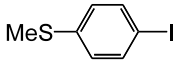
Experimental

Formation of SMOPS ***2***

To a solution of methyl vinyl ketone (18.3 mL, 220 mmol) and methyl 3-mercaptopropionate (22.2 mL, 200 mmol) in THF (300 mL) was added Et_3N (2.8 mL, 20 mmol). After heating for 4.5 h at 50°C under a nitrogen

Table 2. Formation of aryl sulfonamides



entry	Ar—X	% Yields[a] 7	8[b]
a		93	67
b		62	92
c		44	54
d		47	50
e		64	0
f		76	0

[a] All yields are isolated yields. [b] Isolated yelds from **7**

atmosphere, the solvent was removed under reduced pressure to yield the sulfide **4** (37.5 g, 99%). The sulfide **4** (35.5 g, 187 mmol) was placed in a 500 mL, three-necked round-bottom flask, along with $Na_2WO_4 \cdot 2H_20$ (3.1 g, 9.3 mmol), Aliquat® 336 (tricaprylylmethylammonium chloride, 3.8 g, 9.3 mmol), EtOAc (100 mL), cyclohexane (50 mL) and H_2O (20 mL) under a nitrogen atmosphere. The reaction mixture was then heated to 60°C and 30% aqueous solution of H_2O_2 (77 mL, 655 mmol) was added dropwise over a 1 h period. After stirring for 4 h at 60°C, the reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and filtered through a pad of silica. After concentration under reduced pressure, the crude product was stirred as a suspension in a mixture of EtOAc (25 mL) and hexanes (25 mL) overnight and collected by filtration to yield sulfone **5** (29.8 g, 72%). Sulfone **5** (22.65 g, 102 mmol) was dissolved in a mixture of THF (1100 mL) and MeOH (225 mL) at rt, and NaOMe (23.2 mL of a 25% solution in MeOH, 102 mmol) was added dropwise while stirring. After stirring for 15 min, the solvent was removed by evaporation under reduced pressure. The crude product was stirred as a suspension in a mixture of ether (150 mL), EtOAc (10 mL), and MeOH (10 mL) for 30 min and collected by suction filtration to yield the titled sulfinate **2** as a white powder (16.27 g, 92%, or 66% overall yield from methyl 3-mercaptopropionate). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.57 (s, 3H), 2.43 (t, 2H), 2.05 (t, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.96, 56.01, 51.22, 25.96. MS (APCI, neg.) m/z: 151.1 $(M-Na)^-$.

Typical procedure for alkyl sulfonamide formation: 2-methoxy-4-nitrobenzyl sulfonamide ***6c***

2-Methoxy-4-nitrobenzyl bromide (295 mg, 1.20 mmol) was added to a solution of SMOPS **2** (250 mg, 1.44 mmol) in DMSO (2 mL) at room temperature under a nitrogen atmosphere. The reaction was stirred for 10 min and then treated with dropwise addition of NaOMe (275 μL of 25% in MeOH, 1.20 mmol).[12] After stirring for 15 min, a solution of NH_2OSO_3H (679 mg, 6.00 mmol), NaOAc (375 mg) in H_2O (5 mL) was added to the reaction mixture, which was prevented from heating up with a cool water bath. After stirring at room temperature for 20 h, the reaction mixture was diluted with EtOAc (10 mL) and H_2O (15 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were then washed with H_2O (15 mL) and brine (15 mL), dried with Na_2SO_4, filtered through a pad of silica, and concentrated to give the titled sulfonamide **6c** as a white solid (252 mg, 85%).[13] ^{1}H NMR (500 MHz, acetone-d_6): δ 8.38 (s, 1H), 8.30 (d, 1H), 7.32 (d, 1H), 6.29 (bs, 2H), 4.52 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 163.98, 141.85, 128.63, 126.51, 121.42, 112.19, 57.08, 54.4. MS (ESI, neg.) m/z: 245.0 $(M-H)^-$.

Typical procedure for aryl sulfonamide formation: 4-methoxybenzene sulfonamide ***8b***

4-Iodoanisole (234 mg, 1.0 mmol) was added to a solution of CuI (571 mg, 3.0 mmol) and SMOPS (522 mg, 3.0 mmol) in DMSO (2 mL).[14] After stirring for 20 h at 110°C under a nitrogen atmosphere, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and filtered through a pad of silica. The resulting filtrate was washed with H_2O (2×20 mL) and brine (1×20 mL), dried over Na_2SO_4, filtered through a pad of silica, and concentrated to yield the intermediate sulfone **7b** (160 mg, 62%). To a solution of sulfone **7b** (160 mg, 0.62 mmol) in DMSO (1 mL) was added NaOMe (0.142 mL, 25% in MeOH, 0.62 mmol). After stirring at room temperature for 10 min, a solution of NH_2OSO_3H (351 mg, 3.1 mmol), NaOAc (200 mg) in H_2O (4 mL) was added to the reaction mixture, which was prevented from heating up by immersion of the reaction vessel in a cool water bath. After 20 h of stirring at room temperature, the reaction mixture was diluted with EtOAc (10 mL) and H_2O (15 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were then washed further with H_2O (15 mL) and brine (15 mL), dried with Na_2SO_4, filtered through a pad of silica, and concentrated to give the titled sulfonamide **8b** as a white solid (107 mg, 57%).[13] ^{1}H NMR (500 MHz, acetone-d_6): δ 7.85 (d, 2H), 7.10 (d, 2H), 6.44 (bs, 2H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 163.18, 137.04, 128.89, 114.70, 55.96. MS (APCI, neg.) m/z: 186.1 $(M-H)^-$.

Acknowledgements

The authors wish to thank the Merck Frosst Centre for Therapeutic Research for providing financial support for J.M.B.'s summer work-term.

References

1. Korolkovas, A. *Essentials of Medicinal Chemistry*; Wiley-Interscience Publication: New York, 1988; pp. 699–716.
2. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
3. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775–777.
4. Anderson, K. K. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, p. 345.
5. Graham, S. L.; Scholz, T. H. *Synthesis* **1986**, 852–854.
6. Chan, W. Y.; Berthelette, C. *Tetrahedron Lett.* **2002**, *43*, 4537–4540.

7. For preparation of sulfinic acids and their derivatives see: (a) *Org. Chem. Sulfur*; Oae, S., Ed.; Plenum Press: New York, 1977; pp. 603–647; (b) *Compr. Org. Chem.*; Jones, D. N., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, pp. 317–329; (c) Pinnick, H. W.; Reynolds, M. A. *J. Org. Chem.* **1979**, *44*, 160; (d) Huang, H.-C.; Reinhard, E. J.; Reitz, D. B. *Tetrahedron Lett.* **1994**, *35*, 7201–7204; (e) De Vleeschauwer, M.; Gauthier, J. Y. *Synlett* **1996**, 375–377; (f) Sato, R.; Akutsu, Y.; Goto, T.; Saito M. *Chem. Lett.* **1987**, 2161–2162; (g) Ueno, Y.; Kojima, A.; Okawara, M. *Chem. Lett.* **1984**, 2125–2128.
8. (a) Huang, P.-Q.; Zhou, W.-S. *Synth. Comm.* **1991**, *21*, 2369–2376; (b) Gibson, S. E.; Tustin, G. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2427–2432.
9. For a review on preparation of sulfones from sulfinates and alkyl halides, see Patai, S.; Rappaport, Z.; Stirling, C. J. M., Wiley & Sons: New York, 1988, 177–188.
10. Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, *36*, 6239–6242.
11. For preparation of arenesulfinic acids by an electrochemical method, see: Moinet, C.; Raoult, E. *Bull. Soc. Chim. Fr.* **1991**, *128*, 214–221.
12. In the cases of benzyl chlorides, secondary benzyl bromides, and primary non-benzyl bromides, the reaction time was longer, up to 24 h.
13. In some cases, further purification (flash chromatography or recrystallization) was required; however, all reported yields are based on isolated products of satisfactory purity as assessed by ^{1}H, ^{13}C NMR and MS.
14. In the case of aryl bromides, 5 equiv. of CuI and of SMOPS were used instead of 3 equiv.