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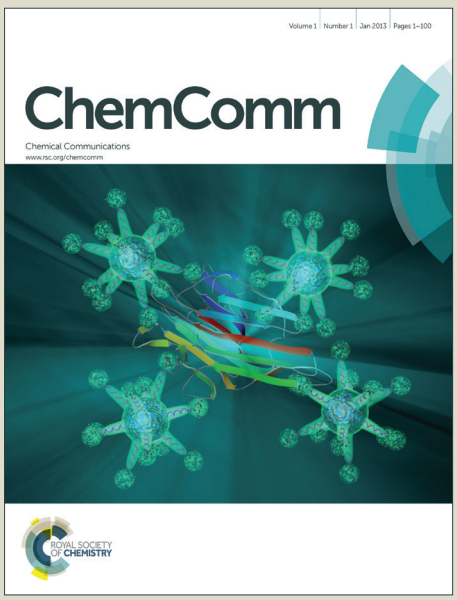

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Catalytic conversion of aryl triazenes into aryl sulfonamides using sulfur dioxide as the sulfonyl source

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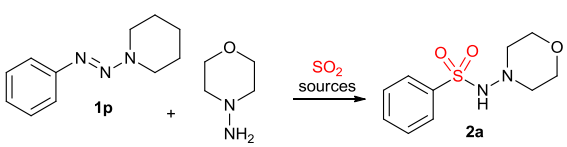
Various sulfonylamides have been synthesized from triazenes and sulfur dioxide. In the presence of even catalytic amount of $BF_3{\cdot}OEt_2$, a series of 1-aryl-triazenes were converted into sulfonyl hydrazines in good to excellent yields. When using $CuCl_2$ as the catalyst, the corresponding sulfonamides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

Sulfonamides are widely present in biologically active molecules and sulfa drugs have been used as antimicrobial agents for a long history.[1] They were typically prepared through sulfonylations of amines with sulfonyl chlorides.[2] Considering that the most common starting materials for sulfonyl chlorides, i.e. oleum and chlorosulfonic acid,[3] were produced either directly or indirectly from sulfur dioxide (SO_2), it would be interesting if SO_2 can be directly applied as a sulfonyl source. And it's true, as early as in 1957, Meerwein *et al.* reported the chlorosulfonylation of aryl diazonium salts with SO_2 in the presence of catalytic amount of $CuCl_2$.[4] Afterwards, some modified procedures using CuCl were developed and applied in large scale preparation of some aryl sulfonyl chlorides.[5] But 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 continuous flow reactor in a more controllable and safer way.[5c] More recently, J. Wu and co-workers reported an interesting radical aminosulfonylation of aryl diazonium tetrafluoroborates with DABCO $(SO_2)_2$ and hydrazines under metal-free conditions.[6]

On the other hand, aryl triazenes is a very useful and versatile class of compounds, which 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.[8, 7b] Although aryl diazonium salts have a very broad application in organic synthesis,[9] they are prone to decompose upon storage and this character make more stable diazonium salt equivalents more 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 sulfonyl source.

Recently we developed a Pd-catalyzed hydrazinosulfonylation 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 supporting information for details) and initialized the study by 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 was added to form diazonium salts, the isolated yields of **2a** were 49% and 90% respectively (Table 1, entries 1 and 2). This may be explained by the poorer stabilities of the diazonium chlorides. Trifluoric acid and sulfamic acid led to 39% and 84% yield of **2a** respectively. To our glad, when 1.5 equivalent of $BF_3{\cdot}OEt_2$ was added, the reaction went smoothly to give almost quantitatively **2a** (Table 1, entry 5). To our surprise, when the amount of $BF_3{\cdot}OEt_2$ was reduced to 0.2 equivalent, the yield of **2a** was still as good as 86%, which suggested that the $BF_3{\cdot}OEt_2$ might worked as 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 $BF_3{\cdot}OEt_2$ (Table 1, entries 8-12). In the control experiment where no additives was 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 using of water as the additive for the reaction (entry 13, Table 1). Therefore, the best reaction conditions were based on using $BF_3{\cdot}OEt_2$ as the additive and SO_2 solution in acetonitrile as the sulfonyl source (Table 1, entry 5).

Table 1. Optimization of the reaction with **1p**, *N*-aminomopholine and SO_2.[a]

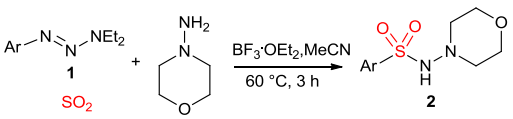


Entry	Additive (equiv.)	SO_2 source	Yield[b]
1	20% aq. HCl (2)	SO_2 in MeCN	49
2	HBF_4[c] (1.5)	SO_2 in MeCN	90
3	CH_3COOH (2)	SO_2 in MeCN	39
4	NH_2SO_3H (1.5)	SO_2 in MeCN	84
5	$BF_3{\cdot}OEt_2$ (1.5)	SO_2 in MeCN[d]	97
6[e]	$BF_3{\cdot}OEt_2$ (0.2)	SO_2 in MeCN	86
7	$BF_3{\cdot}OEt_2$ (1.5)	SO_2 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

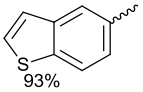
[a]**1p** (45 mg, 237 μmol), 4-aminomorpholine (36 mg, 356 μmol), MeCN (1 mL). All reaction was carried out at 60 ℃ for 3 h. [b]Isolated yield. [c]51-57% HBF_4 in diethyl ether. [d]The concentration of SO_2 is *ca.* 0.5 mol/L (see supporting information). [e]12 h.

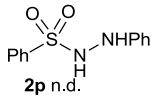
Having the optimized reaction conditions in hand, we next extended the substrates scope to other 1-aryl 3,3-diethyltriazenes (Table 2). In most cases, the reaction proceeded smoothly to give the desired products in good to excellent yields. For example, the reaction of **1a** and **1b** were converted to **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. The strong electron with-drawing group like trifluoromethyl (**1c**), cyano (**1e**), and aminocarbonyl (**1g**) decreased the yields in a large extent. It was noteworthy that iodide and ethynyl group were tolerated and make further functionalization of the products possible. Triazene derived from 5-amino benzothiophenone (**1n**) lead to **2n** in excellent yield. Notably, the nitro group (**2h**) can also be tolerated for this aminosulfonylation.[13, 6a] But other types of substituted hydrazines like 1,1-dimethylhydrazine and phenylhydrazine were not suitable for the reaction, only traces amount of products were detected (**2o** and **2p**). The procedure was ineffective for amines (like aniline, **2q**), which was still a limitation for amimosulfonylations using various SO_2 sources.[13, 6a] The uniqueness of hydrazine in these aminosulfonations prompted us to explain the ineffectiveness of amines in these reactions. Under our conditions, we noticed that when aniline, piperidine or pyrrolidne were added to the reaction, some white solid precipitated on the wall of the Schlenk tubes. We believed that it was these salts formation between SO_2 and amines that depleted the nucleophility of these amines.[14] In the charge transfer complex between substituted hydrazines and SO_2, the free amino groups can still react as nucleophiles.[15]

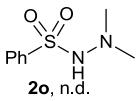
Table 2. Scope of the hydrazinosulfonylation of triazene **1** with SO_2.[a]



(**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%

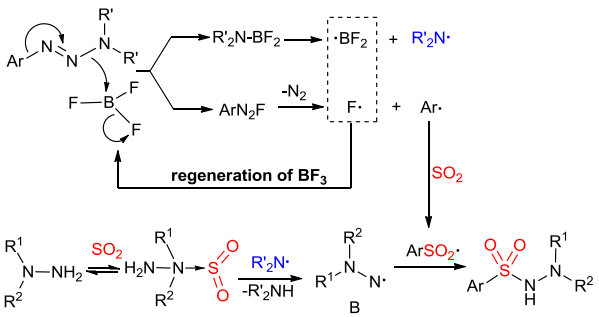
(**2n**) Ar =  93%





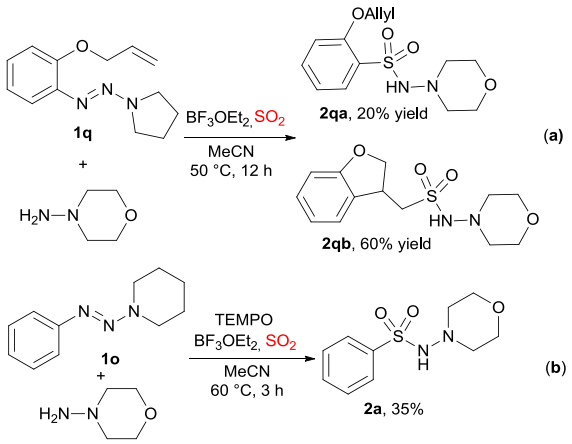
[a] All the reactions were carried out with 0.2 mmol scale. Isolated yields. n. d.= not detected due very unselective reaction. n.r.= no reaction.

After successful hydrazinosulfonation in Table 2, we hypothesized a reaction pathway in Scheme 1 to account for the catalytic role of BF_3. 1-Aryltriazenes was initially activated by boron trifluoride to form aryl diazonium fluoride and dialkylaminoboro difluoride (R_2N-BF_2).[16, 10c] The former species converted into sulfonyl radical in the presence of sulfur dioxide[9a, 17] and the latter homolyzed to difluoroboro and dialkylamino radicals. 1,1-disubstituted hydrazine could form a charge transfer complex $R^1R^2N(SO_2)$-NH_2 with sulfur dioxide.[15d] The amino hydrogen of this complex was abstracted by the dialkylamino radical to produce a hydrazino radical, which then recombined with the arylsulfonyl radicals to give the final product. Meanwhile, the difluroboron radical[18] coupled with the fluoro radical to regenerate the catalyst BF_3.



Scheme 1. Proposed reaction pathway for the $BF_3{\cdot}OEt_2$-catalyzed hydrazinosulfonylation of **1**.

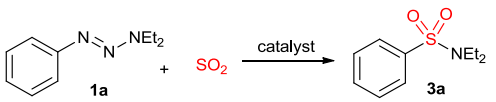
To prove the above radical process, triazene **1q** was synthesized and reacted with 4-amino morpholine. Both the normal product **2qa** and cyclolized **2qb** were separated in a *ca.* 1:3 ratio (Eq. **a**, Scheme 2), which revealed that radical intermediate was involved in the process. Besides, when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



Scheme 2. Some proof for the radical pathway.

According to the above discussions, free amines lost 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 SO_2 solution in MeCN, benzenesulfonyl chloride was produced in 60% yield. Interestingly, the de-nitrogen/sulfonylations product *N*, *N*-diethylbenzenesulfonamide (**3a**) was detected in 33% yield (Table 3, entry 1). After optimization of the amount of $CuCl_2$ and reaction temperature, the yield of **3a** was improved to 75% (Table 3, entry 7). Other metal salts and much less effective (Table 3, entries 9-12). Control experiment showed that $CuCl_2$ was essential for this reaction, as no product was obtained when no metal was added.

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

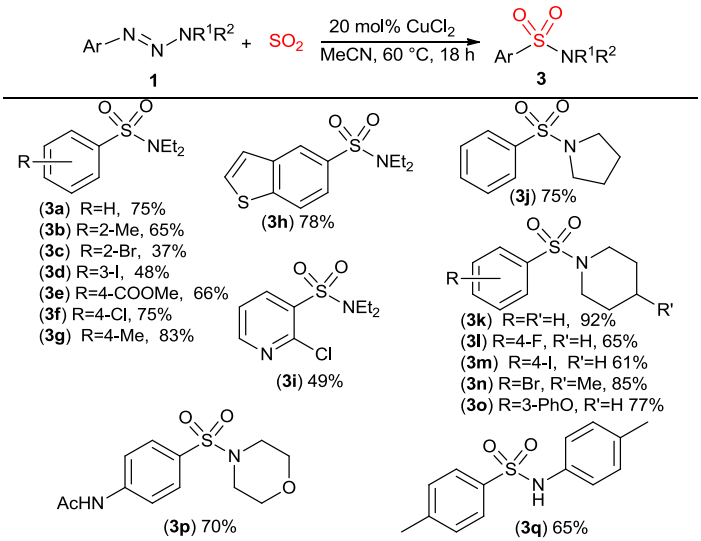


Entry	Catalyst	Temp.	Time	Yield(%)[b]
1	$CuCl_2$ (100%)	60	10	33[c]
2	$CuCl_2$ (10%)	60	10	43
3	$CuCl_2$ (20%)	60	10	57
4	CuCl (20%)	60	10	53
5	None	60	10	0
6	$CuCl_2$ (5%)	70	18	63
7	$CuCl_2$ (10%)	70	18	71 (75[d])
8	$CuCl_2$ (20%)	70	18	30[e]
9	$FeCl_3$ (20%)	70	18	50
10	$CuCl_2$ (10%)	80	7	64
11	CuI (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**, 1 mL SO_2 solution MeCN (1 mL). [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.

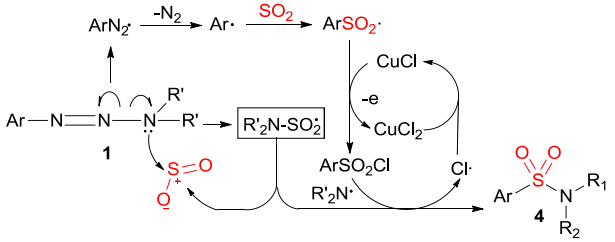
Afterwards, we subsequently extended the $CuCl_2$ catalyzed de-nitrogen/sulfonylations reactions to other aryl triazenes (Table 4). Nine 3,3-diethyl-1-phenyl triazenes were converted into the corresponding sulfonamides (**3a-i**) under the optimized conditions in moderate to good yields. The heterocycles containing sulfur and nitrogen atoms were also tolerated under our conditions. Other secondary sulfonamides can be prepared as well 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.

Table 4. Substrates scope of the $CuCl_2$-catalyzed de-nitrogen/sulfonylations.[a]

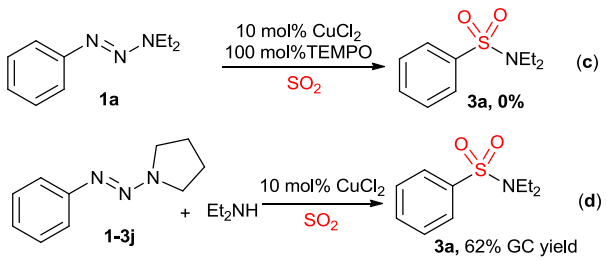


[a] 0.2 mmol of **1**, 1 mL SO_2 solution MeCN (1 mL). Isolated yields.

Finally, a possible reaction mechanism for this catalytic transformation is been proposed in Scheme 3. Initially, the triazene **1** underwent homolysis[19] in the presence of SO_2 to produce diazo aryl and dialkylamino sulfonyl radicals.[20] The former radical released a molecule of N_2 to give an aryl radical, which converted to aryl sulfonyl chlorides catalyzed by $CuCl_2$, which could be reduced to CuCl by SO_2.[9a, 5c] The dialkylamino sulfonyl radical decomposed to dialkyl amino radical, which reacted with aryl chlorides to produce the product **4** and chloro radical. This chloro radical participated in the catalysis regeneration or combined with the aryl radical to produce chlorobenzene, which can be detected by GC-Mass, together with trace amount benzenesulfonyl chloride, during the reaction between **1a** catalyzed by $CuCl_2$. Besides, when one equivalent of TEMPO was added, no product (**3a**) was obtained (eq. **c,** Scheme 4). When **1**-**3j** and diethylamine were subjected to the same reaction condition in Table 4, **3a** was obtained in 62% yield (eq. **d,** Scheme 4).



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



Scheme 4 Some proof for the reaction pathway.

Conclusions

In summary, we realized the first transformation of triazenes into sulfonamides catalyzed by boron trifluoride etherate or copper chloride. One of the advantages of our procedures was the using sulfur dioxide as the sulfonyl source. We also found that the triazenes were more than an equivalent to the diazonium salts, they could produce aryl amino radicals under our conditions, and the utilization of these two types of radicals would be valuable for the other C-C and C-N bond formation reactions.

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†Electronic Supplementary Information (ESI) available: [NMR spectrums and data, reaction procedure]. See DOI: 10.1039/c000000x/

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