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ARTICLE TYPE

Iodine-induced synthesis of sulfonate esters from sodium sulfinates and phenols under mild conditions

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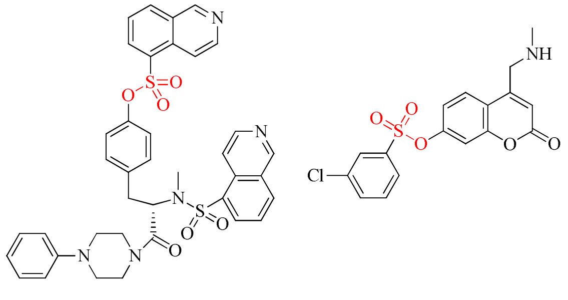
An iodine-induced synthesis of sulfonate esters via cross-coupling reactions of sodium sulfinates with phenols is reported. This synthetic route is low-cost, facile, green and efficient, and could afford the target products with good to excellent yields under mild conditions.

Sulfonate esters are well-known ester compounds and crucial pharmaceutical ingredients which work as bridge structures or ligands and have presented particular biological activities (such as antitumor and monoamine oxidase inhibitory activities) in medicinal chemistry (Fig. 1).[1–4] Besides, sulfonate esters play a unique role in coupling reactions because sulfonate ester groups are removed easily.[5] To date, many methods have been developed to synthesize sulfonate esters, mainly including the reaction of phenols with sulfonic acids,[6] or with thiols using H_2O_2–$POCl_3$ system,[7] and with sulfonyl chlorides in ionic liquid,[8] or under microwave-assistance [9] and catalyzed by copper oxide.[10] Other routes have been also reported.[11] Nevertheless, most of these methods suffer from harsh reaction conditions. In addition, expensive and instable sulfonyl chlorides as sulfonylating reagents would lead to some drawbacks. Hence, it is necessary to search for a low-cost, green and efficient sulfonylating reagents (sulfonyl sources) for the synthesis of sulfonate esters.

In recent years, many chemists became interested in the direct sulfonylation reaction using various sulfonylation reagents.[12] Among various sulfonylation reagents, sodium sulfinates seem to be more attractive due to their stability, low price and convenience handling. Actually, sodium sulfinates have been widely applied in sulfonylations,[13] C–H arylations[14] and sulfenylations.[15] In addition, iodine-mediated synthesis has attracted more and more attention because iodine is cheap, readily available and eco-friendly.[16] Recently, some interseting reactions related phenols in organic chemistry have been also reported.[17]



KN62 MAO-Is Compound

Fig. 1 Selected examples for bioactive and pharmaceutical compounds containing sulfonate ester group.

Based on our research interest in iodine-mediated reactions,[18] herein we reported an iodine-induced the synthesis of sulfonate esters from sodium sulfinates and phenols under mild conditions. To our knowledge, such a route for the synthesis of sulfonate esters has not been reported to date.

To optimize the reaction conditions, the reaction of 4-chlorophenol (**1a**) with sodium *p*-toluenesulfinate (**2a**) was selected as the model reaction, and the results were shown in Table 1. When the reaction of **1a** and **2a** was carried out in the presence of I_2 in CH_3CN for 5 h, the yield of 4-chlorophenyl 4-methylbenzenesulfonate (**3a**) was only 10% (entry 1). Pinhey's investigations indicated that base additives could efficiently promote the coupling reaction of phenols with aryllead triacetates.[19] Based on this idea, we suppose that base may act as the similar role in the present system. Thus, we examined the effect of various inorganic and organic bases on the coupling reaction of 4-chlorophenol with sodium *p*-toluenesulfinate. In the presence of CH_3COONa, the yield of **3a** was raised to 36% (entry 2). Very pleasedly, Cs_2CO_3, especially K_2CO_3, could dramatically improve the yield of **3a** (entries 3 and 4). However, a strong inorganic base KOH and organic bases (Et_3N and pyridine) gave unsatisfactory results (entries 5–7). The effect of solvents were further investigated. Compared with other solvents (H_2O, DMF, EtOH and DMSO), CH_3CN or CH_3OH gave the better results (entries 8–12). Considering the toxicity of CH_3CN, we chose CH_3OH as the solvent for this transformation. When the temperature was elevated to 50°C, the yield of **3a** was not influenced (entry 13), so room temperature was found as the optimal temperature. In addition, the amount of I_2 and K_2CO_3 has a great influence on the reaction (see SI). When 1 equiv. of I_2 or K_2CO_3 was used

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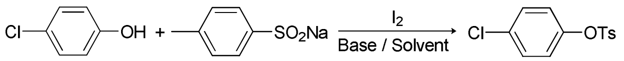
† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, characterization of products, and NMR spectral charts. See DOI: 10.1039/b000000x/

Table 1 Optimization of reaction conditions[a]

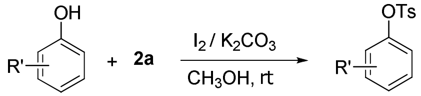


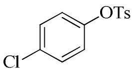
1a **2a** **3a**

Entry	Base	Solvent	Time (h)	Yield [b] (%)
1	No base	CH_3CN	5	10
2	CH_3COONa	CH_3CN	5	36
3	Cs_2CO_3	CH_3CN	5	80
4	K_2CO_3	CH_3CN	5	98
5	KOH	CH_3CN	5	19
6	Et_3N	CH_3CN	5	6
7	Pyridine	CH_3CN	5	14
8	K_2CO_3	CH_3OH	5	**98**
9	K_2CO_3	H_2O	5	11
10	K_2CO_3	DMF	5	57
11	K_2CO_3	EtOH	5	75
12	K_2CO_3	DMSO	5	69
13[c]	K_2CO_3	CH_3OH	5	94
14[d]	K_2CO_3	CH_3OH	5	89
15[e]	K_2CO_3	CH_3OH	5	trace
16[f]	K_2CO_3	CH_3OH	5	trace
17[g]	K_2CO_3	CH_3OH	5	77
18[h]	K_2CO_3	CH_3OH	5	90
19[i]	K_2CO_3	CH_3OH	5	88

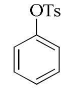
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), I_2 (1 equiv.), base (1 equiv.), solvent (2 mL) and room temperature. [b] GC yield based on **1a**. [c] At 50°C. [d] Reaction in a dark background. [e] Adding TEMPO. [f] Adding BHT. [g] Using tosyl iodide (0.6 mmol) instead of **2a** and I_2. [h] Under N_2 atmosphere. [i] Reaction on a 10 mmol scale.

Table 2 Synthesis of sulfonate esters with various phenols[a,b]

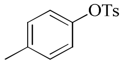




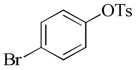
3a, 5h, 93%



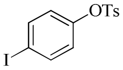
[c]**3b**, 6 h, 85%



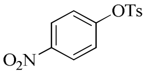
[c]**3c**, 10 h, 70%



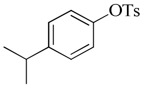
3d, 5 h, 93%



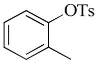
3e, 5 h, 91%



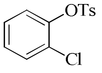
3f, 5 h, 95%



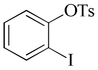
[c]**3g**, 10 h, 62%



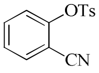
[c]**3h**, 10 h, 63%



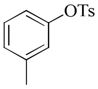
3i, 5 h, 87%



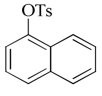
3j, 5 h, 86%



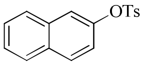
3k, 5 h, 90%



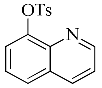
[c]**3l**, 10 h, 60%



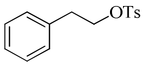
[c]**3m**, 6 h, 71%



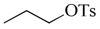
[c]**3n**, 6 h, 74%



[c]**3o**, 6 h, 67%



[c, d]**3p**, 5h, 71%



[c,d] **3q**, 5h, 63%

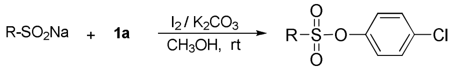
[c,d]**3r**, 5 h, 67%

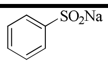
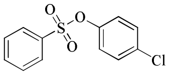
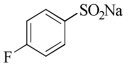
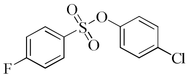
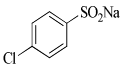
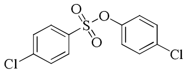
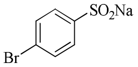
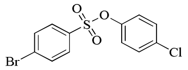
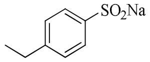
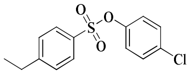
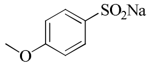
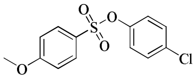
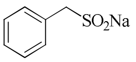
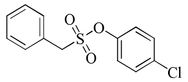
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), I_2 (0.5 mmol), K_2CO_3 (1 equiv.), CH_3OH (2 mL), room temperature. [b] Isolated yield based on **1**. [c] CH_3CN (2 mL) as the solvent. [d] Using CH_3ONa (0.5 mmol) instead of K_2CO_3.

in the present system, the best result could be obtained (entry 8). Moreover, when the reaction was performed on a 10.0 mmol scale (Table 1, entry 19), an excellent yield (88%) of **3a** was obtained. This means that the reaction could be scalable and has a potential application for the preparation of more complex molecules.

Under the optimized reaction conditions, the scope of synthesis of sulfonate esters by using various phenols with **2a** was investigated (Table 2). A series of ortho and para-substituted phenols by electron-withdrawing groups (R = F, Br, I, NO_2, CN) all proceeded smoothly to afford the corresponding products (**3d**–**3f**, **3i**–**3k**) in excellent yields. However, when some electron-donating groups (R = CH_3, isopropyl) substituted phenols were used, a long reaction time was needed, a lower yield was obtained, and some by-products substituted by iodine were observed (**3c**, **3g**, **3h**, **3l**). This result may be attributed to the fact that the presence of electron-donating groups is not favourable for the conversion of phenols to aryloxy anion. In the present reaction system, the aryloxy anion may be one of key intermediates. To our delight, naphthol and quinolin-8-ol performed with good yields (**3m**–**3o**). Specially, aliphatic alcohols could react well with sodium *p*-toluenesulfinate (**2a**) in CH_3CN solvent to afford the target products (**3p**–**3r**) with good yields when K_2CO_3 was replaced by CH_3ONa. These results indicate that aliphatic alcohols are also suitable for this transformation in the presence of a strong base CH_3ONa.

Table 3 Scope of various sodium sulfonates[a,b]



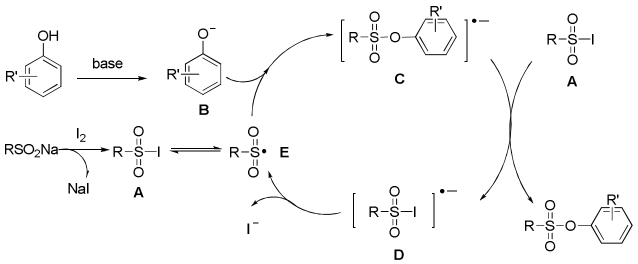
Sodium sulfinate	Product		Yield (%)
		**3s**	86
		**3t**	90
		**3u**	88
		**3v**	89
		**3w**	74
		**3x**	77
		**3y**	82

[a] Reaction conditions: **1a** (0.5 mmol), sodium sulfinate (0.6 mmol), I_2 (0.5 mmol), K_2CO_3 (1 equiv.), CH_3OH (2 mL), 5 h and room temperature. [b] Isolated yield based on sodium sulfinate.

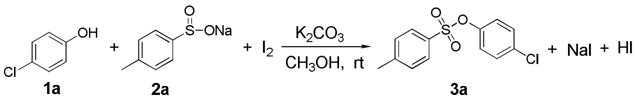
On the other hand, the reactions of some sodium sulfinates with **1a** were examined, and the result was summarized in

Table 3. Various sodium sulfinates with 4-fluoro, 4-chloro, 4-bromo, 4-methoxyl and 4-ethyl groups substituted on aryl rings all proceeded smoothly to give good to excellent yields (**3s–3x**). In addition, 4-chlorophenylphenylmethane sulfonate (**3y**) was also obtained in a high yield.

To investigate the reaction mechanism, several controlled experiments were performed (Table 1, entries 14–18). Firstly, when radical scavenger TEMPO or BHT was added to this reaction system (Table 1, entries 15 and 16), no desired **3a** was obtained, indicating that the reaction involves a radical pathway. Besides, when the reaction of tosyl iodide instead of molecule iodine with **2a** was carried out (Table 1, entry 17), **3a** was still obtained in a high yield, revealing that tosyl iodide may be an intermediate in this transformation. Even if the reaction was proceeded in a dark background or under N_2 atmosphere, the yield of **3a** was almost unchanged (Table 1, entries 14 and 18). This means that visible light and oxygen were irrelevant for this transformation. As a result, a possible mechanism is proposed in Scheme 1. Sodium sulfinate firstly reacts with I_2 to form sulfonyl iodide (**A**),[20] which is easily subjected to homolysis to give a sulfonyl radical (**E**). At the same time, phenols is transformed to aryloxy anion (**B**) in alkaline medium. Then, the aryloxy anion **B** is combined with the radical **E** to generate the radical anion **C**, followed by the reaction with **A** to afford the desired sulfonate ester, together with radical anion **D**.[21] The radical anion **D** could generate the radical **E** to enter into the next reaction cycle. In the present reaction system, molecular I_2 practically is a reactant or an inducer, which is delineated in Scheme 2. The total reaction equation (Scheme 2) could explain well why the full conversion of 0.5 mmol of **1a** to **3a** requires 0.5 mmol of I_2 (See SI, Table S1, entry 6).



Scheme 1 Proposed reaction mechanism.



Scheme 2 A total reaction equation for this transformation.

In conclusion, we have developed a simple, metal-free and eco-friendly synthesis of sulfonate esters from sodium sulfinates and phenols. Compared with the reported methods (such as using sulfonyl chlorides as starting materials), the present route appears to be more attractive and efficient for the synthesis of sulfonate esters. Further study on this reaction's application is ongoing currently in our laboratory.

Acknowledgements

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Iodine-induced synthesis of sulfonate esters from sodium sulfinates and phenols under mild conditions

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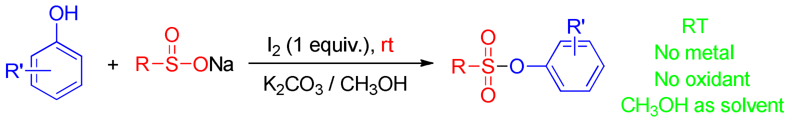
A facile and highly efficient method for the synthesis of sulfonate esters mediated by iodine at room temperature has been developed, without transition metal catalysts and oxidants.



R, R'= H or halogen, alkyl, aryl groups

25 examples, up to 98% yield