Non-Expensive, Open-Flask and Selective Catalytic Systems for the Synthesis of Sulfinate Esters and Thiosulfonates

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Graphical Abstract

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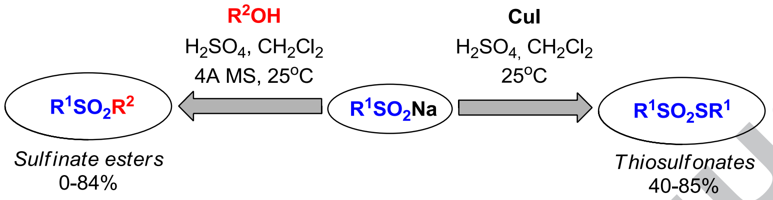

- R^1, R^2 = alkyl, aryl
- open flask
- mild reaction conditions
- broad substrate scope
- upscalability

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Non-Expensive, Open-Flask and Selective Catalytic Systems for the Synthesis of Sulfinate Esters and Thiosulfonates

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ABSTRACT

Two simple and efficient methods for the synthesis of sulfinate esters and thiosulfonates from sodium salts of sulfinic acids are described. Different alcohols were converted into the corresponding sulfinate esters in good yields and purity in an open flask. By the adjustment of the reaction conditions thiosulfonates could also be obtained in a very short reaction time.

Sulfur compounds are widely used in organic synthesis and the importance of sulphides, sulfoxides and sulfones not only to increase the structural complexity of organic molecules but also in asymmetric reactions is unquestionable.[1]

Tricoordinate sulfur compounds such as sulfinate esters and sulfoxides can adopt a trigonal pyramidal structure, however, the presence of an electron lone pair gives to the sulfur centre a tetrahedral framework and unlike amines, sulfoxides and sulfinate esters are configurationally stable at ambient temperatures.[2]

The synthesis of sulfinate esters is mainly based on the seminal work developed by Douglass using sulfinyl chlorides.[3] Some other methods for the synthesis of this class of compounds such as the use of N-nitroso sultams,[4] substitution of benzyl alcohols with arylsulfonylmethyl isocyanides,[5] reaction of sulfonyl hydrazides with alcohols,[6] alcoholysis of sulfinamides,[7] the use of disulfides[8] were also described.

More recently, the oxidation of sulphides to the corresponding sulfinyl radicals[9] and the use of equimolar amounts of $BF_3{\bullet}Et_2O$ and sodium sulfinates[10] were also described. These methods, however, have some limitations such as the need of inert atmosphere, the generation of sulfur dioxide as by product or the use of unpleasant sulphides.

Thus, despite the plethora of methods for the synthesis of sulfinate esters, the development of a simple and reliable method, based on the use of easy to handle reagents and mild reaction conditions would be of the great interest.

The use of Brønsted acids as catalysts in academic laboratories and chemical manufacturing plants is universal and, this fact, together with the use of sodium salts of sulfinic acids and alcohols as starting materials would be a more appropriate choice due to their commercial availability, low cost and high stability. In addition, sulfinic acids can act as nucleophiles or electrophiles, depending on the conditions used.[1c]

For preliminary optimization of the reaction conditions, sodium *p*-toluenesulfinate, **1a** (1 mmol) and methanol (1 mL) were submitted to acidic conditions using CH_2Cl_2 as solvent at room temperature. The results are depicted on Table 1.

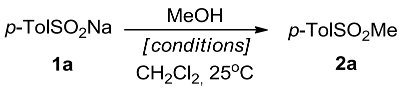
When the reaction was performed without the use of H_2SO_4 in CH_2Cl_2, the desired product was not observed after 24 h (Table 1, entry 1). The addition of 0.5 equiv. of H_2SO_4 gave the desired sulfinate ester **2a** in low yield after 24 h (Table 1, entry 2).

By increasing the amount of H_2SO_4 in the reaction higher conversions of **1a** to **2a** were observed (Table 1, entries 2-5). However, when 4 equiv. of H_2SO_4 were used, a significant decrease in the conversion together with the formation of the corresponding sulfone was observed after 24 h (Table 1, entry 6). This result is in agreement with the literature where the acid-catalysed reaction of sulfinic acids and benzyl alcohols at 100°C gave the corresponding sulfones.[11] A dramatic effect was observed when 4 Å molecular sieves were used in the reaction, where the reaction time decreased to 8h and the desired product **2a** was obtained in a conversion of 80% (Table 1, entry 7).

The optimized reaction conditions namely: **1a** (1 mmol) and methanol (1.2 mmol) using H_2SO_4 (2 equiv.) and 4 Å molecular sieves in CH_2Cl_2 were then applied to different alcohols.[12]

An interesting fact to be observed is that, depending on the structure of the alcohol, it can be used as the solvent in the reaction without the need of CH_2Cl_2. The results are described on Table 2.

Table 1. Effect of the amount of H_2SO_4 on the synthesis of methyl benzenesulfinate, **2a**[a]



$$p\text{-TolSO}_2\text{Na} \xrightarrow[\text{CH}_2\text{Cl}_2,\ 25^\circ\text{C}]{\text{MeOH [conditions]}} p\text{-TolSO}_2\text{Me}$$

1a **2a**

Entry	conditions		**5a** (%)[b]
	H_2SO_4 (equiv.)	Time (h)	
1	-	24	-
2	0.5	24	36
3	1.0	24	42
4	1.5	24	65
5	2.0	24	88
6	4.0	24	78
7	2.0	8	80[c]

[a] *Reaction conditions:* Reactions were performed with **1a** (1 mmol) and MeOH (1.0 mL) using the indicated amount of H_2SO_4 in CH_2Cl_2 (4 mL) at the temperature indicated. [b] Determined by GC analysis; [c] 4 Å molecular sieves (200 mg) was added to the reaction.

From Table 2 it can be seen that the method was efficient for most of the alcohols used. When primary aliphatic alcohols such as methanol, ethanol and *n*-propanol were used, good yields were observed in all cases (Table 2, entries 1-3).

A similar yield was observed when a secondary aliphatic alcohol was used (Table 2, entry 4). The effect of alcohol bulkiness was more evident when *t*-butanol was used, where only traces of **2e** were observed together with a complex mixture of compounds after 16 h (Table 1, entry 5).

Allyl and propargyl alcohols also gave the corresponding sulfinate esters **2f** and **2g** in good yields (Table 1, entries 6 and 7). This result is important while **2g** is a precursor for the synthesis of allenic sulfones through a [2,3]-sigmatropic rearrangement.[13] Benzyl alcohol also gave the corresponding product **2h** also in good yield (Table 1, entry 8).

An interesting result was obtained when (-)-menthol was used as the alcohol source where (1*R*,2*S*,5*R*)-(−)-Menthyl (*S*)-*p*-toluenesulfinate, **2i** was obtained in 50% yield in a 53:47 diastereomeric ratio (Table 1, entry 9). The synthesis of **2i** is generally carried out by converting **1a** into the corresponding *p*-toluenesulfinyl chloride using thionyl chloride in benzene followed by the addition of (-)-menthol. The less soluble (*S*)-(−) diastereomer can be isolated by recrystallization from the mixture using acetone at −20°C.[14]

In order to explore the scope of the reaction other sodium sulfinates were used. For example, sodium benzenesulfinate **1b** gave similar results for primary (Table 2, entries 12-13) and secondary alcohols (Table 2, entry 14) indicating that the method is general for aromatic sulfinic acids.

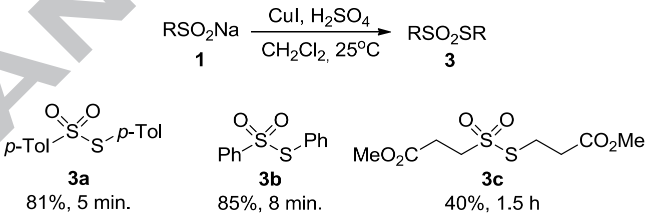
When sodium 1-methyl 3-sulfinopropanoate, **1c** was submitted to the optimized reaction conditions using methanol, the corresponding product **2p** was obtained in 52% after 12 h (Table 2, entry 15). However, when *n*-propanol was used, a mixture corresponding to the desired product **2q** and the product resulting from the transesterification reaction **2r** were obtained in 56% yield in a 60:40 ratio (Table 2, entry 16). Finally, when sodium trifluoromethylsulfinate was used, the corresponding product **2s** was not obtained (Table 1, entry 17).

Another factor that must be taken into account in the development of new synthetic methods is the scale-up of the reaction. Thus, when the synthesis of chiral sulfinate ester **2i** was performed using 1.0 g (6 mmol) of **1a** under the conditions described on Table 2, the desired product was obtained in 72% yield, indicating that the developed reaction conditions could be also applied to carry out reactions on a larger scale.

More recently, the use of thiosulfonates gained particular attention due to the fact that these reagents are more effective in sulfenylation reactions when compared to disulfides.[15] In addition, these compounds exhibit greater stability and ease of handling when compared to sulfenyl chlorides.[16] Moreover, interesting biological activities and industrial applications in fine chemicals,[17] photographic processes[18] and as protecting groups[19] were described.

These facts led to the development of several methods for the synthesis of thiosulfonates, being the most common approach based on the oxidation of the corresponding disulfides.[20] Other approaches based on the use of sulfides,[21] sulfonic acids,[22] sulfonyl chlorides,[23] and sulfinic acids[24] and esters[25] were also described.

The synthesis of methyl and diaryl sulfones using salts of sulfinic acid and aryl iodides promoted by copper was described by Wang.[26] By analogy, the adjustment of the reaction conditions developed for the synthesis of sulfinate esters by using 0.5 equiv. of copper iodide (I) and an excess of H_2SO_4 (7.5 equiv.) gave the corresponding thiosulfonates in good yield, purity and in a very short reaction time compared to the methods previously described on the literature (Scheme 1).



Scheme 1. Synthesis of thiosulfonates

In summary, we have shown an efficient and versatile method for the synthesis of sulfinate esters and thiosulfonates from commercially available and low cost sulfinic acids in a very chemoselective way.

In the case of sulfinate esters, the use of different alcohols gave the corresponding products in good to moderate yields without the need of anhydrous solvents or sulfonyl chlorides as precursors.

The method is simple, fast and general, allowing further applications in the synthesis of more complex compounds. By changing the reaction conditions, thiosulfonates can be obtained in a reaction promoted by cooper iodide in an open flask. The products were obtained in a very short reaction time when compared to the previously described methods.

Acknowledgments

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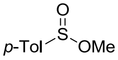
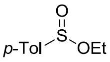
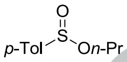
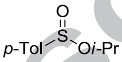
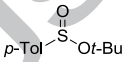
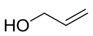
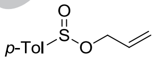
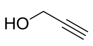
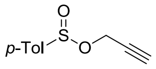
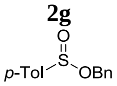
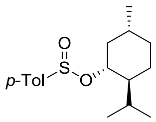
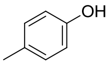
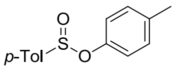
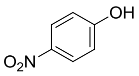
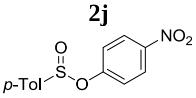
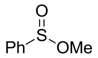
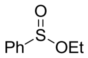
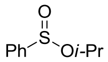
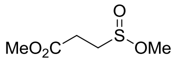
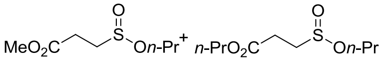
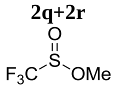
Table 2. Synthesis of different sulfinate esters **2** from the corresponding sulfinic acid sodium salts, **1** and alcohols[a]

$$\underset{\mathbf{1}}{R^1SO_2Na} \xrightarrow[\substack{H_2SO_4,\ CH_2Cl_2 \\ 4A\ MS,\ 25^oC}]{R^2OH} \underset{\mathbf{2}}{R^1SO_2R^2}$$

entry	**1**	R^{2}OH	Time (h)	**2**	Yield (%)[b]
1	*p*-TolSO$_2$Na, **1a**	MeOH	8	 **2a**	76[c]
2	**1a**	EtOH	8	 **2b**	70[c]
3	**1a**	*n*-PrOH	8	 **2c**	69[c]
4	**1a**	*i*-PrOH	8	 **2d**	67[c]
5	**1a**	*t*-BuOH	16	 **2e**	-[d]
6	**1a**		5	 **2f**	63[e]
7	**1a**		8	 **2g**	65[e]
8	**1a**	BnOH	4	 **2h**	65[e]
9	**1a**	(-)-menthol	4	 **2i**	50[e]
10	**1a**		16	 **2j**	-[f]
11	**1a**		16	 **2l**	-[f]
12	PhSO$_2$Na, **1b**	MeOH	8	 **2m**	84[c]
13	**1b**	EtOH	8	 **2n**	73[c]
14	**1b**	*i*-PrOH	8	 **2o**	71[c]
15	MeCO$_2$(CH$_2$)$_2$SO$_2$Na, **1c**	MeOH	12	 **2p**	52
16	**1c**	*n*-PrOH	15	 **2q+2r**	56[g]
17	CF$_3$SO$_2$Na, **1d**	MeOH	16	 **2s**	-[f]

[a] *Reaction conditions:* Reactions were performed with **1** (1 mmol), ROH (3 mmol), H$_2$SO$_4$ (106 µL, 2 equiv.) and 4 Å molecular sieves (200 mg) in CH$_2$Cl$_2$ (4 mL) at room temperature. [b]isolated yields; [c] The reaction was performed using 1.0 mL of the alcohol without losses in the yield. [d]Only traces observed after 16h; [e]1.5 equiv. of H$_2$SO$_4$ was used; [f] The product was not observed after 16 h; [g]Obtained as an inseparable mixture in a 60:40 ratio determined by GC analysis.

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12 *Representative Procedure for the Synthesis of methyl 4-methylbenzenesulfinate* (**2a**): In a test tube containing sodium *p*-toluenesulfinate, **1a** (178 mg, 1 mmol) was added methanol (1 mL, 25 mmol) followed by dichloromethane (4 mL). Under stirring, sulfuric acid (106 μL, 2 equiv.) was added, dropwise. After 30 minutes, powdered 4 Å molecular sieves (200 mg) was added. The mixture was stirred for additional 8 h period and then diluted with dichloromethane (10 mL) and transferred to a separation funnel. The organic phase was washed with water (2 x 20 mL), dried over anhydrous $MgSO_4$ and filtered through a pad of silica. The solvents were removed *in vacuo* to yield 129 mg (76%) of the tittle compound sufficiently pure for characterization. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9 Hz, 2H); 7.33 (d, *J* = 9 Hz, 2H); 3.45 (s, 3H); 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 140.9, 129.7, 125.4, 49.4, 21.5.

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Supplementary Material

Additional experimental procedures and spectra associated with this article can be found in the online version.

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Non-Expensive, Open-Flask and Selective Catalytic Systems for the Synthesis of Thiosulfonates and Sulfinates

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Highlights:

- A versatile method for the synthesis of sulfinate esters and thiosulfonates is described;
- The methodology is simple and flexible in design;
- Sulfinate esters were obtained in good yields without the need of anhydrous solvents;
- Thiosulfonates were obtained in a reaction promoted by cooper iodide in an open flask.