Aminosulfonylation

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Metal-Free Aminosulfonylation of Aryldiazonium Tetrafluoroborates with DABCO·$(SO_2)_2$ and Hydrazines**

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Abstract: *The coupling of aryldiazonium tetrafluoroborates, DABCO·$(SO_2)_2$, and hydrazines under metal-free conditions leads to the formation of aryl N-aminosulfonamides. The reaction proceeds smoothly at room temperature and shows broad functional-group tolerance. A radical process is proposed for this transformation.*

The sulfonamide group is widely present in top-selling pharmaceuticals.[1] Celecoxib,[2] Tipranavir,[3] and Zonisamide[4] are some examples of marketed drugs that feature this functional group. Sulfonamides can be generally prepared by direct amination of sulfonyl chlorides with the corresponding amines.[1a] However, traditional methods to access sulfonyl chloride, including electrophilic aromatic substitution with chlorosulfonic acid and oxidative chlorination of organosulfurs, usually suffer from significant limitations.[5–7] Harsh conditions are often required and the substrate scope is limited. Therefore, the development of efficient methods for the formation of sulfonamides is of great importance.

To obviate these problems, recent efforts were directed to the transition-metal-catalyzed aminosulfonylation.[1a,8,9] An interesting result was reported by Willis and co-workers, who described a Pd-catalyzed coupling reaction of aryl iodides, DABCO·$(SO_2)_2$, and hydrazines to generate *N*-aminosulfonamides.[8a] The application of the bench-stable solid DABCO·$(SO_2)_2$ as the source of sulfur dioxide was a breakthrough, as other reagents for sulfonylation were usually harmful. Additionally, this method opens a pathway to introduce sulfur dioxide into small organic molecules. We also conducted studies in this field to expand the scope of the reported process.[9] Recently, an alternative route to aryl sulfonamides through Pd-catalyzed chlorosulfonylation of arylboronic acids was achieved by Buchwald and co-workers.[10] As these approaches required expensive metal catalysts, ligands, bases, and relatively high temperatures, it is still highly desirable to explore new methods for this transformation.

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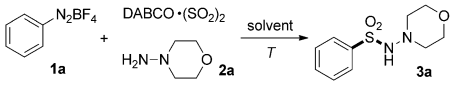
It is well known that aryldiazonium salts are commonly used chemicals and important intermediates in organic chemistry because of their relatively high reactivity and several possible functional-group transformation.[11,12] Additionally, aryldiazonium salts can be easily prepared by diazotization of aromatic amines, which are available in great structural diversity. Recently, aryldiazonium salts were used as starting materials or key intermediates in trifluoromethylations under mild conditions through a new type of Sandmeyer reaction.[13] Inspired by this result, we envisioned that aryldiazonium salts might be employed in the aminosulfonylation as well. Herein, we report the simple preparation of *N*-aminosulfonamides under metal-free conditions through the coupling of aryldiazonium tetrafluoroborates, DABCO·$(SO_2)_2$, and hydrazines at room temperature.

We began our investigation with the addition of morpholin-4-amine (**2a**) to a solution of $Pd(OAc)_2$ (10 mol%), phenyldiazonium tetrafluoroborate (**1a**), and DABCO·$(SO_2)_2$ in 1,4-dioxane at 25 °C. Pleasingly, the desired product **3a** was obtained in 35% yield. To our surprise, the reaction also proceeded smoothly in a control experiment without the addition of the Pd catalyst. A similar yield of 37% was obtained under the conditions (Table 1, entry 1). This unexpected result showed that the Pd catalyst was not involved in

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



Entry	Solvent	*T* [°C]	DABCO·$(SO_2)_2$	Yield [%][b]
1	1,4-dioxane	25	1.2 equiv	37
2	toluene	25	1.2 equiv	trace
3	CH_3OH	25	1.2 equiv	trace
4	MeCN	25	1.2 equiv	54
5	DCE	25	1.2 equiv	34
6	DMF	25	1.2 equiv	36
7	DMSO	25	1.2 equiv	28
8[c]	MeCN	25	1.2 equiv	39
9[d]	MeCN	25	1.2 equiv	94
10[d]	MeCN	25	0.8 equiv	94
11[d]	MeCN	25	0.6 equiv	93
12[d]	MeCN	0	0.6 equiv	81
13[d]	MeCN	40	0.6 equiv	85

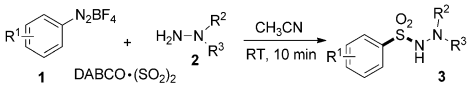
[a] Reaction conditions: DABCO·$(SO_2)_2$ (0.36 mmol) and **1a** (0.30 mmol) in solvent (4.0 mL), followed by the dropwise addition of **2a** (0.36 mmol) under N_2 in 10 min. [b] Yield of isolated product based on **1a**. [c] Under air atmosphere. [d] Reaction conditions: DABCO·$(SO_2)_2$ and **2a** (0.36 mmol) in CH_3CN (3.0 mL), followed by dropwise addition of **1a** (0.30 mmol) in CH_3CN (1.0 mL) under N_2 in 10 min.

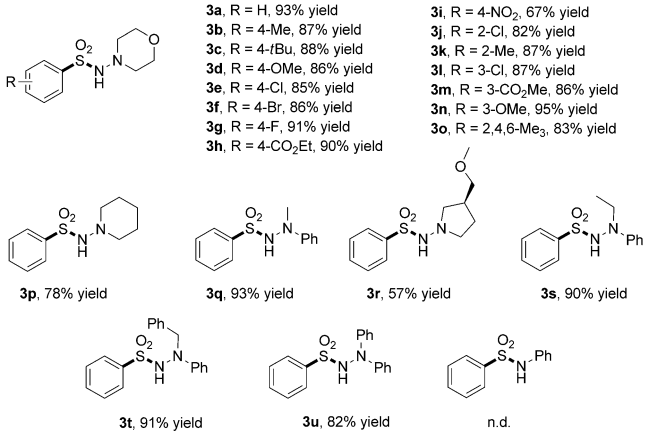
this transformation, thus suggesting that this transformation is different from the one previously reported by Willis.[8] Considering that this process involved a totally different reaction route, and the advantage of non-metal catalysis, we continued to further optimize this reaction. The reaction failed when toluene and methanol were used as the solvent (Table 1, entries 2 and 3). Further screening of solvents showed that the reaction proceeded efficiently in acetonitrile, furnishing the expected product **3a** in 54% yield (Table 1, entry 4). No improvement was observed when the reaction was performed under air atmosphere (Table 1, entry 8). Considering the relatively high reactivity of aryldiazonium tetrafluoroborates, we suspected that the experimental procedure had a significant influence on the outcome of the reaction. When **1a** in 1.0 mL of CH_3CN was added in a dropwise manner to a solution of DABCO·$(SO_2)_2$ and **2a** in 3.0 mL of CH_3CN, the yield was significantly increased to 94% (Table 1, entry 9). Similar results were obtained when the amount of DABCO·$(SO_2)_2$ was decreased to 0.8 or 0.6 equivalents (Table 1, entries 10 and 11). The reaction proceeded smoothly at 0 °C as well, while the yield decreased to 81% (Table 1, entry 12). No better result was obtained at a higher temperature (Table 1, entry 13).

With the optimized reaction conditions in hand, we next investigated the scope of the aminosulfonylation reaction of aryldiazonium tetrafluoroborates **1** with DABCO·$(SO_2)_2$ and hydrazines **2** (Table 2). A range of aryldiazonium tetrafluoroborates were examined first. Interestingly, all reactions were complete within 10 minutes. Various aryldiazonium tetrafluoroborates **1** reacted with DABCO·$(SO_2)_2$ and **2a**, giving rise to the aminosulfonylation products **3a**–**3o** in good to excellent yields. Both electron-withdrawing and electron-donating groups on the aromatic ring of aryldiazonium tetrafluoroborates were compatible under the standard conditions, leading to the products in similarly high yields. Moreover, substrates that feature common functional groups, including ethers, esters, halogen atoms, and even a nitro group, were smoothly coupled. Aryldiazonium tetrafluoroborates that bear *ortho* substitutents, including methyl and chloro groups, also reacted well to give the desired products **3j** and **3k** in good yields. Polysubstituted aryldiazonium tetrafluoroborates could be utilized in this transformation too. Other hydrazines **2** were subsequently explored, and the reactions proceeded efficiently to produce the corresponding products **3p**–**3u** in good yields. However, no reaction took place when anilines and aliphatic amines were employed in the transformation under the optimal conditions, which was similar to the previous reports.[8,9]

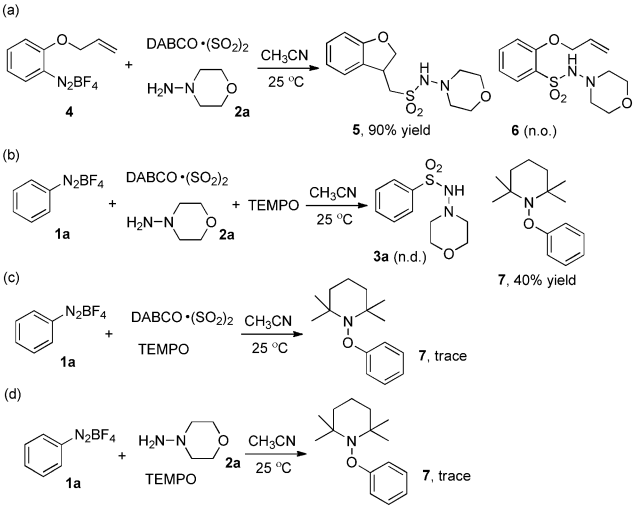
To understand the mechanism of this metal-free coupling reaction, preliminary mechanistic investigation was carried out. When we used 2-(allyloxy)phenyldiazonium tetrafluoroborate (**4**) in this aminosulfonylation, only the cyclized product **5** was obtained in 90% yield, whereas the normal product **6** was not detected [Scheme 1, Eq. (a)]. This result suggested that an aryl radical is involved as the intermediate, which was presumably produced from the aryldiazonium salt. In the Sandmeyer-type reaction, it is plausible that copper-mediated single-electron transfer (SET) generates the aryl radical.[14] Therefore, we were curious about the pathway through which the aryl radical was formed without a metal catalyst. Thus, we tested the reaction with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the additive under the standard reaction conditions [Scheme 1, Eq. (b)]. After subjecting TEMPO to the standard aminosulfonylation procedure, TEMPO-Ph **7** was isolated in 40% yield, further proving that a phenyl radical was produced under the reaction conditions. Only a trace amount of TEMPO-Ph **7** was observed when DABCO·$(SO_2)_2$ or **2a** were absent [Scheme 1, Eq. (c) and (d)], thus demonstrating that both DABCO·$(SO_2)_2$ and **2a**

Table 2: Scope of the aminosulfonylation reaction of aryldiazonium tetrafluoroborates **1** with DABCO·$(SO_2)_2$ and hydrazines **2**.[a,b]





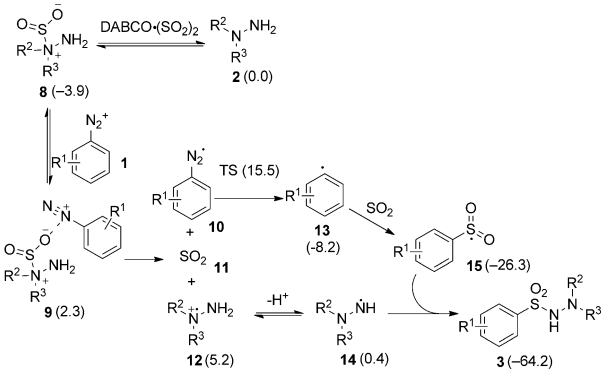
[a] Reaction conditions: DABCO·$(SO_2)_2$ (0.18 mmol) and **2** (0.36 mmol) in CH_3CN (3.0 mL), followed by dropwise addition of **1** (0.30 mmol) in CH_3CN (1.0 mL) under N_2 atmosphere in 10 min. [b] Yields of isolated products based on **1**.



Scheme 1. Investigation of the mechanism. n.d. = not determined, n.o. = not observed.

were indispensable in the introduction of the phenyl radical. Additionally, it was known that **2a** could be employed as an SO_2 carrier with the formation of an *N*-aminomorpholine/SO_2 complex.

On the basis of the above-mentioned experimental observations and according to our own theoretical calculations, we suggest that the metal-free aminosulfonylation reaction proceeds through the route shown in Scheme 2. First, barrierless exchange of sulfur dioxide occurs between



Scheme 2. Proposed mechanism for the aminosulfonylation reaction of aryldiazonium tetrafluoroborates **1** with DABCO·$(SO_2)_2$ and hydrazines **2**. The numbers in brackets are the changes in Gibbs free energy relative to those of the initial reactants at 298 K. TS = transition state.

DABCO·$(SO_2)_2$ and hydrazine to generate the hydrazine-SO_2 complex **8**. Then complex **9** is formed through electrostatic interaction between the hydrazine–SO_2 complex **8** and the arydiazonium cation **1**. Homolytic cleavage of the N–S bond[15] and a single-electron transfer produces the arydiazonium radical **10**, SO_2 (**11**) and radical cation intermediate **12**. Then, the arydiazonium radical **10** releases one equivalent of nitrogen, leading to the aryl radical **13**. The aryl radical attacks sulfur dioxide to give the radical intermediate **15** (also a barrierless process), which reacts with the hydrazinium radical **14** (generated from deprotonation of the radical cation intermediate **12**) to afford the desired product **3**. Orbital analysis suggests that the electrostatic interaction in complex **9** makes the homolytic cleavage of the N–S bond more favorable (the structure and Cartesian coordinates of complex **9** are shown in Supporting Information). According to our theoretical calculations, the overall Gibbs free energy barrier of this route is 19.4 kcal mol^{-1} (at 298 K), which is reasonable from the perspective of thermodynamics. When hydrazine was replaced by morpholine as a representative of simple amines, the theoretical calculations showed that the overall Gibbs free energy barrier of this route is 37.7 kcal mol^{-1} (at 298 K), which indicates that this process is infeasible (the Gibbs free energy of each step is provided in Supporting Information). This theoretical result might explain why only hydrazines were efficient and amines were unsuccessful in this transformation.

In conclusion, we have described an efficient route to aryl *N*-aminosulfonamides by coupling aryldiazonium tetrafluoroborates, DABCO·$(SO_2)_2$, and hydrazines under metal-free conditions. The reaction proceeds smoothly at room temperature and shows broad functional-group tolerance. A plausible mechanism is proposed as well, which involves a radical process. We believe that the efficiency of the transformation, the extremely mild conditions, and the broad reaction scope will make the method attractive for further applications.

Experimental Section

General experimental procedure for the aminosulfonylation reaction of aryldiazonium tetrafluoroborates **1** with DABCO·$(SO_2)_2$ and hydrazines **2**: Aryldiazonium tetrafluoroborate **1** (0.30 mmol) in CH_3CN (1.0 mL) was added in a dropwise manner to a solution of DABCO·$(SO_2)_2$ (0.18 mmol) and hydrazine **2** (0.36 mmol) in CH_3CN (3.0 mL) under N_2 atmosphere in 10 min. The mixture was stirred at room temperature for another 10 min. The solvent was evaporated and the residue was purified directly by flash column chromatography (eluent: EtOAc/*n*-hexane = 1:2) to give the desired product **3**.

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[1] a) M. Bartholow, Top 200 Drugs of 2011. Pharmacy Times. http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011, accessed on Jan 9, **2013**; b) For a list of topdrugs by year, see: http://cbc.arizona.edu/njardarson/group/toppharmaceuticals-poster, accessed on Jan 9, **2013**; c) J. Drews, *Science* **2000**, *287*, **1960**.

[2] T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347.

[3] S. Thaisrivongs, H. I. Skulnick, S. R. Turner, J. W. Strohbach, R. A. Tommasi, P. D. Johnson, P. A. Aristoff, T. M. Judge, R. B. Gammill, J. K. Morris, K. R. Romines, R. A. Chrusciel, R. R. Hinshaw, K.-T. Chong, W. G. Tarpley, S. M. Poppe, D. E. Slade, J. C. Lynn, M.-M. Horng, P. K. Tomich, E. P. Seest, L. A. Dolak, W. J. Howe, G. M. Howard, F. J. Schwende, L. N. Toth, G. E. Padbury, G. J. Wilson, L. Shiou, G. L. Zipp, K. F. Wilkinson, B. D. Rush, M. J. Ruwart, K. A. Koeplinger, Z. Zhao, S. Cole, R. M. Zaya, T. J. Kakuk, M. N. Janakiraman, K. D. Watenpaugh, *J. Med. Chem.* **1996**, *39*, 4349.

[4] H. Uno, M. Kurokawa, Y. Masuda, H. Nishimura, *J. Med. Chem.* **1979**, *22*, 180.

[5] a) K. Bahrami, M. M. Khodaei, D. Khaledian, *Tetrahedron Lett.* **2012**, *53*, 354; b) G. K. S. Prakash, T. Mathew, G. A. Olah, *J. Org. Chem.* **2007**, *72*, 5847; c) S. W. Wright, K. N. Hallstrom, *J. Org. Chem.* **2006**, *71*, 1080.

[6] a) V. Percec, T. K. Bera, B. B. De, Y. Sanai, J. Smith, M. N. Holerca, B. Barboiu, B. B. B. Grubbs, J. M. J. Fréchet, *J. Org. Chem.* **2001**, *66*, 2104; b) R. J. Watson, D. Batty, A. D. Baxter, D. R. Hannah, D. A. Owen, J. G. Montana, *Tetrahedron Lett.* **2002**, *43*, 683.

[7] a) S. O. Alapafuja, S. P. Nikas, V. G. Shukla, I. Papanastasiou, A. Makriyannis, *Tetrahedron Lett.* **2009**, *50*, 7028; b) K. Bahrami,

M. M. Khodaei, M. Soheilizad, *J. Org. Chem.* **2009**, *74*, 9287; c) H. Woolven, C. González-Rodrígues, I. Marco, A. L. Thompson, M. C. Willis, *Org. Lett.* **2011**, *13*, 4876.

[8] a) B. Nguyen, E. J. Emmet, M. C. Willis, *J. Am. Chem. Soc.* **2010**, *132*, 16372; b) A. J. Emmett, C. S. Richards-Taylor, B. Nguyen, A. Garcia-Rubia, B. R. Hayter, M. C. Willis, *Org. Biomol. Chem.* **2012**, *10*, 4007; c) C. S. Richards-Taylor, D. C. Blakemore, M. C. Willis, *Chem. Sci.* **2014**, *5*, 222; d) E. J. Emmett, B. R. Hayter, M. C. Willis, *Angew. Chem.* **2013**, *125*, 12911; *Angew. Chem. Int. Ed.* **2013**, *52*, 12679; e) A. S. Deeming, C. J. Rusell, A. J. Hennessy, M. C. Willis, *Org. Lett.* **2014**, *16*, 150; f) B. N. Rocke, K. B. Bahnck, M. Herr, S. Lavergne, V. Mascitti, C. Perreault, J. Polivkova, A. Shavnya, *Org. Lett.* **2014**, *16*, 154.

[9] a) S. Ye, J. Wu, *Chem. Commun.* **2012**, *48*, 7753; b) S. Ye, J. Wu, *Chem. Commun.* **2012**, *48*, 10037.

[10] J. R. DeBergh, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 10638.

[11] For reviews on arene diazonium salts, see: a) F. Mo, G. Dong, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582; b) D. P. Hari, B. König, *Angew. Chem.* **2013**, *125*, 4832; *Angew. Chem. Int. Ed.* **2013**, *52*, 4734.

[12] a) P. Allongue, M. Delamar, B. Desbat, O. Fagebaume, R. Hitmi, J. Pinson, J.-M. Savéant, *J. Am. Chem. Soc.* **1997**, *119*, 201; b) C. Galli, *Chem. Rev.* **1988**, *88*, 765; c) S. Milanesi, M. Fagnoni, A. Albini, *J. Org. Chem.* **2005**, *70*, 603.

[13] a) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem.* **2013**, *125*, 8130; *Angew. Chem. Int. Ed.* **2013**, *52*, 7972; b) J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436; c) X. Wang, Y, Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330.

[14] a) H. H. Hodgson, *Chem. Rev.* **1947**, *40*, 251; b) E. B. Merkushev, *Synthesis* **1988**, 923.

[15] F. Eugène, B. Langlois, E. Laurent, *J. Org. Chem.* **1994**, *59*, 2599.

