The Addition of α-Metalated Chloromethanesulfonamides to Unsaturated Linkages

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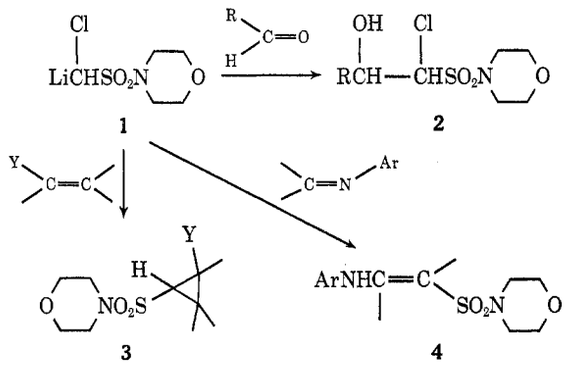
In the course of our investigations utilizing sulfur-stabilized carbanions in synthesis,[1] the reactions of 1-metalated 1-halosulfonic acid derivatives have offered unique synthetic potential.[2] These species couple the advantage of an extremely reactive carbanionic site while maintaining a functionality at the α position which is available for subsequent modification.[2b] Thus, facile, high-yield routes to a variety of novel 1- and 1,2-functionalized sulfur compounds are provided. We wish to report on the diverse reactivity of α-haloalkyllithium systems such as **1** with various classes of unsaturated substrates. Table I and Scheme I

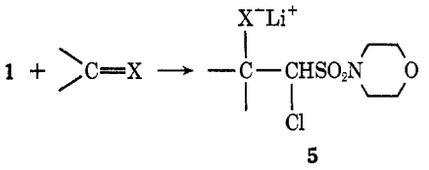
SCHEME I



summarize the results of the reactions of α-lithiochloromethanesulfonmorpholide with such acceptors. Clearly each unsaturated system demonstrates both characteristic and unique behavior. All reactions were carried out in tetrahydrofuran at −65° to minimize side reactions of the "carbenoid" **1**. Characterization of the products is based on chemical properties, elemental analyses, molecular-weight determinations, and infrared and well-defined proton magnetic resonance spectra.

Condensation of **1** with aldehydes afforded a mixture of diastereomeric alcohols. A similar preparation of diastereomeric β-hydroxy-α-chlorosulfones has been reported.[3]

That diastereomeric mixtures are obtained is evidenced both by the wide melting range of analytically pure adduct (Table I) and examination of the nmr spectra, which shows a variation in chemical shift accompanied by a pronounced difference in coupling constants for the erythro and threo isomers.[4,5] However, in most cases separation and isolation of the pure erythro and threo isomers was not systematically attempted. The nature of the products in this condensation parallels directly the interaction of **1** with ketones.[2] This reaction can be pictured as an initial addition of **1** to the unsaturated system giving the ion-pair intermediate **5**. No epoxide could be detected in



the crude reaction mixture, indicating that, under the reaction conditions when X is oxygen, ring closure with displacement of chloride ion is not favored.

By contrast, the reaction of **1** with Michael acceptors gives the ring-closed cyclopropanes under the same reaction conditions. Thus, an attractive route is provided to cyclopropanes which are 1,2 disubstituted with electron-withdrawing groups. Such systems are difficult to synthesize or unavailable by alternative cyclopropyl ring forming reactions.[6] It should be noted that, if the reaction proceeds *via* the intermediate carbanion, **5**, a facile intramolecular nucleophilic displacement α to a sulfonamide group must ensue.[7] It is evident that this method of forming disubstituted cyclopropanes is useful synthetically and its extension to other α-halosulfur-containing reactants and diverse Michael acceptor olefins constitutes a general approach to such cyclopropyl systems.

Distinct to these two modes of reactivity, the interaction of **1** with an imine affords a sulfonyl-substituted enamine as product[8] rather than the amine (analogous to carbonyl reactivity) or the aziridine (analogous to carbon–carbon double bond reactivity). The three individual modes of behavior of **1** toward various acceptors may reflect the differences in nucleophilicity and basicity expected for the three different anionic intermediates, **5**. Although such a correlation is attractive, we have little additional data to support such speculation at this time. An indication that perhaps more subtle factors govern the change in the nature of the products is suggested by the lack of reaction between **1** and *N*-benzylidenemethylamine.

These reactions, while providing convenient routes to novel sulfonic acid derivatives, also illustrate the diverse behavior of sulfur-stabilized α-haloalkyllithiums.

(1) (a) W. E. Truce and L. W. Christensen, *Tetrahedron*, **25**, 181 (1969); (b) W. E. Truce and D. J. Vrencur, *J. Org. Chem.*, **35**, 1226 (1970); (c) W. E. Truce and T. C. Klingler, *ibid.*, **35**, 1834 (1970).

(2) (a) W. E. Truce and L. W. Christensen, *Tetrahedron Lett.*, 3075 (1969); (b) *J. Org. Chem.*, **36**, 2538 (1971); (c) *Chem. Commun.*, 588 (1971).

(3) (a) F. Bohlmann and G. Haffer, *Chem. Ber.*, **102**, 4017 (1969); (b) T. Durst and K. C. Tin, *Tetrahedron Lett.*, 2369 (1970); (c) D. F. Tavares, R. E. Estep, and M. Blezard, *ibid.*, 2373 (1970).

(4) Assignment of stereochemistry *via* nmr spectroscopy has been reported: (a) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961); (b) M. E. Munk, M. K. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968). Also see ref 1c for similar assignments in diastereomeric sulfones.

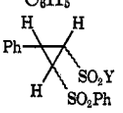
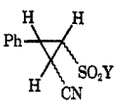
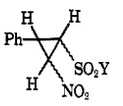
(5) The terms erythro and threo refer to *dl*-erythro and *dl*-threo, respectively.

(6) For analogous reactions of carboxylic acid derivatives, see (a) G. Bonavent, M. Causse, M. Guitard, and R. Fraisse-Jullian, *Bull. Soc. Chim. Fr.*, 2462 (1964); (b) T. Kawakami and T. Tsuruta, *Tetrahedron Lett.*, 1173 (1971).

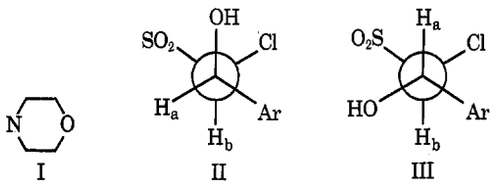
(7) For a comparison of the ease of intra- and intermolecular displacement α to a sulfonyl group, see (a) F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968); (b) W. E. Truce, T. C. Klingler, J. E. Paar, H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969), and ref 2b.

(8) (a) J. G. Lombardino, *J. Org. Chem.*, **33**, 3938 (1968); (b) W. E. Truce, R. H. Bavry, and P. S. Bailey, Jr., *Tetrahedron Lett.*, 5651 (1968).

TABLE I
REACTION PRODUCTS OF α-LITHIOCHLOROMETHANESULFONMORPHOLIDE WITH DOUBLE BONDS

Registry no.	Acceptor	Product	Product no.	Mp, °C	Yield, %[i]
75-07-0	CH_3CHO	$CH_3CHCHClSO_2Y$[a] (OH)	6	b	90[c]
78-84-2	$(CH_3)_2CHCHO$	$(CH_3)_2CHCHCHClSO_2Y$ (OH)	7	114–120[c]	68
100-52-7	C_6H_5CHO	$PhCHCHClSO_2Y$ (OH)	8	138–155[d]	39
89-98-5	o-ClC_6H_4CHO	o-$ClC_6H_4CHCHClSO_2Y$ (OH)	9	122–134[c]	93
591-31-1	m-$CH_3OC_6H_4CHO$	m-$CH_3OC_6H_4CHCHClSO_2Y$ (OH)	10	110.5–111.5[e]	81
538-51-2	$C_6H_5CH{=}NC_6H_5$	$C_6H_5NHC{=}CHSO_2Y$ (C_6H_5)	11	53.5–55	69
16212-06-9	*trans*-$C_6H_5CH{=}CHSO_2C_6H_5$		12	175.5–177[f]	73[g]
1885-38-7	*trans*-$C_6H_5CH{=}CHCN$		13	143–148[h]	70
5153-67-3	*trans*-$C_6H_5CH{=}CHNO_2$		14	104–109[h]	21

[a] Y is the group designated as structure I below. [b] Isolated as a viscous oil which could not be crystallized. [c] An analytically pure mixture of erythro and threo isomers. [d] A single isomer (structure II) was isolated from this mixture, having mp 156.5–158°. This



I II III

isomer is assigned the erythro configuration having the gauche conformation on the basis of the coupling constant J_{ab} = 1.6 Hz. [e] This isomer is tentatively assigned the threo configuration having the anti conformation designated as structure III on the basis of the coupling constant J_{ab} = 9.0 Hz. (See ref 1c and references cited therein for discussion of spectral methods of structural assignment.) [f] Stereochemistry about the cyclopropyl ring has not been determined. [g] 12% of a lower melting (142–143°) geometrical isomer was also isolated. [h] Mixture of geometrical isomers. [i] Isolated products, yields not optimized.

Experimental Section

All melting points are uncorrected. The nmr spectra were obtained in $CDCl_3$ using a Varian A-60 spectrometer with TMS = 0. Microanalyses and molecular weight determinations were performed by Dr. C. S. Yeh and staff of the Purdue University Microanalysis Laboratories or Atlantic Microlab, Inc. *n*-Butyllithium was purchased from Alfa Inorganics as a 2.1 *M* solution in hexane. Reagent grade THF was distilled from $LiAlH_4$ prior to use and all reactions were carried out under a dry nitrogen atmosphere. Aldehydes, olefins, and imines were obtained commercially in reagent grade purity.

Chloromethanesulfonmorpholide.—To a solution of triethylamine (9.58 g, 0.11 mol) and morpholine (11.12 g, 0.11 mol) in 200 ml of tetrahydrofuran stirred under nitrogen at 0° was slowly added a solution of chloromethanesulfonyl chloride (16.30 g, 0.11 mol) in 50 ml of tetrahydrofuran. The mixture was stirred for 1 hr, the precipitated triethylamine hydrochloride was filtered, and the filtrate was evaporated *in vacuo*. The resultant solid was recrystallized from 90% ethanol to afford 16.68 g (76%) of the amide, mp 70.5–71.0°, nmr δ 3.48 (m, 4), 3.72 (m, 4), 4.52 (s, 2).

Anal. Calcd for $C_5H_{10}ClNSO_3$: C, 30.18; H, 5.05; Cl, 17.79. Found: C, 30.30; H, 5.10; Cl, 17.70.

General Procedure for the Condensation of α-Chloromethyllithiumsulfonmorpholide with Carbonyl Compounds.—To a solution of 0.01 mol of chloromethanesulfonmorpholide in 30 ml of THF at −78° was added *n*-butyllithium (0.01 mol, in hexane) while maintaining the temperature below −60°. Immediately upon completion of the addition, the carbonyl compound (0.011 mol) was added and the resulting mixture was stirred at −60 to −65° for 15–20 min, and quenched with 100 ml of a 3% aqueous solution of NH_4Cl. The resultant mixture was extracted with four 50-ml portions of chloroform; the chloroform extracts were dried over Na_2SO_4 and evaporated *in vacuo* to yield the β-hydroxy-α-chlorosulfonamide as either a white solid or a light yellow oil which was purified by appropriate procedures.

1-Chloro-2-hydroxypropanesulfonmorpholide (6).—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol) and acetaldehyde (0.62 ml, 0.011 mol) gave 2.30 g of a viscous yellow oil which could not be induced to crystallize. The oil was therefore washed with cold hexane and cold diethyl ether and subjected to evaporation *in vacuo* for 24 hr. The resultant yellow oil, 2.20 g (90%), gave analytical and spectral evidence of being a diastereomeric mixture of **6**: nmr δ 1.30 (overlapping d, 6, J = 5.0 Hz, $-CH_3$), 3.60 (m, 9, morpholine ring protons plus −OH), 4.42 (m, 1, −CHOH), 4.72 (d, 1, J = 1.5 Hz, erthyro isomer), 4.82 (d, 1, J = 5.0 Hz, threo isomer); mol wt calcd 243, found (mass spectrum) 243.

Anal. Calcd for $C_7H_{14}ClNO_4S$: C, 34.53; H, 5.75; Cl, 14.58. Found: C, 34.40; H, 5.90; Cl, 14.29.

1-Chloro-2-hydroxy-3-methylbutanesulfonmorpholide (7).—Chloromethanesulfonmorpholide (3.00 g, 0.015 mol), *n*-butyllithium (0.015 mol), and isobutylaldehyde (1.23 g, 0.017 mol) afforded a light yellow oil which was taken up in an ether–petroleum ether (bp 30–60°) mixture and cooled to afford a white solid, 2.75 g (68%), which was a diastereomeric mixture of **7**, mp 114–120°, nmr δ 1.00 (m, 6), 2.22 (m, 1), 3.61 (m, 9), 4.02 (m, 1), 4.66 (m, 1).

Anal. Calcd for $C_9H_{18}ClNO_4S$: C, 39.88; H, 6.84; S, 11.40; mol wt, 272. Found: C, 39.98; H, 6.70; S, 11.58; mol wt (in benzene), 269.

1-Chloro-2-hydroxy-2-phenylethanesulfonmorpholide (8).—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and benzaldehyde (1.17 g, 0.011 mol) afforded a yellow oil which upon crystallization and recrystallization from 95% ethanol gave 1.19 g (39%) of diastereomeric **8**, mp 138–155°, nmr δ 3.65 (m, 9), 4.90–5.80 (m, 2), 7.50 (s, 5).

Anal. Calcd for $C_{12}H_{16}ClNO_4S$: C, 47.12; H, 5.24; Cl, 11.61. Found: C, 46.72; H, 5.34; Cl, 11.52.

Repeated fractional crystallization from 95% ethanol gave 0.62 g (20%) of one pure diastereomer, mp 156.5–158°, which was assigned the erythro configuration (see Table I) on the basis of the nmr spectrum: δ 3.21 (d, 1, J = 4.0 Hz, –OH), 3.70 (m, 8), 4.87 d, 1, J = 1.6 Hz, >CHCl), 5.67 (m, 1, >CHOH). This isomer also gave a satisfactory analysis for $C_{12}H_{16}ClNO_4S$.

1-Chloro-2-hydroxy-2-(*o*-chlorophenyl)ethanesulfonmorpholide (9).—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol) and *o*-chlorobenzaldehyde (1.55 g, 0.011 mol) gave, after recrystallization of the crude product from 95% ethanol, 3.16 g (93%) of diastereomeric **9**, mp 108–141°, nmr δ 3.62 (m, 10), 5.30 (m, 1), 7.60 (m, 4).

Anal. Calcd for $C_{12}H_{15}Cl_2NO_4S$: C, 42.50; H, 4.41; Cl, 20.82. Found: C, 42.46; H, 4.56; Cl, 21.01.

1-Chloro-2-hydroxy-2-(*m*-methoxyphenyl)ethanesulfonmorpholide (10).—Chloromethanesulfonmorpholide (2.20 g, 0.011 mol), *n*-butyllithium (0.011 mol), and *m*-methoxybenzaldehyde (1.53 g, 0.0112 mol) afforded a yellow oil which was recrystallized from 90% ethanol to give a white solid, which was further recrystallized from benzene–hexane to yield 3.00 g (81%) of **10**, tentatively assigned the threo configuration (see Table I), mp 110–111.50°, nmr δ 3.50 (m, 5), 3.72 (m, 4), 3.82 (s, 3), 4.82 (d, 2, J = 9.0 Hz), 5.14 (d, 2, J = 9.0 Hz), 7.12 (m, 4).

Anal. Calcd for $C_{13}H_{18}ClNO_5S$: C, 46.50; H, 5.49; Cl, 10.59; S, 9.56. Found: C, 46.47; H, 5.61; Cl, 10.81; S, 9.27.

General Procedure for Cyclopropane Formation from α-Chloromethyllithium Sulfonamides and Activated Olefins.—To chloromethanesulfonmorpholide (0.020 mol) in 50 ml of dry THF at −75° under N_2 was added *n*-butyllithium (0.020 mol in hexane) while maintaining the temperature below −60°. The olefin (0.021 mol) was then added in THF and the reaction mixture was stirred for 10–15 min and quenched with 150 ml of 3% aqueous NH_4Cl. The resultant mixture was extracted with 5 × 40 ml of chloroform, and the combined chloroform extracts were dried over Na_2SO_4 and then evaporated *in vacuo*, yielding the cyclopropane as a white solid which was recrystallized from ethanol.

Reaction of α-Chloromethyllithiumsulfonmorpholide with *trans*-1-Phenylsulfonyl-2-phenylethene.—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and *trans*-1-phenylsulfonyl-2-phenylethene (2.68 g, 0.011 mol) afforded 2.92 g (73%) of **12**, mp 175–176.5° (geometric stereochemistry was undefined). In addition 0.45 g (12%) of a second cis–trans configurational isomer was obtained, mp 142–143°. The minor component was much more soluble in 95% ethanol than the major component, nmr of which showed δ 3.10 (m, 4), 3.38 (m, 2), 3.63 (m, 5), 7.28 (s, 5), 7.82 (m, 5).

Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C, 56.28; H, 5.19; N, 3.43; S, 15.69; mol wt, 409. Found: C, 56.10; H, 5.28, N, 3.28; S, 15.55; mol wt (in acetone), 410.

Reaction of α-Chloromethyllithiumsulfonmorpholide with *trans*-Cinnamonitrile.—Chloromethanesulfonmorpholide (2.00 g, 0.01 mol), *n*-butyllithium (0.01 mol), and *trans*-cinnamonitrile (1.42 g, 0.011 mol) gave 2.06 g (70%) of a mixture of geometrical isomers of **13**, mp 143–148 and 165–169°, nmr δ 2.58 (q. 1, J = 5.0 Hz), 3.38 (m, 5), 3.78 (m, 4), 7.40 (s, 5).

Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.55; H, 5.48; N, 9.58; S, 10.95; mol wt, 292. Found: C, 57.63; H, 5.67; N, 9.88; S, 10.91; mol wt (in benzene), 297.

Reaction of α-Chloromethyllithiumsulfonmorpholide with β-Nitrostyrene.—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and β-nitrostyrene (1.53 g, 0.011 mol) gave 0.72 g (21%) of geometric isomers of **14**, mp 162–171°, nmr δ 4.26 (q, 1), 3.38 (m, 5), 3.80 (m, 4), 7.40 (s, 5).

Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 50.01; H, 5.14; S, 10.22. Found: C, 49.87; H, 5.26; S, 10.25.

Reaction of α-Chloromethyllithiumsulfonmorpholide with *N*-Benzylideneaniline.—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and *N*-benzylideneaniline (1.99 g, 0.011 mol) gave 2.36 g (69%) of **11**, nmr δ 3.60 (m, 8), 5.20 (m, 2), 7.50 (m, 10).

Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.95; H, 5.82. Found: C, 62.80; H, 5.96.

Registry No.—**1**, 23917-17-1; (*R**,*R**)-**6**, 39542-15-9; (*R**,*S**)-**6**, 39542-16-0; (*R**,*R**)-**7**, 39542-17-1; (*R**,*S**)-**7**, 39542-18-2; *erythro*-**8**, 39542-19-3; (*R**,*R**)-**9**, 39542-20-6; (*R**,*S**)-**9**, 39542-21-7; *threo*-**10**, 39542-22-8; **11**, 39542-23-9; **12**, 39542-24-0; **13**, 39542-25-1; **14**, 39542-26-2; chloromethanesulfonmorpholide, 39542-27-3; triethylamine, 121-44-8; morpholine, 110-91-8; chloromethanesulfonyl chloride, 3518-65-8; *n*-butyllithium, 109-72-8.

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A Stereospecific Synthesis of (±)-(*E*)-Nuciferol *via* the [2,3]-Sigmatropic Rearrangement of Allylic Sulfoxides

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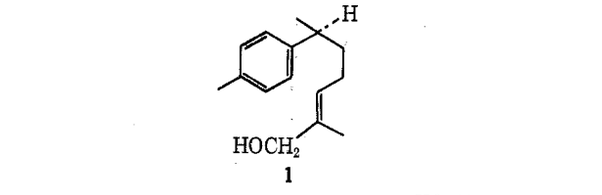
We wish to report a convenient four-step synthesis of racemic (*E*)-nuciferol (**1**)[1] utilizing the concerted nature of the [2,3]-sigmatropic rearrangement[2] of allylic sulfoxides to allylic sulfenate esters (eq 1).



The completely stereospecific nature of the allylic sulfoxide–sulfenate interconversion resulting in the synthesis of trisubstituted olefins of type **5** was recently reported by one of us.[3]

Reduction[4] of β-methyl-4-methylcinnamic acid with excess lithium in liquid ammonia proceeded cleanly to give a 98% yield of the crystalline saturated acid **2a**, mp 90–90.5° (lit.[5] mp 91°). Further reduction of acid **2a** with lithium aluminum hydride afforded a nearly quantitative yield of alcohol **2b**. Standard

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