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Radical-mediated thiodesulfonylation of the vinyl sulfones: access to (α-fluoro)vinyl sulfides

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ABSTRACT

Radical-mediated thiodesulfonylation of the vinyl and (α-fluoro)vinyl sulfones, derived from aldehydes and ketones, with aryl thiols in organic or aqueous medium provided access to vinyl and (α-fluoro)vinyl sulfides. The vinyl sulfides were formed predominantly with *E* stereochemistry independent of the stereochemistry of the starting vinyl sulfones.

Vinyl sulfides are valuable tools in organic synthesis and are used as enolate ion equivalents,[1] as components of [2+2] cycloadditions,[2] and as substrates in transition metal-catalyzed carbon–carbon bond forming reactions.[3] Methods for the synthesis of 1-alkenyl sulfides include Wittig reaction,[4] ionic and radical additions of thiols to alkynes,[5] coupling of 1-alkenyl halides with thiols,[6–9] and transition metal-catalyzed *anti*-Markovnikov hydrothiolation[9–12] of alkynes with arenethiols and alkanethiols to produce *E* isomers, including hydrothiolation in water medium.[13]

Vinyl sulfonium ions, generated via the biological methylation of the corresponding vinyl sulfides, act as inhibitors of thioether *S*-methyltransferase[14] and proteolytic enzyme papain.[15] They are highly reactive toward nucleophiles and bind covalently to DNA, RNA, and proteins in vivo.[16] Moreover, vinyl sulfonium salts are more electrophilic than the corresponding vinyl sulfones, which are known for their ability to inhibit cysteine proteases.[17,18]

The (α-halo)vinyl sulfides can be prepared by Wittig–Horner reactions with diethyl chloro(phenylthio)methanephosphonate[19] or by addition of the hydrogen halides (HI, HBr, and HCl) to acetylenic sulfides (chalcogenides).[20] The regioselectivity and stereoselectivity of such additions were improved when equivalent quantities of hydrogen halide, generated in situ from trimethylsilyl halides and anhydrous methanol, were utilized[21] instead of excess aqueous HX or saturated gaseous HX in benzene. The (α-halo)vinyl sulfides have been employed in Stille,[21,22] Negishi,[22] and Sonogashira[23] couplings, Friedel–Crafts vinylation,[24] and other transformations.[21,25,26]

Removal of the sulfonyl group from the vinylic carbon is usually achieved by reductive methods[27] or by addition–elimination processes in which the sulfonyl group is replaced, for example, with tributylstannyl substituent.[28–30] The latter can be then conveniently removed by protiodestanylation or utilized in other synthetic transformations.[29,31] Heating of the vinyl arylsulfones with tris(trimethylsilyl)silane or germane at reflux in benzene or toluene effected substitution of a sulfonyl group with a silyl or germyl group to give vinyl silanes or germanes including α-fluoro substituted analogues.[32,33]

Herein, we report stereoselective radical-mediated thiodesulfonylations of vinyl and (α-fluoro)vinyl sulfones with aryl thiols to provide access to vinyl and (α-fluoro)vinyl sulfides. Such thiodesulfonylation provides a flexible alternative to the hydrothiolation of alkynes with thiols under radical or metal catalysis conditions. It also offers convenient preparations of (α-fluoro)vinyl sulfides—a class of interesting fluoroalkenes which remain unexplored.[34] The thiodesulfonylation can also be viewed as reductive deoxygenation of sulfones to the corresponding sulfides—a transformation which requires harsh conditions incompatible with most functional groups.[35]

Treatment of the sulfonyl-stabilized enolates generated from diethyl (phenylsulfonyl)methylphosphonate with aliphatic and aromatic aldehydes and ketones **1a–g** gave the corresponding *E*-vinyl sulfones **2a–f** and vinyl sulfone **2g** (72–95%, Scheme 1).[32] Analogous treatment of **1a–h** with diethyl fluoro(phenylsulfonyl)methylphosphonate produced (α-fluoro)vinyl sulfones **3a–h**.[31,32]

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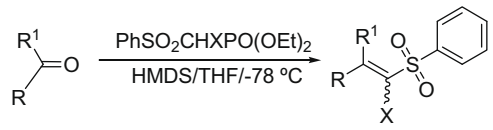


1

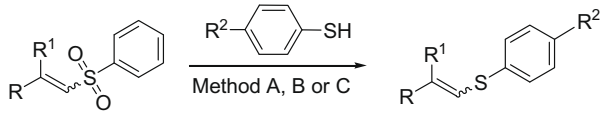
Series:	R	R^1
a	C_6H_5	H
b	4-$(CH_3)C_6H_4$	H
c	4-$(CF_3)C_6H_4$	H
d	3,4-$(MeO)_2C_6H_3$	H
e	$C_6H_5CH_2CH_2$	H
f	*c*-C_6H_{11}	H
g	-$(CH_2)_5$-	
h	C_6H_5	CH_3

Scheme 1. Synthesis of *E*-vinyl and (*E*/*Z*)-(α-fluoro)vinyl sulfones.

Reaction of the conjugated vinyl sulfone *E*-**2a** with benzenethiol (2 equiv) in the presence of ACCN as a radical initiator at reflux in toluene (12 h) produced the vinyl sulfide **4a** (61%; Scheme 2; Table 1, entry 1). The radical thiodesulfonylation was also effective in aqueous[36] medium. Thus, treatment of *E*-**2a** with benzenethiol/ACCN or AIBN in water (100 °C) produced sulfide **4a** in 71% and 65% yields (entry 2). Replacement of water with MeOH or EtOH produced a homogenous reaction mixture and did not affect the yield of the thiodesulfonylation reaction (entry 3). The reaction has a general character since the presence of the alkyl (series b), electron-withdrawing (CF_3, series c), or electron-donating (MeO, series d) groups on the phenyl ring attached to the double bond had only modest effect on rate and yield of thiodesulfonylation reactions with benzenethiol (entries 11–15, 18–20).

Treatment of the vinyl sulfones derived from the aliphatic aldehydes (series e and f) with benzenethiol/AIBN or ACCN under protic and aprotic conditions did not yield the corresponding vinyl sulfides (entries 21 and 22). However, sulfone **2g**, derived from cyclohexanone, underwent thiodesulfonylation reaction affording sulfide **4g** (entries 23 and 24), demonstrating that the thiodesulfonylation can serve as a convenient method for the synthesis of the trisubstituted vinyl sulfides.

Thermal reaction of *E*-**2a** with benzenethiol without radical initiators produced **4a** but in lower yield (entry 2). Likewise, the replacement of benzenethiol with phenyl disulfide also effected conversion of the sulfone **2a** to the sulfide **4a** in low yield, although reaction required longer time (entry 4). However, reaction of **2a** with phenyl disulfide without radical initiator failed to afford **4a**.



2

Series:	R	R^1
a	C_6H_5	H
b	4-$(CH_3)C_6H_4$	H
c	4-$(CF_3)C_6H_4$	H
d	3,4-$(MeO)_2C_6H_3$	H
e	$C_6H_5CH_2CH_2$	H
f	*c*-C_6H_{11}	H
g	-$(CH_2)_5$-	

4 R^2 = H
5 R^2 = CH_3
6 R^2 = NH_2
7 R^2 = CO_2Me

Scheme 2. Thiodesulfonylation of vinyl sulfones. Synthesis of vinyl sulfides.

Table 1
Synthesis of vinyl sulfides via thiodesulfonylation of vinyl sulfones

Entry	Sulfone	Method[a]	Product[b]	(*E*/*Z*)[c]	Yield[d]
1	**2a** (*E*)	A	**4a**	(95:5)	61
2	**2a** (*E*)	B	**4a**	(95:5)	71[e], 65[e,f], 10[e,g]
3	**2a** (*E*)	C	**4a**	(95:5)	70[e]
4	**2a** (*E*)	C	**4a**	(95:5)	20[e,h]
5	**2a** (*E*)	B	**5a**	(95:5)	61
6	**2a** (*E*)	B	**6a**	(98:2)	55
7	**2a** (*E*)	C	**7a**	(95:5)	85
8	**2a** (*Z*)	A	**4a**	(95:5)	65[e]
9	**2a** (*Z*)	B	**4a**	(95:5)	95[e]
10	**2a** (*Z*)	C	**4a**	(95:5)	70, (80[e])
11	**2b** (*E*)	A	**4b**	(85:15)	55[e]
12	**2b** (*E*)	B	**4b**	(85:15)	54, (63[e])
13	**2c** (*E*)	A	**4c**	(95:5)	59, (70[e]), 5[e,g]
14	**2c** (*E*)	B	**4c**	(95:5)	85[e], 80[e,f], 50[g]
15	**2c** (*E*)	C	**4c**	(95:5)	94[e], 96[e,i]
16	**2c** (*E*)	B	**5c**	(95:5)	58
17	**2c** (*E*)	B	**6c**	(95:5)	40, (55[e])
18	**2d** (*E*)	A	**4d**	(75:25)	55
19	**2d** (*E*)	B	**4d**	(75:25)	64[e]
20	**2d** (*E*)	C	**4d**	(85:15)	70[e]
21	**2e** (*E*)	A,B,C	**4e**		n.r.
22	**2f** (*E*)	A,B,C	**4f**		n.r.
23	**2g**	B	**4g**		55
24	**2g**	C	**4g**		76[e]
25	**2g**	C	**5g**		62

[a] Method A: thiol/ACCN/toluene/110 °C/12 h; Method B: thiol/ACCN/H_2O/100 °C/10 h; Method C: thiol/ACCN/MeOH/65 °C/10 h.
[b] Reactions were performed on 0.1–1.0 mmol scale of sulfones (0.05 mM) with 1.25–2.0 equiv of thiols and 0.1–0.5 equiv of ACCN or AIBN.
[c] Determined by GC–MS and/or ^{1}H NMR.
[d] Isolated yield.
[e] Based on GC–MS.
[f] AIBN instead of ACCN.
[g] Without ACCN.
[h] Disulfide instead of thiol, 16 h.
[i] In EtOH.

Treatment of *E*-**2a** with 4-methylbenzenethiol or 4-aminobenzenethiol in H_2O/ACCN produced the corresponding vinyl sulfides **5a** (61%) and **6a** (55%) (entries 5 and 6). Analogously, *E*-**2c** was converted to **5c** and **6c** (entries 16 and 17). Thiodesulfonylation of *E*-**2a** with 4-mercaptobenzoic acid ($R^2 = CO_2H$) in MeOH produced the methyl ester **7a** (85%; entry 7). Thus, thiodesulfonylation protocol is compatible with amino and carboxylate functional groups vulnerable to the oxidative and reductive procedures. Attempted thiodesulfonylations of **2a** or **2c**, as well as **3a**, with alkanethiols (2-mercaptoethanol, 1-propanethiol) or thioacetic acid under radical conditions did not produce the corresponding vinyl sulfides.

Radical-mediated thiodesulfonylation of the vinyl sulfones **2** occurred basically with retention of the *E* stereochemistry although small amounts of the *Z* isomers were detectable by GC–MS and ^{1}H NMR of the crude reaction mixtures (Table 1). In order to study stereochemical outcome of the thiodesulfonylation reactions *Z*-vinyl sulfone **2a** was prepared by anti-Markovnikov addition of PhSH/NaOH to phenylacetylene followed by the oxidation of the resulting (*Z*)-2-phenyl-1-phenylthioethene.[37] Treatment of *Z*-**2a** with PhSH in aqueous or organic medium produced sulfide **4a** in very good yields with inversion of stereochemistry (*E*/*Z*, 95:5; entries 8–10). Thus, the vinyl sulfides are formed predominantly with *E* stereochemistry independent of the stereochemistry of the starting vinyl sulfones.

Radical thiodesulfonylation permitted synthesis of the sparsely developed[34] (α-fluoro)vinyl sulfides **8**–**11** in high yields (Scheme

3). Thus, treatment of **3a** (*E*/*Z*, 96:4) with benzenethiol in organic or protic medium in the presence of ACCN gave *E*/*Z*-**8a** in good to excellent yields with the 'overall' retention of stereochemistry (Table 2, entries 1 and 2).

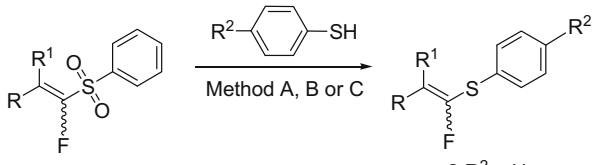
Thiodesulfonylation appears fairly general since sulfones **3b**, **3c,** and **3d** with the alkyl (Me), electron-withdrawing (CF_3), or electron-donating (MeO) substituents on the phenyl ring attached to the double bond also produced (α-fluoro)vinyl sulfides (entries 4–6, 9, and 10).[38] Thiodesulfonylation of α-fluoro sulfone **3b** (*E*/*Z*, 84:16; 0.5 equiv) with PhSH (1.0 equiv; Method C) in the presence of the parent α-H sulfone *E*-**2b** (0.5 equiv) showed that product **8b** [30 min (70%; *E*/*Z*, 93:7; with all *Z*-**3b** being consumed); 1 h (88%; *E*/*Z*, 93:7); 2 h (95%; *E*/*Z*, 93:7)] is formed faster than **4b** [30 min (35%, *E*/*Z*, 90:10), 1 h (45%, *E*/*Z*, 88:12); 2 h (48%; *E*/*Z*, 88:12)].

Treatment of the unconjugated sulfone **3e** or **3f** with benzenethiol produced the vinyl sulfide **8e** or **8f** in low yields (entries 11 and 12). Careful analysis of the crude reaction mixture indicated that Z-**3e** or *Z*-**3f** isomer was consumed during reactions to produce primarily *E*-sulfides, while the *E*-sulfones remained mostly unreacted. These results are in agreement with the lack of reactivity of *E*-**2e** and *E*-**2f** vinyl sulfones. Sulfone **3g** produced tetrasubstituted sulfide **8g** (entry 13).

Reaction of **3h** (*E*/*Z*, 57:43) with benzenethiol also afforded tetrasubstituted (α-fluoro)vinyl sulfide **8h** (*E*/*Z*, 50:50; entries 14 and 15). Thiodesulfonylation was not stereospecific since reactions of pure *E*-**3h** or *Z*-**3h** with benzenethiol also gave **8h** as mixture of *E*/*Z*-isomers (entries 16 and 17). Thiodesulfonylation occurred with other aromatic thiols to yield various vinyl sulfides (entries 3, 7, and 8, 18–20). It is noteworthy that hydrothiolation approaches are inapplicable for the synthesis of (α-fluoro)vinyl sulfides since the 1-fluoroalkynes are unstable and virtually unknown.[39]

Desulfonylation occurred probably via β-elimination of the sulfonyl radical from the radical intermediates formed after addition of PhS· to vinyl sulfones (presumably via a radical addition–elimination mechanism).[30,32] Lack of stereochemistry is probably the result of cis–trans isomerization of a radical intermediate leading predominantly to the formation of the more stable *E* isomers under thermal conditions.[5]

In summary, we have developed radical-mediated thiodesulfonylations of the vinyl and (α-fluoro)vinyl sulfones with aryl thiols to provide access to vinyl and (α-fluoro)vinyl sulfides. This method offers for the first time a general and bench-friendly procedure for the synthesis of (α-fluoro)vinyl sulfides.



3

8 R^2 = H
9 R^2 = CH_3
10 R^2 = NH_2
11 R^2 = CO_2Me

		R	R^1
Series:	**a**	C_6H_5	H
	b	4-$(CH_3)C_6H_4$	H
	c	4-$(CF_3)C_6H_4$	H
	d	3,4-$(MeO)_2C_6H_3$	H
	e	$C_6H_5CH_2CH_2$	H
	f	*c*-C_6H_{11}	H
	g	-$(CH_2)_5$-	
	h	C_6H_5	CH_3

Scheme 3. Thiodesulfonylation of (*E*/*Z*)-(α-fluoro)vinyl sulfones. Synthesis of (*E*/*Z*)-(α-fluoro)vinyl sulfides.

Table 2
Synthesis of (α-fluoro)vinyl sulfides via thiodesulfonylation of (α-fluoro)vinyl sulfones

Entry	Sulfone	Method[a]	Product[b]	(*E*/*Z*)[c]	Yield[d]
1	**3a** (96:4)	A	**8a**	(92:8)	92
2	**3a** (96:4)	B	**8a**	(94:6)	65[e]
3	**3a** (94:4)	A	**10a**	(83:17)	50
4	**3b** (86:14)	A	**8b**	(93:7)	82, 62[f]
5	**3b** (86:14)	B	**8b**	(92:8)	56
6	**3b** (86:14)	C	**8b**	(92:8)	92[f]
7	**3b** (86:14)	C	**9b**	(92:8)	90
8	**3b** (86:14)	C	**11b**	(94:6)	69[f]
9	**3c** (90:10)	B	**8c**	(93:7)	60[f], 72
10	**3d** (97:3)	B	**8d**	(93:7)	73
11	**3e** (88:12)	B	**8e**	(70:30)	10[g]
12	**3f** (84:16)	C	**8f**	(70:30)	12[h]
13	**3g**	B	**8g**		65
14	**3h** (57:43)	B	**8h**	(50:50)	58
15	**3h** (57:43)	C	**8h**	(50:50)	68
16	**3h** (100:0)	C	**8h**	(50:50)	85
17	**3h** (0:100)	C	**8h**	(33:67)	70
18	**3h** (100:0)	C	**9h**	(64:36)	96
19	**3h** (57:43)	B	**9h**	(50:50)	59
20	**3h** (57:43)	C	**11h**	(55:45)	42

[a] Method A: thiol/ACCN/toluene/110 °C/6 h; Method B: thiol/ACCN/H_2O/100 °C/6 h; Method C: thiol/ACCN/MeOH/65 °C/5 h.
[b] Reactions were performed on 0.1–0.5 mmol scale of sulfones (0.05 mM) with 1.25–2.0 equiv of thiols and 0.25–0.50 equiv of ACCN or AIBN.
[c] Determined by GC–MS and ^1H or ^{19}F NMR.
[d] Isolated yield.
[e] Reaction with phenyl disulfide gave **8a** (55%, Method B or C).
[f] AIBN instead of ACCN.
[g] 83% based on *Z*-**3e**.
[h] 75% based on *Z*-**3f**.

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38. *Typical procedure for thiodesulfonylation: (E/Z)-1-Fluoro-2-(3,4-dimethoxyphenyl)-1-phenylthioethene* (**8d**). Method B. Sulfone **3d**[40] (32 mg, 0.1 mmol; *E*/*Z*, 97:3) was suspended in H_2O (2 mL) under a N_2 atmosphere in a sealed tube and the resulting mixture was degassed for 30 min at rt. PhSH (18 mg, 17 μL, 0.2 mmol) and ACCN (7 mg, 0.03 mmol) were added and the heterogenous reaction mixture was heated at 105 °C (oil bath) for 6 h. The resulting brownish residue was partitioned ($CHCl_3$/H_2O/brine), and the organic layer was dried ($MgSO_4$), evaporated, and purified by column chromatography (hexane/EtOAc, 9:1) to give **8d** (21 mg, 73%: *E*/*Z*, 93:7): ^{19}F NMR ($CDCl_3$) δ −81.5 (d, J = 16.3 Hz, 0.07F), −88.2 (d, J = 32.4 Hz, 0.93F); HRMS calcd for $C_{16}H_{15}FNaO_2S$ [M+Na]$^+$: 313.0675; found: 313.0687; GC–MS (EI) *m*/*z* 290 (M$^+$; t_R = 29.32 min, *E*, t_R = 30.04 min, *Z*). *E*-**8d** had: ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 3.88 (s, 3H), 6.24 (d, J = 32.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.04 (dd, J = 2.1, 8.4 Hz, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.24–7.35 (m, 3H), 7.42–7.46 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.8 and 55.9 (CH_3), 110.1 (C5), 111.6 (d, J = 10.1 Hz, C2), 118.3 (d, J = 13.2 Hz, C_β), 122.2 (d, J = 7.5 Hz, C6), 125.9 (d, J = 6.0 Hz, C1), 127.5 (C4′), 129.3 (C3′), 129.5 (C2′), 132.6 (d, J = 3.7 Hz, C1′), 148.8 (C4), 149.1 (d, J = 3.1 Hz, C3), 150.6 (d, J = 301.7 Hz, C_α); *Z*-**8a** had: ^{1}H NMR δ 6.74 (d, J = 16.4 Hz).
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