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ARTICLE TYPE

Synthesis of sulfonamides via I_2-mediated reaction of sodium sulfinates with amines in aqueous medium at room temperature

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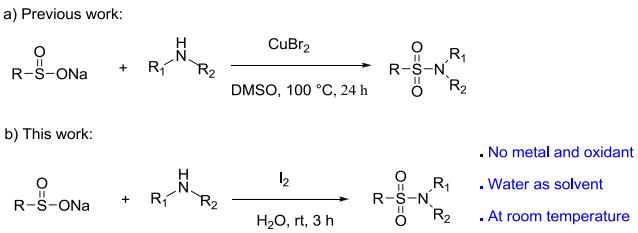
An efficient I_2-mediated approach to the synthesis of sulfonamides at room temperature using water as the solvent has been developed. This method for the synthesis of sulfonamides is quite convenient and environment friendly. In addition, the purification procedure of the desired products becomes very easy.

As HIV protease inhibitors, calcitonin inducers and anticancer, antibacterial and anti-inflammatory agents, sulfonamides have a wide range of applications in pharmaceutical industry.[1] During the past decade, various methods have been developed for the synthesis of sulfonamides, including the reaction of thiols or sulfonyl chlorides with amino compounds and sulfonamides with organic halides, alcohols or hydrocarbons via metal-catalyzed coupling.[2] Recently, a new and attractive protocol for the synthesis of sulfonamides from sodium sulfinates and amines has also been reported (Scheme 1a).[3] However, in most of these methods, the reaction was carried out using transition metals as catalyst and toxic solvents as reaction media. In addition, some of them also suffer from harsh reaction conditions and tedious procedures in the purfication of the products. To overcome these drawbacks, it is still highly desired to search for a greener and sustainable method for the synthesis of sulfonamides.

In recent years, iodine-mediated[4] or iodine-catalyzed[5] reactions have been widely studied because iodine is cheap, readily available and eco-friendly. Undoubtedly, it is very attractive that iodine could substitute for transition metals as catalysts. Some successful cases have comfirmed that iodine could effectively replace the transition metals to catalyze some organic reactions.[6] In addition, water as reaction media has attracted increasing attention in organic synthesis due to its environmental acceptability, abundance, safety and low cost.[7] We are interested in I_2-mediated or catalyzed organic reactions performed in the aqueous phase. Herein, we report an efficient I_2-mediated reaction of sodium sulfinates with amines for the synthesis of sulfonamide in aqueous media at



Scheme 1 Two different methods for the synthesis of sulfonamides.

room temperature (Scheme 1b). The present synthetic route could afford the target products in good to excellent yields under green and mild conditions, showing its fascinating application prospect.

Initially, we utilized N-methylbenzylamine (**1a**) and sodium p-tolylsulfinate (**2a**) as model substrates to optimize the reaction conditions, and the results are summarized in Table 1. To our delight, in the presence of iodine (0.2 equiv), the reaction of **1a** with **2a** at room temperature in H_2O for 3 h gave sulfonamides (**3a**) in 42% yield (Table 1, entry 2). When the amount of iodine was increased to twice (0.4 equiv), the yield of **3a** was also nearly raised to twice (Table 1, entry 4). When the reaction time was prolonged from 3 h to 30 h, the yield of **3a** was almost unchanged (Table 1, entry 5). This interesting result attracted our attention. We guessed that the yield of **3a** would be directly related to the amount of iodine. In order to confirm this point, different amounts of iodine were added into the reaction system. When the amount of iodine was increased to 0.5 equiv, more than 98% yield of **3a** was obtained (Table 1, entry 6). Decreasing the stoichiometric amount of iodine to 0.3 and 0.1 equiv led to the declined yield of 61% and 18% (Table 1, entries 3 and 1), respectively. Next, the effect of solvents on the reaction was examined. Screening of various solvents indicated that water was the most suitable solvent for this transformation (Table 1, entries 7–15). Unfortunately, with the use of AcOH as the solvent, no desired product was detected by GC-MS (Table 1, entry 16). In addition, the yield of **3a** could be hardly improved by increasing reaction temperature (Table 1, entry 17). Thus, the optimized conditions for this reaction was summarized as

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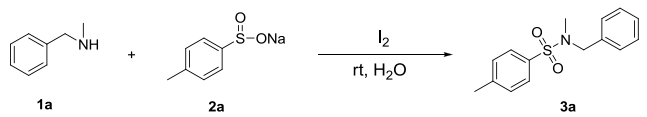
follows: **1a** (0.5 mmol), **2a** (0.6 mmol), I_2 (0.25 mmol), at room temperature in water medium under air for 3 h.

Table 1 Optimization of reaction conditions.[a]

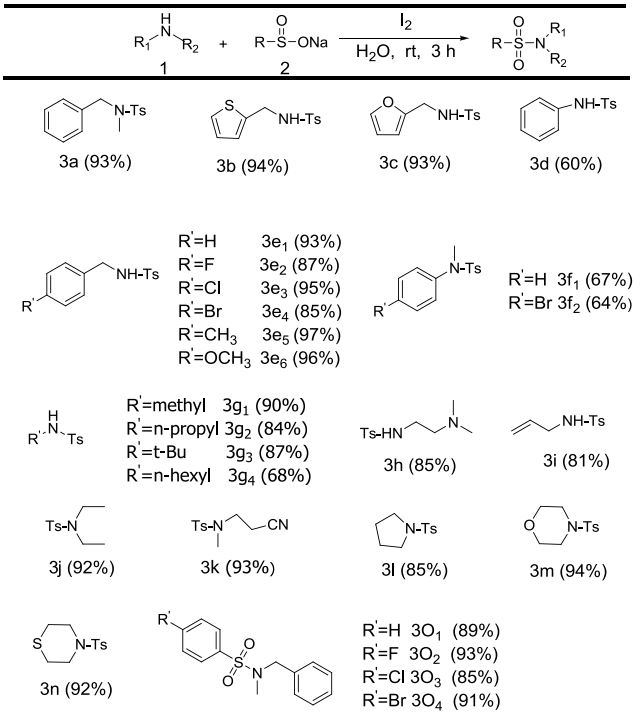


Entry	I_2 (equiv)	Solvent	Time (h)	Yield (%) [b]
1	0.1	H_2O	3	18
2	0.2	H_2O	3	42
3	0.3	H_2O	3	61
4	0.4	H_2O	3	79
5	0.4	H_2O	30	81
6	0.5	H_2O	3	>98
7	0.5	MeOH	3	92
8	0.5	EtOH	3	89
9	0.5	CH_3CN	3	93
10	0.5	DMF	3	98
11	0.5	DMSO	3	87
12	0.5	EtOAC	3	87
13	0.5	CH_2Cl_2	3	96
14	0.5	THF	3	88
15	0.5	pyridine	3	91
16	0.5	AcOH	3	trace
17[c]	0.1	H_2O	3	19
18[d]	0.5	H_2O	3	96
19[e]	0.5	H_2O	3	>98

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), solvent (2.0 mL), room temperature, 3 h, under air. [b] Determined by GC based on **1a**. [c] Reaction temperature 80 ℃. [d] Under N_2 in a sealed tube. [e] The reaction was carried out in the dark background.

With the optimal reaction conditions established, we then examined the scope of the reaction between different amines and sodium p-tolylsulfinate (**2a**). As listed in Table 2, both aromatic and aliphatic amines reacted smoothly with sodium p-tolylsulfinate under the optimal reaction conditions, giving the corresponding sulfonamides from moderate to excellent yields. It was worth mentioning that benzylamine could be effective to afford the corresponding sulfonamide in an excellent yield (93%), which indicated that some unwanted phenomenon such as self-polymerization almost did not occur in this process. Moreover, benzylamine with either electron-donating groups (R′=OMe, Me) or electron-withdrawing groups (R′=F, Cl, Br) on aryl rings all afforded the corresponding sulfonamides in good to excellent yields. When aliphatic amines such as methylamine, allylamine and n-hexylamine were utilized as the substrates, giving the desired products ($3g_1$–3n) in moderate to excellent yields. Nevertheless, lower yields were obtained when the aromatic amines coupled with **2a** (3d, $3f_1$ and $3f_2$) under the same reaction conditions. We further investigated the scope of substrates of sulfinic acid sodium salts in this reaction. Para-substituted sulfinic acid sodium salts with electron-withdrawing groups (R′=F, Cl, Br), were suitable for this transformation and afforded the desired products in high yields.

Table 2 Synthesis of sulfonamides under the optimum conditions.[a,b]

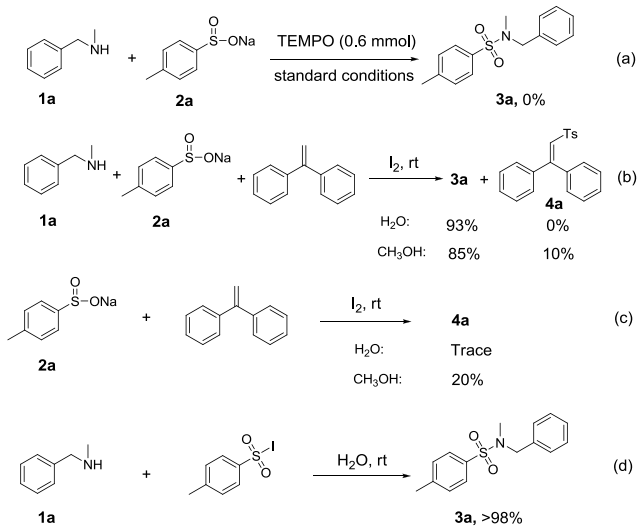


[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol) and I_2 (0.25 mmol) in 2.0 mL of H_2O at room temperature for 3 h. [b] Isolated yield.

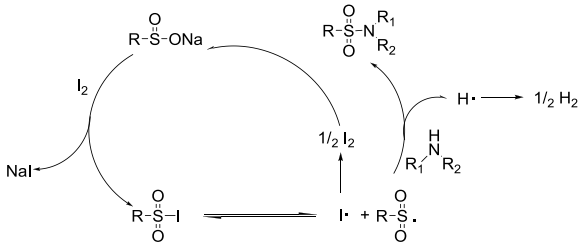
In order to better understand the reaction mechanism, several controlled experiments were carried out (Scheme 2). The reaction was totally inhibited in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), indicating that this transformation proceeded via a radical pathway (Scheme 2, eq (a)). To find more evidence tosupport this point, we utilized 1,1-diphenylethylene to capture the radical. Unfortunately, no desired product (**4a**) was detected in the presence or absence of N-methylbenzylamine under the optimal reaction conditions (Scheme 2, eq (b) and eq (c)). However, the yields of **4a** increased to 10% and 20%, respectively, using methanol as solvent (Scheme 2, eq (b) and eq (c)). This is mainly due to an intrinsically better solubility of the 1,1-diphenylethylene in methanol. Subsequently, instead of sodium p-tolylsulfinate, freshly prepared p-toluenesulfonyl iodide[8] reacted smoothly with N-methylbenzylamine in the absence of iodine, affording the desired product in an excellent yield (Scheme 2, eq (d)). This result indicates that p-toluenesulfonyl iodide was an intermediate for this transformation. Under the protection of N_2, the reaction was carried out to afford the target product **3a** in an excellent yield (96%, Table 1, entry 18), demonstrating that oxygen did not act as a oxidant in this transformation. When the reaction was performed in the dark background, the yield of the target product was not influenced (Table 1, entry 19). This means that the radicals in this reaction system does not originate from the light induction. Further testing pH value of the solution after the reaction of **1a** (0.5 mmol) with **2a** (0.5 mmol), we found that the solution exhibits a slightly alkaline (pH=7.3), which was close to the pH value of NaI solution (pH=7.0). This indicated that no HI existed in the

solution after the reaction.

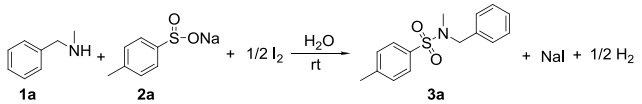
According to the experimental results described the above, a proposed reaction pathway is depicted in Scheme 3. Initially, the sulfinic acid sodium salt reacts with iodine, affording the sulfonyl iodide intermediate **A**.[9c] Due to its instability, the sulfonyl iodide intermediate **A** is easily subjected to homolysis, giving a sulfonyl radical **B** and a iodine radical (I ·).[9] Then, the sulfonyl radical **B** attacks on hydrogen of amine to afford the desired sulfonamide, together with the formation of hydrogen atom (H ·).[10] Meanwhile, the molecular iodine is partly re-generated via the self-coupling of the iodine radical, which could participate in the reaction untill I_2 is fully transformed to NaI. In this sense, I_2 has no catalytic characteristics in this process. In addition, the formed hydrogen atom is finally converted into molecular hydrogen via a self-coupling process. In the present reaction system, I_2 practically is a reactant or inducer, which is depicted in Scheme 4. The total reaction equation (Scheme 4) could well explain why the full conversion of 0.5 mmol of **1a** to **3a** requires 0.25 mmol of I_2 (Table 1, entry 6).



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism.



Scheme 4 A total reaction equation for this transformation.

In conclusion, we have developed a green and sustainable method for the synthesis of sulfonamides from sodium sulfinates and amines. Compared with previous works, this work shows its simplicity, environmental friendliness and low-cost, which could meet the requirement of green chemistry. The research on iodine-mediated or iodine-catalyzed reactions for the synthesis of other important compounds is ongoing in our laboratory.

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Synthesis of sulfonamides via I_2-mediated reaction of sodium sulfinates with amines in aqueous medium at room temperature

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A convenient and green synthetic route has been developed to synthesize sulfonamides in aqueous medium at room temperature, without the use of transition metal catalysts and oxidants.