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One-Pot Synthesis of Sulfonamides from Sodium Sulfinates and Amines via Sulfonyl Bromides

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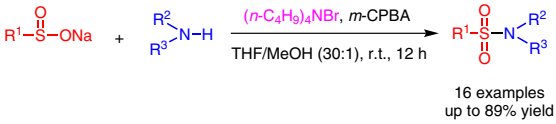

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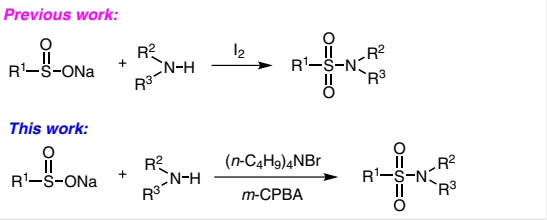
Abstract a new and convenient procedure has been developed for the preparation of sulfonamides from sodium sulfinates and amines with $(n\text{-}C_4H_9)_4NBr$ as bromine source and *m*-chloroperbenzoic acid as oxidant. This S–N bond formation reaction proceeds efficiently via sulfonyl bromides under neutral conditions to afford the corresponding sulfonamides in good yields at room temperature.

Key words sulfonamides, sodium sulfinates, amines, $(n\text{-}C_4H_9)_4NBr$, sulfonyl bromides

Sulfonamides are very important organic compounds and have been broadly applied in pharmaceutical industry due to their effective antifungal, anticancer, antibacterial, antipsychotic anticonvulsant, and HIV protease inhibitory activities.[1] They are also used as nitrogen protecting groups in organic synthesis.[2] The traditional method for the formation of sulfonamides is by the nucleophilic reaction of amino compounds on sulfonyl chlorides in the presence of a base.[3] However, this method has some limitations, such as hazardous starting materials, harsh reaction conditions, and the difficulty to obtain some sulfonyl chlorides. To obviate these drawbacks, alternative methods have been developed, including the metal-catalyzed coupling reaction of sulfonamides with organic halides, arylboronic acids, alcohols, or hydrocarbons[4] and copper-catalyzed oxidative coupling of amines and sodium sulfinates.[5] Nevertheless, the above methods for the preparation of sulfonamides usually use transition-metal catalysts and toxic solvents as reaction media, which might increase the risk or cause pollution in the final products. In addition, some of them also suffer from hardly available reactants, multistep reactions, complex reaction conditions, high reaction temperatures, and long reaction times.

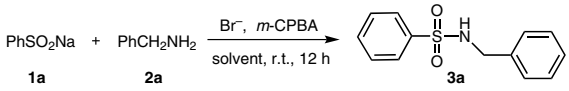
The catalytic utilization of molecular iodine and its salts in organic synthesis is increasing in importance, with growing interest in the development of environmentally benign synthetic transformations.[6] Due to the ease of handling, low toxicity, commercial availability, and mild reactivity, especially the metal-like behavior of iodine, a number of recent studies have demonstrated the utility of iodine catalysis as an efficient and powerful tool for the formation of carbon–carbon and carbon–heteroatom bonds.[7] Using iodine as the catalyst, the construction of carbon–sulfur bond methods also have been developed from sodium sulfinates.[8] Very recently, the iodine-mediated or iodine-catalyzed one-pot synthesis of sulfonamides from readily available sodium sulfinates and amines has been reported, which is demonstrated via sulfonyl iodide intermediates (Scheme 1).[9] It is very interesting because this nitrogen–sulfur bond-formation method is general, efficient, and environmentally friendly. To extend the application scope of this methodology, we have investigated a similar route for the synthesis of sulfonamides via sulfonyl bromide intermediates. Fortunately, a new and convenient procedure has been developed for accessing sulfonamides from sodium sulfinates and amines, which is promoted by $(n\text{-}C_4H_9)_4NBr$ combined with oxidant *m*-chloroperbenzoic acid (*m*-CPBA, Scheme 1). To the best of our knowledge, this method has not been reported before.



Scheme 1 Methods for the synthesis of sulfonamides

Although similar to iodine, molecular bromine is difficult to handle due to its strong volatility and corrosiveness. Using sodium bromide (NaBr) combined with *m*-CPBA to replace bromine, we first explored the one-pot procedure for the preparation of sulfonamides from sodium benzenesulfinate (**1a**) and benzylamine (**2a**) at room temperature. We were pleased to find that simply stirring of a mixture of 2.0 equivalents of **1a** with 1.0 equivalent of **2a**, NaBr and *m*-CPBA in CH_2Cl_2 for 12 hours, the desired product, *N*-benzylbenzenesulfonamide (**3a**) was obtained, albeit in 26% yield (Table 1, entry 1). Then, the reaction conditions were optimized. Among various solvents screened, tetrahydrofuran (THF) led to the best yield, 47%, for **3a** (Table 1, entries 1–9). Due to the bad solubility of **1a** in THF, water was added to improve the reaction. The experiment indicated that when the volume ratio of THF to H_2O was 30:1, the mixed solvent was not beneficial to the reaction. However, using MeOH to replace H_2O, the yields increased, and finally the mixed solvent THF–MeOH (30:1) was selected as a suitable solvent for the reaction (Table 1, entries 10–13). In this sol-

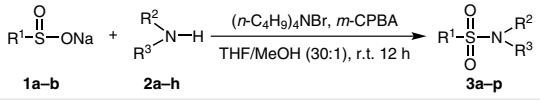
Table 1 Optimization of the Reaction Conditions for the Preparation of *N*-Benzylbenzenesulfonamide



Entry	$PhSO_2Na$ (equiv)	*m*-CPBA (equiv)	Br^- (equiv)	Solvent	Yield (%)[a]
1	2.0	1.0	NaBr (1.0)	CH_2Cl_2	26
2	2.0	1.0	NaBr (1.0)	MeCN	35
3	2.0	1.0	NaBr (1.0)	EtOAc	38
4	2.0	1.0	NaBr (1.0)	H_2O	–
5	2.0	1.0	NaBr (1.0)	TFA	30
6	2.0	1.0	NaBr (1.0)	MeOH	32
7	2.0	1.0	NaBr (1.0)	THF	47
8	2.0	1.0	NaBr (1.0)	DCE	35
9	2.0	1.0	NaBr (1.0)	1,4-dioxane	44
10	2.0	1.0	NaBr (1.0)	THF–H_2O (30:1)	45
11	2.0	1.0	NaBr (1.0)	THF–MeOH (30:1)	76
12	2.0	1.0	NaBr (1.0)	THF–MeOH (20:1)	56
13	2.0	1.0	NaBr (1.0)	THF– MeOH (10:1)	50
14	2.0	1.0	KBr (1.0)	THF–MeOH (30:1)	69
15	2.0	1.0	NH_4Br (1.0)	THF–MeOH (30:1)	72
16	2.0	1.0	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	83
17	2.0	THBP (1.0)	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	–
18	2.0	H_2O_2 (1.0)	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	–
19	2.0	$K_2S_2O_8$ (1.0)	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	12
20	2.0	1.2	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	82
21	2.0	1.3	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	78
22	2.0	1.5	$(n\text{-}C_4H_9)_4NBr$ (1.0)	THF–MeOH (30:1)	70
23	2.0	1.0	$(n\text{-}C_4H_9)_4NBr$ (1.2)	THF–MeOH (30:1)	86
24	2.0	1.0	$(n\text{-}C_4H_9)_4NBr$ (0.8)	THF–MeOH (30:1)	80
25	2.0	1.0	$(n\text{-}C_4H_9)_4NBr$ (0.2)	THF–MeOH (30:1)	30
26	1.8	1.0	$(n\text{-}C_4H_9)_4NBr$ (1.2)	THF–MeOH (30:1)	86
27	1.5	1.0	$(n\text{-}C_4H_9)_4NBr$ (1.2)	THF–MeOH (30:1)	86
28	1.2	1.0	$(n\text{-}C_4H_9)_4NBr$ (1.2)	THF–MeOH (30:1)	80
29	1.5	–	$(n\text{-}C_4H_9)_4NBr$ (1.2)	THF–MeOH (30:1)	–
30	1.5	1.0	–	THF–MeOH (30:1)	–

[a] Isolated yields.

vent mixture, other bromides such as KBr, NH_4Br, and $(n\text{-}C_4H_9)_4NBr$ were examined. Among them, $(n\text{-}C_4H_9)_4NBr$ was the most efficient with regard to the yield of **3a**, and 1.2 equivalents of it was the optimized amount (Table 1, entries 11, 14–16, 23–25). Compared with *m*-CPBA, other oxidants such as *tert*-butyl hydroperoxide (TBHP), hydrogen peroxide (H_2O_2), and dipotassium persulfate ($K_2S_2O_8$) were not active in the reaction or resulted in lower yield of **3a**. Therefore, *m*-CPBA was the most suitable oxidant and the optimized amount of it was also determined (Table 1, entries 16–22). In addition, the quantity of sodium benzenesulfinate was optimized: 1.5 equivalents of it was the best choice (Table 1, entries 23, 26–28). Under the optimized conditions, the reaction proceeded smoothly and was completed in 12 hours. The control experiment also indicated that in the absence of *m*-CPBA or $(n\text{-}C_4H_9)_4NBr$, no desired product was obtained (Table 1, entries 29 and 30).



Scheme 2 Preparation of sulfonamides **3** from sodium sulfinates **1** and amines **2** promoted by $(n\text{-}C_4H_9)_4NBr$

Based on the extensive screening process, we arrived at the optimal reaction conditions (Scheme 2). Then, with 1.5 equivalents of sodium sulfinates **1**, 1.0 equivalent of amines **2** and *m*-CPBA in the presence of 1.2 equivalents of $(n\text{-}C_4H_9)_4NBr$, the one-pot reaction proceeded smoothly in THF–MeOH (30:1) at room temperature, and after 12 hours a series of the corresponding sulfonamides **3** were obtained.[10] The results are summarized in Table 2.

Table 2 Preparation of Sulfonamides **3** from Sodium Sulfinates **1** and Amines **2** Promoted by $(n\text{-}C_4H_9)_4NBr$

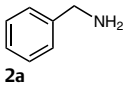
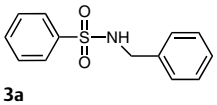
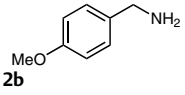
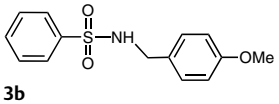
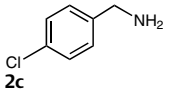
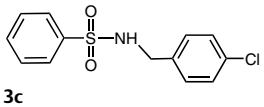
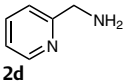
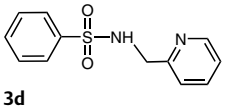
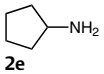
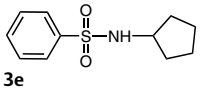
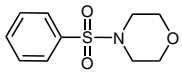
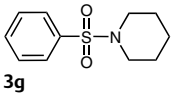
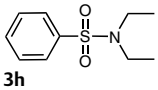
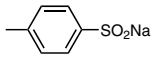
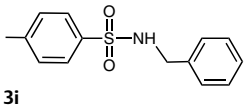
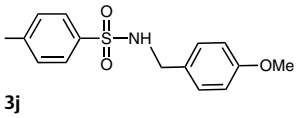
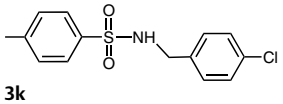
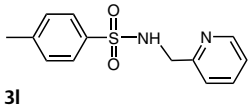
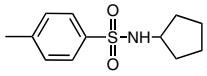
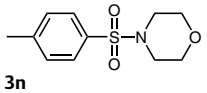
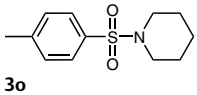
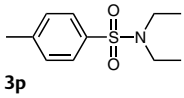
Entry	Sodium sulfinates **1**	Amines **2**	Products **3**	Yield (%)[a]
1	$PhSO_2Na$ **1a**	 **2a**	 **3a**	86
2	**1a**	 **2b**	 **3b**	89
3	**1a**	 **2c**	 **3c**	72
4	**1a**	 **2d**	 **3d**	55
5	**1a**	 **2e**	 **3e**	63
6	**1a**	 **2f**	 **3f**	78
7	**1a**	 **2g**	 **3g**	58
8	**1a**	 **2h**	 **3h**	45

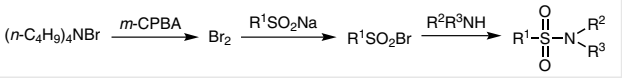
Table 2 (continued)

Entry	Sodium sulfinates **1**	Amines **2**	Products **3**	Yield (%)[a]
9	 **1b**	**2a**	 **3i**	81
10	**1b**	**2b**	 **3j**	84
11	**1b**	**2c**	 **3k**	70
12	**1b**	**2d**	 **3l**	50
13	**1b**	**2e**	 **3m**	62
14	**1b**	**2f**	 **3n**	72
15	**1b**	**2g**	 **3o**	54
16	**1b**	**2h**	 **3p**	39

[a] Isolated yields.

As shown in Table 2, the one-pot reaction was compatible with the studied primary and secondary amines when sodium sulfinates **1a** and **1b** were treated, affording the corresponding sulfonamides **3** in moderate to excellent yields (Table 2, entries 1–16). It is obvious that sodium benzenesulfinate **1a** had a better effect in the reaction than sodium *p*-tolylsulfinate (**1b**). In a similar manner, when sodium methylsulfinate, an aliphatic sodium sulfinate, was used to replace **1a** or **1b**, the one-pot reaction nearly did not proceed, in agreement with Wei's report.[9c] The results also demonstrated that amine **2b**, bearing an electron-donating group on benzene ring, usually resulted in the products with higher yields than **2c** and **2d**, those having electron-withdrawing groups on aromatic rings (Table 2, entries 2–4, 10–12). Among three secondary amines, both cyclic amines **2f** and **2g** gave the corresponding products in moderate to good yields; while as a representative of acyclic amines, **2h** normally let to the products in somewhat low yields (Table 2, entries 6–8, 14–16).

When radical scavenger, 2,2,6,6-tetramethyl-piperidine1-oxyl (TEMPO), was added in the reaction of sodium benzenesulfinate (**1a**) and benzylamine (**2a**) under the optimized reaction conditions, the one-pot reaction still proceeded well, resulting in the product **3a** in good yield. This result suggests that the mechanism may undergo a nucleophilic substitution pathway. A plausible mechanism for the preparation of sulfonamides is depicted in Scheme 3. Initially, $(n\text{-}C_4H_9)_4NBr$ is oxidized by *m*-CPBA into molecular bromine that reacts with sodium sulfinate immediately to form the active sulfonyl bromide.[11] Then, the in situ generated sulfonyl bromide intermediate is attacked by the nucleophilic amine, affording the desired product sulfonamide.



Scheme 3 Proposed mechanism for the preparation of sulfonamides

In summary, we have developed a now and convenient procedure for the preparation of sulfonamides from sodium sulfinates and amines in the presence of $(n\text{-}C_4H_9)_4NBr$ and *m*-CPBA at room temperature in air. This one-pot reaction has some advantages such as readily available starting materials, mild reaction conditions, simple procedure, and good yields. Furthermore, the one-pot reaction via sulfonyl bromides under neutral conditions will extend the application scope of molecular iodine in organic synthesis.

References and Notes

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(10) **A Typical Procedure for the Preparation of Sulfonamides**

In mixed solvent THF–MeOH (30:1, 2.0 mL), sodium sulfinates **1** (0.45 mmol), amines **2** (0.30 mmol), $(n\text{-Bu})_4NBr$ (0.36 mmol), and *m*-CPBA (0.3 mmol) were added successively. The suspension mixture was vigorously stirred at r.t. for 12 h. Upon completion, the reaction was quenched by addition of sat. aq $Na_2S_2O_3$ (2 mL), sat. aq Na_2CO_3 (8 mL), and H_2O (5 mL), respectively. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified on a silica gel plate (PE–EtOAc = 3:1) to furnish products **3**.

***N*-Benzylbenzenesulfonamide (3a)**

White solid; mp 82–83 °C (lit.[12] 85–87 °C). IR (KBr): 3329, 1326, 1162, 1093, 1061, 750, 687 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.2 Hz, 2 H), 7.59–7.54 (m, 1 H), 7.50–7.45 (m, *J* = 7.7 Hz, 2 H), 7.27–7.21 (m, 3 H), 7.20–7.16 (m, 2 H), 5.43 (t, *J* = 6.1 Hz, 1 H), 4.12 (d, *J* = 6.3 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.8, 136.2, 132.5, 129.0, 128.5, 127.7, 127.6, 126.9, 47.0. ESI-MS: *m/z* (%) = 265 (100) $[M + NH_4]^+$.

***N*-(4-Methoxybenzyl)benzenesulfonamide (3b)**

White solid; mp 71–72 °C (lit.[13] 72–75°C). IR (KBr): 3281, 1513, 1321, 1254, 1158, 1091, 1031, 858, 730, 685, 590 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85–7.81 (m, 2 H), 7.57–7.52 (m, 1 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 5.38 (t, *J* = 6.1 Hz, 1 H), 4.04 (d, *J* = 6.1 Hz, 2 H), 3.73 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 139.8, 132.4, 129.1, 128.9, 128.2, 126.9, 113.8, 55.1, 46.5. ESI-MS: *m/z* (%) = 295 (100) $[M + NH_4]^+$.

4-(Phenylsulfonyl)morpholine (3f)

White solid; mp 107–108 °C (lit.[14] 117–119 °C). IR (KBr): 2979, 2862, 1450, 1347, 1261, 1168, 1109, 943, 746, 693, 579, 532 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.73 (m, 2 H), 7.66–7.60 (m, 1 H), 7.58–7.53 (m, 2 H), 3.73 (t, *J* = 4.8 Hz, 4 H), 3.00 (t, *J* = 4.7 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.1, 133.0, 129.1, 127.8, 66.0, 45.9. ESI-MS: *m/z* (%) = 228 (100) $[M + H]^+$.

***N*-(4-Chlorobenzyl)-4-methylbenzenesulfonamide (3k)**

White solid; mp 92–93 °C (lit.[15] 88 °C). IR (KBr): 3234, 1641,

1492, 1319, 1157, 1091, 816, 549 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 3 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 5.27 (t, *J* = 6.3 Hz, 1 H), 4.07 (d, *J* = 6.4 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.6, 136.8, 135.0, 133.6, 129.8, 129.2, 128.7, 127.1, 46.5, 21.5. ESI-MS: *m/z* (%) = 313 (73) $[M + NH_4]^+$.

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