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Iodine-catalysed regioselective synthesis of β-hydroxysulfides

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A metal-free, and environment benign iodine-catalysed protocol has been developed for the regioselective synthesis of β-hydroxysulfides in good to excellent yields from easily accessible styrenes and thiophenols. The reaction involves single step C—S and C—O bonds construction.

Introduction

Carbon–heteroatom bond formation has a great importance in synthetic organic chemistry because of its presence in many natural products. Consequently, it is attracting much attention in recent times.[1] Various methods have been developed for the synthesis of C—X bonds. However, some protocols involve transition metals, expensive reagents or additives[2] and therefore this process is still under exploration to develop environment friendly and affordable strategies for the construction of these bonds.

Over the last few years, difunctionalization methodologies such as alkoxythiolation,[3] hydroxythiolation,[4] acetoxythiolation,[5] sulfamination[6] and disulfidation[7] have been performed successfully. The generation of difunctionality in a single step is itself a challenging task in synthetic organic chemistry. Further, sulfide functionalization raises its importance[8] as the sulphide unit is present in numerous natural compounds.[9] Sulfur-containing organic compounds have various applications in the area of medicinal chemistry for their antibiotic, antioxidant, calcium channel antagonist, antimicrobial, anti-inflammatory, antitumor, and anti-HIV activities.[10] β-Hydroxysulfides act as precursors in the synthesis of compounds having biological importance such as pharmacophores[11] including bexarotene,[12] tamoxifen,[13] iso-combretastin (iso CA-4),[14] ratanhine,[15] and in the synthesis of β-hydroxysulfoxides which can be obtained by the oxidation of β-hydroxysulfides using conventional oxidising agents.[16] β-Hydroxysulfides are important building blocks for the synthesis of thioketones, allylic alcohols, cyclic sulfides, benzothiazepines, benzoxathiepines and many other highly functionalized organic scaffolds[17] specially in the synthesis of Leukotriene LTC4 and LTD4.

Several reports are available in literature for the construction of β-hydroxysulfides (Scheme 1), which can be broadly divided in two categories on the basis of the reactants used: i) styrenes and disulfides/thiols, and ii) epoxides and disulfides/thiols. Some of them are associated with certain drawbacks such as use of toxic metals or solvents. Movassagh et al. synthesized β-hydroxysulfides using styrenes and disulfides by employing zinc/aluminium chloride as a promoter under oxygen.[17] Singh et al. synthesized β-hydroxysulfides using silver nitrate catalyst in DMF.[18] Later Chandrasekaran and co-workers reported the synthesis of β-hydroxysulfides with rongalite, potassium carbonate in DMF[19] and Lanke et al. synthesized β-hydroxysulfides using amberlyst-15 in toluene.[20] Use of iodine as a catalyst in oxidation reactions is one of the upcoming advances of the recent time in terms of environmental sustainability and cost effectiveness.[21] As iodine is environmentally benign, we envisaged that it would provide us a green path towards the synthesis of β-hydroxysulfides.

Initially the reaction was carried out with styrene (**1a**) and thiophenol (**2a**) as model substrates in DMSO at room temperature and 80 °C (Table 1, entry 1). However, no reaction was observed under these conditions. When **1a** and **2a** were treated in the presence of iodine at room temperature the reactants were recovered (entry 2). Later the reaction was performed with 50 mol% of iodine in DMSO at 80 °C. To our delight β-hydroxysulfide **3a** was obtained in 51% yield (entry 3). When we performed the reaction of thiophenol with excess of styrene (2 equiv), **3a** was obtained in 90% yield (entry 5). After that we screened different reagents such as

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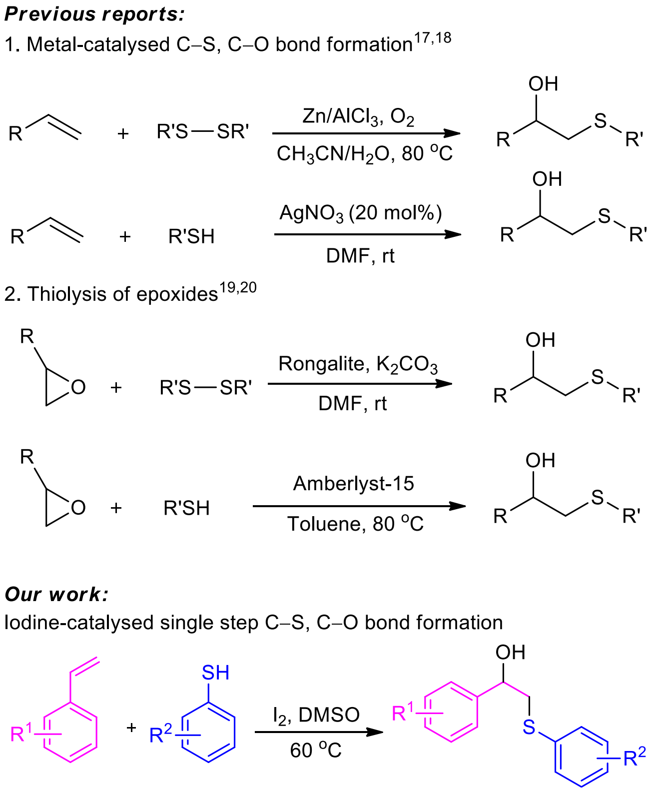
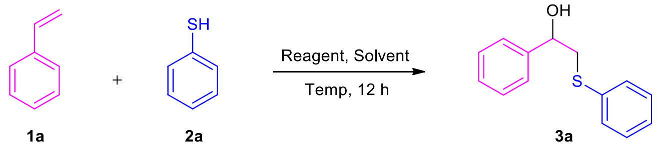


Scheme 1. Protocols for the synthesis of β-hydroxysulfides.

potassium iodide, diacetoxyiodobenzene (DIB), *N*-chlorosuccinimide and molecular iodine. When reaction was carried out in the presence of KI and DIB, no reaction was observed (entries 6 and 7), while in the presence of NCS, traces of product was observed (entry 8). To improve the yield of the product further, the reaction was carried out by loading iodine in 1.0 and 0.25 equivalents and **3a** was isolated in 92 and 75% yield, respectively (entries 9 and 10). To evaluate the effect of temperature on reaction, we carried out the reaction at different temperatures and we observed that yield of product was dropped to 58% at 100 °C while at 60 °C yield of product was slightly increased from 92 to 98% (entries 11 and 12). Further decrease of temperature of the reaction to 40 °C did not provide encouraging results (entry 13). Then we screened different solvents by using 0.5 equiv of iodine and 1:2 equiv of thiophenol and styrene, product was obtained in traces when DMF and ACN were used as solvents (entries 14 and 15), while no reaction was observed when H_2O was used as solvent (entry 16). Thereafter another reaction was performed in 1:1 mixture of DMSO/H_2O at 60 °C and the product **3a** was obtained in 50% yield (entry 17). The optimum results were obtained when DMSO was used as solvent. Thus the iodine (0.5 equiv) at 60 °C in DMSO as solvent emerged as the optimal set of conditions (entry 12) for subsequent studies Table 1.

With the optimized reaction conditions in hand, we investigated functional group compatibility and scope of the present iodine catalysed protocol for the synthesis of β-hydroxysulfides using a variety of styrenes **1a–e** and thiophenols **2a–d** (Table 2). Styrenes as well as thiophenols both bearing electron-withdrawing and electron-donating groups proceeded well with the present protocol. *p*-Chlorostyrene furnished chlorophenyl substituted β-hydroxysulfides **3e–h** in yields 57–75% and *p*-fluoro substituted styrene afforded the corresponding products **3i–l** in 62–70% with both electron-withdrawing and electron-donating groups on thiophenols. The presence of bulky isopropyl group did not affect much and the reaction proceeded well to produce the sulfides **3m–p** in 60–94% yield. To test the applicability of the present methodology with poly-substituted styrene, the reaction was performed with trimethoxy-styrene, and the corresponding sulfides **3q** and **3r** were obtained in 64 and 70% yields. These results indicated that the type of substituent and their bulkiness had no regular effect on the yields of products.

Table 1
Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Reagent (equiv)	Solvent	Temp (°C)	Yield[b] (%)
1	–	DMSO	80	–
2	I_2 (0.5)	DMSO	rt	–
3[c]	I_2 (0.5)	DMSO	80	51
4[d]	I_2 (0.5)	DMSO	80	56
5	I_2 (0.5)	DMSO	80	90
6	KI (0.5)	DMSO	80	nr
7	DIB (0.5)	DMSO	80	nr
8	NCS (0.5)	DMSO	80	Traces
9	I_2 (1.0)	DMSO	80	92
10	I_2 (0.25)	DMSO	80	75
11	I_2 (0.5)	DMSO	100	58
12	I_2 (0.5)	DMSO	60	98
13	I_2 (0.5)	DMSO	40	70
14	I_2 (0.5)	DMF	80	Traces
15	I_2 (0.5)	ACN	80	Traces
16	I_2 (0.5)	H_2O	80	nr
17	I_2 (0.5)	H_2O/DMSO	60	50

[a] All reactions were performed with **1a** (1.0 mmol), **2a** (0.5 mmol), reagent and solvent (2 mL) on heating.
[b] Isolated yield. nr = no reaction.
[c] **1a** (0.5 mmol) and **2a** (0.5 mmol) were used.
[d] **1a** (0.5 mmol) and **2a** (1.0 mmol) were used.