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Catalytic conversion of aryl triazenes into aryl sulfonamides using sulfur dioxide as the sulfonyl source†

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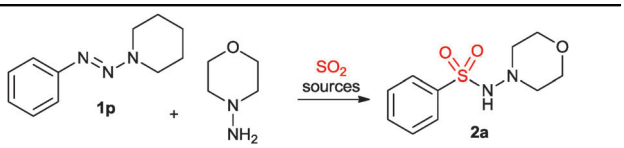
Various sulfonamides have been synthesized from triazenes and sulfur dioxide. In the presence of just a catalytic amount of $BF_3{\cdot}OEt_2$, a series of 1-aryl-triazenes were converted into sulfonyl hydrazines in good to excellent yields. When using $CuCl_2$ as the catalyst, the corresponding sulfonamides can be produced from the 1-aryl triazenes in good yields.

Sulfonamides are often present in biologically active molecules and sulfa drugs have been used as antimicrobial agents for a long time.[1] They were typically prepared through sulfonylation reactions of amines with sulfonyl chlorides.[2] Considering that the most common starting materials for sulfonyl chlorides, *i.e.* oleum and chlorosulfonic acid,[3] are produced either directly or indirectly from sulfur dioxide (SO_2), it would be interesting if SO_2 can be used directly as a sulfonyl source. In fact, as early as 1957, Meerwein *et al.* reported the chlorosulfonylation of aryl diazonium salts with SO_2 in the presence of a catalytic amount of $CuCl_2$.[4] Afterwards, some modified procedures using CuCl were developed and applied to large scale preparations of some aryl sulfonyl chlorides.[5] However, these Sandmeyer-like reactions using SO_2 have not been widely utilized, possibly due to the unstable and potentially explosive nature of the diazonium intermediates. To solve this problem, Laia Malet-Sanz *et al.* ran this reaction using a continuous flow reactor in a more controllable and safer way.[5c] More recently, J. Wu and co-workers reported an interesting radical aminosulfonylation reaction of aryl diazonium tetrafluoroborates with $DABCO{\cdot}(SO_2)_2$ and hydrazines under metal-free conditions.[6]

Aryl triazenes are a very useful and versatile class of compounds, which have found many applications in organic synthesis.[7] They can be easily prepared from various aryl amines and converted to the corresponding diazonium salts in the presence of Lewis or protic acids.[7b,8] Although aryl diazonium salts have a very broad range of applications in organic synthesis,[9] they are prone to decomposing upon storage and this characteristic makes more stable diazonium salt equivalents interesting and demanded.[10] Herein, we wish to report our recent results on the transformation of 1-aryl triazenes into aryl sulfonamides using SO_2 gas as the sulfonyl source.

Recently we developed a Pd-catalyzed hydrazinosulfonylation reaction of aryl halides using *ex situ* generated SO_2 in a two-chamber reactor.[11] For easier manipulation, we prepared the SO_2 stock solution in organic solvents (see ESI† for details) and initialized the study by investigating the reaction of 1-(phenyldiazenyl)piperidine (**1p**) and 4-aminomorpholine in the presence of various additives in the SO_2 solution. Firstly, inorganic protic acids like HCl or HBF_4 were added to form diazonium salts, and the isolated yields of **2a** were 49% and 90% respectively (Table 1, entries 1 and 2). This difference in yield may be explained by the poorer stabilities of diazonium chlorides. Trifluoric acid and

Table 1 Optimization of the reaction with **1p**, 4-aminomorpholine and SO_2[a]



Entry	Additive (equiv.)	SO_2 source	Yield[b]
1	20% aq. HCl (2)	SO_2 in MeCN	49
2	HBF_4[c] (1.5)	SO_2 in MeCN	90
3	CH_3COOH (2)	SO_2 in MeCN	39
4	NH_2SO_3H (1.5)	SO_2 in MeCN	84
5	$BF_3{\cdot}OEt_2$ (1.5)	SO_2 in MeCN[d]	97
6[e]	$BF_3{\cdot}OEt_2$ (0.2)	SO_2 in MeCN	86
7	$BF_3{\cdot}OEt_2$ (1.5)	SO_2 in dioxane	53
8	$ZnCl_2$ (1.5)	SO_2 in MeCN	48
9	$AlCl_3$ (1.5)	SO_2 in MeCN	72
10	$FeCl_3$ (1.5)	SO_2 in MeCN	33
11	$CuCl_2$ (1.5)	SO_2 in MeCN	62
12	None	SO_2 in MeCN	27
13	H_2O (5)	SO_2 in MeCN	45

[a] **1p** (45 mg, 237 μmol), 4-aminomorpholine (36 mg, 356 μmol) and SO_2 in solution (1 mL). All reactions were carried out at 60 °C for 3 h. [b] Isolated yield. [c] 51–57% HBF_4 in diethyl ether. [d] The concentration of SO_2 was *ca.* 0.5 mol L^{-1} (see ESI). [e] 12 h.

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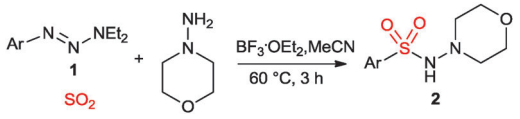
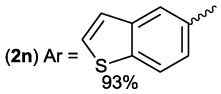
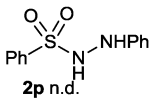
† Electronic supplementary information (ESI) available: NMR spectra and data, and the reaction procedure. See DOI: 10.1039/c4cc03481c

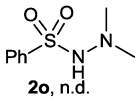
Table 2 Scope of the hydrazinosulfonylation of triazene **1** with SO_2[a]

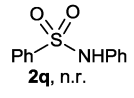


(2a) R=H 97%
(2b) R=4-Me 98%
(2c) R=4-CF_3 78%
(2d) R=4-Cl 89%
(2e) R=4-CN 49%
(2f) R=4-COOMe 85%
(2g) R=4-$CONH_2$ 25%
(2h) R=4-NO_2 67%
(2i) R=2-Me 91%
(2j) R=2-Br 63%
(2k) R=2,6-Di-Me 67%
(2l) R=3-I 89%
(2m) R=3-Ethynyl 55%

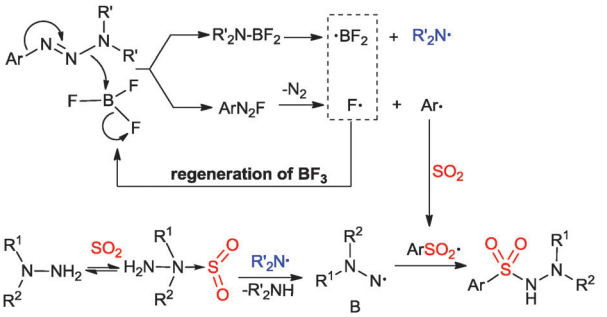








[a] All the reactions were carried out on a 0.2 mmol scale. Yields recorded are the isolated yields (n.d. = not detected due to a very unselective reaction, n.r. = no reaction).



Scheme 1 Proposed reaction pathway for the BF_3·OEt_2-catalyzed hydrazinosulfonylation of **1**.

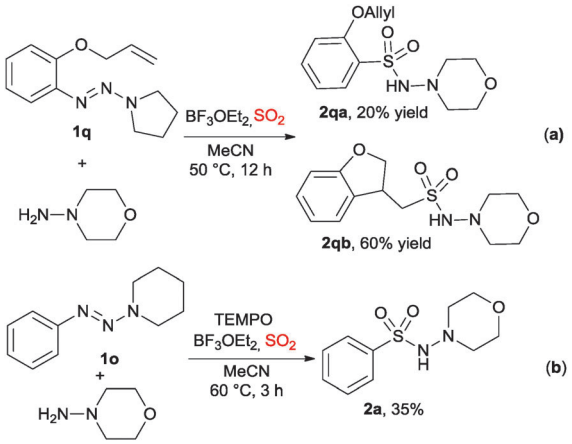
sulfamic acid led to 39% and 84% yields of **2a** respectively (Table 1, entries 3 and 4). To our delight, when 1.5 equivalents of BF_3·OEt_2 was added, the reaction proceeded smoothly to give almost quantitatively **2a** (Table 1, entry 5). To our surprise, when the amount of BF_3·OEt_2 was reduced to 0.2 equivalents, the yield of **2a** was still as high as 86% (Table 1, entry 6), which suggested that BF_3·OEt_2 might work as a catalyst in this reaction. Acetonitrile was a much better solvent than 1,4-dioxane for this transformation (Table 1, entry 7 *vs.* 5). Other additives proved less effective than BF_3·OEt_2 (Table 1, entries 8–11). In the control experiment where no additives were added, the yield dropped to 27% (Table 1, entry 12), which may be caused by the acid formation from SO_2 and incidental water in the system.[12] This was further illustrated by the use of water as the additive for the reaction (Table 1, entry 13). Therefore, the best reaction conditions were based on using BF_3·OEt_2 as the additive and SO_2 solution in acetonitrile as the sulfonyl source (Table 1, entry 5).

Having the optimized reaction conditions in hand, we next extended the substrate scope to other 1-aryl 3,3-diethyltriazenes (Table 2). In most cases, the reaction proceeded smoothly to give the desired products in good to excellent yields. For example, the reactions with **1a** and **1b** produced **2a** and **2b** in nearly quantitative yields. The nature of the substituents on the phenyl rings had obvious effects on the efficiency of the reaction. Strong electron withdrawing groups like trifluoromethyl (**1c**), cyano (**1e**), and aminocarbonyl (**1g**) decreased the yields to a large extent. It is noteworthy that iodide and ethynyl groups were tolerated and make further functionalization of the products possible. The triazene derived from 5-amino benzothiophenone (**1n**) lead to **2n** in an excellent yield. Notably, the nitro group (**2h**) can also be tolerated in this aminosulfonylation reaction.[6a,13] However, other types of substituted hydrazines like 1,1-dimethylhydrazine and phenylhydrazine were not suitable for the reaction, and only trace amounts of the products were detected (**2o** and **2p**). The procedure was ineffective for amines (like aniline, **2q**), which is also a limitation for aminosulfonylation reactions using various SO_2 sources.[6a,13] The unique behaviour of hydrazines in these aminosulfonation reactions prompted us to explain the ineffectiveness of amines in these reactions. Under our conditions, we noticed that when aniline, piperidine or pyrrolidine were added to the reaction, some white solid precipitated on the wall of the Schlenk tubes. We believe that it was the formation of these salts between SO_2 and the amines that depleted the nucleophilicity of the amines.[14] In the charge transfer complexes formed between substituted hydrazines and SO_2, the free amino groups can still act as nucleophiles.[15]

After the successful hydrazinosulfonation reactions in Table 2, we hypothesized a reaction pathway (shown in Scheme 1) to account for the catalytic role of BF_3. The 1-aryltriazene molecule is initially activated by boron trifluoride to form aryl diazonium fluoride and dialkylaminoborodifluoride (R_2N–BF_2).[10c,16] The former species converts into a sulfonyl radical in the presence of sulfur dioxide[9a,17] and the latter homolyzes to form difluoroboro and dialkylamino radicals. 1,1-Disubstituted hydrazine can form a charge transfer complex $R^1R^2N(SO_2)$–NH_2 with sulfur dioxide.[15d] The amino hydrogen of this complex is abstracted by the dialkylamino radical to produce a hydrazino radical, which then recombines with an arylsulfonyl radical to give the final product. Meanwhile, the difluoroboron radical[18] couples with a fluoro radical to regenerate the catalyst BF_3.

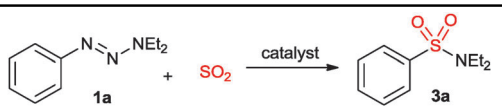
To prove the above radical process, triazene **1q** was synthesized and reacted with 4-amino morpholine. Both the normal product **2qa** and the cyclolized product **2qb** were separated in a *ca.* 1 : 3 ratio (eqn (a), Scheme 2), which revealed that a radical intermediate was involved in the process. Besides, when 1 equivalent of TEMPO was added to the reaction with **1o** under standard conditions (eqn (b), Scheme 2), the yield of **2a** was decreased from 97% to 35%.

According to the above discussions, free amines loose their nucleophilities in the presence of SO_2 solution. The results in Table 1 showed that copper salts like $CuCl_2$ may also induce a radical process of triazenes. When one equivalent of $CuCl_2$ was added to **1a** and a SO_2 solution in MeCN, benzenesulfonyl chloride was produced in 60% yield. Interestingly, the de-nitrogen/sulfonylation product *N*,*N*-diethylbenzenesulfonamide (**3a**) was detected in 33% yield (Table 3, entry 1). After optimizing the amount of $CuCl_2$ and the reaction temperature, the yield of **3a** was improved to 75% (Table 3, entry 7). Other metal salts were much less effective (Table 3, entries 9–14). A control experiment showed that $CuCl_2$ was essential for this reaction, as no product was obtained when no metal was added (Table 3, entry 5).



Scheme 2 Some proof for the radical pathway.

Table 3 Optimization of the catalytic sulfonation of **1a**[a]



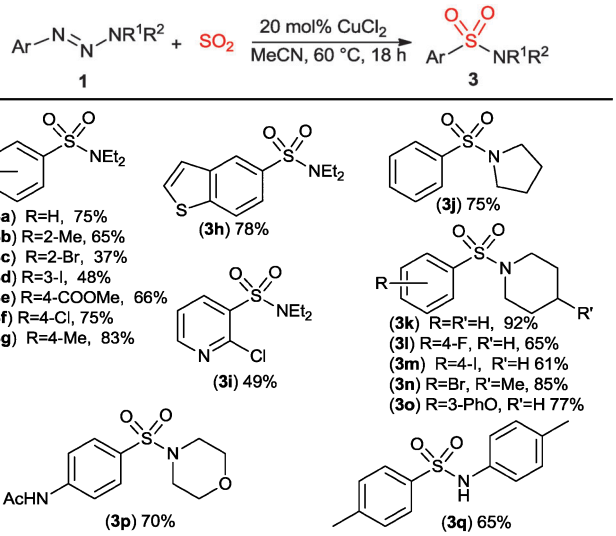
Entry	Catalyst	Temp.	Time	Yield[b] (%)
1	$CuCl_2$ (100%)	60	10	33[c]
2	$CuCl_2$ (10%)	60	10	43
3	$CuCl_2$ (20%)	60	10	57
4	CuCl (20%)	60	10	53
5	None	60	10	0
6	$CuCl_2$ (5%)	70	18	63
7	$CuCl_2$ (10%)	70	18	71 (75[d])
8	$CuCl_2$ (20%)	70	18	30[e]
9	$FeCl_3$ (20%)	70	18	50
10	$CuCl_2$ (10%)	80	7	64
11	CuI (10%)	70	18	31
12	$Cu(OAc)_2$ (10%)	70	18	19
13	$PdCl_2$ (10%)	70	18	0
14	FeF_2 (10%)	70	18	0

[a] 0.2 mmol of **1a** and 1 mL of SO_2 solution (MeCN). [b] Yield determined by GC using hexadecane as the internal standard. [c] 60% $PhSO_2Cl$ was detected by GC. [d] Isolated yield. [e] DABSO was used as the SO_2 source.

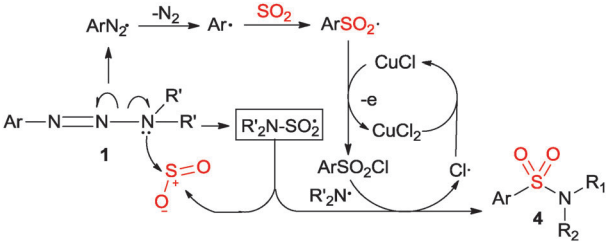
Afterwards, we extended the $CuCl_2$ catalyzed de-nitrogen/sulfonylation reaction to other aryl triazenes (Table 4). Nine 3,3-diethyl-1-phenyl triazenes were converted into the corresponding sulfonamides (**3a–i**) under the optimized conditions in moderate to good yields. The heterocycles containing sulfur and nitrogen atoms were also tolerated under our conditions. Other secondary sulfonamides can also be prepared by this method in good to excellent yields (**3k–p**). Remarkably, the *N*-aryl sulfonamide (**3q**) could also be obtained from the corresponding 1,3-diaryl triazene.

Finally, a possible reaction mechanism for this catalytic transformation is proposed in Scheme 3. Initially, the triazene **1** undergoes homolysis[19] in the presence of SO_2 to produce diazo aryl and dialkylamino sulfonyl radicals.[20] The former radical releases a molecule of N_2 to give an aryl radical. This converts to an aryl sulfonyl chloride compound catalyzed by $CuCl_2$, which can be reduced to CuCl by SO_2.[9a,5c] The dialkylamino sulfonyl radical decomposes to a dialkyl amino radical,

Table 4 Substrate scope of the $CuCl_2$-catalyzed de-nitrogen/sulfonylation reaction[a]

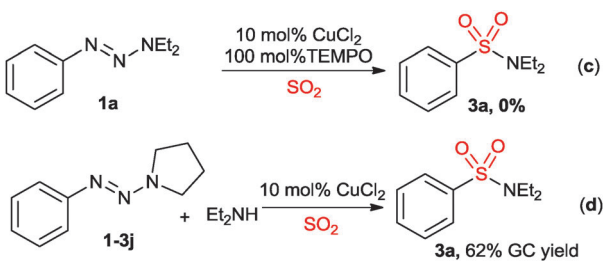


[a] 0.2 mmol of **1** and 1 mL of the SO_2 solution (MeCN). Yields recorded are the isolated yields.



Scheme 3 Proposed mechanism for the $CuCl_2$-catalyzed aminosulfonylation of **1**.

which reacts with the aryl chloride to produce the product **4** and a chloro radical. This chloro radical participates in the catalyst regeneration process or combines with the aryl radical to produce chlorobenzene, which can be detected by GC-mass spectroscopy, together with a trace amount of benzenesulfonyl chloride, during the reaction of **1a** catalyzed by $CuCl_2$. Besides, when one equivalent of TEMPO was added, no product (**3a**) was obtained (eqn (c), Scheme 4). When **1–3j** and diethylamine were subjected to the same reaction conditions as in Table 4, **3a** was obtained in 62% yield (eqn (d), Scheme 4).



Scheme 4 Some proof for the reaction pathway.

In summary, we have shown the first transformation of triazenes into sulfonamides catalyzed by boron trifluoride etherate or copper chloride. One of the advantages of our procedure is the use of sulfur dioxide as the sulfonyl source. We also found that the triazenes were more stable than the equivalent diazonium salts, they could produce aryl amino radicals under our conditions, and the utilization of these two types of radicals may be valuable for other C–C and C–N bond formation reactions.

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