Metal-Free Direct Construction of Sulfonamides via Iodine-Mediated Coupling Reaction of Sodium Sulfinates and Amines at Room Temperature

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Abstract: A simple, practical, and metal-free protocol has been developed for the synthesis of sulfonamides from sodium sulfinates and various amines through an iodine-mediated S–N bond formation reaction at room temperature. This green reaction is cost-effective, operationally straightforward, and especially proceeds under very mild conditions to afford the target products in good to excellent yields (up to 98%).

Keywords: metal-free conditions; molecular iodine; S–N bond formation; sodium sulfinates; sulfonamides

Introduction

Sulfonamides are highly valuable structural motifs in numerous natural products, bioactive molecules, and pharmaceuticals, since they can exhibit a wide range of bioactivities, such as antifungal, anticancer, antibacterial, antipsychotic anticonvulsant, and HIV protease inhibitory activities.1 Also, they have been used as potent COX-2,2 caspase,3 and carbonic anhydrase inhibitors.4 Particularly, in light of their importance in drug discovery, considerable efforts have been devoted to the synthesis of sulfonamides in the past few decades. Traditionally, sulfonamides are prepared by the nucleophilic attack by amines on sulfonyl chlorides in the presence of a base (Scheme 1, A).5 This method, although effective, requires the availability of sulfonyl chlorides, some of which are hard to prepare, water sensitive, and difficult to store or handle. Alternative methods, such as the triphenylphosphine ditriflate-mediated coupling reaction of sulfonic acids with amines,6 transition metal-catalyzed cross-coupling of sulfonamides separately with organic halides,7 arylboronic acids,8 aryl nonaflates,8 alcohols or esters10 and hydrocarbons,11 the amidation and oxidation of methyl sulfinates,12 and the aminosulfonylation reactions of aryl halides, boronic acids and diazonium salts13 have thus been developed. Nevertheless, most

Scheme 1. Methods for the construction of sulfonamides.
established reactions usually suffer from some drawbacks, such as hardly available reactants, multistep reactions, strong oxidants, toxic wastes and relatively harsh or complex reaction conditions. Therefore, the development of a simple, mild, convenient, economic, and especially, environmentally friendly strategy to access sulfonamides is still highly desirable.

Very recently, Jiang and co-workers reported an elegant work for CuBr$_2$-catalyzed oxidative synthesis of sulfonamides from readily available sodium sulfinites and amines with DMSO or O$_2$ (balloon) as the oxidant (Scheme 1, B).$^{[15]}$ In 2014, Pan et al. described CuCl-mediated sulfonamide formation from thiols and formamides in the presence of a stoichiometric amount of Cu(OAc)$_2$, and cinnamic acid (Scheme 1, C).$^{[16]}$ Nevertheless, the two well-developed reactions still require high reaction temperatures and transition metal catalysts, which might thereby increase the risk for traces of toxic metals in the products, and limit their wide applications on a large scale in the field of organic synthesis and pharmaceutical chemistry.

### Results and Discussion

Molecular iodine has attracted considerable attention in modern synthetic chemistry because of its low cost, water tolerance, non-toxicity and commercial availability.$^{[17]}$ With our continuing efforts towards the development of new methods for the construction of sulfone-containing organic compounds$^{[17]}$ herein, we report a simple, cost-effective, and metal-free protocol for the direct construction of sulfonamides from sodium sulfinites$^{[18]}$ and various amines via molecular iodine-mediated S–N bond formation reaction. The present reaction could be performed at room temperature under air to give the corresponding products in good to excellent yields, moreover, it can avoid the risk of metal contamination, high temperatures, and the use of an inert gas or pure oxygen atmosphere (Scheme 1, D).

Initially, the reaction of sodium benzenesulfinate 1a with benzylamine 2a was performed in the presence of molecular iodine (0.2 equiv.) in 1,2-dichloroethane (DCE) at room temperature under air (Table 1, entry 2). To our delight, the desired sulfonamide 3aa was isolated in 26% yield.

Increasing the amount of iodine led to a significant increase in product yields, so that a 95% yield of 3aa was obtained when iodine was increased to 1 equiv. (Table 1, entry 5). It should be noted that no conversion was observed in the absence of iodine (Table 1, entry 1). Next, the effect of solvent on the reaction efficiency was investigated. It was found that DCE was the most appropriate reaction medium for the present transformation, while other solvents gave lower yields of the targets (Table 1, entries 5–15). Further optimization of reaction temperature showed that room temperature was the best choice, in contrast, higher temperatures could result in relatively lower reaction efficiency (Table 1, entries 5, 16 and 17). In addition, the proportion of the substrates also exerted an influence on the efficiency. The optimal proportion of sodium benzenesulfinate and benzylamine was 2:1, and a decrease of the amount of 1a (Table 1, entry 18) or increase of 2a (Table 1, entry 19) would inhibit this transformation. The desired product was still obtained in 79% yield when the reaction was performed under N$_2$. This suggested that air (oxygen) is not required for the efficient progress of the reaction (Table 1, entry 20).

With the optimized conditions in hand, the scope and limitations of the reaction of benzenesulfinate 1a with various alkylamines were investigated, with the results shown in Table 2. Generally, benzylamine and its derivatives, which have electron-rich or electron-poor groups on the aryl rings, could readily participate in the reactions, producing the desired products in high yields (3aa–3ag). In addition to benzylamines,
various primary and secondary amines including amines with long aliphatic chains, acyclic amines such as di-n-butylamine, and cyclic amines such as piperidine and morpholine could also afford the corresponding sulfonamides 3ah–3ar in good to excellent yields. Moreover, the participation of aromatic amines in this protocol was examined (Table 3), as a series of substituted aromatic amines containing either electron-rich or electron-deficient groups were all suitable for this process, affording the corresponding products in good yields (5aa–5ak).

The scope of this coupling reaction was further expanded to a variety of sodium sulfinates (Table 4). In addition to sodium benzenesulfinate 1a, various substituted sodium arenesulfinates were all favorable substrates to generate the corresponding products in moderate to good yields (5al–5ao). Notably, heteroaromatic amines (i.e., pyridin-2-amine) and secondary aromatic amines (i.e., indoline, N-methylaniline and 1H-benzo[d]imidazole) could be tolerated in this reaction, achieving the desired products in moderate to good yields (5al–5ao).

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Table 4. Iodine-mediated reaction of various sodium sulfinates with amines[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sodium sulfinates</th>
<th>Products</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>3ba</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>5ba</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>3ca</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3da</td>
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<td>5</td>
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<td>56</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>3ga</td>
<td>85</td>
</tr>
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<td>3ha</td>
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</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>3ia</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>3ja</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>1a</td>
<td>3aa</td>
<td>46[c]</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: sodium arenesulfinate 1 (1 mmol), amine 2 (0.5 mmol), I₂ (1 equiv.), DCE (2 mL), 25°C, 24–30 h, under air.
[b] Isolated yields based on 2a.
[c] 1a (20 mmol), 2a (10 mmol).

also compatible with this reaction, and the corresponding product was obtained in 56% yield (Table 4, entry 9). Unfortunately, none of the desired product was obtained when aliphatic sodium sulfinates such as sodium methanesulfinate were used as the substrate (Table 4, entry 10). It should be noted that this reaction could be effectively scaled up to the gram scale with a similar efficiency (Table 4, entry 11). Thus, this simple protocol could be employed as a practical and efficient method to access various sulfonamides.

It is known that the sulfinate sodium salts on reaction with iodine could produce sulfonyl iodide.[19] Remarkably, when the reaction of sulfonyl iodide[20] with benzylamine was conducted in DCE at room temperature, the corresponding sulfonamide 3ba was obtained in 67% yield (Scheme 2). Based on the above experimental results and referring to the previous reports,[19] a possible reaction pathway was proposed and is shown in Scheme 3. Firstly, sodium sulfinate interacted with molecular iodine to generate sulfonyl iodide. Then, sulfonyl iodide was attacked by amine leading to the desired sulfonamide.

Conclusions

In conclusion, we have developed a new, metal-free method for the synthesis of sulfonamides via the molecular iodine-mediated coupling reaction of sodium sulfinates and amines. The reaction proceeds smoothly at room temperature under air and shows broad functional group tolerance. It provides a practical, cost-effective, efficient, and green approach to various sulfonamides. It is believed that the merits of extremely mild reaction conditions, high efficiency of transformation, and broad substrate scope will make the developed method highly attractive in the field of synthetic chemistry and for the pharmaceutical industry.

Experimental Section

General Procedure

A mixture of sodium sulfinate 1 (1 mmol), alkylamine 2 or arylamine 4 (0.5 mmol), I₂ (0.5 mmol), and DCE (2 mL) was charged in a 25-mL round-bottomed flask at room temperature under air. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then cooled to 0 °C, and the resulting precipitate was filtered off and washed with hexane. The combined filtrate and washings were concentrated to give a dark oil, which was purified by flash column chromatography on silica gel using DCM/MeOH (98:2) as eluent to afford the desired product.
temperature for 12–36 h. After the reaction, the resulting mixture was extracted with EtOAc. The combined organic phase was dried over anhydrous Na$_2$SO$_4$ and the solvent was then removed under vacuum. The residue was purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired product 3 and 5.

Acknowledgements

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References


[20] Tosyl iodide was prepared according to the ref.19b,c