A New Synthesis of α-Chloro Sulfoxides. The Reaction of Diazo Compounds with Sulfinyl Chlorides[1a]

CLIFFORD G. VENIER,* HSIN-HSIONG HSIEH,[1b] AND HOWARD J. BARAGER, III[1c]

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

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A new and facile synthesis of α-chloro sulfoxides involving the reaction of sulfinyl chlorides and diazo compounds has been developed. A comparison with previously known methods shows that this new method is superior for the preparation of many of the α-chloro sulfoxides whose reactions have generated much recent interest. In particular, methyl chloromethyl (**1**), bis(chloromethyl) (**2**), benzyl chloromethyl (**4**), and methyl chlorobenzyl (**5**) sulfoxides are produced in superior yields. A yield equal to that obtained by chlorination of phenyl methyl sulfoxide is realized for the preparation of phenyl chloromethyl sulfoxide (**3**). A number of new α-chloro sulfoxides have been synthesized, including *n*-butyl chloromethyl (**6**), *sec*-butyl chloromethyl (**7**), 9-fluorenyl chloromethyl (**8**), 9-chloro-9-fluorenyl methyl (**9**), and 1-chloroethyl chloromethyl (**10**) sulfoxides. This method is of particular merit for the preparation of α-chloro sulfoxides in cases where both the α and α′ positions of the product may bear a chlorine substituent, since only one of the possible chlorine positional isomers is formed.

Recently, there has been widespread interest in the reactions of α-halo sulfoxides.[2,3] Naturally, interest has also been generated in the synthesis of various members of this series of compounds. We wish to report in this paper, a new and facile synthesis of α-chloro sulfoxides.

Most of the early workers chose to synthesize α-chloro sulfoxides by oxidation of the corresponding α-chloro sulfides with a variety of oxidizing reagents: ozone,[4] peroxy acids,[5] $NaOCl$,[6,7a] HNO_3,[7] and N_2O_5.[8] It is also worthwhile to note the synthesis of bis(1,2-dichloroethyl) sulfoxide by the addition of chlorine to divinyl sulfoxide.[9]

Since 1968, α-chloro sulfoxides have received much more attention. Additional oxidation methods include the use of *m*-chloroperbenzoic acid[10] and vanadium pentoxide[11] as oxidants. More importantly, α-chloro sulfoxides have been prepared by the α-chlorination of the corresponding unhalogenated sulfoxides by a variety of reagents. *N*-Chlorobenzotriazole,[12] sulfuryl chloride,[13] *p*-toluenesulfonyl chloride,[3] iodobenzene dichloride,[14] *N*-chlorosuccinimide,[15] *tert*-butyl hypochlorite,[16] nitrosyl chloride,[17] and molecular chlorine[18] have all been used as sources of chlorine. A novel preparation of chloromethyl sulfoxides involving the hydrolysis of α,β-dichlorovinyl sulfoxides has been described recently.[19]

Although the reaction of diazomethane with sulfinyl chlorides is mentioned in the literature directly in one place,[20] and indirectly in another,[21] previous authors have reported this reaction simply as a slight diversion from the main topic of their work. Ayca,[20] in an attempt to modify the Arndt-Eistert reaction as a synthesis of α-diazo sulfoxides, reported that diazomethane and *p*-toluenesulfinyl or benzenesulfinyl chlorides react to give low yields of *p*-tolyl chloromethyl sulfoxide and phenyl chloromethyl sulfoxide, respectively. Saunders, *et al.*,[21] reported that diazomethane reacts with thionyl chloride to give a 40% yield of bis(chloromethyl) sulfoxide (**2**). In this last reaction, chloromethanesulfinyl chloride is undoubtedly an intermediate. In fact, we have been able to show that chloromethanesulfinyl chloride is the product of the reaction when diazomethane is added to an excess of thionyl chloride.[22] Recently, Senning and his coworkers[23] have synthesized trichloromethyl bromomethyl sulfoxide in 15% yield from trichloromethanesulfinyl bromide and diazomethane.

In this paper, we describe experiments which show that the reaction of diazo compounds with sulfinyl chlorides is a useful synthetic method for the preparation of α-chloro sulfoxides.[24]

Results and Discussion

Although two general methods for the preparation of α-chloro sulfoxides are available, namely, the oxidation of α-chloro sulfides and the chlorination of sulfoxides,

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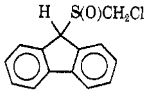
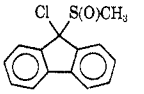
TABLE I

DATA ON α-CHLORO SULFOXIDES PREPARED BY ADDITION OF DIAZO COMPOUNDS TO SULFINYL CHLORIDES[a]

$$RR'CN_2 + R''S(O)Cl \longrightarrow RR'CClS(O)R''$$

Compd	Mp or bp, °C (mm)	Lit. mp or bp, °C (mm)	Yield, %	Ir, –S(O)–, cm⁻¹	Nmr Data, δ, ppm
$CH_3S(O)CH_2Cl$ (**1**)	61–62 (2)	49–50 (0.03)[b]	90	1040	2.68 (s, 3 H), 4.58, 4.71 (AB q, *J* = 11 Hz, 2 H)
$ClCH_2S(O)CH_2Cl$ (**2**)	38–39	39[c]	99	1050	4.52, 4.64 (AB q, *J* = 11 Hz)
$PhS(O)CH_2Cl$ (**3**)	Oil	38.5–39.5[d]	78	1045, 1075	4.35, 4.43 (AB q, *J* = 11 Hz, 2 H), 7.50 (m, 5 H)
$PhCH_2S(O)CH_2Cl$ (**4**)	56–58	54–55[e]	99	1050	3.89, 3.98 (AB q, *J* = 13 Hz, 2 H), 4.05, 4.16 (AB q, *J* = 11 Hz, 2 H), 7.20 (m, 5 H)
$PhCHClS(O)CH_3$ (**5**)[f]	Oil	50–51[e]	49	1055	**5a**, 2.26 (s, 3 H), 5.74 (s, 1 H), 7.36 (m, 5 H), **5b**, 2.43 (s, 3 H), 5.70 (s, 1 H), 7.36 (m, 5 H)
n-$BuS(O)CH_2Cl$ (**6**)	Dec	*g*	77	1030	0.90 (m, 3 H), 1.60 (m, 4 H), 2.83 (t, 2 H), 4.47, 4.59 (AB q, *J* = 11 Hz, 2 H)
sec-$BuS(O)CH_2Cl$ (**7**)[h]	Dec	*g*	68	1040	0.83–1.30 (complex, 6 H), 1.30–2.15 (complex, 2 H), 2.85 (m, 1 H), **7a**, 4.47, 4.55 (AB q, *J* = 11 Hz, 0.9 H), **7b**, 4.52, 4.71 (AB q, *J* = 11 Hz, 1.1 H)
 (**8**)	101–103	*g*	47	1050	3.70 (s, 2 H), 5.26 (s, 1 H), 7.40 (m, 8 H)
 (**9**)	91–93	*g*	25	1060	1.70 (s, 3 H), 7.50 (m, 8 H)
$CH_3CHClS(O)CH_2Cl$ (**10**)[i]	63–64 (3)	*g*	90	1065	**10a**, 1.88 (d, 3 H), 4.69, 4.73 (AB q, *J* = 12 Hz, 2 H), 4.89 (q, 1 H), **10b**, 1.88 (d, 3 H), 4.48 (s, 2 H), 5.05 (q, 1 H)
$PhCHClS(O)Ph$ (**11**)[j]	106–114	**11a**, 101–102[k] **11b**, 122–123[k]	36	1050, 1085	**11a**, 5.35 (s, 1 H), 7.25 (m, 10 H), **11b**, 5.43 (s, 1 H), 7.25 (m, 1 H)

[a] Compounds **1**, **3**, **4**, **5**, and **11** had properties consistent with those reported in the literature. Compounds **2**, **6**, **7**, **8**, **9**, and **10** gave satisfactory C and H analyses (±0.4%). Compounds **2**, **6**, **8**, and **9** gave satisfactory S analyses (±0.4%). **7** required 20.7, gave 20.0 S. **10** required 19.9, gave 18.3 S. Compounds **2**, **7**, **8**, and **9** gave satisfactory Cl analyses (±0.4%). **6** required 23.0, gave 21.2 Cl. **10** required 44.0, gave 41.4 Cl. [b] Reference 18b. [c] Reference 21. [d] Reference 17. [e] Reference 14a. [f] Two diastereomers in the ratio **5a**:**5b** = 4:1. [g] Previously unknown. [h] Two diastereomers in the ratio **7a**:**7b** = 4:5. [i] Two diastereomers in the ratio **10a**:**10b** = 2:1. [j] Two diastereomers in the ratio **11a**:**11b** = 1:4. [k] Reference 16.

each of these methods has some drawbacks which make the elaboration of still another general method desirable. In either of the previous preparations, an important step is the oxidation of a sulfide to a sulfoxide. Even in the most skilled hands, these oxidations are treacherous. Overoxidation to the sulfone occurs with exasperating ease. In the reaction of diazo compounds with sulfinyl chlorides described herein, the oxidation of sulfur occurs in the sulfinyl chloride preparation, an easily carried out, high-yield procedure which has been thoroughly worked out by Douglass and his coworkers.[25] Additionally, a procedure avoiding the malodorous α-chloro sulfides is desirable.

An inspection of Table I reveals the high yields of α-chloro sulfoxides achievable by the diazoalkane–sulfinyl chloride reaction. In fact, for most of the compounds in Table I, the yields are equivalent to or superior to the best yields obtainable by other methods. Only in the case of phenyl chlorobenzyl sulfoxide is another method superior to this new method. In order to compare the efficacy of two routes to a single product, one must compare the yields from commonly available starting materials and not just the yields in the last step of a sequence. From the divalent sulfur compounds, mercaptans, sulfides, and disulfides, which are the commonly available starting materials for all three of the general methods of α-chloro sulfoxide preparation, the overall yields for the diazoalkane–sulfinyl chloride sequence are clearly superior in almost every case.

A further inspection of Table I will reveal that the diazoalkane–sulfinyl chloride reaction gives its highest yields when diazomethane is the diazo compound. Thus, this method is particularly well suited for the preparation of chloromethyl sulfoxides.

Since the α-chlorine of the product α-chloro sulfoxide must be on the nitrogen-bearing carbon of the reactant diazo compound, the addition of diazoalkane to sulfinyl chloride must, of necessity, give only one of the two possible chlorine positional isomers. Chlorination of sulfoxides can, and does,[14a,16] lead to mixtures of the isomers. A good example of positional specificity is illustrated in Table II. This tabulation shows the yields of the two monochloro derivatives of benzyl methyl sulfoxide (**12**) as prepared by a variety of means. Note that only in the case of the diazomethane–phenylmethanesulfinyl chloride reaction is **4** produced without contamination from **5**. Although **5** can be prepared free of contaminating **4** by the chlorination of the sulfoxide **12**, in the absence of added base, the overall yields suffer drastically, and so, for this isomer, the relatively low yield phenyldiazomethane–methanesulfinyl chloride reaction is the superior method of preparation.

Tin and Durst[13b] have shown that the chlorination of dialkyl sulfoxides can be made to give a single mono-

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TABLE II

COMPARISON OF YIELDS FOR THE PREPARATION OF MONOCHLORO DERIVATIVES OF BENZYL METHYL SULFOXIDE

Method	**4**, %	**5**, %	Ref[a]
$PhCH_2S(O)Cl + CH_2N_2$	99	0	This work
t-BuOCl, pyridine + $PhCH_2S(O)CH_3$ (**12**)	45	15	16
N-Chlorobenzotriazole, pyridine + **12**	44	37	11
$PhICl_2$, pyridine + **12**	32	30	14
SO_2Cl_2, no base + **12**	0	25	12b
t-BuOCl, KOAc + **12**	0	40	16
$PhCHN_2 + CH_3S(O)Cl$	0	49	This work

[a] Reference numbers refer to footnotes in text.

chloro isomer in good yield. For example, they were able to prepare methyl 1-chlorobutyl sulfoxide in 75% yield by the reaction of the parent methyl butyl sulfoxide with SO_2Cl_2 in the absence of added base. There is apparently no contamination from chlorine substitution on the methyl group. The diazoalkane–sulfinyl chloride reaction nicely complements this result, since it allows the production of the other isomer, butyl chloromethyl sulfoxide, in 77% yield from *n*-butanesulfinyl chloride and diazomethane.

It is important to note that the order of addition of the reagents is quite critical to the success of the preparation. While addition of diazoalkane to sulfinyl chloride leads to the high yields reported here, inverse addition leads to complex mixtures of products and consequently to greatly lowered yields of the desired α-chloro sulfoxides.

Experimental Section

Infrared spectra were recorded on a Beckman IR-33 spectrophotometer. Nmr spectra were run on a Varian A-60A spectrometer using tetramethylsilane as an internal standard. Melting and boiling points are uncorrected. Combustion analyses were performed by Chemalytics, Inc., Tempe, Ariz. Diazomethane was generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich Chemical Co.)[26] and dried over KOH for at least 2 hr prior to use. Phenyldiazomethane and 9-diazofluorene were prepared by the method of Smith and Howard[27] from benzalhydrazine and 9-fluorenone hydrazone, respectively. Sulfinyl chlorides were prepared by the chlorination of disulfides in the presence of acetic anhydride according to the procedure of Douglass and Norton,[25] except as noted.

Chloromethane- and 1-Chloroethanesulfinyl Chlorides.—A slurry of the requisite *sym*-trithiane and Ac_2O (1 equiv) was chlorinated at 0°. Excess Cl_2 and AcCl were removed at reduced pressure and the sulfinyl chlorides were purified by distillation. Chloromethanesulfinyl chloride (55%) had bp 42–62° (15 mm); nmr ($CDCl_3$) δ 4.90 (s); ir 1150 cm^{-1} (–S=OCl). 1-Chloroethanesulfinyl chloride (two diastereomers in the ratio of 2:1 A:B) (80%) had bp 26–27° (0.5 mm) [lit.[28] bp 36–38° (3.7 mm)]; nmr (CCl_4) δ 1.93 (d, J = 6.5 Hz, 3 H), 4.95 (isomer B), 5.11 (isomer A) (2 q, J = 6.5 Hz, 1 H); ir 1150 cm^{-1} (–S=OCl).

β-(9-Fluorenesulfonyl)propionitrile (13).[29]—β-Thioacetylpropionitrile[30] (12.9 g, 0.1 mol) was added dropwise to a sodium ethoxide solution prepared by dissolving sodium (2.3 g, 0.1 g-atom) in 50 ml of absolute EtOH. 9-Bromofluorene[31] (24.6 g, 0.1 mol), dissolved in 200 ml of hot absolute EtOH, was then added in portions over a 1-hr period. After stirring overnight, the NaBr was filtered off and the solvent was removed *in vacuo*. The crude sulfide was oxidized to the sulfone **13** with H_2O_2 in HOAc.[32]

9-Fluorenesulfinyl Chloride (14).—**13** was converted to 9-fluorenesulfinic acid, which was converted to **14** as previously described.[29] **14** was used without purification and the yield of **8** was based on **13** as the limiting reagent.

General Procedure for the Preparation of Chloromethyl Sulfoxides.—Excess diazomethane was added dropwise over a period of 30 min *via* a pressure-equalizing dropping funnel fitted with a $CaCl_2$ drying tube to a stirred, ice-cold solution of 0.07 mol of sulfinyl chloride in 50 ml of absolute ether. Stirring was continued for an additional 30 min. The ether was removed on a rotary evaporator. Liquid sulfoxides were purified by silica gel chromatography, except for chloromethyl methyl sulfoxide, which was distilled. Solid sulfoxides were recrystallized. Properties of the sulfoxides are presented in Table I.

General Procedure for the Preparation of α-Chloro Sulfoxides.—The procedure for the preparation of chloromethyl sulfoxides was followed, except that a stoichiometric amount of the diazo compound was used rather than an excess. The properties of these sulfoxides are presented in Table I.

Registry No.—**1**, 21128-88-1; **2**, 5031-59-4; **3**, 7205-94-9; **4**, 24824-97-3; **5a**, 36963-17-4; **5b**, 36963-18-5; **6**, 36963-19-6; **7a**, 36963-20-9; **7b**, 36963-21-0; **8**, 36963-22-1; **9**, 36963-23-2; **10a**, 36963-24-3; **10b**, 36963-25-4; **11a**, 36963-26-5; **11b**, 36963-27-6; chloromethanesulfinyl chloride, 36963-28-7; 1-chloroethanesulfinyl chloride (isomer A), 36963-29-8; 1-chloroethanesulfinyl chloride (isomer B), 36963-30-1.

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