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## COMMUNICATION

## Metal-free Oxidative Coupling of Amines with Sodium Sulfinates: A Mild Access to Sulfonamides

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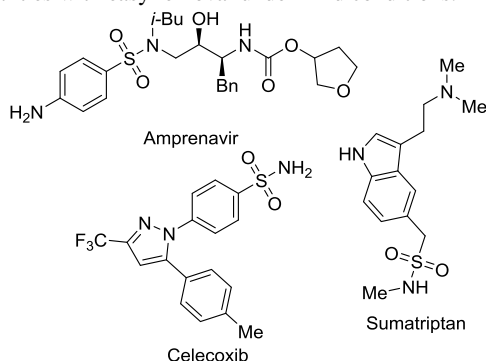
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**A practical and mild procedure for the preparation of sulfonamides through TBAI-catalyzed oxidative coupling of amines with sodium sulfinates using TBHP as an oxidant was presented. A variety of amines and sodium sulfinates could go through the transformation, without impacting hydroxyl group.**

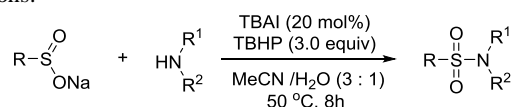
Sulfonamides are often present in pharmaceuticals and bioactive compounds. Sulfa drugs have been used as antimicrobial agents for a long time, and sulfonamide compounds exhibit several other type biological activities such as hypoglycemic, diuretic, anti-carbonic anhydrase(CA), anti-thyroid, anti-inflammatory, anti-cancer, anti-hypertensive and anticonvulsant properties.<sup>1</sup> Pharmaceutically important examples include the protease inhibitor amprenavir, the analgesic celecoxib, sildenafil for erectile dysfunction and the antimigraine agent sumatriptan (Figure 1). Sulfonamides also have a wide range of applications in herbicides and dyes.<sup>2</sup> Furthermore, sulfonamides have been used as protecting groups for NH functionalities with easy removal under mild conditions.<sup>3</sup>



**Figure 1.** Examples of bioactive sulphonamides

Although a number of processes for the synthesis of sulfonamides have been developed,<sup>4</sup> the traditional methods for the synthesis of

sulfonamides principally involve the reaction of amines with sulfonyl chlorides and the alkylation of sulfonamides.<sup>5,6</sup> Transition metal-catalyzed oxidative cross-coupling have been a new strategy to obtain sulfonamides.<sup>7</sup> In 2013, Jiang group reported an elegant process for the synthesis of sulfonamides from sodium sulfinates and amines under the catalysis of copper.<sup>8</sup> Later, Pan group disclosed that sulfonamides could be synthesized from thiols and formamides using stoichiometric Cu(OAc)<sub>2</sub> and CuCl.<sup>9</sup> Although these methods are useful to produce sulfonamides, they suffer from drawbacks such as harsh conditions, requirement for excess base to balance the generated acid, poor tolerance of functional groups, difficulty in handling and possible metal contamination. Therefore, there is a great demand for the development of a clean and facile methodology for the synthesis of sulfonamides. Herein, we wish to report a metal-free procedure for the synthesis of sulfonamides through TBAI-catalyzed (tetra-*n*-butylammonium iodide) oxidative coupling of sodium sulfinates with amines using TBHP (*tert*-butyl hydroperoxide) as an oxidant (Scheme 1). This protocol affords a variety of sulfonamides in satisfactory yields under mild reaction conditions.



**Scheme 1.** TBAI-catalyzed oxidative coupling of amines and sodium sulfinates using TBHP as an oxidant.

Our studies began by optimizing the reaction conditions for the synthesis of sulfonamides, choosing sodium *p*-toluenesulfinate (**1a**) and morpholine (**2a**) as model substrates. The results are tabulated in Table 1. When the reaction proceeded at 50 °C for 8h under the catalysis of 10 mol% molecular iodine in DMSO using TBHP as an oxidant, the desired sulfonamide **3aa** was obtained in 65% yield (Table 1, entry 1). Employing 20 mol% KI as catalyst improved the yield to 79% and TBAI was found to be the best catalyst for the oxidative coupling (Table 1, entries 2 and 3). Our experimental results showed that the tested solvents including DMF, water,

dioxane and acetonitrile all afforded the target compound in lower yields compared with DMSO (Table 1, entries 4-7). To our delight, aqueous acetonitrile gave **3aa** in an excellent yield (Table 1, entry 8). Various oxidants were then screened. As shown in table 1, the examined oxidants, such as dioxxygen, DMSO, oxone and  $K_2S_2O_8$  had almost no effect on the transformation except that hydrogen peroxide produced the corresponding molecule in a lower 78% yield (Table 1, entries 9-13). It was finally found that increasing the loading of *n*-Bu<sub>4</sub>NI could not elevate the yield and 3.0 equivalent of TBHP was most beneficial for the coupling reaction (Table 1, entries 14-16).

**Table 1.** Optimizing the reaction conditions for the coupling of amines and sodium sulfates. <sup>a</sup>

Entry	Catalyst (mol%)	Oxidant (equiv)	Solvent	Yield (%) <sup>b</sup>
1	I <sub>2</sub> (10)	TBHP (2)	DMSO	65
2	KI (20)	TBHP (2)	DMSO	79
3	TBAI (20)	TBHP (2)	DMSO	86
4	TBAI (20)	TBHP (2)	DMF	74
5	TBAI (20)	TBHP (2)	H <sub>2</sub> O	30
6	TBAI (20)	TBHP (2)	dioxane	trace
7	TBAI (20)	TBHP (2)	MeCN	70
8	TBAI (20)	TBHP (2)	MeCN /H <sub>2</sub> O (3 : 1)	92
9	TBAI (20)	H <sub>2</sub> O <sub>2</sub> (2)	MeCN /H <sub>2</sub> O (3 : 1)	78
10	TBAI (20)	O <sub>2</sub> <sup>c</sup>	MeCN /H <sub>2</sub> O (3 : 1)	trace
11	TBAI (20)	DMSO (2)	MeCN /H <sub>2</sub> O (3 : 1)	trace
12	TBAI (20)	oxone (2)	MeCN /H <sub>2</sub> O (3 : 1)	0
13	TBAI (20)	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (2)	MeCN /H <sub>2</sub> O (3 : 1)	0
14	TBAI (30)	TBHP (2)	MeCN /H <sub>2</sub> O (3 : 1)	92
15	TBAI (20)	TBHP (3)	MeCN /H <sub>2</sub> O (3 : 1)	96
16	TBAI (20)	TBHP (4)	MeCN /H <sub>2</sub> O (3 : 1)	96

<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), solvent (2 mL), 8 h. <sup>b</sup> Isolate yield based on **1a**. <sup>c</sup> The reaction was carried out with a O<sub>2</sub> balloon.

The generality and scope of the methodology was then examined after establishing the optimal reaction conditions, and the results are listed in Table 2. Aliphatic amines all went through the oxidative coupling smoothly to give the desired products (Table 2, **3ab-3al**). Among them, although steric hindrance had negative impact on the yield, bulky *tert*-butylamine and di-*iso*-butylamine produced the target sulfonamides in the yields of 78% and 80% respectively (Table 2, **3ae, 3aj**). Benzylamine furnished the corresponding sulfonamide in lower 60% yield because of the side reaction of benzylic oxidation (**3af**). Aromatic amines were also able to undergo the coupling reaction in lower yields compared against aliphatic primary amines for the possible reason that aromatic amine has less nucleophilicity than aliphatic amine (Table 2, **3am-3ao**). Unexpectedly, amines containing a hydroxyl selectively gave the sulfonylation products of amino groups in good to excellent isolated yields (Table 2, **3ap-3ar**), which could not be easily prepared with the traditional methods. These experimental result suggested that sodium sulfinate coupled exclusively with the amino group without impacting the hydroxyl group.

**Table 2.** Scope of amines for the oxidative coupling. <sup>a, b</sup>

 <b>3aa</b> (96%)	 <b>3ab</b> (91%)	 <b>3ac</b> (90%)
 <b>3ad</b> (87%)	 <b>3ae</b> (78%)	 <b>3af</b> (60%)
 <b>3ag</b> (80%)	 <b>3ah</b> (94%)	 <b>3ai</b> (92%)
 <b>3aj</b> (80%)	 <b>3ak</b> (95%)	 <b>3al</b> (94%)
 <b>3am</b> (70%)	 <b>3an</b> (74%)	 <b>3ao</b> (81%)
 <b>3ap</b> (82%)	 <b>3aq</b> (90%)	 <b>3ar</b> (83%)

<sup>a</sup> Conditions: **1a** (1.0 mmol), **2** (1.5 mmol) in aqueous acetonitrile (2mL). <sup>b</sup> Isolated yield.

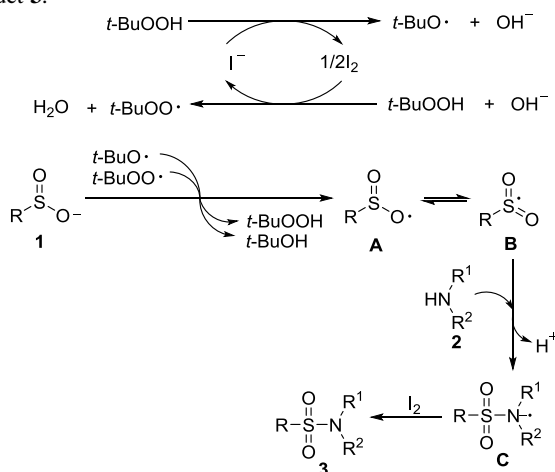
A variety of sodium sulfates were then examined under the standard reaction conditions and the results are recorded in table 3. Sodium naphthalene-2-sulfinate and 4-chlorobenzenesulfinate reacted efficiently with morpholine to provide the target sulfonamide in 95% and 93% yield, respectively (Table 3, **3ba** and **3ca**). When sodium 4-methoxybenzenesulfinate was subjected to the optimized reaction conditions, an excellent yield was obtained while sodium 4-(trifluoromethyl)benzenesulfinate furnished a moderate yield (Table 3, **3da, 3ea**). These results revealed that electronic effect had a considerable effect on the coupling reaction. To our delight, it was found that aliphatic sulfonic acid sodium salts were all outstanding coupling partners (Table 3, **3fa-3ha**). However, sodium trifluoromethanesulfonate failed to yield the desired sulfonamide as expected (Table 3, **3ia**).

**Table 3.** Scope of sodium sulfates for the oxidative coupling. <sup>a, b</sup>

 <b>3ba</b> (95%)	 <b>3ca</b> (93%)	 <b>3da</b> (98%)
 <b>3ea</b> (63%)	 <b>3fa</b> (98%)	 <b>3ga</b> (98%)
 <b>3ha</b> (98%)	 <b>3ia</b> (0%)	

<sup>a</sup> Conditions: **1** (1.0 mmol), **2 a** (1.5 mmol) in aqueous acetonitrile (2mL). <sup>b</sup> Isolated yield.

Based on the above experimental results and the relevant reported works,<sup>10</sup> a proposed reaction mechanism is outlined in scheme 2. Firstly, I<sup>-</sup>/I<sub>2</sub> redox cycle promotes TBHP to furnish *tert*-butoxyl and *tert*-butylperoxyl radicals. Sulfinate **1** is oxidized by these oxidative species into an oxygen-centered radical **A** that can resonate with the sulfonyl radical **B**. Then, amine **2** attacks sulfonyl radical to generate radical anion **C** with the loss of a proton. Intermediate **C** is able to be oxidized by molecular iodine to produce the final sulfonamide product **3**.



**Scheme 2.** Proposed mechanism for TBAI-catalyzed oxidative coupling of amines with sodium sulfinates

## Conclusions

In conclusion, we have developed a practical procedure for the preparation of sulfonamides through TBAI-catalyzed coupling of amines with sodium sulfinates under mild conditions. This methodology tolerates various functional groups including hydroxyl.

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## Notes and references

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