Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1283–1286

TETRAHEDRON LETTERS

Novel synthesis of sulfones from α,α-dibromomethyl aromatics

Feng Xu,* Kimberly Savary, J. Michael Williams, Edward J. J. Grabowski and Paul J. Reider

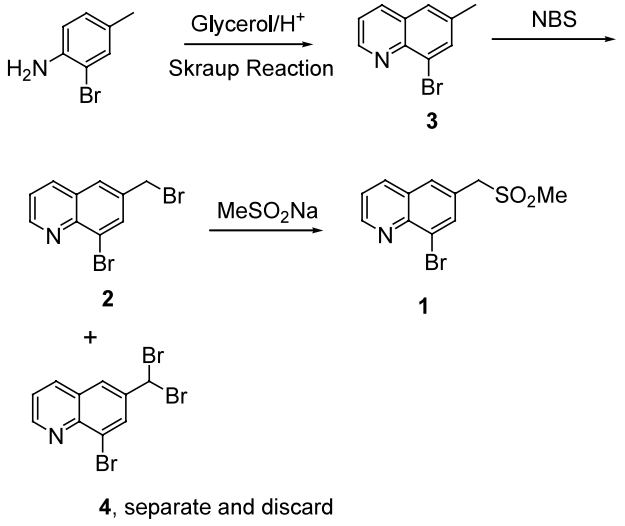
Department of Process Research, Merck Research Laboratory, Rahway, NJ 0706, USA

Received 18 October 2002; revised 4 December 2002; accepted 5 December 2002

Abstract—A novel, high yielding preparation of sulfones from α,α-dibromomethyl aromatics through reaction with a sulfinate salt is reported. © 2003 Published by Elsevier Science Ltd.

Sulfones are widely used intermediates in organic synthesis.[1] Many procedures can be applied in the preparation of sulfones.[1] One of the most commonly used methods involves formation of the C–S bond by reacting an alkyl halide with a sulfinate salt. As part of synthetic efforts to support a drug development program at Merck, a practical synthesis of the key intermediate sulfone **1** was required. The initial synthesis of **1** is shown in Scheme 1.

The by-product **4**, which resulted from bromination of the desired product competitive with bromination of **3**, was separated as waste in isolation of **2**. The selectivity and conversion in the bromination step heavily depended on the NBS charge, reaction temperature, and solvents. The overall yield in the synthesis of **1** is limited by the bromination step. Table 1 illustrates some selected bromination results. To date, the best selectivity/conversion achieved is about 90:5:5 (**2**:**3**:**4**) with 80–85% isolated yield. Full conversion could be achieved by treatment of **3** with 1.4 equiv. of NBS in PhCl in the presence of 10 mol% of Vazo® 67[2] at 70°C, but selectivity suffered (**2**:**4** = 70:30).



Scheme 1. Initial synthesis of sulfone **1**.

Although extensive studies have been carried out in the past, selectivity clearly remains a common problem in radical bromination.[3] α,α-Dibromomethyl aromatics are often observed in the radical bromination of methyl aromatics used to prepare monobromomethyl aromatics.[3] It is also known that α-bromomethyl sulfones can be reduced to the corresponding sulfones in the presence of suitable reducing reagents such as cat. $(PhSe)_2$/$NaBH_4$.[4] In principal, the oxidation state of sulfur in a sulfinic acid allows it to act as a reducing agent. However, one-step synthesis of sulfones from α,α-dibromomethyl aromatics in the presence of sulfinate salt has not been reported. Therefore, we initiated studies to determine the potential for converting the α,α-dibromomethyl quinoline **4** into the desired sulfone **1** using $MeSO_2Na$.

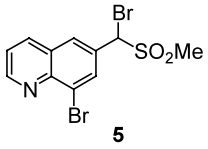
No reaction was observed between the tribromide **4** and $MeSO_2Na$ in aqueous DMAc at ambient temperature. However, the bromosulfone **5** was observed as an intermediate in the formation of the desired sulfone **1** when the reaction was carried out at higher temperature. The bromosulfone **5** was isolated and characterized. At 70–90°C, **4** was completely converted to the desired sulfone product **1** in 95% yield. Figure 1 illustrates the conversion versus time for sulfone formation at 70°C.

* Corresponding author. Tel.: 732-594-3211; fax: 732-594-1499; e-mail: feng_xu@merck.com

0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02769-7

Table 1. Bromination of **3**: selectivity versus conversion

Entry	Reagents	Temp. (°C)	Solvents	Conversion/selectivity **3**:**2**:**4**
1	1.05 equiv. NBS/AIBN	65–70	PhCl	12:77:11
2	1.4 equiv. NBS/Vazo® 67[2]	70	PhCl	0:70:30
3	1.2 equiv. NBS/$(BzO)_2$	65	EtOAc	10:80:10
4	1.2 equiv. NBS/$(BzO)_2$	65	*t*-$BuCO_2Me$	8:75:17
5	1.2 equiv. NBS/$(BzO)_2$	65	$MeCO_2Bu$-*t*	5:83:12
6	1.2 equiv. NBS/$(BzO)_2$	65	*i*-PrOAc	10:80:10
7	1.05 equiv. NBS/Vazo® 52[2]	50–55	*i*-PrOAc	5:90:5
8	1.05 equiv. NBS/AIBN or $(BzO)_2$	65–70	CF_3CO_2Pr-*i* or CF_3CO_2Pr-*i*/CF_3Ph	5:90:5



5

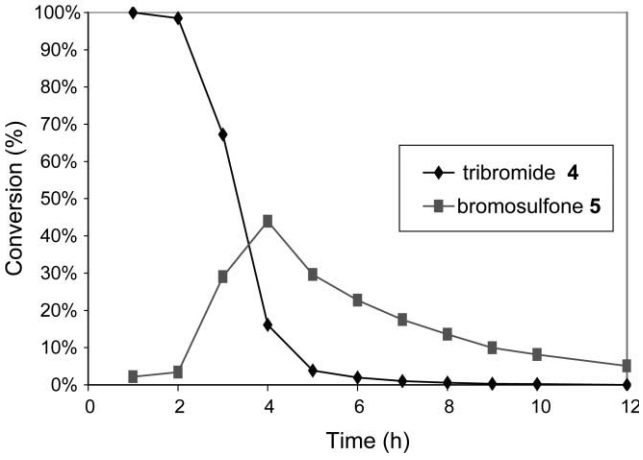
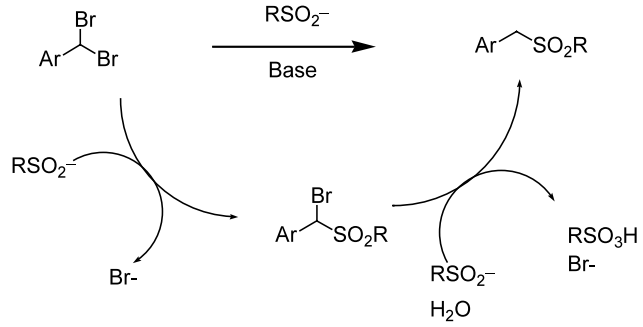


Figure 1. Plot of conversion versus time for sulfone formation at 70°C.

During the reaction, 1 equiv. of sulfinate salt (RSO_2^-) is oxidized to sulfonic acid (RSO_3H) (Scheme 2), the detailed mechanism for reduction of α-bromosulfone to sulfone with sulfinate salt (RSO_2^-) has not been further investigated. Sulfinic acid is a weaker acid and is not stable under acidic conditions,[5] therefore, addition of a base such as $NaHCO_3$ is required to improve efficiency in use of the sulfinate salt (RSO_2^-) and prevent formation of sulfinic acid during the reaction. A plausible reaction pathway is shown in Scheme 2.



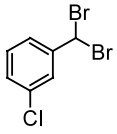
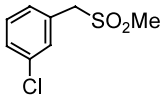
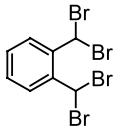
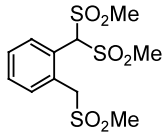
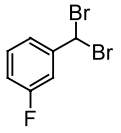
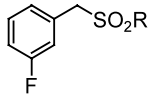
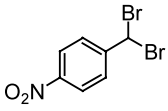
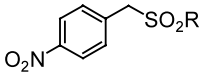
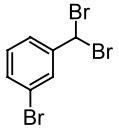
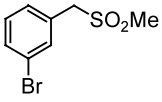
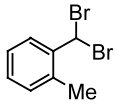
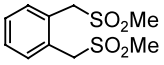
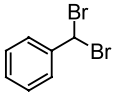
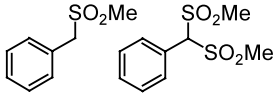
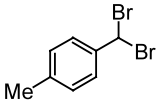
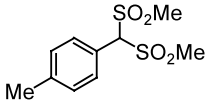
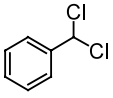
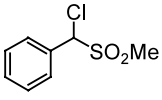
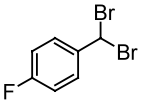
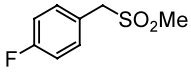
Scheme 2. Reaction pathway for formation of sulfone.

Applying this new approach coupled with sulfone formation from monobromomethyl quinoline **2**, the improved synthesis of sulfone **1** turns out to be robust and allows the use of a mixture of **2**,**4**, and succinimide as isolated directly from the bromination reaction. The presence of succinimide does not affect the reaction. Thus, bromination of **2** (1.4 equiv. NBS, 5–10 mol% Vazo® 67[2]/PhCl/70°C) is carried out in nearly full conversion (entry 2, Table 1). Then, heptane is added to the reaction mixture and a solid mixture of **2**,**4**, and succinimide is isolated in 94% yield. The above mixture (typical mole ratio of **2**:**4** is about 2.5:1; succinimide is about 30 wt%) is treated with $MeSO_2Na$ (1.1 equiv. for **2** and 2.5 equiv. for **4**) at ambient temperature in DMAc containing 20% water in the presence of 2.5 equiv. $NaHCO_3$. Sulfone formation can be carried out in aqueous DMAc without suffering hydrolysis of α-mono/α,α-dibromides. The reaction solution is aged at ambient temperature until all the α-monobromide **2** is consumed (about 2 h). The reaction solution is then heated at 90°C for approximately 10 h to convert **4** to **1**. The crystalline sulfone product **1** is isolated in 92% yield and 98 A% purity by adding water at the end of the reaction.[6]

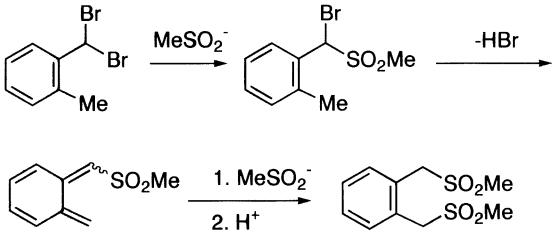
The scope of the new sulfone formation reaction was examined with commercially available or easily prepared α,α-dibromomethyl compounds.[7] Table 2 summarizes the results for the reactions using various α,α-dibromomethyl aromatics and sulfinate salts. In a typical experiment, 2.5 equiv. of the sulfinate salt and $NaHCO_3$ are charged. The reaction is typically run in DMAc containing 20% water at elevated temperature (70–110°C). In most of the cases, the product is crystallized by addition of water at the end of the reaction.

As shown in Table 2, the sulfone formation works extremely well when the aromatics bear electron-withdrawing groups. The reduction of the corresponding α-bromosulfone is faster relative to displacement. In fact, the displacement competition product, α,α-disulfonylmethyl aromatics, was not observed.[8] Without having an electron-withdrawing group, the reduction of α-bromosulfone slows down and requires going to higher reaction temperatures, while the formation of the bromosulfone is still fast. The displacement product, α,α-disulfonylmethyl aromatics, starts to form as the reaction temperature is increased so that the

Table 2. Synthesis of sulfones from dibromides

Entry	Starting Material	Products[9]	Conditions	Assay Yield
1			100 °C, 12 h	83%
2			70 °C, 8 h	98%
3		 R = Me, Ph	110 °C, 8 h	96%, R = Me 99%, R = Ph
4		 R = Me, Ph	80 °C, 3 h	93%, R = Me 97%, R = Ph
5			100 °C, 8 h	87%
6			100 °C, 8 h	94%
7		 2.5 : 1	110 °C, 1 day	70%
8			110 °C, 2 days	89%
9			80 °C, 4 h	95%
10			100 °C, 8 h	92%

reduction reaction could take place. In entry 7, α,α-dibromotoluene was allowed to reacted with $NaSO_2Me$ at 110°C for 1 day to give a mixture of the monosulfone and the displacement product α,α-disulfone (2.5:1). If the reaction is carried out at 70°C, the bromosulfone is the only product. Aromatic sulfinate salt $PhSO_2Na$ works as well as $MeSO_2Na$, as shown in entries 3 and 4.



Scheme 3. Proposed reaction pathway for formation of 1,2-bis[(methylsulfonyl)methyl]benzene.[9]

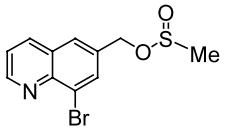
For *o*-methyl α,α-dibromo-*o*-xylene (entry 6) the reaction proceeds via a different pathway, formation of the disulfone product is believed to take place via an elimination–addition sequence (Scheme 3). Formation of the trisulfone product in entry 2 is believed to involve a combination of elimination–addition and reduction pathway.

α,α-Dichloromethyl aromatics are easily converted to the chlorosulfone, but the chlorosulfone is not reduced to the sulfone.

In conclusion, a novel method for high yielding preparation of sulfones simply by reacting α,α-dibromomethyl aromatics with sulfinate salts has been demonstrated. The new method makes it possible to use mixtures of mono- and dibromomethyl aromatics to prepare sulfones in high yields. Since α,α-dibromomethyl aromatics are often obtained in the radical bromination used to prepare monobromomethyl aromatics, this discovery eliminates the need to achieve high selectivity in the bromination.

References

1. For recent reviews, see: (a) Najera, C.; Sansano, J. M. *Recent Res. Dev. Org. Chem.* **1998**, 637; (b) Simpkins, N. S. *Sulphones in Organic Synthesis*; Baldwin, J. E.; Magnus, P. D., Eds.; *Tetrahedron Org. Chem. Series*, *Vol. 10*; Pergamon Press: Oxford, 1993.
2. Vazo® is a DuPont registerted name for free radical sources. Vazo® 67: 2,2′-azobis(2-methylbutanenitrile); Vazo® 52: 2,2′-azobis(2,4-dimethylpentanenitrile).
3. For recent examples, see: (a) Noda, K.; Matsui, N.; Miyazaki, H. *Jpn. Kokai Tokkyo Koho* 20020522, **2002**; (b) Schneider, H. *Ger. Offen.* 19917025, **2000**; (c) Lehmann, B. *Ger. Offen.* 19757995, **1999**; (d) Awano, H.; Shimoda, A.; Kubo, M. *Jpn. Kokai Tokkyo Koho* 11130708, **1999**; (e) Kikichi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023; (f) Shaw, H.; Perlmutter, H. D.; Gu, C. *J. Org. Chem.* **1997**, *62*, 236; (g) Yoneda, Y.; Yamamoto, Y.; Okamura, S.; Ataka, K. *Jpn. Kokai Tokkyo Koho* 09031059, **1997**; (h) Kleiner, H.-J.; Regnat, D. *Ger. Offen.* 9531164, **1997**; (i) Waykole, L.; Prashad, M.; Palermo, S.; Repic, O.; Blacklock, T. J. *Synth. Commun.* **1997**, *27*, 2159.
4. Yashimatsu, M.; Ohara, M. *Tetrahedron Lett.* **1997**, *38*, 5651.
5. (a) Oae, S.; Kunieda, N. *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, 1977; Chapter 11; (b) Truce, W. E.; Murphy, A. M. *Chem. Rev.* **1951**, *48*, 69.
6. Interestingly, at elevated temperature the *O*-alkylated by-product **6** (typically 3–4 A%, generated from **2**) was also converted to the desired sulfone **1**. This was confirmed by subjecting the isolated **6** to the reaction conditions. Sulfinate ester is a by-product often observed by reacting an alkyl bromide with a sulfinate salt. For mechanistic studies on converting sulfinate esters to sulfones, see: Hendrickson, J. B.; Skipper, P. L. *Tetrahedron* **1976**, *32*, 1627.



6

7. α,α-Dibromomethyl compounds can be prepared in various ways, see: (a) Hoffmann, R. W.; Bovicelli, P. *Synthesis* **1990**, 657; (b) Guo, W.; Duann, Y. F. *Org. Prep. Proced. Int.* **1990**, *23*, 85; (c) Lansinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341; (d) Hase, T. *Acta Chem. Scand.* **1970**, *24*, 2263.
8. For a recent review on reactivity and application of α-halo sulfonyl compounds, see: Paquette, L. A. *Synlett* **2001**, 1.
9. **Spectral data for new compounds**:
1-[Bis(methylsulfonyl)methyl]-2-[(methylsulfonyl)methyl]-benzene: ^{1}H NMR ($CDCl_3$): δ 8.05 (m, 1H), 7.58 (m, 2H), 7.43 (m, 1H), 6.43 (s, 1H), 4.62 (s, 2H), 3.26 (s, 3H), 2.90 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 134.2, 131.1, 130.7, 130.5, 129.3, 125.9, 80.0, 55.8, 42.4.
1,2-Bis[(methylsulfonyl)methyl]benzene: ^{1}H NMR ($CDCl_3$): δ 7.44 (m, 4H), 4.66 (s, 4H), 2.94 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 133.5, 129.9, 128.5, 58.4, 40.4.
1-[Bis(methylsulfonyl)methyl]-4-methylbenzene: ^{1}H NMR ($CDCl_3$): δ 7.52 (d, $J=8$ Hz, 2H), 7.29 (d, $J=8.0$ Hz, 2H), 5.25 (s, 1H), 3.20 (s, 6H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 141.5, 130.7, 130.4, 121.6, 86.2, 41.0, 21.4.