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Aminosulfonylation of aromatic amines, sulfur dioxide and hydrazines†‡

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A facile route to aryl *N*-aminosulfonamides under mild conditions is provided. The reaction of aromatic amines (including heteroaromatic amines), sulfur dioxide, and hydrazines proceeds efficiently with good functional group tolerance. The *in situ* generated diazonium ion is involved in the aminosulfonylation process.

Aromatic amines are a type of readily available and abundant organic synthon either in transition metal-catalyzed coupling reactions or non-metal-mediated transformations, as represented by the Ullmann reaction and the Buchwald–Hartwig coupling reaction. During the past century, these thriving achievements in the realm of transition metal-catalyzed (especially copper and palladium) C–N coupling reactions, have been witnessed.[1] However, enough emphasis has not been put on the transformations involving the free amino group of aromatic amines as a formal leaving group, in part probably because of the relatively inert nature of the C–N bond in aromatic amines. It's generally accepted that conversion of the C–N bonds in aromatic amines into carbon–carbon bonds and carbon–heteroatom bonds represents a significant and attractive strategy due to the aromatic amines' easy accessibility, low-toxicity, relatively high stability, and applicability in numerous transformations.[2a,b] One initially elegant example involving the reaction of an aromatic amine with acrylonitrile was developed in 1977 by Doyle and co-workers.[2c] In 2013, another copper-catalyzed example was described for the direct arylation of pyrroles and benzoquinone *via* C–H activation using aromatic amines as the aryl source.[2d,e] Palladium-catalyzed direct arylation using aryl amines as the aryl source was also developed,[3] and direct arylation of styrene,[3a,d,e] alkynes,[3b] and arylboronic acids[3c] was successfully achieved. According to the findings, stoichiometric acids including Lewis acid and protonic acid were crucial for the process, and the *in situ* generated diazonium ion was shown to be the key intermediate. As an emerging technique, a continuous-flow technique was successfully employed by Buchwald and co-workers in the direct Wagner-Meerwein-type arylation of vinyl ether using aromatic amines as the aryl group donors.[4] Further important progress involving copper- and silver-mediated Sandmeyer trifluoromethylation of aromatic amines, was reported by Wang and Fu.[5] Direct Sandmeyer-type borylation and stannylation of aromatic amines was subsequently accomplished.[6]

On the other hand, aminosulfonylation has been utilized as an efficient approach for the generation of sulfonamides, which are widespread in drugs and natural products.[7] Although direct amination of sulfonyl chlorides with amines could afford the corresponding sulfonamides, much attention has been paid to the insertion of sulfur dioxide[8,9] for the preparation of sulfonamides. So far, aryl halides, arylboronic acids, as well as aryldiazonium tetrafluoroborates, have been used in the coupling of sulfur dioxide with hydrazines. Sources of sulfur dioxide include DABCO-bis(sulfur dioxide) and inorganic metal sulfides. Very recently, we reported a radical process for the synthesis of *N*-aminosulfonamides through a reaction of an aryldiazonium salt, DABCO·$(SO_2)_2$, with hydrazines.[9c] As mentioned above, during the coupling of aromatic amines, the *in situ* generated diazonium ion was identified as the key intermediate. We therefore envisioned that aromatic amines might also be utilized as the substrate in the insertion reaction of sulfur dioxide.

As a source of sulfur dioxide, DABCO·$(SO_2)_2$ is stable and easy to handle, therefore, we initially studied the transformation of *p*-toluidine **1a** in the reaction of DABCO·$(SO_2)_2$ and morpholin-4-amine **2a** (Table 1). We began our exploration with the addition of HBF_4 and ^{t}BuONO. To our delight, the desired product **3a** was obtained in 33% yield (Table 1, entry 1). The reaction proceeded very fast within 15 min. This exciting result encouraged us to undertake further investigations. The yield was higher when the amount of acid was increased (Table 1, entries 2 and 3).

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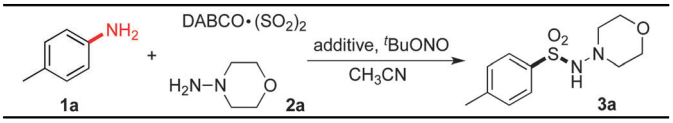
‡ Electronic supplementary information (ESI) available: Experimental procedure, characterization data, and ^{1}H & ^{13}C NMR spectra of compound **3**. See DOI: 10.1039/c4cc03032j

Table 1 Optimizing conditions for the reaction of *p*-toluidine **1a**, DABCO·$(SO_2)_2$, and morpholin-4-amine **2a**[a]



Entry	Additive	Molecular ratio (**1a**/^{t}BuONO/additive/**2a**)	T (°C)	Yield[b] (%)
1	HBF_4	1.2/1.4/2.4/1.0	5	33
2	HBF_4	1.2/1.4/1.4/1.0	5	40
3	HBF_4	1.5/1.8/1.8/1.0	5	53
4	HCl	1.5/1.8/1.8/1.0	5	35
5	CF_3SO_3H	1.5/1.8/1.8/1.0	5	45
6	CH_3SO_3H	1.5/1.8/1.8/1.0	5	43
7	CH_3CO_2H	1.5/1.8/1.8/1.0	5	40
8	$BF_3{\cdot}OEt_2$	1.5/1.8/1.8/1.0	5	64
9	$BF_3{\cdot}OEt_2$	1.5/1.8/1.8/1.0	30	85
10	$BF_3{\cdot}OEt_2$	1.5/1.8/1.8/1.0	50	83

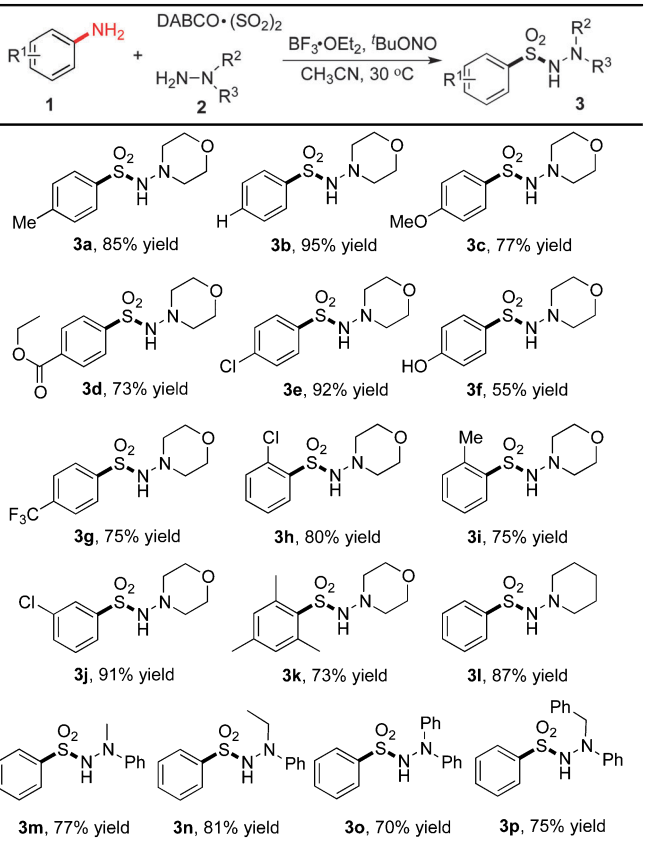
[a] Reaction conditions: *p*-toluidine **1a** and acid in CH_3CN (1.0 mL), followed by dropwise addition of ^{t}BuONO at 0 °C. After 5 min, the above mixture was slowly added into a mixture of DABCO·$(SO_2)_2$ (0.18 mmol) and morpholin-4-amine **2a** (0.30 mmol) in CH_3CN (3.0 mL), under N_2 protection at the temperature as indicated in the table. [b] Isolated yield based on morpholin-4-amine **2a**.

No better results were obtained when the acid was changed to HCl, CF_3SO_3H, CH_3SO_3H, or CH_3CO_2H (Table 1, entries 4–7). Gratifyingly, when Lewis acid $BF_3{\cdot}OEt_2$ was used as a replacement for protonic acid, the corresponding product **3a** was obtained in 64% yield (Table 1, entry 8). The yield improved (85%) when the reaction temperature was changed to 30 °C (Table 1, entry 9). A similar result was observed when the reaction occurred at a higher temperature (Table 1, entry 10).

The reaction scope of anilines **1**, DABCO·$(SO_2)_2$, and hydrazines **2** was then explored under the above optimized conditions (1.8 equiv. of ^{t}BuONO, 1.8 equiv. of $BF_3{\cdot}OEt_2$, MeCN). The results of the aminosulfonylation are shown in Table 2.[10] A range of anilines reacted well with DABCO·$(SO_2)_2$ and the hydrazines, leading to the expected aryl *N*-aminosulfonamide **3** in good to excellent yields. It was found that different functional groups were all compatible under the standard conditions, and the sensitive ester and hydroxy groups all survived during the transformation. For instance, the ester-substituted product **3d** was afforded in 73% yield and the hydroxy-substituted compound **3f** was generated in 55% yield. The yields did not show big differences when anilines with electron-withdrawing or electron-donating groups on the aromatic ring were employed. Additionally, reactions of anilines bearing *ortho*-substituents also worked smoothly to give the desired products. For example, 2,4,6-trimethylaniline reacted with DABCO·$(SO_2)_2$ and morpholin-4-amine **2a** and afforded the corresponding product **3k** in 77% yield. We also examined other hydrazines **2** in the coupling of sulfur dioxide with aniline. As expected, not only aliphatic but also aryl hydrazines could be incorporated well during the reaction process. It is noteworthy that all reactions finish in 15 min under mild conditions to generate the desired aryl *N*-aminosulfonamides **3**.

The aminosulfonylation of heteroaromatic amines with sulfur dioxide and morpholin-4-amine **2a** was investigated next (Table 3). Unfortunately, no desired products (**5a** and **5b**) were

Table 2 Scope investigation for the aminosulfonylation reaction of anilines **1**, DABCO·$(SO_2)_2$ and hydrazines **2**[a]



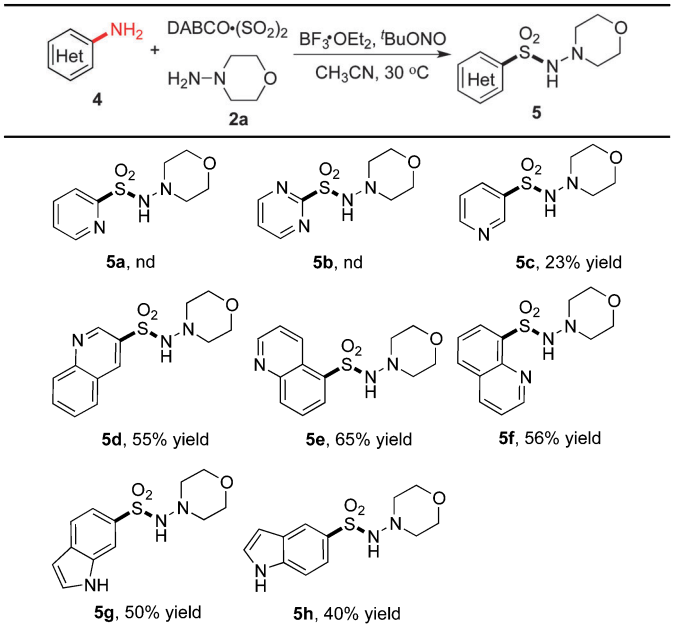
[a] Isolated yield based on hydrazine **2**.

observed when 2-aminopyridine or 2-aminopyrimidine was applied in the reaction. For 3-aminopyridine, the reaction only produced a low yield of the corresponding product **5c**. Further investigation showed that in the case of quinolines and indoles, the desired products **5d–5h** could be formed in moderate yields. These transformations indicate that this new method is an important supplement to the previous reports,[8,9] considering the significance of heterocycles.

For the mechanism of the above transformations, it was recognized that the aryldiazonium salt would be the key intermediate, and would be generated from aniline in the presence of ^{t}BuONO and $BF_3{\cdot}OEt_2$.[11] The subsequent radical process, with the insertion of sulfur dioxide, would produce the expected aryl *N*-aminosulfonamides.[9c]

In summary, coupling of aromatic amines (including heteroaromatic amines) with DABCO·$(SO_2)_2$ and hydrazines under mild conditions, leading to aryl *N*-aminosulfonamides in good to excellent yields, has been described. Different functional groups including ester, hydroxyl, chloro, and trifluoromethyl groups are compatible under these conditions. Moreover, some heteroaromatic amines proceeded well in this transformation. This thriving chemistry involving the formal removal of an amino group from an aromatic amine, represents an alternative aryl source for the insertion of sulfur dioxide. Further exploration of sulfur dioxide insertion is ongoing in our laboratory.

Table 3 Aminosulfonylation reaction of heteroaromatic amines **4**, DABCO·$(SO_2)_2$ and morpholin-4-amine **2a**[a]



[a] Isolated yield based on morpholin-4-amine **2a**.

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10 General experimental procedure for the aminosulfonylation reaction of anilines **1** with DABCO·$(SO_2)_2$ and hydrazines **2**: ^{t}BuONO (0.54 mmol) was added to a solution of aniline **1** (0.45 mmol) and BF_3·Et_2O (0.54 mmol) in CH_3CN (1.0 mL) dropwisely at 0 °C. After 5 min, the solution was slowly added into a mixture of DABCO·$(SO_2)_2$ (0.18 mmol) and hydrazine **2** (0.30 mmol) in CH_3CN (3.0 mL) at 30 °C. The mixture was stirred at 30 °C for another 10 minutes. The solvent was then evaporated and the residue was purified directly by flash column chromatograph (EtOAc/*n*-hexane, 1 : 2) to give the desired product **3**.

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