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One-pot synthesis of β-hydroxysulfides from styrenes and disulfides using the $Zn/AlCl_3$ system

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ABSTRACT

A simple, general, and highly regioselective procedure has been developed for the one-pot synthesis of β-hydroxysulfides in good yields from various styrenes and disulfides by cleavage of the S–S bond with a $Zn/AlCl_3$ system in aqueous acetonitrile at 80 °C and in the presence of oxygen.

β-Hydroxysulfides are important intermediates in organic synthesis.[1] These compounds are versatile building blocks for synthesizing thioketones,[2] allylic alcohols,[1] cyclic sulfides,[3] benzothiazepines,[4] and benzoxathiepines.[5] They also exhibit great synthetic utility in the field of pharmaceuticals[6] and natural products.[7] The most important synthetic procedure for the preparation of β-hydroxysulfides is the thiolysis of epoxides in the presence or absence of a catalyst.[8] However, some of the procedures reported were performed using Lewis acid catalysts, but these methods suffer from various disadvantages such as lower yields, poor regioselectivity, harsh reaction conditions, and undesirable side products via rearrangement of oxiranes and oxidation of thiols.[9]

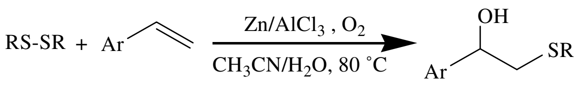
Thiol–oxygen cooxidation (TOCO) reaction[10] of olefins and reactive arenes is another method commonly used for the straightforward synthesis of β-hydroxysulfides. Notable features of TOCO reactions are their susceptibility to initiation by free-radical precursors, their propensity to afford high yields of products rapidly, and their relative freedom from side reactions. However, these reactions usually require a base catalyst, a large excess of thiol and are initiated by UV irradiation or peroxides. Major drawbacks of this methodology are undesirable side products, and low regioselectivity and yields. Hence, the development of a direct transformation of olefins to β-hydroxysulfides would be a useful contribution to the preparation of this class of compounds. In two recent reports, β-hydroxysulfides were synthesized from alkenes and thiols in the presence of β-cyclodextrin/H_2O/O_2[11] and [bmim][BF_4]/H_2O/O_2[12] in good to high yields. Also, combination of metal salts (Pb^{4+} and Cu^{2+}) and disulfides provides a convenient approach to hydroxysulfenylation of olefins via transfer of the equivalent of RS^+.[13]

As part of our interest in zinc chemistry,[14,15] we continue to seek novel applications of zinc thiolates and zinc selenolates in chemical reactions. Very recently, we investigated a convenient, catalyst-free method for the anti-Markovnikov addition of thiols to styrenes at room temperature in water.[16] We have now examined a new methodology for the synthesis of β-hydroxysulfides via the anti-Markovnikov addition of thiolate anions, generated in situ by reductive cleavage of diaryl disulfides in the presence of $Zn/AlCl_3$, to styrenes in aqueous acetonitrile in the presence of oxygen (Scheme 1). To the best of our knowledge, no study has been made using the reaction of thiolate anions (RS^-) with styrenes for the synthesis of β-hydroxysulfides.

The experiments were initially conducted with styrene and diphenyl disulfide, as a model reaction, by varying the molar ratios, solvents, and temperatures under ambient atmosphere. We found that the reactants were converted readily to the corresponding β-hydroxysulfide using the $Zn/AlCl_3$ system with a molar ratio of disulfide/$AlCl_3$/Zn/styrene = 0.5:1:3.5:1.2 in acetonitrile/water (4:1) at 80 °C.

The formation of β-hydroxysulfides may be explained as follows: the oxygen may complex with the styrene assisted by hydrogen bonding with the water hydroxyls,[11] and this would be followed by nucleophilic attack by zinc thiolate, $(RS)_2Zn$, prepared via reductive cleavage of the disulfide with $Zn/AlCl_3$.[15]

Table 1 presents the results of the regioselective addition of various diaryl disulfides to several substituted styrenes in an anti-Markovnikov fashion leading to the corresponding β-hydroxysulfides in good to high yields. The yields reported in Table 1 are of



Scheme 1.

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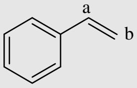
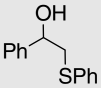
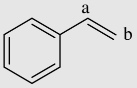
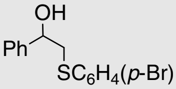
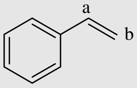
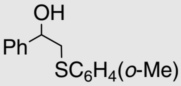
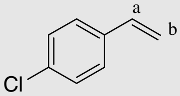
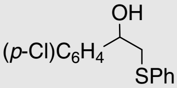
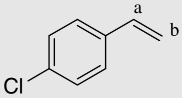
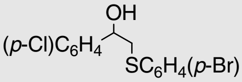
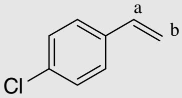
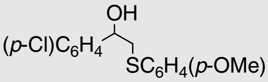
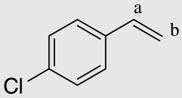
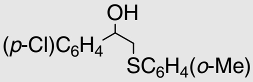
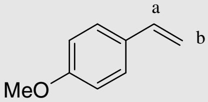
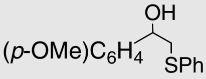
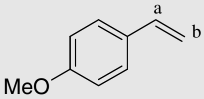
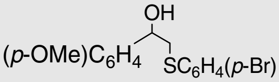
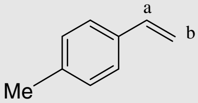
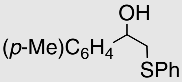
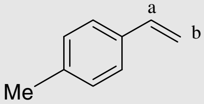
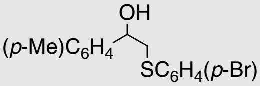
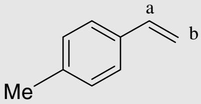
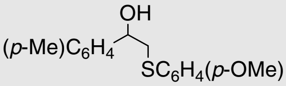
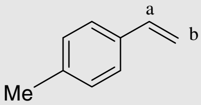
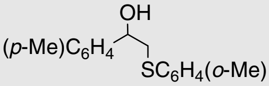
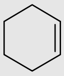
Table 1
Synthesis of β-hydroxysulfides from styrenes and disulfides (RS–SR) in the presence of the Zn/$AlCl_3$ system in acetonitrile/water

Entry	Styrene	R	Product	Time (h)	Yield[a] (%)	Regioselectivity[b]
1		Ph		2	80	a/b:4/96
2		*p*-BrC_6H_4		2	75	a/b:15/85
3		*o*-MeC_6H_4		2.4	63	a/b:10/90
4		Ph		2.2	73	a/b:25/75
5		*p*-BrC_6H_4		2.5	71	a/b:19/81
6		*p*-$MeOC_6H_4$		3.7	66	a/b:4/96
7		*o*-MeC_6H_4		3	61	a/b:17/83
8		Ph		3.5	70	a/b:10/90
9		*p*-BrC_6H_4		3.2	65	a/b:18/82
10		Ph		2.7	65	a/b:13/87
11		*p*-BrC_6H_4		2.25	66	a/b:33/67
12		*p*-$MeOC_6H_4$		3.8	63	a/b:9/91
13		*o*-MeC_6H_4		3.5	60	a/b:17/83
14		Ph	No reaction	24	—	—

[a] Yield of the isolated major product.

[b] Refers to the ratio of thiolate anion attack at carbon-a and carbon-b determined by ^1H NMR analysis of the crude reaction mixture.

the isolated major product. Also, the regioselectivity was evaluated by ^1H NMR analysis of the crude reaction mixture; the results clearly show preferential attack at the β-position (carbon-b) by the thiolate anion. However, under the same conditions, the much less-reactive cyclohexene (Table 1, entry 14) did not produce the expected product even after prolonged reaction time. Generally, the reaction goes to completion in a short time (2–4 h). This procedure is compatible with various substituted styrenes and substituted aromatic disulfides with functionalities such as methyl, chloro, and methoxy. When the reaction was conducted, under the same reaction conditions, but under an argon atmosphere, the addition product, that is, the sulfide ($PhCH_2CH_2SPh$) alone was formed in 44% yield. This indicates that aerial oxygen is involved in the formation of the β-hydroxysulfides. All the products are known,[11] and the structures of the β-hydroxysulfides were established from their IR, ^1H, and ^{13}C NMR spectral data.

In conclusion, we have shown that the addition of a thiolate anion (RS^-) to styrenes takes place regioselectively giving β-hydroxysulfides in an anti-Markovnikov manner. This reaction is simple and proceeds under relatively mild conditions with short reaction times and high selectivity. To our knowledge, this is the first example of the reaction of thiolate anions with styrenes for the synthesis of β-hydroxysulfides. This protocol may lead to a new dimension in terminal olefin functionalization.

Typical experimental procedure: A mixture of diphenyl disulfide (109 mg, 0.5 mmol), zinc powder (229 mg, 3.5 mmol), and finely ground anhydrous $AlCl_3$ (133 mg, 1.0 mmol) was suspended in MeCN (8 mL) and H_2O (2 mL). The mixture was stirred at 80 °C for 2 h, during which time the zinc powder was almost completely consumed. Then, 4-methoxystyrene (161 mg, 1.2 mmol) was added in one portion and stirring was continued at that temperature for 3.5 h in air. After completion of the reaction, the solution was filtered, acetonitrile was evaporated, EtOAc (20 mL) was added, and the mixture was washed with water (2×10 mL), and the organic layer was dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the crude mixture was purified by preparative TLC (silica gel; eluent, *n*-hexane/EtOAc = 4: 1) to afford pure 1-(4-methoxyphenyl)-2-(phenylsulfanyl)-1-ethanol (182 mg, 70%, Table 1, entry 8) as a pale yellow oil. IR (neat) ν 1513, 1584, 3429 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.82 (br s, 1H), 3.11 (dd, $J = 13.7$, 9.3 Hz, 1H), 3.30 (dd, $J = 13.7$, 3.7 Hz, 1H), 3.81 (s, 3H), 4.70 (dd, $J = 9.3$, 3.7 Hz, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 7.22–7.44 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.87, 55.30, 71.34, 113.95, 126.70, 127.13, 129.11, 130.15, 134.29, 135.02, 159.36.

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