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β-Sulfinyl acrylate esters as a convenient source of alkane- and arenesulfenate anions

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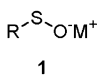
Abstract—Methyl acrylate esters bearing alkane- and arenesulfinyl units on the 2-carbon liberate sulfenate anions upon nucleophilic attack. The sulfenates are readily captured through sulfur alkylation. When a sulfenate derived from *R*-cysteine is generated, diastereoselective benzylation is observed.

Sulfenic acid anions, compounds possessing the general structure **1**,[1–3] have well established value in organic chemistry as precursors to sulfoxides,[4–15] sulfenamides[9,10] and protected[16] as well as unprotected thiols.[17] Furthermore, these species have been implicated in important biological mechanisms[18–23] particularly as intermediates in the oxidation of cysteine residues of proteins[18–20] and as a reactive component along the mechanistic pathway by which thiols activate leinamycin for DNA alkylation.[22,23]

Modern approaches to selected sulfenate anions involve sulfur oxidation chemistry,[7,24] an addition–elimination approach,[5] ring opening[4,6,8,11,13–15] or ring manipulation protocols,[12] a [2,3]-sigmatropic rearrangement[17] and a metal insertion reaction ultimately creating a zinc sulfenate.[25] These different methods have produced 1-alkenesulfenates,[6,8–11,13,14] dienesulfenates,[15] (het)arenesulfenates[5,7,25] and a limited number of alkanesulfenates.[5,12,17] In the latter cases, cyclopropanesulfenate (**2**) is available through an anionic ring contraction protocol[12] and sulfenates with a homoallyl component attached to sulfur arise from the aforementioned sigmatropic rearrangement.[17]



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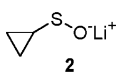

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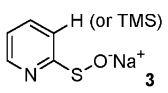

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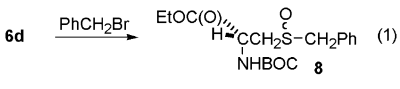
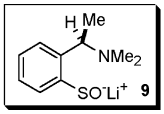
Once a sulfenate has been generated in solution, the common method for establishing its structure is through alkylation at sulfur[1] and characterization of the resulting sulfoxide. The alkylation can proceed in a diastereoselective fashion under suitable conditions.[24] Furukawa has described particular heteroaromatic sulfenate anions **3** which can be isolated and characterized directly by IR spectroscopy.[5] Despite the number of interesting and useful advances in this area, it would appear as recently stated,[24] that a general procedure to sulfenic acid anions, one suitable for a large and varied selection of substituents on sulfur, has yet to be established.

While our group was pursuing the Grignard reactions of optically enriched α,β-unsaturated esters, we noted that an alkenyl sulfoxide possessing a (*E*)-2-carbomethoxyethenyl unit displayed electrophilic character toward alkoxide and that chemistry led to a sulfenate anions.[26] For this communication, we have examined this reaction and demonstrate its general relevance as a valuable and straightforward method for the generation of both alkane- and arenesulfenate anions.

The requisite starting materials (**4**, Table 1) are easily prepared by treating methyl propiolate with a thiol under basic conditions.[27] This protocol usually affords both *E*/*Z* isomers which are immediately oxidized to a mixture of isomeric sulfoxides. Experiments show that the makeup of the isomeric mixture is not critical to the outcome of the next reaction.





Keywords: sulfenate; sulfoxide; alkylation; sulfinylcysteine.
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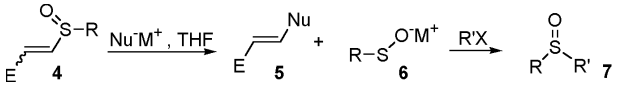
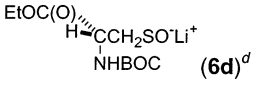
Table 1. Yields of sulfoxide recovered in the sulfenate generation reactions



Entry	RSO⁻M⁺(**6**)[a]	Nu⁻M⁺ (equiv.)	R′X	Yield of **7**[b]
1	*p*-TolSO⁻Na⁺	MeO⁻Na⁺ (1.02)	BnBr	84
2	*p*-MeC(O)NHC$_6$H$_4$SO⁻Na⁺		BnBr	50
3	BnSO⁻Na⁺		BnBr	13–84
4	*n*-C$_6$H$_{13}$SO⁻Na⁺		BnBr	77
5	*n*-C$_6$H$_{13}$SO⁻Na⁺		MeI	83
6	*n*-C$_{16}$H$_{33}$SO⁻Na⁺		BnBr	61
7	*n*-C$_{16}$H$_{33}$SO⁻Na⁺		MeI	63
8	c-C$_6$H$_{11}$SO⁻Na⁺		BnBr	65
9	MeSO⁻Na⁺		BnBr	0–27
10	*p*-TolSO⁻Li⁺	*c*-C$_6$H$_{11}$O⁻Li⁺ (1.2)	MeI	71
11	*p*-TolSO⁻Li⁺		BnBr	85
12	*cis*-*p*-TolSO⁻Li⁺		BnBr	88
13	*trans*-*p*-TolSO⁻Li⁺		BnBr	81
14	BnSO⁻Li⁺		BnBr	63–80
15	*n*-C$_6$H$_{13}$SO⁻Li⁺		BnBr	85
16	*n*-C$_{16}$H$_{33}$SO⁻Li⁺		BnBr	76
17	MeSO⁻Li⁺ (**6a**)		BnBr	75
18	MeSO⁻Li⁺ (**6a**)	*c*-C$_6$H$_{11}$S⁻Li⁺ (1.0)	BnBr	62
19	BnSO⁻Li⁺ (**6b**)		BnBr	75
20	CH$_2$(CH$_2$SO⁻Li⁺)$_2$ (**6c**)[c]		BnBr	74
21	 (**6d**)[d]		BnBr	46

[a] The starting sulfoxide was a mixture of double bond isomers in each case unless otherwise indicated.
[b] Yield of chromatographically pure sulfoxides recovered from the two step reaction sequence of sulfenate liberation and then alkylation. All new sulfoxides (**7** and **4**) gave suitable spectroscopic and analysis data.
[c] Bissulfenate **6c** was liberated with 2 equiv. of *c*-C$_6$H$_{11}$S⁻Li⁺ and captured with 2 equiv. of PhCH$_2$Br to give two diastereomeric bissulfoxides in a 3:4 ratio.
[d] Benzylation of sulfenate **6d** gave a mixture of diastereomers, see text.

Three sets of conditions were chosen to effect nucleophile induced liberation of sulfenates from the acrylate substrates. After base addition, each mixture was quenched with a reactive alkyl halide and was warmed slowly to room temperature. The results of several reactions are outlined in Table 1. Following the lead of Furukawa,[5] sodium methoxide was initially tried. A commercial source proved convenient, but yields of isolated sulfoxide rarely reached 80% and the benzyl and methyl systems routinely gave irreproducible results. Lithium cyclohexanolate, the nucleophile that introduced us to this chemistry,[26] gave improved yields and was a reliable source of lithium methanesulfenate (**6a**) as judged by dependable sulfoxide yield, yet benzyl sulfoxide recovery was still somewhat variable. Since deprotonation α to the sulfinyl was viewed as a possible competitive reaction, lithium cyclohexanethiolate was also employed as a more nucleophilic, less basic alternative. That reagent successfully liberated benzyl sulfenate **6b** and brought about eventual sulfoxide formation in a reproducible 76% yield. A by-product in all reaction mixtures was the product of displacement of the sulfenate unit as indicated in the reaction equation (Table 1). The alkene so obtained (**5**) is consistent with an addition–elimination pathway for this chemistry.[†]

[†] **Spectral date for new sulfoxides**. Precursor sulfoxide to **6c**, one diastereomer, *E*,*E*-configuration. ^{1}H NMR (400 MHz), δ: 7.54 (d, *J*=15.0 Hz, 2H), 6.57 (d, *J*=15.0 Hz, 2H), 3.74 (s, 6H), 3.06 (m, 2H), 2.82 (m, 2H), 2.37 (m, 1H), 2.17 (m, 1H); ^{13}C NMR (100.6 MHz), δ: 163.9, 148.8, 126.6, 52.3, 50.0, 15.7; IR ($CDCl_3$), cm^{-1}: 3071, 2954, 1728, 1622, 1437, 1068, 1031, 959; MS (EI), *m*/*z* (%): 308 (M$^+$, <1), 191 (5), 175 (100), 102 (8), 89 (11), 59 (8). Anal. calcd for C$_{11}$H$_{16}$O$_6$S$_2$: C, 42.84; H, 5.23. Found: C, 42.67; H, 5.11.

Precursor sulfoxide to **6d**, one diastereomer, *E*-configuration. ^{1}H NMR (400 MHz), δ: 7.63 (d, *J*=15.0 Hz, 1H), 6.63 (d, *J*=14.9 Hz, 1H), 5.78 (br m, 1H), 4.58 (br m, 1H), 4.18 (q, *J*=6.7 Hz, 2H), 3.76 (s, 3H), 3.43 (dd, *J*=13.3 and 8.6 Hz, 1H), 3.22 (m, 1H), 1.39 (s, 9H), 1.24 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100.6 MHz), δ: 169.9, 163.9, 155.2, 149.6, 126.0, 80.5, 62.2, 54.3, 52.3, 49.7, 28.1, 14.0; IR ($CDCl_3$), cm^{-1}: 3428, 3058, 2983, 1746, 1715, 1695, 1061; MS (EI), *m*/*z* (%): no M$^+$ peak, 276 (5), 249 (7), 217 (7), 176 (7), 160 (94), 159 (10), 116 (17), 114 (8), 102 (8), 57 (100). Anal. calcd for C$_{14}$H$_{23}$NO$_7$S: C, 48.13; H, 6.64; Found: C, 48.13; H, 6.56.

n-Hexadecyl benzyl sulfoxide. ^{1}H NMR (400 MHz), δ: 7.32 (m, 5H), 3.97 (AB$_q$, *J*=12.9 Hz, 2H), 2.55 (t, *J*=8.0 Hz, 2H), 1.72 (m, 2H), 1.29 (m, 2H), 1.24 (br s, 24H), 0.86 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100.6 MHz), δ: 130.1, 130.0, 128.9, 128.3, 58.2, 50.9, 31.9, 29.7, 29.6 (2C), 29.5 (4C), 29.3 (2C), 29.2, 28.8, 22.7, 22.4, 14.1; IR

To our knowledge, methanesulfenate (**6a**) has been reported once before, and was produced under the very harsh setting of reducing metal conditions. The reduction of DMSO affords sodium (or potassium) methanesulfenate and a dimsyl anion.[28] Clearly a synthetic manipulation of the sulfenate requires first voiding the higher reactivity of the dimsyl anion. The formation of all sulfenates **6** including methanesulfenate in this work happens under substantially milder conditions and the trapping chemistry is not affected by the by-product, an unreactive, comparatively non-polar, push–pull alkene (**5**). The addition–elimination sequence of Furukawa[5] which is suitable for arenesulfenates was applied to adamantanesulfenate as the lone alkanesulfenate and the yield of sulfoxide was only 26%. Overall, the method reported herein is a general approach for the formation of alkanesulfenate anions.

A number of organometallic sulfenato complexes have been prepared and characterized[29–32] and have shown utility, for example, as models for nickel containing enzymes.[29] Their preparation can be viewed as being achieved through complexation of a sulfenate with a metal although they are commonly arrived at through sulfur oxidation of thiolato complexes.[29–32] Bifunctional species **6c** and **6d** or close derivatives of them may possess the necessary structure to serve as metal chelating agents and accordingly introduce a new preparative motif for these important organometallic compounds.

As a final note, amino acid derivative **8** was isolated in 46% yield, in a diastereomeric ratio of 82:18 (Eq. (1)). Crystallization of that sample gave 73% mass recovery (ca. 55 mg) of an optically pure (^{1}H NMR) material ($[\alpha]_D^{23} = -69.4°$ ($CHCl_3$)). The absolute configuration of enantiopure **8** has been tentatively assigned (R_S,R_C), based on comparison to a related compound.[33] Such diastereoselective alkylations have been observed by the Perrio group who noted that sulfenate **9** could be alkylated with *dr*'s of ca. 4:1 to 49:1. Those authors suggest that internal complexation contributes to the observed selectivity.[24] Since *S*-alkylcysteine sulfoxides are important substances with a variety of applications,[34] our system will be the subject of a full investigation in order to optimize this chemistry and establish the origin of the stereoinduction.

In summary, we unveil β-alkanesulfinyl acrylates as the first general source of alkanesulfenates anions. By demonstrating the broad applicability of this chemistry we have introduced what appears to be the first bifunctional sulfenate dianion (**6c**). The discovery that sulfenate **6d** shows stereoselection during alkylation opens the door to a conceptually novel preparative mode for sulfoxides of *S*-alkylcysteines.

General experimental: To a solution of α,β-unsaturated sulfoxide (**4**, ca. 100 mg, 1 equiv.) in dry THF (1 mL/10 mg) at −78°C was added a solution of *c*-$C_6H_{11}S^-$ (or O^-)Li^+ in THF (1–2 mL) (or MeO^-Na^+ as a 25% solution in MeOH) and stirring proceeded for 20 min. A −78°C solution of RX (1.2 equiv.) in THF (1–2 mL) was then added and the reaction mixture stirred overnight with slow warming to rt. The mixture was filtered through a bed of Celite,™ and concd crude sulfoxide (**7**) was purified by flash chromatography on SiO_2 using EtOAc/hexanes as the eluant.

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($CDCl_3$), cm^{-1}: 2928, 2855, 1029, 791; MS (CI, NH_3), *m*/*z* (%): 365 ($(M+H)^+$, 53), 292 (33), 292 (86), 291 (28), 289 (12), 258 (92), 257 (13), 256 (100), 176 (14), 116 (21), 91 (92). Anal. calcd for $C_{23}H_{40}OS$: C, 75.76; H, 11.06; Found: C, 75.59; H, 10.96.

1,3-Bis(benzylsulfinyl)propane, mixture of diastereomers. ^{1}H NMR (400 MHz), δ: 7.35 (m 6H), 7.26 (m, 4H), 3.98 (AB_q, J=12.0 Hz, 4H, major isomer), 3.97 (AB_q, J=12.9 Hz, 4H, minor isomer), 2.68 (m, 4H), 2.27 (m, 2H); ^{13}C NMR (100.6 MHz), δ: 129.9, 129.3, 129.0, 128.5, 58.3, 58.2, 49.1, 48.9, 16.6, 16.1; IR (CH_2Cl_2), cm^{-1}: 3054, 2987, 1422, 1255, 1045, 896. Anal. calcd for $C_{17}H_{20}O_2S_2$: C, 63.71; H, 6.24; Found: C, 63.52; H, 6.28.

Sulfoxide **8**. $[\alpha]_D^{23}$: −69.4° (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz), δ: 7.33 (m, 5H), 5.72 (br d, J=7.8 Hz, 1H), 4.65 (br m, 1H), 4.19 (q, J=7.1 Hz, 2H), 4.04 (ABq, J=13.0 Hz, 2H), 3.09 (ABX pattern, J_{AB}=13.0 Hz, J_{AX}=7.8 Hz, J_{BX}=3.4 Hz, 2H) 1.42 (s, 9H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz), δ: 170.3, 155.3, 130.1, 129.3, 129.0, 128.6, 80.3, 62.0, 59.0, 52.0, 50.2, 28.2, 14.0; IR ($CDCl_3$), cm^{-1}: 3432, 3033, 2983, 2934, 1740, 1711, 1503, 1369, 1311, 1254, 1161, 1029, 855, 790. Anal. calcd for $C_{17}H_{25}O_5NS$: C, 57.44; H, 7.03; Found: C, 57.66; H, 7.17.

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