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Metal-free synthesis of sulfonamides via iodine-catalyzed oxidative coupling of sulfonyl hydrazides and amines

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ABSTRACT

A novel, rapid and environmentally-friendly protocol for the synthesis of sulfonamides using iodine as catalyst under solvent-free conditions is described. This method involves the oxidative coupling of sulfonyl hydrazides and amines in the presence of catalytic amount of iodine using TBHP as oxidant. This protocol does not require purification techniques such as column chromatography and recrystalization.

Sulfonamides have received significant relevance in modern organic chemistry and are very privileged class of compounds in synthetic and medicinal chemistry.[1] Sulfonamides are ubiquitous motif seen in many of natural products and pharmaceutically active compounds. Sulfonamide derivatives become popular ever since the discovery of their activity towards antibacterial, anticancer, antiviral, anticonvulsant, anti-inflamatory, antiviral, antitumor and HIV protease inhibitory[1,2] (Figure 1). Furthermore, sulfonamides can also be used as inhibitors for the enzymes carbonic anhydrase, potent COX-2 and caspase.[3] Azo dyes containing sulfonamide moiety are used for the improvement of fibre fixation and light-stability.[4] Because of the easy removal of sulfonamide group under mild conditions, these arylsulfonyls can be used as protecting groups for amino functionalities.[5] Due to their significance, over the last several years many endeavours have been made for the synthesis of sulfonamides. Most commonly, these sulfonamides can be synthesized by the reaction of sulfonyl chlorides with amines[6] and by the coupling of sulfonamides separately with organic alcohols or esters,[7] halides,[8] aryl boronic acids[9] and by aminosulfonation of hydrocarbons[10] under transition metal catalysis. Pan and his co-workers developed an oxygen-activated radical protocol for the synthesis of sulfonamides from aryl thiols under copper catalysis in the presence of stiochiometric amounts of $Cu(OAc)_2$ and cinnamic acid.[11] Chan-Lam coupling of sulfonyl azides and boronic acids under copper-catalysis is another alternative.[12] Though these methods are efficient for the synthesis of sulphonamides, most of them suffer from one or another drawback such as harsh and complex reaction conditions, slow reactivity, poor functional group tolerability, tedious purification procedures and usage of transition metals which may cause contamination in pharmaceutical industry. The title compounds can also be synthesized from the reactions of sodium sulfinates

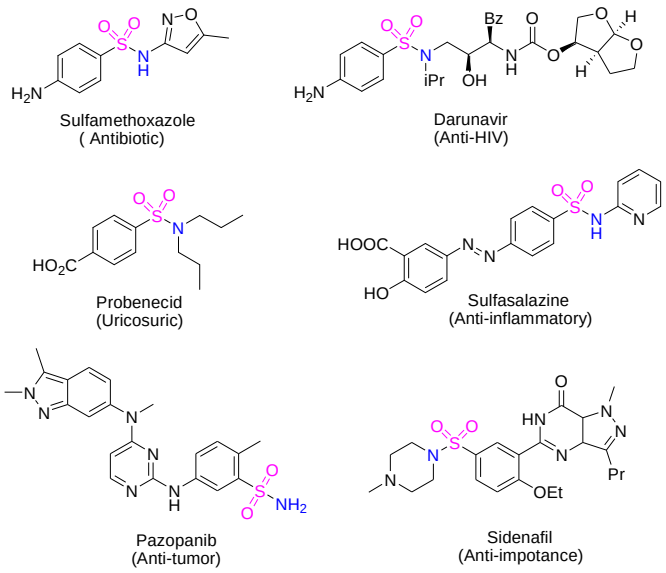
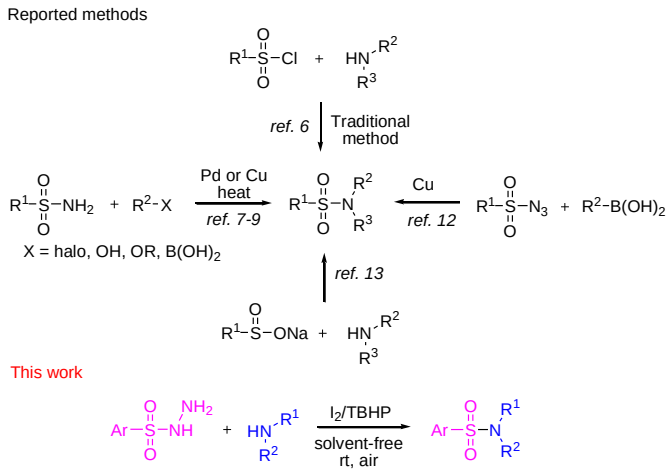


Figure 1. Drugs containing sulfonamide moiety.

with amines under metal and metal-free conditions.[13] Therefore, to overcome these problems it is highly desired to develop a novel, green and sustainable methods for the construction of sulfonamides.

In continuation of our work towards the development of green protocols,[14] herein, we report an efficient, rapid and green method for the construction of sulfonamides by iodine catalyzed[15] oxidative coupling reaction of sulfonyl hydrazides with amines under metal- and solvent-free conditions. The present metal- and solvent-free protocol has various advantages

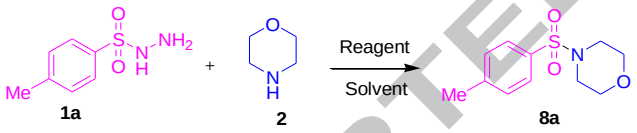


Scheme 1. Synthetic approaches for sulfonamides.

over the literature methods, and could be performed rapidly under air at room temperature to afford the target products in excellent yields. Also, this method does not require purification techniques such column chromatography and recrystalization.

We began our studies by selecting *p*-toluenesulfonyl hydrazide (**1a**) and morpholine (**2**) as model reactants to get the optimized conditions. The results were shown in Table 1. In an initial attempt we performed the reaction in CH_3CN in the presence of catalytic amount of tetrabutylammonium iodide (TBAI) using *tert*-butyl hydroperoxide (TBHP, 70% in H_2O) as an oxidant at room temperature. We were pleased to find that the sulfonamide **8a** was formed in 97% yield in 6 h (Table 1, entry 1). Replacement of TBAI with tetrabutylammonium bromide (TBAB) and potassium iodide (KI) as catalysts yielded the desired product in trace amount and 78%, respectively (Table 1, entries 2 and 3). Molecular iodine as a catalyst afforded the corresponding sulfonamide **8a** in 98% yield in 45 min (Table 1, entry 4). When we replaced the oxidant TBHP with H_2O_2 and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), the reaction was completely inefficient to produce the desired sulfonamide **8a** (Table 1, entries 5 and 6). In the case of oxone and potassium persulfate ($K_2S_2O_8$) as oxidants, the sulfonamide **8a** was obtained in 84 and 62% yield, respectively (Table 1, entries 7 and 8). After getting the maximum yield in the case of iodine and TBHP, we studied the solvent effect. For this purpose, we have performed the model reaction in various solvents such as EtOH, DMF, DMSO, toluene, CH_2Cl_2, DCE, 1,4-dioxane and EtOAc under iodine catalysis using TBHP as oxidant. All the results were summarized in Table 1 (entries 9–16). Among all the solvents used, 1,4-dioxane gave the desired sulfonamide **8a** in maximum yield in 5 min (Table 1, entry 15). When we performed the reaction under solvent-free conditions, to our surprise, the sulfonamide derivative **8a** was obtained in quantitative yield in less than a minute (Table 1, entry 17). By decreasing the amount of iodine (10 mol%) and TBHP (2 equiv), the yield of the desired product **8a** was decreased slightly whereas the reaction time was increased to 3–5 min (Table 1, entries 18 and 19).

Table 1. Optimization of reaction conditions[a]

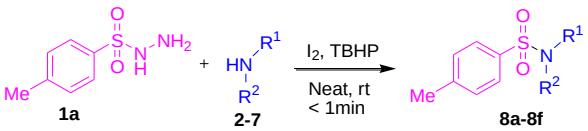


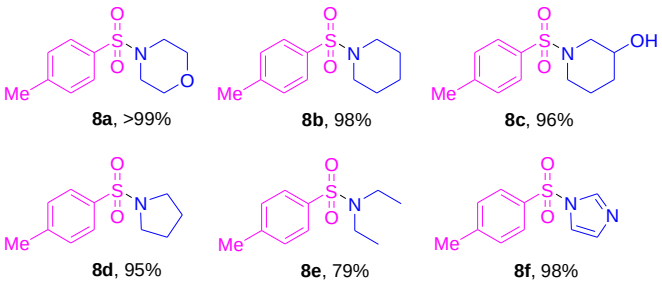
Entry	Reagent	Solvent	Time	Yield (%)[d]
1	TBAI/TBHP	CH_3CN	6 h	97
2	TBAB/TBHP	CH_3CN	6 h	Trace
3	KI/TBHP	CH_3CN	6 h	78
4	I_2/TBHP	CH_3CN	45 min	98
5	I_2/H_2O_2	CH_3CN	3 h	0
6[b]	I_2/DDQ	CH_3CN	3 h	0
7[b]	I_2/Oxone	CH_3CN	1 h	84
8[b]	$I_2/K_2S_2O_8$	CH_3CN	6 h	62
9	I_2/TBHP	EtOH	45 min	94
10	I_2/TBHP	DMF	30 min	93
11	I_2/TBHP	DMSO	1 h	Trace
12	I_2/TBHP	Toluene	1 h	81
13	I_2/TBHP	CH_2Cl_2	10 min	97
14	I_2/TBHP	DCE	15 min	95
15	I_2/TBHP	1,4-dioxane	5 min	>99
16	I_2/TBHP	EtOAc	10 min	98
17	**I_2/TBHP**	**Neat**	**<1 min**	**>99**
18[c]	I_2 /TBHP	Neat	3 min	96
19[b]	I_2/TBHP	Neat	5 min	97

[a] Reaction conditions: **1a** (0. 5 mmol), **2** (0.75 mmol), iodine (0.10 mmol), oxidant (2.0 mmol), solvent (3 mL) stirred at rt. [b] 2.0 equiv of oxidant. [c] 10 mol% iodine. [d] Isolated yields.

After having the optimized conditions in hand, we explored the scope of reaction with respect to amines. Thus, we have performed the reaction of *p*-toluenesulfonyl hydrazide (**8a**) with various amines **2**–**7** under optimized reaction conditions. All the reactions were undergone cleanly within a minute and the corresponding sulfonamides **8a-f** were obtained in excellent yields (Table 2).

Table 2. Scope of amines[a]

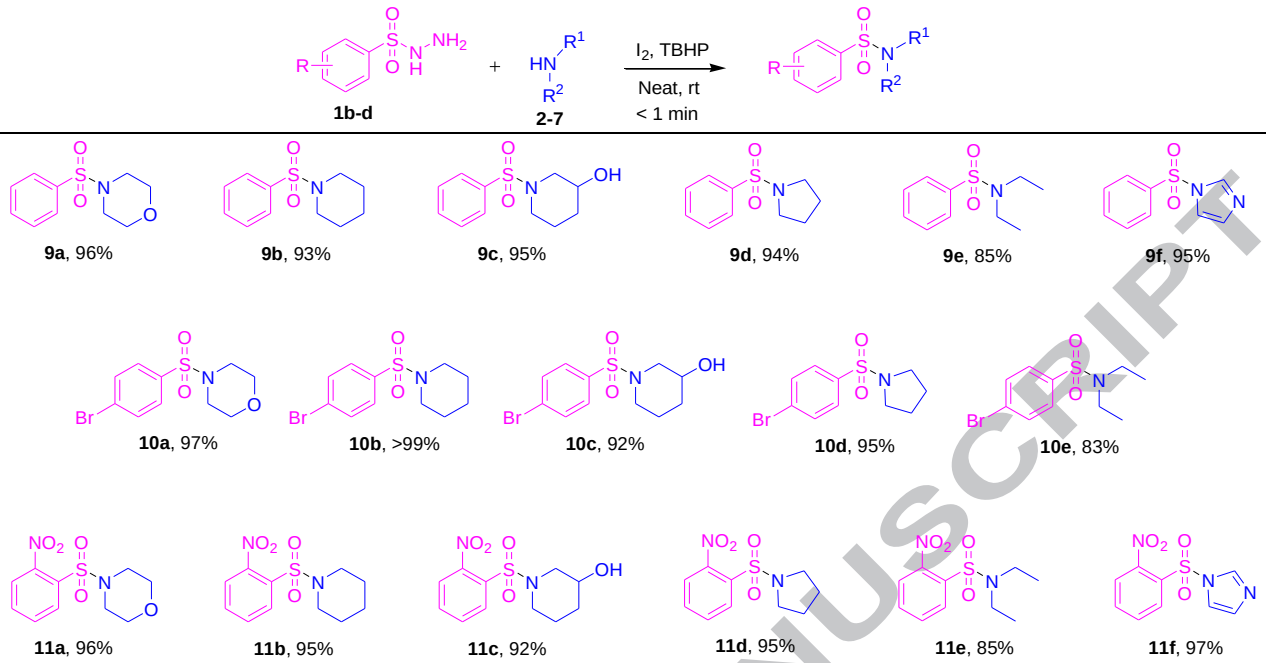




[a] Conditions: **1a** (0.5 mmol), **2** (0.75 mmol), iodine (0.10 mmol), TBHP 70% in H_2O (2.0 mmol).

On the basis of promising results obtained in the case of *p*-toluenesulfonyl hydrazide and various amines, we further extended the present oxidative S–N coupling protocol for the reactions of other sulfonyl hydrazides **1b-d** with amines **2**–**7**. To achieve this, we have chosen parent, 4-bromo- and 2-nitro-benzenesulfonyl hydrazides and performed their reactions with various amines under standard reaction conditions. All the reactions were reached completion within a minute and the corresponding sulfonamide derivatives **9**–**11** were formed in very high to excellent yields (Table 3).

Table 3. Scope of sulfonyl hydrazides[a]



[a] Conditions: **1** (0.5 mmol), amine (0.75 mmol), iodine (0.10 mmol), TBHP 70% in H_2O (2.0 mmol).

In order to show our present protocol is compatible with primary amines, we have carried out the reaction of *p*-toluenesulfonyl hydrazide (**1a**) with propyl amine and *t*-butyl amine under set conditions. In both cases, the reaction were completed within a minute to afford the sulfonamides **12a,b**, respectively, in excellent yields (Figure 2).

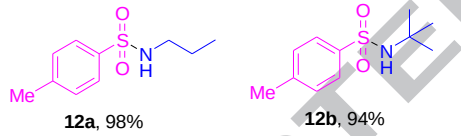
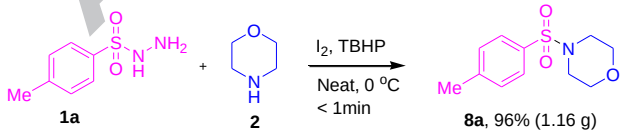


Figure 2: Sulfonamides derived from primary amines.

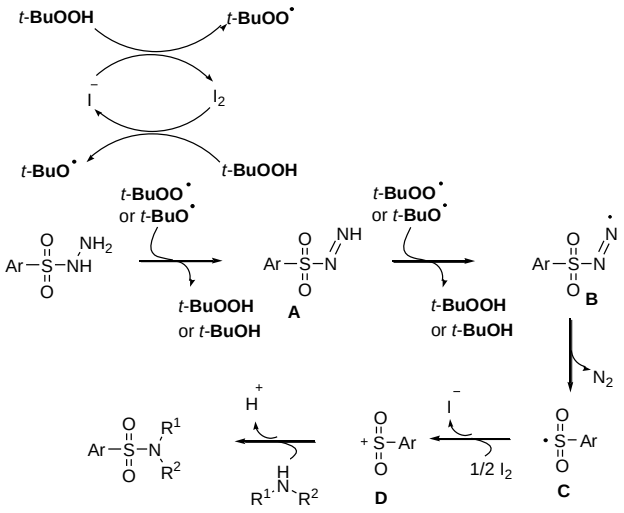
Inspired by the novel and rapid protocol for the synthesis of sulfonamides, we demonstrated the efficiency of the present methodology by conducting the scale up experiment. For this we carried out the reaction of *p*-toluenesulfonyl hydrazide (**1a**, 5 mmol) and morpholine (**2**, 7.5 mmol) under standard reaction conditions at 0 °C. The reaction was reached completion within a minute and after usual work up, the product **8a** was obtained in 96% yield. This shows that the present protocol is amenable towards the gram-scale synthesis of sulphonamides (Scheme 2).



Scheme 2. Gram-scale synthesis of sulfonamide **8a**.

A tentative mechanism is proposed for the formation of sulfonamides in Scheme 3. Initially, TBHP generates the *tert*-butoxyl radical and iodide ion in the presence of iodine. The formed iodide ion reacts with TBHP and generates the *tert*-butyl peroxy radical by the regeneration of iodine. Then the aryl sulfonyl hydrazide in the presence of *tert*-butoxyl and *tert*-butyl peroxy radicals generates the intermediate **A** through H-abstraction which further reacts with *tert*-butoxyl and *tert*-butyl peroxy radicals to give intermediate **B**. Then the radical intermediate **B** is converted into arylsulfonyl radical **C** by the concomitant elimination of molecular nitrogen. The arylsulfonyl radical **C** in the presence of iodine turns into arylsulfonyl cation **D**, which can act as electrophile. Thus formed electrophilic arylsulfonyl cation **D** couples with amine nucleophiles to give the sulfonamide derivative.

In conclusion, for the first time, we have developed an efficient, mild and green protocol for the synthesis of sulfonamides through the oxidative coupling of arylsulfonyl hydrazides and amines using molecular iodine as catalyst and TBHP as oxidant under metal- and solvent-free conditions. In addition, the present reaction conditions are tolerable with amines bearing hydroxy functionality. This protocol is free from purification techniques such as column chromatography and recrystalization.



Scheme 3. Plausible mechanism.

Acknowledgments

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15. Similar work to construct sulfonamides with I_2/TBHP in dichloroethane in 1 h yielding 48–98% after column chromatography has been reported while our manuscript was under preparation: Yotphan, S.; Sumunnee, L.; Beukeaw, D.; Buathongjan, C.; Reutrakul, V. *Org. Biomol. Chem.* **2016**, *14*, 590..

Supplementary Material

Electronic Supplementary Information (ESI) available: [Experimental procedures, spectroscopic data, copies of 1H NMR and 13C NMR]. See DOI: 10.1039/x0xx00000x.

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