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I_2/TBHP Mediated C−N and C−H Bond Cleavage of Tertiary Amines toward Selective Synthesis of Sulfonamides and β-Arylsulfonyl Enamines: The Solvent Effect on Reaction

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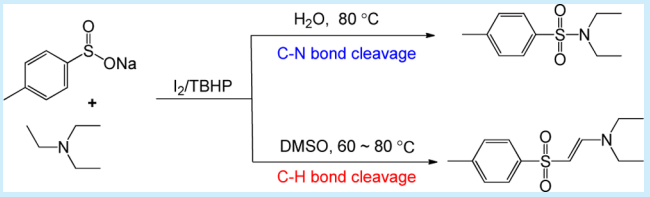
Supporting Information

ABSTRACT: A novel method toward synthesis of sulfonamides and β-arylsulfonyl enamines has been developed via I_2/TBHP mediated C−N and C−H bond cleavage of tertiary amines, which features highly selective formation of two different target products depending on the reaction solvent. The experimental results reveal that H_2O as the solvent could effectively achieve the C−N bond cleavage to produce sulfonamides due to H_2O participating in the reaction process where H_2O plays a dual role. Differing from H_2O, organic solvents (such as dimethyl sulfoxide) could promote the C−H bond cleavage of tertiary amines to yield β-arylsulfonyl enamines.



The activation of C−N and C−H bonds plays an important role in organic synthesis since these bonds are abundant and unreactive in organic molecules. An efficient control over cleavage of C−N and C−H bonds toward synthesis of target products has been an active research area.[1,2] However, previous investigations mainly focused on transition−metal catalysis processes. In contrast, nontransition metal catalysis for the activation of C−N and C−H bonds has been rarely explored. Only a few examples have been reported to date.[3] Thus, it is highly desirable to develop a new and efficient metal-free method for realizing cleavage of C−N or C−H bonds.

The synthesis of sulfonamides and β-arylsulfonyl enamines has attracted much attention due to their highly biological activities such as anticancer, antithyroid, antiinflamatory, hypoglycemic, and diuretic agents.[4] Sulfonamides were typically synthesized by the reaction of thiols or sulfonyl chlorides with amino compounds and sulfonamides with organic halides, alcohols, or hydrocarbons.[5] Recently, Jiang and co-workers reported an attractive process for the synthesis of sulfonamides from sodium sulfinates and amines by $CuBr_2$ catalyst.[6] Very recently, Song and our group further developed a green and sustainable method for the synthesis of sulfonamides from sodium sulfinates and primary/secondary amines via I_2-mediated approach (Scheme 1a).[7] Our previous investigation has revealed that the formation of sulfonamides practically underwent a radical process via I_2-induced N−H bond cleavage. Following our continuous interest in radical reactions, we found that the combination of I_2 and *t*-butyl hydroperoxide (TBHP) with H_2O or dimethyl sulfoxide (DMSO) as the reaction solvent could realize a selective cleavage of C−N and C−H bonds of tertiary amines toward synthesis of sulfonamides and β-arylsulfonyl enamines (Scheme 1b). Herein, we report this interesting finding.

The reaction of sodium 4-methylbenzenesulfinate (**1a**) with triethylamine (**2a**) was chosen as a model to initiate our investigations. In the presence of iodine, the reaction was carried out in H_2O solvent at room temperature, affording the product *N*,*N*-diethyl-4-methylbenzenesulfonamide (**3a**) related with the C−N bond cleavage of **2a** in 13% yield (Table 1, entry 1). When I_2 with TBHP was used as the inducer at the same time, the yield of **3a** was raised to 34% (Table 1, entry 2). In addition, reaction temperature has a great impact on the formation of **3a** (Table 1, entries 2−5). At 80 °C, the yield of **3a** was drastically improved, up to 96% (entry 5). It is noteworthy that (*E*)-*N*,*N*-diethyl-2-tosylethenamine (**4a**) corresponding to the C−H bond cleavage of **2a** was not observed at all in the H_2O solvent case (Table 1, entries 1−5). Surprisingly, it was found that **4a** could be obtained in moderate to high yields besides **3a** if reaction medium H_2O was replaced by organic solvents such as *N*,*N*-dimethylformamide (DMF), dimethylacetamide (DMA), CH_3CN, toluene, EtOH, and DMSO (Table 1, entries 12−17). These

Scheme 1. Synthesis of Sulfonamides and β-Arylsulfonyl Enamines

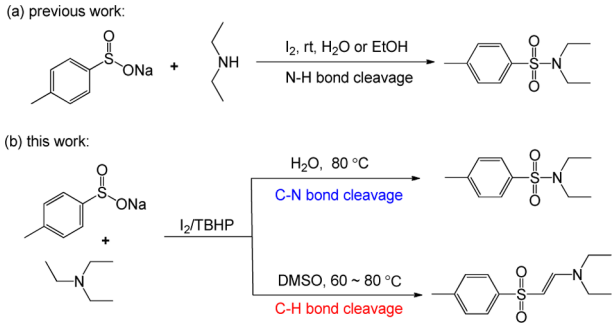


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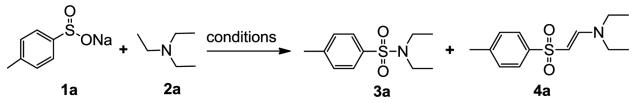
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 4a

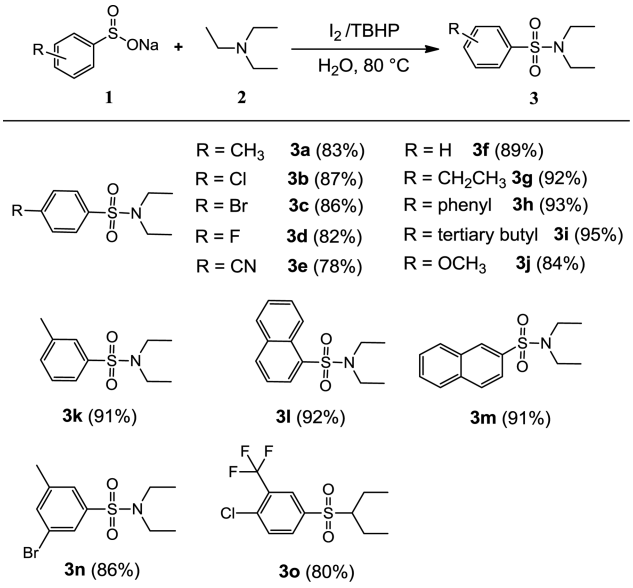
entry	I_2 (equiv)	TBHP (equiv)	solvent	temp (°C)	yield[b] (3a/4a, %)
1	1	0	H_2O	rt	13/0
2	1	3	H_2O	rt	34/0
3	1	3	H_2O	40	60/0
4	1	3	H_2O	60	78/0
5	1	3	H_2O	80	96/0
6	0.5	3	H_2O	80	75/0
7	0.1	3	H_2O	80	19/0
8	0	3	H_2O	80	NR
9	1	5.5	H_2O	80	95/0
10	1	1.5	H_2O	80	84/0
11	1	0	H_2O	80	27/0
12	1	3	DMF	80	29/49
13	1	3	DMA	80	34/66
14	1	3	CH_3CN	80	55/45
15	1	3	toluene	80	49/51
16	1	3	EtOH	80	53/47
17	0.5	3	DMSO	80	10/83
18	0.5	4	DMSO	80	6/89
19	0.5	5.5	DMSO	80	trace/90
20	0.5	5.5	DMSO	60	trace/90
21	0	5.5	DMSO	60	trace/30
22	0.5	0	DMSO	60	trace/32

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), solvent (2 mL), TBHP (70% in water), and 8 h under air in a sealed tube. [b]Determined by GC.

experimental results clearly indicate that solvents have a remarkable effect on the C−N and C−H bond cleavage of **2a**. Further investigation demonstrated that the formation of **3a** was negligible and that **4a** became almost a sole product when the amount of TBHP was increased to 5.5 equiv in the DMSO solvent case (Table 1, entries 19−21). Moreover, the yield of **3a** or **4a** obviously declined in the absence of TBHP or I_2 (Table 1, entries 11, 21, and 22). This means that the combination of I_2 with TBHP is very important for the formation of **3a** and **4a**. In addition, only 19% yield of **3a** was obtained when 0.1 equiv (catalytic amount) of I_2 was used (Table 1, entry 7), indicating that I_2 could not act as a catalyst in the present system.

For the reaction of C−N bond cleavage of tertiary amines in H_2O solvent, we further investigated the substrate scope with respect to sodium sulfinate salts. As shown in Scheme 2, a wide range of sodium sulfinate salts with triethylamine (**2a**) could be applicable to this reaction system under the optimized conditions. The sodium sulfinate salts with electron-withdrawing and electron-donating groups reacted with **2a** to afford the corresponding sulfonamides in good to excellent yields smoothly (Scheme 2, **3a**−**3j**). This process could tolerate various functional groups such as halogen, −CN, and $-OCH_3$ (Scheme 2, **3b**−**3e** and **3j**), which provided the possibility for further functionalization. Moreover, the substituted group at different positions on the phenyl ring of sodium sulfinates had no obvious effect on the reaction (Scheme 2, **3a** and **3k**). Besides, the substrates bearing two substituted groups (especially trifluoromethyl group) such as sodium 3-bromo-5-methylbenzenesulfinate and sodium 4-chloro-3-(trifluoromethyl)benzenesulfinate could smoothly perform as well (Scheme 2, **3n** and **3o**). In

Scheme 2. Scope of Sodium Sulfinate Salts[a,b]

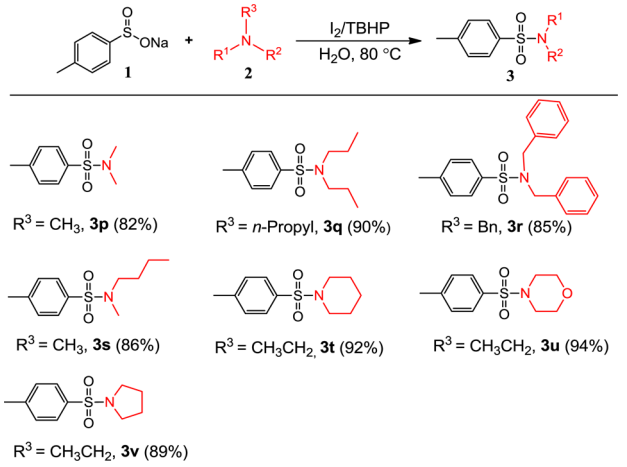


[a]Reaction conditions: sodium sulfinate salts (0.6 mmol), **2a** (0.5 mmol), I_2 (1 equiv), TBHP (3 equiv), H_2O (2 mL), and 8 h under air in a sealed tube. [b]Isolated yield.

addition, sodium naphthalene-1-sulfinate and sodium naphthalene-2-sulfinate were proven to be good substrates for this process (Scheme 2, **3l** and **3m**).

To determine whether other tertiary amines could be applicable to this reaction process, various tertiary amines were investigated under the optimized conditions. It was found that both aliphatic and aromatic tertiary amines reacted smoothly with sodium 4-methylbenzoate to afford the target products in good yields (Scheme 3, **3p**−**3r**). When the tertiary amine with

Scheme 3. Scope of Tertiary Amines[a,b]



[a]Reaction conditions as shown in Scheme 2. [b]Isolated yield.

different substituent groups like *N*,*N*-dimethylbutan-1-amine was involved, the target product (**3s**) was also obtained in a high yield. Delightfully, the reaction could afford the corresponding products in excellent yields (Scheme 3, **3t**−**3v**) when cyclic and heterocyclic tertiary amines, such as 1-ethylpiperidine, 4-ethylmorpholine, and 1-ethylpyrrolidine, were used as the substrates.

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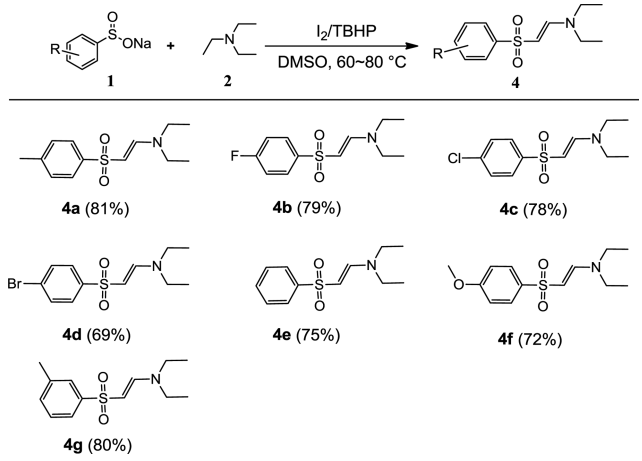
For the activation of C−H bond of tertiary amines toward synthesis of β-arylsulfonyl enamines in DMSO solvent, we further investigated the reaction of various sodium sulfinate salts with triethylamine (**2a**). As shown in Scheme 4, sodium sulfinate

Scheme 4. Synthesis β-Arylsulfonyl Enamines[a,b]



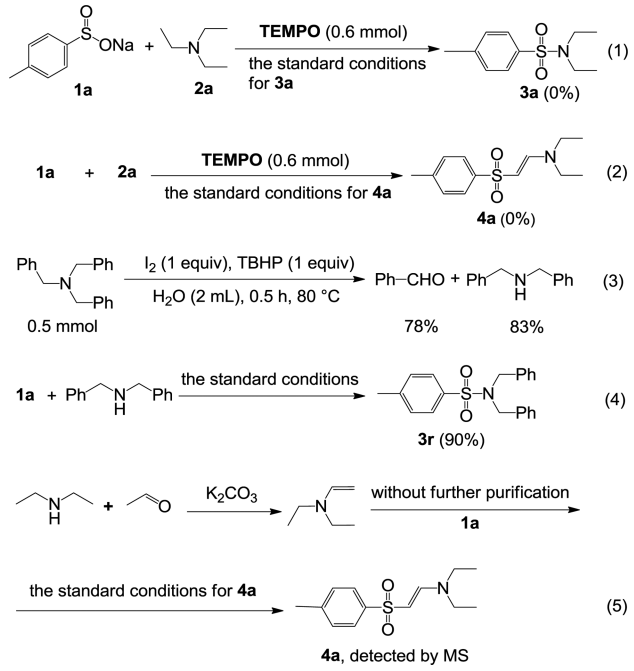
[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), I_2 (0.5 equiv), TBHP (5.5 equiv), DMSO (2 mL), and 8 h under air in a sealed tube. [b]Isolated yield.

salts bearing electron-withdrawing and electron-donating groups with **2a** were well converted to the corresponding β-arylsulfonyl enamine products in good yields. Using *N*,*N*-diisopropylethylamine as the substrate, the reaction of sodium 4-methylbenzenesulfinate (**1a**) with *N*,*N*-diisopropylethylamine gave a mixture of β-arylsulfonyl enamines in DMSO solvent, while the target product sulfonamides were not obtained at all in H_2O solvent (Scheme S1, see the Supporting Information).

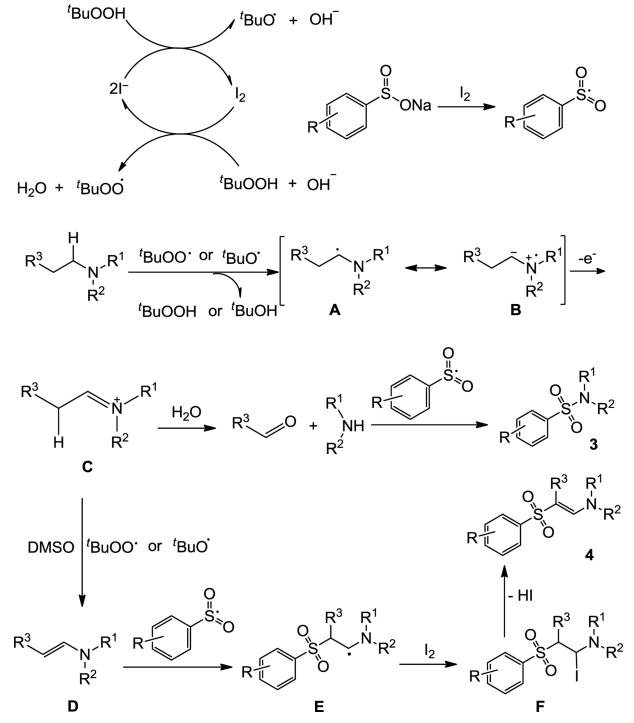
To gain further insight into the mechanism, a series of control experiments were carried out. No desired product was detected in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), indicating that the formation of **3a** or **4a** presumably underwent a radical pathway (Scheme 5, eqs 1 and 2). In the absence of sodium 4-methylbenzoate (**1a**), tribenzylamine was changed to dibenzylamine and benzaldehyde via the C−N bond cleavage (Scheme 5, eq 3). Dibenzylamine with **1a** could be smoothly converted to sulfonamide **3r** (Scheme 5, eq 4). In addition, benzaldehyde could also be detected during the reaction of **1a** with tribenzylamine for the synthesis of **3r** under the standard conditions (Scheme 3). Therefore, we deduce that the formation of sulfonamide may involve the conversion of tertiary amine to secondary amine. The C−N bond cleavage of tertiary amine is contributed to H_2O participating in this reaction process. In the present system, H_2O could serve not only as the solvent but also as the reactant. In addition, we deduce that enamine may be the intermediate product in the DMSO solvent case. In order to confirm this point, *N*,*N*-diethylethenamine was synthesized via the reaction of diethylamine with acetaldehyde by using K_2CO_3 as the dehydrating agent at 40 °C for 4 h,[8] followed by the reaction with **1a** without further purification. As shown in Scheme 5 (eq 5), (*E*)-*N*,*N*-diethyl-2-tosylethenamine (**4a**) could be obtained, which indicates that *N*,*N*-diethylethenamine may be the intermediate product.

Based on our experimental results and previous publications, a plausible mechanism is depicted in Scheme 6. Initially, I^-/I_2 redox cycle promotes TBHP to furnish *tert*-butoxyl and *tert*-

Scheme 5. Control Experiments



Scheme 6. Possible Mechanism



butylperoxyl radicals. Meanwhile, the sulfinic acid sodium is activated by I_2, providing a sulfonyl radical.[9] *tert*-Butoxyl and *tert*-butylperoxyl radicals then abstract hydrogen from the tertiary amine to generate a radical **A** or **B**, followed by an electron transfer to form intermediate **C**. Because of its instability, the intermediate **C** is readily hydrolyzed to produce an aldehyde and a secondary amine in water.[10] Then, the sulfonyl radical attacks the secondary amine to afford the target product **3**.[7] However, the intermediate **C** is converted into enamine **D** by deprotonation in DMSO solvent.[11] Enamine **D** combines with

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a sulfonyl radical to give a radical **E**, followed by the reaction with I_2 to form intermediate product **F**. Finally, HI elimination from **F** provides the target product **4**.[9c,12]

In summary, the preparation of sulfonamides and β-arylsulfonyl enamines via I_2/TBHP-mediated reaction between tertiary amines and sodium sulfinates has been achieved. In this reaction system, the combination of I_2 with TBHP induces a radical reaction, and solvents have a great effect on the reaction. H_2O takes part in the reaction to result in the C−N bond cleavage of tertiary amines so that sulfonamides could be formed. In the DMSO solvent case, the C−H bond cleavage of tertiary amines readily occurred to give β-arylsulfonyl enamines. The present work provides a new strategy for the synthesis of sulfonamides and β-arylsulfonyl enamines. The strategy is of interest and has potential applications due to selective cleavage of C−N and C−H bonds of tertiary amines for achieving desirable synthetic purposes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01412.

Typical experimental procedure and characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

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