SmI_2-Mediated Addition Reaction of α-Halomethylsulfones to Carbonyl Compounds. A Convenient Synthesis of β-Hydroxysulfones†

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Due to the chemoselective dehalogenation by SmI_2, the addition of α-halomethylsulfones to carbonyl compounds afforded β-hydroxysulfones. Those reactions with α-bromomethylsulfones gave the products in moderate to good yields. The SmI_2-mediated addition of *gem*-dihalomethylsulfones to ketones also afforded α-halo-β-hydroxysulfones in moderate yields.

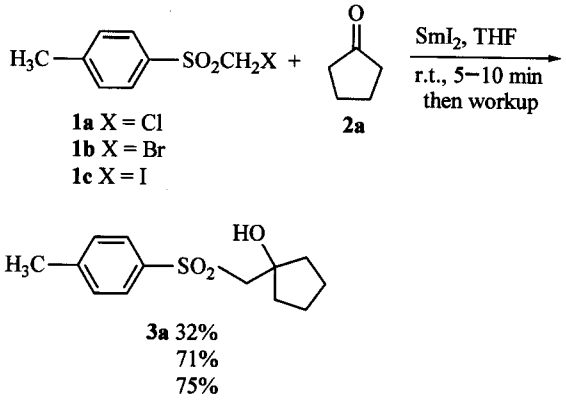
Keywords SmI_2-mediated addition, synthesis, β-hydroxysulfones, α-halo-β-hydroxysulfones

The SmI_2-mediated organic reactions exhibit great potential in the construction of new carbon-carbon bonds.[1] In SmI_2-Barbier conditions, the addition reactions of organic iodides to carbonyl compounds have become one of excellent alkylation protocols.[2] With an activating group such as oxygen[3] or sulfur[4] at the adjacent α-position, organic chlorides also served well as the alkylation reagents. By the reductive desulfonylation with SmI_2, some research groups realized the alkylation of carbonyl compounds with organic sulfones.[5]

On the other hand, β-hydroxysulfones, usually as the precursor of vinyl sulfones,[6] were prepared by the addition of α-metalized sulfones and carbonyl compounds[7] or the reduction of β-sulfonyl-substituted ketones.[8] With three different functional groups, α-halo-β-hydroxysulfones could be transformed into many organic compounds, while few methods were established to synthesize these compounds.[9] Herein, we wish to report a convenient synthesis of β-hydroxysulfones and α-halo-β-hydroxysulfones by the SmI_2-mediated addition reaction of α-halomethylsulfones or *gem*-dihalomethylsulfones to carbonyl compounds. Here, the following two challenges would be the key to the success of this strategy: (1) Chemoselective dehalogenation other than reductive desulfonylation will be required when halomethylsulfones are treated with SmI_2. (2) To synthesize α-halo-β-hydroxysulfones, the SmI_2-Barbier reaction of *gem*-dihalomethylsulfones and ketones must avoid over-reduction.

The reaction of α-chloromethyl *p*-tolylsulfone (**1a**) and cyclopentanone (**2a**) gave β-hydroxysulfones (**3a**) in only 32% yield and some low-polarity side products, which shows that dechlorogination and desulfonylation may co-exist in the reaction. Using α-bromomethylsulfone **1b**, the yield of compound **3a** increased to 71% although a small amount of desulfonylation products was also observed. When α-bromomethylsulfone **1b** was replaced with α-iodomethylsulfone **1c**, the product **3a** was obtained in 75% yield and desulfonylation reaction could not be completely suppressed yet (Scheme 1). So the bromide **1b** was more appropriate substrate, since it is inexpensive and easily available.[10]

Scheme 1



These reactions with acetone, cyclic ketones and alkyl aldehydes led to good results, which are summarized in Table 1. The alkylation of aryl aldehydes or ketones did not yield the expected products under the same conditions.

gem-Dihalomethylsulfones (**4**) can also undergo the same reaction to synthesize α-halo-β-hydroxysulfones (**5**). The results are summarized in Table 2. Two points should be noticed: (1) Two equiv. of SmI_2 were enough when synthesizing target products **5** (Entry 1, Table 2). More amount of SmI_2 led to the further dehalogenation to yield β-hydroxysulfones **3** (compare Entries 2 and 3 with

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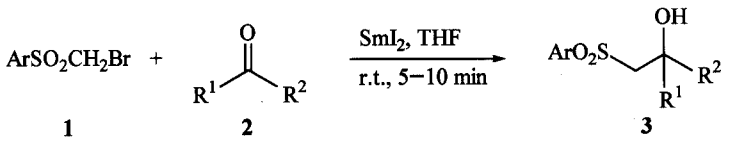
Table 1 Synthesis of β-hydroxysulfones by the SmI_2-mediated addition of α-bromomethylsulfones to carbonyl compounds[a]

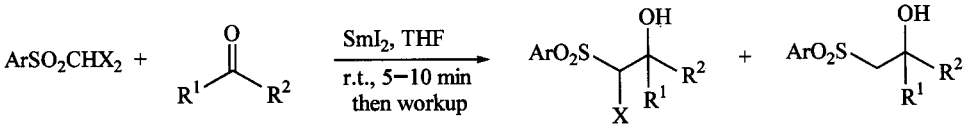


1 2 3

Entry	Ar (1)	R^1, R^2(2)	Product (3)	Yield[b](%)
1	4-MeC_6H_4(**1a**)	Me, Me (**2b**)	**3b**	61
2	**1a**	H, *n*-Pr (**2c**)	**3c**	78
3	**1a**	H, *n*-Bu (**2d**)	**3d**	70
4	Ph (**1d**)	**2b**	**3e**	60
5	**1d**	—$(CH_2)_5$— (**2e**)	**3f**	67

[a] To 2.0 equiv. of SmI_2/THF solution prepared *in situ* was added the mixture of 1.0 equiv. of α-bromomethylsulfone **1** and 1.0 equiv. of carbonyl compound **2** under a nitrogen atmosphere. The reaction was finished at room temperature in 5—10 min. [b] Pure compounds.

Table 2 Synthesis of α-halo-β-hydroxysulfones by the SmI_2-mediated addition of *gem*-dihalomethylsulfones to ketones[a]



4 2 5 3

Entry	Ar, X (4)	R^1, R^2(2)	SmI_2 (equiv.)	Product (5)	Yield[b](%) (5, 3)
1	4-MeC_6H_4, Br (**4a**)	—$(CH_2)_4$— (**2a**)	2	**5a**	50, 12
2	**4a**	**2a**	3	**5a**	45, 22
3	**4a**	**2a**	4	**5a**	15, 44
4	**4a**	Me, Me (**2b**)	2	**5b**	52, 15
5	4-MeC_6H_4, Cl (**4b**)	**2b**	2	**5c**	35, 0
6	Ph, Cl (**4c**)	**2b**	2	**5d**	40, 0

[a] To 2.0 equiv. of SmI_2/THF solution prepared *in situ* was added the mixture of 1.0 equiv. of *gem*-dihalomethylsulfone **4** and 1.0 equiv. of ketone **2** under a nitrogen atmosphere. The reaction was finished at room temperature in 5—10 min. [b] Pure compounds.

Entry 1, Table 2). (2) As what was observed with α-halomethylsulfones **1**, the reactions with *gem*-dibromides **4a** gave better results than those with *gem*-dichlorides **4b** and **4c** (compare Entry 4 with Entries 5 and 6, Table 2).

In conclusion, by the chemoselective debromination using SmI_2, the addition of α-bromomethylsulfones to carbonyl compounds provided a convenient synthesis of β-hydroxysulfones in good yields. In the presence of 2 equiv. of SmI_2, the addition reaction of *gem*-dihalomethylsulfones to ketones afforded α-halo-β-hydroxysulfones in moderate yields.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. THF was distilled from sodium/benzophenone immediately before use. α-Halomethylsulfones **1** and *gem*-dihalomethylsulfones **4** were prepared according to the reported methods.[10] All reactions were performed under a nitrogen atmosphere.

General procedure for the SmI_2*-mediated addition reaction of α-Halomethylsulfones* **1** *or gem-dihalomethylsulfones* **4** *to carbonyl compounds* **2**

Under a nitrogen atmosphere, to a dark blue SmI_2 (2.2 mmol) solution in THF, a mixture of carbonyl compound **2** (1.0 mmol), anhydrous THF (5 mL) and α-Halomethylsulfone **1** (or a *gem*-dihalomethylsulfone **4**) (1.0 mmol) were added at room temperature. After 5—10 min, the initial blue solution of SmI_2 turned yellow, indicating the end of the reaction. The mixture was worked up with the dilute HCl (0.1 N). Organic product was extracted twice with ether. The organic layers were washed with water, sodium thiosulfate, water and brine. After the solution was dried over $MgSO_4$, the solvent was removed. The product was separated from the residue through preparative TLC (silica gel) with petroleum ether (60—90 ℃)/ethyl

acetate as eluent to give β-hydroxysulfones **3** or α-halo-β-hydroxysulfones **5**.

1-[(*p-Tolylsulfonyl*) *methyl*]-*cyclopentan*-1-*ol* (**3a**) Oil; IR (neat) ν: 3560, 2990, 2900, 1615, 1310, 1150, 1090 cm^{-1}; ^1H NMR δ: 1.48—1.91 (m, 8H), 2.37 (s, 3H), 3.23 (s, 2H), 3.38 (s, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H); MS (EI) m/z (%): 255 (M^+ + 1, 4), 81(100). Anal. calcd for $C_{13}H_{18}O_3S$: C 61.39, H 7.13; found C 61.76, H 7.33.

2-[(*p-Tolylsulfonyl*) *methyl*]*propan*-2-*ol* (**3b**) Solid, m.p. 47—48 ℃ (Lit.[11] 49 ℃); IR (KBr) ν: 3560, 2999, 1615, 1315, 1150, 1090 cm^{-1}; ^1H NMR δ: 1.30 (s, 6H), 2.37 (s, 3H), 3.09 (s, 2H), 3.45 (brs, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H).

1-(*p-Tolylsulfonyl*)-*pentan*-2-*ol* (**3c**) Oil; IR (neat) ν: 3570, 2980, 2900, 1615, 1430, 1310, 1150, 1090 cm^{-1}; ^1H NMR δ: 1.87 (t, J = 7.0 Hz, 3H), 1.26—1.50 (m, 4H), 2.36 (s, 3H), 3.10 (d, J = 6.0 Hz, 2H), 3.30 (brs, 1H), 3.83—4.12 (m, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.7 (d, J = 8.4 Hz, 2H); MS (EI) m/z (%): 243 (M^+ + 1, 18), 91 (100). Anal. calcd for $C_{12}H_{18}O_3S$: C 59.48, H 7.49; found C 59.76, H 7.33.

1-(*p-Tolylsulfonyl*)-*hexan*-2-*ol* (**3d**) Oil; IR (neat) ν: 3580, 2980, 2950, 2880, 1615, 1480, 1315, 1150 cm^{-1}; ^1H NMR δ: 0.75—1.45 (m, 9H), 2.40 (s, 3H), 3.03 (d, J = 6.0 Hz, 2H), 3.42 (brs, 1H), 3.78—4.17 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H); MS (EI) m/z (%): 257 (M^+ + 1, 7.1), 91 (100). Anal. calcd for $C_{13}H_{20}O_3S$: C 60.91, H 7.86; found C 60.59, H 7.53.

2-[*Phenylsulfonylmethyl*]-*propan*-2-*ol* (**3e**) Solid, m.p. 78—80 ℃ (Lit.[12] 76—81 ℃); IR (KBr) ν: 3550, 2990, 1460, 1380, 1310, 1150, 1090 cm^{-1}; ^1H NMR δ: 1.33 (s, 6H), 3.15 (s, 2H), 3.47 (s, 1H), 7.43—7.64 (m, 3H), 7.77—8.01 (m, 2H).

1-[(*Phenylsulfonyl*) *methyl*]-*cyclohexan*-1-*ol* (**3f**) Solid, m.p. 58—60 ℃ (Lit.[13] 62 ℃); IR (KBr) ν: 3530, 3400, 2950, 2880, 1650, 1460, 1320, 1160, 1090 cm^{-1}; ^1H NMR δ: 1.17—1.88 (m, 10H), 3.08 (s, 2H), 3.42 (s, 1H), 7.45—7.64 (m, 3H), 7.75—7.99 (m, 2H); MS (EI) m/z (%): 255 (M^+ + 1, 5), 112 (100).

1-[1-*Bromo*-(*p-tolylsulfonyl*) *methyl*]-*cyclopentan*-1-*ol* (**5a**) Oil; IR (neat) ν: 3550, 2980, 1615, 1310, 1150, 1090 cm^{-1}; ^1H NMR δ: 1.16—2.13 (m, 8H), 2.45 (s, 3H), 4.33 (s, 1H), 4.87 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H); MS (EI) m/z (%): 334 (M^+, (^{81}Br), 2), 332 (M^+, (^{79}Br), 2), 157 (100). Anal. calcd for $C_{13}H_{17}$-BrO_3S: C 46.86, H 5.14; found C 46.60, H 5.43.

1-*Bromo*-1-*p-tolylsulfonyl*-2-*methyl*-*propan*-2-*ol* (**5b**) Solid, m.p. 96—97 ℃; IR (KBr) ν: 3540, 3010, 2970, 1610, 1470, 1315, 1150 cm^{-1}; ^1H NMR δ: 1.50 (s, 3H), 1.71 (s, 3H), 2.47 (s, 3H), 4.09 (s, 1H), 4.74 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H); MS (EI) m/z (%): 308 [M^+, (^{81}Br), 3], 306 [M^+, (^{79}Br), 2.1], 91 (100). Anal. calcd for $C_{11}H_{15}BrO_3S$: C 43.01, H 4.92; found C 43.36, H 4.63.

1-*Chloro*-1-*tolylsulfonyl*-2-*methyl*-*propan*-2-*ol* (**5c**) Solid, m.p. 99—100 ℃; IR (KBr) ν: 3570, 3010, 1460, 1330, 1210, 1150, 1090 cm^{-1}; ^1H NMR δ: 1.33 (s, 3H), 1.55 (s, 3H), 2.42 (s, 3H), 3.63 (brs, 1H), 4.40 (s, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H); MS (EI) m/z (%): 264 [M^+, (^{37}Cl), 2], 262 [M^+, (^{35}Cl), 4], 91 (100). Anal. calcd for $C_{11}H_{15}ClO_3S$: C 50.28, H 5.75; found C 50.48, H 5.74.

1-*Chloro*-1-*phenylsulfonyl*-2-*methyl*-*propan*-2-*ol* (**5d**) Solid, m.p. 80—81 ℃ (Lit.[14] 82—83 ℃); IR (KBr) ν: 3565, 3010, 1455, 1330, 1155, 1090 cm^{-1}; ^1H NMR δ: 1.38 (s, 3H), 1.57 (s, 3H), 3.72 (brs, 1H), 4.52 (s, 1H), 7.43—7.70 (m, 3H), 7.85—8.06 (m, 2H).

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