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Copper-Catalyzed Synthesis of Aryldiazo Sulfones from Arylhydrazines and Sulfonyl Chlorides under Mild Conditions

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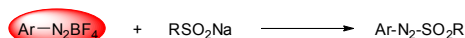
In this paper, the aryldiazo sulfones are prepared from tandem sulfonylation/dehydrogenation reactions of arylhydrazines and sulfonyl chlorides. The transformations proceed well in the presence of catalytic $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, leading to the aryldiazo sulfones in good to excellent yields. It is believed that this protocol represents a safe and convenient model for the synthesis of these versatile aryldiazo sulfones under mild conditions.

As important building blocks, aryldiazo salts have received extensively attention in the community of organic chemists during the past century.¹ Presently, it still remains high interests in these aryldiazonium salts-based transformations (especially, transitional metal-catalyzed cross-coupling reactions). However, aryldiazonium salts are often dangerously explosive and prone to decomposition upon storage. Therefore, it has been one of hot topics in organic chemistry to synthesize diazonium salts with good stability and storage safety and further apply them into the synthesis of useful architectures. To date, aryldiazonium tetrafluoro-borates,² aryldiazonium hexafluorophosphates,³ and aryldiazonium arylsulfonates⁴ have been described as excellent candidates in aryldiazonium salts-based transformations in the bench level or even in industrial stage.

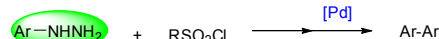
To the best of our knowledge, aryldiazo sulfone is a kind of potential diazonium salts. According to the findings on their thermal⁶ and photochemical⁷ behavior, aryldiazo sulfones show relatively high stability and storage safety, even with acids⁸ and bases.⁹ What's more, aryldiazo sulfones have been demonstrated as electrophilic partners in cycloadditions to construct *N*-containing cyclic compounds,¹⁰ and in some transition-metal-catalyzed cross-coupling reactions.¹¹ Although with broad applications, studies on new methodology development for the synthesis of aryldiazo

sulfones remain rare. Traditionally, aryldiazo sulfones are often derived from the reaction of aryldiazonium salts with sulfinic acid salts (Scheme 1a).⁵ On the other hand, according to our previous results on hydrazine chemistry, we know that palladium catalysis enabled aryl hydrazines as excellent aryl source, resulting in diaryl compounds^{12b} (Scheme 1b). In these transformations, aryldiazo sulfones were proposed as the key intermediates. And sulfonyl chloride was a crucial additive, guaranteeing the formation of aryldiazo sulfones. In view of high importance of aryldiazo sulfones and insights into the mechanism of our previous reactions, we envisioned that the reactions of arylhydrazines and sulfonyl chloride could produce aryldiazo sulfones efficiently under copper catalysis (instead of palladium catalysis), and the generated aryldiazo sulfones was able to survive in the presence of copper (Scheme 1c).

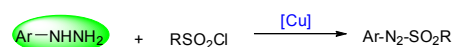
(1a): traditional synthesis of aryldiazo sulfones



(1b): our previous work



(1c): this work



Scheme 1 Reaction Design.

Initially, the model reaction of phenylhydrazine **1a** and *p*-toluenesulfonyl chloride (TsCl) **2a** was carried out in the presence of 20 mol% $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as catalyst, 3.0 equiv Et_3N as base, and CH_2Cl_2 as solvent. Under aerobic conditions, the reaction was stirred at room temperature for 4 h, giving rise to the desired product **3a** in 50% yield (Table 1, entry 1). This reaction represented a formal tandem sulfonylation/dehydrogenation. Encouraged by this result, other Cu sources were evaluated [$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, CuCl , $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{Cu}(\text{OTf})_2$] (entries 2-5). It is pleased to find that $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ was the best choice, affording 70% yield of the product

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3a (entry 4). Other transition-metal catalysts were also examined in the reaction: the reactions using $\text{FeSO}_4 \cdot 5\text{H}_2\text{O}$ and ZnSO_4 only afforded less than 10% desired products (entries 6 and 7); $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ completely shut down this reaction (entry 8). The effect of bases in this reaction was then investigated (entries 9-13), and the use of K_2CO_3 as the base improved the yield to 88% (entry 11 *versus* entries 4, 9-10, and 12-13). Solvents evaluation revealed that no better yields were provided when using MeOH, DMSO, THF and toluene as solvents (entries 14-17). Reducing copper catalyst loading to 10 mol% resulted in a comparable yield (entry 18 *versus* entry 11). However, further reduction of copper catalyst loading to 5 mol % made a significant effect on the yield of the product, forming aryl diazo sulfone **3a** in 66% yield (entry 19). It seems that the oxygen might play an important role as an oxidant in the dehydrogenation process, because a significant drop in yield was observed under N_2 atmosphere (entry 20). Control experiment under oxygen gave a comparable outcome with that of under air (entry 21).

Table 1 Optimization of reaction conditions.^a

$\text{Ph-NHNH}_2 + \text{TsCl} \xrightarrow[\text{rt., 1-4h}]{\text{conditions}} \text{Ph-N=N-Ts}$			
entry	catalyst/base	solvent	yield ^b [%]
1	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\text{Et}_3\text{N}$	CH_2Cl_2	50
2	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}/\text{Et}_3\text{N}$	CH_2Cl_2	46
3	$\text{CuCl}/\text{Et}_3\text{N}$	CH_2Cl_2	24
4	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{Et}_3\text{N}$	CH_2Cl_2	70
5	$\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$	CH_2Cl_2	60
6	$\text{FeSO}_4 \cdot 5\text{H}_2\text{O}/\text{Et}_3\text{N}$	CH_2Cl_2	<10
7	$\text{ZnSO}_4/\text{Et}_3\text{N}$	CH_2Cl_2	<10
8	$\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}/\text{Et}_3\text{N}$	CH_2Cl_2	trace
9	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{DBU}$	CH_2Cl_2	30
10	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{DABCO}$	CH_2Cl_2	65
11	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	CH_2Cl_2	88
12	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{Na}_2\text{CO}_3$	CH_2Cl_2	76
13	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{KOH}$	CH_2Cl_2	24
14	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	MeOH	trace
15	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	DMSO	38
16	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	THF	28
17	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	toluene	46
18 ^c	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	CH_2Cl_2	87
19 ^d	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	CH_2Cl_2	66
20 ^e	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	CH_2Cl_2	40
21 ^f	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{CO}_3$	CH_2Cl_2	86

^aReaction conditions: **1a** (0.5mmol), **2a** (0.5mmol), catalyst (20 mol%), base (3.0 equiv), solvent (3 mL), 1-4 h. ^bIsolated yields of **3a**. ^c $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (10 mol%). ^d $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5 mol%). ^eUnder N_2 . ^fUnder O_2 .

With the optimized conditions in hand (10 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ as catalyst, CH_2Cl_2 as solvent, at room temperature for 1-4 h), the substrate scope for the reactions of arylhydrazines (**1**) with sulfonyl chlorides (**2**) was studied (Table 2). For a wide range of arylhydrazines with either electron-rich or electron-poor aryl groups, the corresponding tandem sulfonylation/dehydrogenation

with **2a** proceeded smoothly, giving arylazosulfones (**3**) with high efficiency. However, the efficiency of the reaction was relatively sensitive to the substituents on the aromatic rings in different arylhydrazines (entries 1-13). Arylhydrazine with an electron-withdrawing group on the aromatic ring gave a better yield than that bearing an electron-donating group on the aromatic ring. For example, the substrates with an electron-donating group, such as CH_3 or CH_3O on the phenyl ring reacted with **2a** to afford the corresponding products in 70-79% yields (entries 2-5). But when arylhydrazines with an electron-withdrawing group (Cl, Br, F or CF_3) on the phenyl ring reacted with **2a**, more than 85% yields of the desired products were obtained (entries 6-12). Interestingly, the steric hindrance effect of the *ortho*-substituents of the substrate **1** was negligible for this reaction. For instance, the compounds **1h** and **1i** could react smoothly in 90% and 94% yields, respectively (entries 8 and 9). Then several other sulfonyl chlorides with different substitutions were next explored (entries 14-18). For the phenylsulfonyl chloride **2b**, the reactions were all successfully proceeded with **1a**, **1b** or **1f** to afford the products in high yields (entries 14-16). What's more, methanesulfonyl chloride (**MsCl**) **2d** could also produce the azosulfone **3r** in 70% yield under the standard conditions (entry 18). However, the **2c** with NO_2 substituent delivered the desired compound **3q** with low yield, in 34% (entry 17). Other hydrazines such as alkyl hydrazines and tosyl hydrazine were not compatible for the reactions, probably due to too high reactivities (data not shown in Table 2).

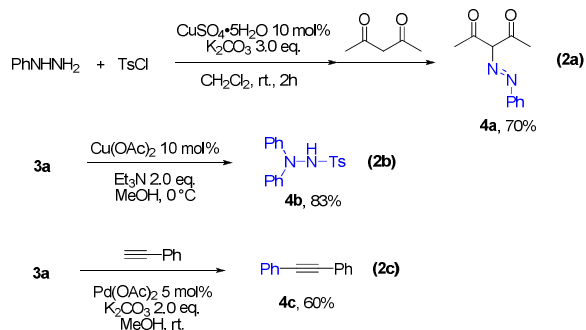
Table 2 Copper-catalyzed synthesis of aryl diazo sulfones.^a

$\text{R-Ph-NHNH}_2 + \text{R}'\text{SO}_2\text{Cl} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt., 1-4h}]{\text{CuSO}_4 \cdot 5\text{H}_2\text{O} 10 \text{ mol\%}, \text{K}_2\text{CO}_3 3.0 \text{ eq.}} \text{R-Ph-N=N-SO}_2\text{R}'$				
entry	R	R'	3	yield ^b [%]
1	H (1a)		3a	87
2	4-Me (1b)		3b	78
3	3-Me (1c)		3c	80
4	3,5-diMe (1d)		3d	75
5	4-OMe (1e)		3e	79
6	4-Cl (1f)		3f	90
7	3-Cl (1g)	4-MePh (2a)	3g	88
8	2-Cl (1h)		3h	91
9	2,4,6-triCl (1i)		3i	92
10	4-Br (1j)		3j	88
11	4-F (1k)		3k	90
12	4-OCF ₃ (1l)		3l	85
13	4-Ms (1m)		3m	82
14	1a		3n	80
15	1b	Ph (2b)	3o	84
16	1f		3p	85
17	1a	4-NO ₂ Ph (2c)	3q	30
18	1a	Me (2d)	3r	70

^aReaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (10

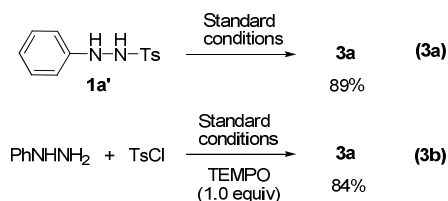
mol%), K₂CO₃ (3.0 equiv), CH₂Cl₂ (3 mL), 1-4 h. ^bIsolated yields of **3**.

To illustrate the synthetic utility of these versatile intermediates in organic chemistry, aryldiazo sulfone **3a** was applied to various Pd/Cu-catalyzed reactions (Scheme 2). Interestingly, aryldiazo sulfone **3a** could react with dicarbonyl compound, producing another aryldiazo **4a** (Scheme 2a). By changing to catalyst Cu(OAc)₂ and base triethylamine, aryldiazo sulfone **3a** converted into *N,N*-diphenylhydrazine **4b** in 83% yield (Scheme 2b). In particular, aryldiazo sulfone **3a** could react with terminal alkyne in the presence of 5 mol% Pd(OAc)₂, giving the desired 1,2-diphenylethyne **4c** in 60% yield (Scheme 2c).



Scheme 2 Synthetic utility of aryldiazo sulfone.

Meanwhile, to understand the mechanism, two control experiments were carried out (Scheme 3). Firstly, we conceived that phenylhydrazine derivatives **1a'** would be the key intermediate for this sulfonylation/dehydrogenation process. As described in Scheme **3a**, *N'*-tosyl phenylhydrazine **1a'** could be oxydehydrogenated by Cu(II) affording **3a** in 89% yield. Secondly, when TEMPO was added to the reaction under the standard conditions, a comparable yield of **3a** was observed as well. This result probably indicated that the copper-promoted oxydehydrogenation did not involve a radical route.



Scheme 3 Control experiments.

In light of the above results and the research findings from other groups, a plausible mechanism for this sulfonylation/dehydrogenation process has been proposed (Fig.1).¹²⁻¹³ *N'*-tosylaryldiazo sulfone **A** was dehydrogenated in the presence of Cu(II)-catalyst and base to provide the copper-complex **B**. Then electron transfer of **B** afforded the corresponding aryldiazo sulfone **C** and gave the Cu(I). Meanwhile, oxygen in the air regenerated the Cu(II)-catalyst.

In summary, a simple and effective procedure for the preparation of aryldiazo sulfones by Cu-catalyzed sulfonylation/dehydrogenation of arylhydrazines and sulfonyl chlorides is presented. As a readily available and effective coupling partner, aryldiazo sulfone exhibits excellent generality in the aforementioned Pd/Cu-catalyzed coupling reactions. Future studies will be focused on extending the synthetic applications.

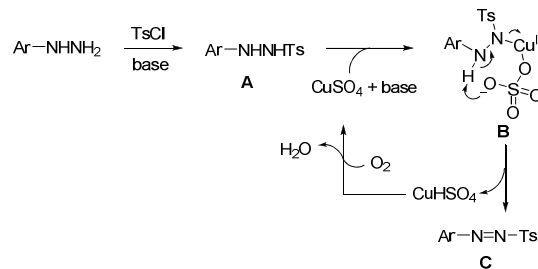


Fig. 1 Proposed mechanism.

Experimental

A mixture of arylhydrazine **1** (0.5 mmol), sulfonyl chloride **2** (0.5 mmol), CuSO₄·5H₂O (10 mol %), and K₂CO₃ (3.0 equiv), was stirred at room temperature in CH₂Cl₂ (3 mL) for 1-4 h. After completion of the reaction (indicated by TLC), the mixture was quenched with saturated NaCl solution, extracted with EtOAc, and dried over Na₂SO₄. The crude product was purified by flash column chromatography to provide the corresponding product **3**.

Acknowledgements

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Graphical Abstract

A simple and effective procedure for the preparation of aryldiazo sulfones by Cu-catalyzed sulfonylation/dehydrogenation is presented.

