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The Triple Role of Rongalite in Aminosulfonylation of Aryldiazonium Tetrafluoroborates: Synthesis of N-aminosulfonamides via a Radical Coupling Reaction

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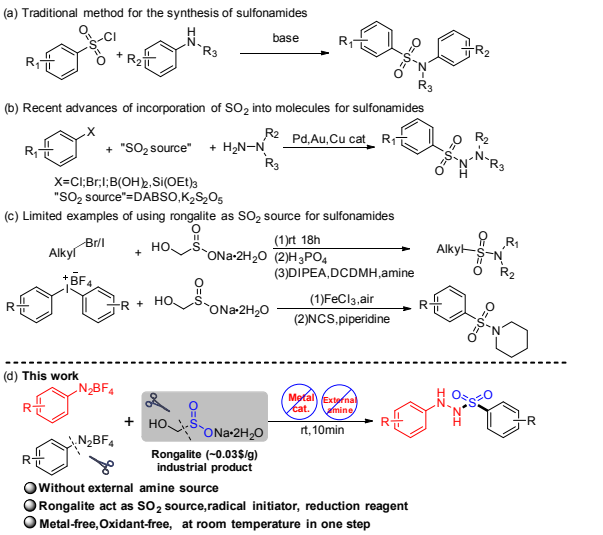
A simple and convenient method for *N*-aminosulfonamide synthesis from the cross-coupling of aryldiazonium tetrafluoroborates and rongalite under metal-free, oxidant-free, and room-temperature conditions is reported. This method does not require an external amine source, with the aryldiazonium tetrafluoroborates participating as both an aryl radical and potential amine source in the transformation. Mechanistic studies revealed that rongalite could act as radical initiator, sulfur dioxide surrogate and reduction reagent simultaneously in this reaction.

Due to their distinctive structural and electronic features, sulfones have been widely applied in pharmaceuticals, agrochemicals, materials, and important synthetic intermediates.[1] Among sulfonyl-containing molecules, sulfonamides are the most important owing to their medical significance.[2] Many anticonvulsants, HIV protease inhibitors, and anticancer, antibacterial, anti-inflammatory, and antiviral agents contain sulfonamide skeletons.[3] Accordingly, many methods for the construction of sulfonamides have been developed. Traditionally, the direct route to sulfonamide construction is the nucleophilic reaction of sulfonyl chlorides and amines (Scheme 1a).[4] However, this method suffers from significant limitations, including a limited substrate scope and the cumbersome procedures necessary to obtain some sulfonyl chlorides. To prevent these problems, recent efforts have been directed toward incorporating sulfur dioxide into molecules for the synthesis of sulfonamides.[5-7] Breakthrough work was reported by Willis and coworkers, who described a Pd-catalyzed coupling reaction of aryl iodides, DABCO·$(SO_2)_2$, and hydrazines to generate *N*-aminosulfonamides (Scheme 1b).[6a] Recently, several groups have reported reacting aryl chlorides/bromides,[7a] arylboronic acids,[7b] and triethoxysilanes[7c] with DABCO·$(SO_2)_2$ or $K_2S_2O_5$[7d] and hydrazines to prepare sulfonamides. Despite this progress, simpler and more convenient methods for sulfonamide synthesis, especially those incorporating new and cheap SO_2 sources into molecules and avoiding the addition of an external amine source, are highly desirable.

Rongalite ($Na^+HOCH_2SO_2^-\cdot 2H_2O$) is a useful and cheap industrial product that has been widely used in the dye, rubber, and veterinary industries.[8] Rongalite is also used as a versatile reagent in synthetic chemistry.[9] However, examples where rongalite is used as a source of SO_2 for incorporation into molecules are rare. In 2016 Shavnya and coworkers reported a three-step method for the preparation of aliphatic sulfonamides using alkyl halides and rongalite.[10a] Furthermore, Luo reported a Fe-catalyzed radical coupling reaction of diaryliodonium salts, rongalite, and amines in a two-step synthesis of sulfonamides (Scheme 1c).[10b] However, the direct using rongalite as SO_2 source incorporate into molecules for sulfonamides under metal-free conditions in one step has not been reported. In conjunction with our ongoing research into



Scheme 1. Tradition Synthesis and Recent Advances for the Preparation of Sulfonamides

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Electronic Supplementary Information (ESI) available: Experimental details, characterization of compounds, copies of ^1H and ^{13}C spectra for selected compounds, and CIF files of **3b**. See DOI: 10.1039/x0xx00000x

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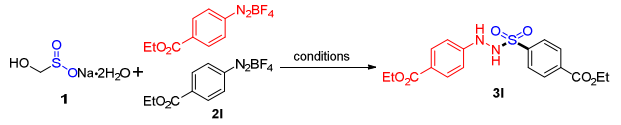
developing methodologies for rongalite-based cleavage and incorporation into molecules to obtain valuable skeletons,[11] we now present a simple preparation of *N*-aminosulfonamides under metal-free and oxidant-free conditions through coupling tetrafluoroborates and rongalite at room temperature (Scheme 1d). Notably, this method did not require an external amine source, with the aryldiazonium tetrafluoroborates participating as both aryl radicals and the potential amine source in the transformation. To our knowledge, this represents the first reported example of rongalite being used as a source of SO_2 for incorporation into two molecules of aryldiazonium tetrafluoroborates to obtain *N*-aminosulfonamides under metal-free, oxidant-free, and room-temperature conditions.

Initial investigations focused on the model reaction of rongalite (**1**) with 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**2l**) in MeCN at 60 °C. To our delight, the desired compound, ethyl-4-((2-(4-(ethoxycarbonyl)phenyl) hydrazinyl)sulfonyl)benzoate (**3l**), was obtained in 41% yield (entry 1). Solvent screening suggested that DMSO was the best solvent for this reaction, increasing the yield of **3l** to 72% (entries 2–9). Next, we investigated the ratios of the two reactants, with the optimum ratio of **1/2l** found to be 2.0:1.0 (entries 10–13). Finally, a range of different temperatures were screened, which showed that the reaction proceeded well at room temperature (entries 14–17).

Table 1. Optimization of the Reaction Conditions[a]

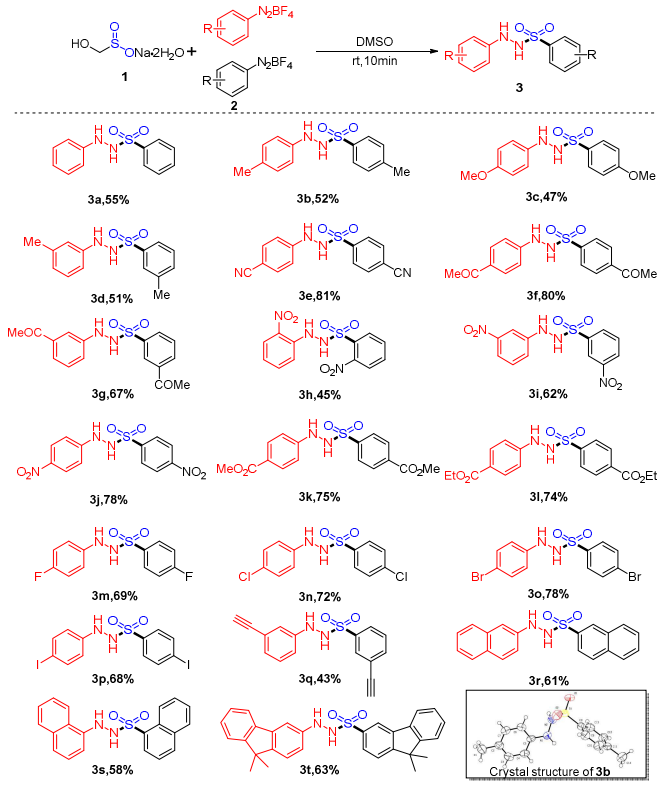


entry	solvent	1a:2l	temp (°C)	yield[b] (%)
1	MeCN	2.0:1.0	60	41
2	DCE	2.0:1.0	60	trace
3	PhMe	2.0:1.0	60	trace
4	$CHCl_3$	2.0:1.0	60	0
5	EtOH	2.0:1.0	60	58
6	DMSO	2.0:1.0	60	72
7	acetone	2.0:1.0	60	37
8	1,4-dioxane	2.0:1.0	60	trace
9	THF	2.0:1.0	60	0
10	DMSO	0.5:1.0	60	trace
11	DMSO	1.0:1.0	60	52
12	DMSO	1.5:1.0	60	69
13	DMSO	2.5:1.0	60	71
14	**DMSO**	**2.0:1.0**	**rt**	**74**
15	DMSO	2.0:1.0	40	72
16	DMSO	2.0:1.0	50	71
17	DMSO	2.0:1.0	70	68

[a]Reaction conditions: **1** (1.2 mmol), **2l** in solvent (3.0 mL) at different temperatures. The reaction was performed for 10miuntes. [b]isolated yields based on **2l**.

The substrate scope of this transformation was then evaluated, with the optimized reaction conditions found to be applicable to a broad range of substrates. As shown in Scheme 2, aryldiazonium tetrafluoroborates bearing electronically neutral (4-H), electron-donating (4-Me, 4-OMe, 3-Me), and electron-withdrawing (4-CN, 4-COMe, 3-COMe, 2-NO_2, 3-NO_2, 4-NO_2, 4-CO_2Me, 4-CO_2Et) substituents all reacted smoothly, affording the corresponding *N*-aminosulfonamides in moderate to excellent yields (45–81%, 3a–3l). Pleasingly, the conditions were mild enough to be compatible with halogenated (4-F, 4-Cl, 4-Br, 4-I) and alkynyl (3-ethynyl) substrates (43–78%, 3m–3q), which provided the potential for further functionalization. Meanwhile, sterically hindered 2-naphthyl diazonium tetrafluoroborates and 1-naphthyl diazonium tetrafluoroborates furnished desired products 3r and 3s in 61% and 58% yields, respectively. Furthermore, the optimal conditions were successfully applied to diazonium tetrafluoroborates bearing fused rings, such as fluorenyl groups, affording the corresponding products in good yields (63%, 3t). The structure of 3b was confirmed by single-crystal X-ray diffraction (see Supporting Information (SI)).

Scheme 2. Scope of aryldiazonium tetrafluoroborates[a,b]



[a]Reaction conditions: **1** (1.2 mmol), **2** (0.6 mmol) in solvent (3.0 mL) at room temperatures. The reaction was performed for 10miuntes. [b]isolated yields based on **2**.

To gain insight into the reaction mechanism, a series of control experiments were performed (Scheme 3). When rongalite (**1**) was treated with 4-(ethoxycarbonyl)benzenediazonium

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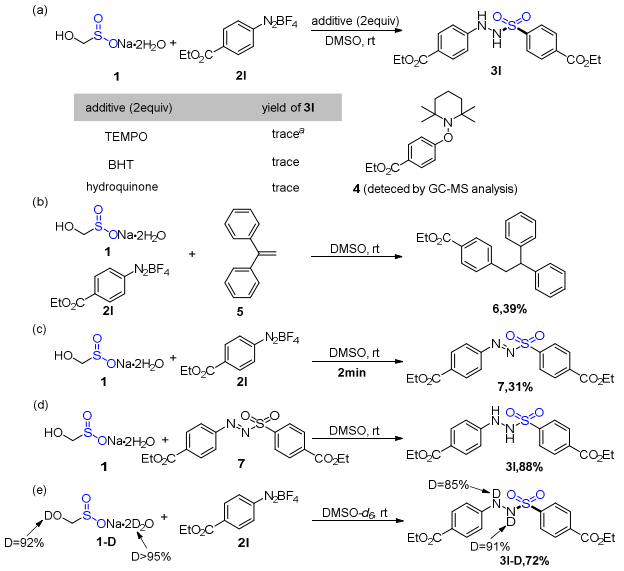
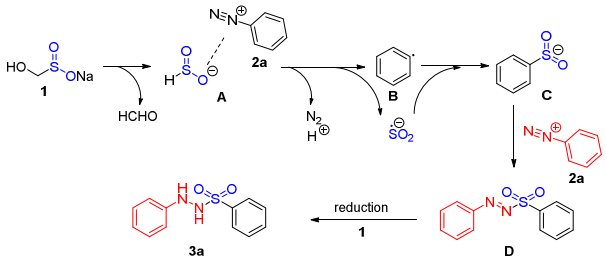
tetrafluoroborate (**2l**) in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), butylhydroxytoluene (BHT), or hydroquinone (Scheme 3a), no desired product (**3l**) was observed. In the reaction containing TEMPO, a TEMPO-PhCO$_2$Et product **4** was detected by GC–MS, which suggested that the reaction might involve a radical process. A further radical trapping experiment using rongalite (**1**), **2l**, and 1,1-diphenylethylene (**5**) under the optimized conditions was performed, with ethane-1,1,2-triyltribenzene (**6**) obtained as a product in 38% yield (Scheme 3b). This result was different to that previously reported for a similar trapping experiment, where the product was triphenylethylene,[10b, 12] which indicated that the reaction system in this reaction might be reducing. Furthermore, when the reaction of rongalite (**1**) and **2l** under the standard conditions was stopped at 2 min, the corresponding sulfonyl diazo (**7**) was obtained in 31% yield (Scheme 3c), which was then reduced to corresponding sulfonyl hydrazide (**3l**) in 88% yield by rongalite (**1**) (Scheme 3d). The reaction of sodium benzenesulfinate and **2l** gave corresponding sulfonyl diazo (**8**) in 95% yield, which can also be reduced to corresponding sulfonyl hydrazide (**9**) in 91% yield by rongalite (**1**) (see Supporting Information (SI)). These results indicated that the benzene sulfonate anion and sulfonyl diazo species might be the key intermediates, and that rongalite could reduce the sulfonyl diazo intermediate to the final sulfonyl hydrazide product. Finally, deuterated rongalite (**1-D**) and **2l** was also reacted in DMSO-d_6 and the deuterated product **3l-D** generated in 72% yield with 85% and 91% deuteration of the two N–H groups, respectively (Scheme 3e). This clearly confirmed that hydrogen atom in the N–H groups of sulfonyl hydrazide (**3l**) was mainly from water.

Scheme 3. Control experiments



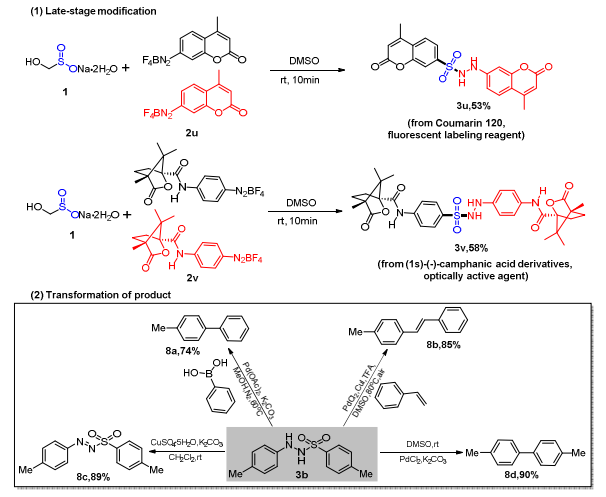
[a]*Ethyl 4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)benzoate (4) was in situ deteced by GC-MS analysis*

Based on the results in the current study and previous reports,[9,13] a possible mechanism has been proposed using **1** and **2a** as examples (Scheme 4). Initially, the decomposition of rongalite generated an HSO_2^- anion, accompanied by the release of a molecule of formaldehyde. Subsequently, arydiazonium cation **2a** would combine with an HSO_2^- anion to generate complex **A** through electrostatic interaction. Next, aryl radical **B** and sulfoxylate anion radical $SO_2^{\bullet-}$ could be produced by single-electron transfer. The radical coupling of sulfoxylate anion radical $SO_2^{\bullet-}$ and aryl radical **B** would provide the desired arylsulfinate **C**, which would then attack another molecule of **2a** to afford intermediate sulfonyl diazo intermediate **D**. Finally, **D** would be reduced by rongalite to give the corresponding sulfonyl hydrazide **3a**.



Scheme 4. Possible mechanism

We further explored the applications of this radical coupling reaction and sulfonyl hydrazide product **3** in organic synthesis, as shown in Scheme 5. This method is attractive for the incorporation of sulfonyl hydrazide groups into natural products and drug candidates containing an aniline backbone. Late-stage modification was conducted using naturally occurring coumarin 120, with corresponding product **3u** obtained in 53% yield. Derivatives of chiral lactone (1S)-(–)-camphanic acid chloride also participated in this reaction to generate desired sulfonyl hydrazide **3v** in 58% yield. Next, transformation of sulfonyl hydrazide product **3** was studied, using **3b** as an example. Compound **3b** was converted into the corresponding sulfonyl diazo compound **10a** in 89% yield in the presence of $CuSO_4 \bullet 5H_2O$ and K_2CO_3. Pleasingly, sulfonyl hydrazide **3b** was successfully used as a coupling partner in classic coupling reactions with an arylboronic acid and aryl olefin, yielding corresponding coupling products **10b** and **10c** in 74% and 85% yields, respectively. Finally, **3b** was also transformed into 4,4'-dimethylbiphenyl (**10d**) in 90% yield accompanied by the release of N_2 and SO_2.



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Scheme 5. Synthetic applications of the methodology

In summary, we have developed a novel method for the synthesis of *N*-aminosulfonamides from aryldiazonium tetrafluoroborates and rongalite under metal-free, oxidant-free, and room-temperature conditions. Notably, aryldiazonium tetrafluoroborates participated as both an aryl radical and potential amine source in the subsequent transformation. This method is facile and highly efficient, with a broad substance scope. Mechanistic studies revealed that rongalite could act as radical initiator, sulfur dioxide surrogate and reduction reagent simultaneously in this reaction. Further applications of rongalite as a source of SO_2 for the synthesis of other interesting sulfones are currently underway in our laboratory.

Acknowledgements

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