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Copper-Catalyzed Nitrogen Loss of Sulfonylhydrazones: A Reductive Strategy for the Synthesis of Sulfones from Carbonyl Compounds

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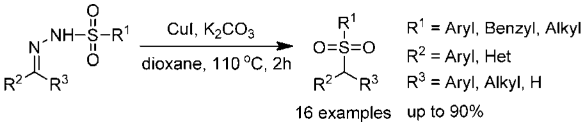
ABSTRACT



An efficient method for the synthesis of sulfones via nitrogen loss of sulfonyl hydrazones is described. The reaction was performed in the presence of simple copper salt and base by utilization of sulfonyl hydrazones, which were easily prepared from carbonyl compounds. A wide variety of aryl and alkyl sulfones were obtained in moderate to good yields.

The synthesis of sulfones has drawn much attention over the years since they constitute useful building blocks in natural products and pharmaceutical compounds. For example, sulfone derivatives were found to be potent inhibitors for several enzymes such as cyclooxygenase-2, HIV-1 reverse transcriptase, matrix metalloproteinase, and γ-secretase.[1] On the other hand, sulfones exhibit interesting chemical properties[2] and are useful intermediates in organic synthesis.[3] Therefore, sulfones have emerged as important synthetic targets in recent years. Known procedures for preparing sulfones are based on the oxidation of corresponding sulfides[4] or by displacement reactions using sulfinate salts as nucleophiles (Scheme 1).[5] However, these methods generally involve drawbacks such as limited substrate sources and sometimes harsh reaction conditions.

Sulfonyl hydrazones are versatile synthetic intermediates that have been used as an in situ source of diazo compounds in different types of transition-metal-catalyzed reactions,[6] such as XH (X = C, N, O) insertion reactions,[7] cyclopro-

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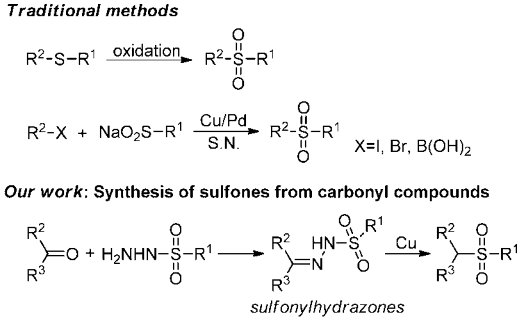
Scheme 1. Methods toward the Preparation of Sulfones

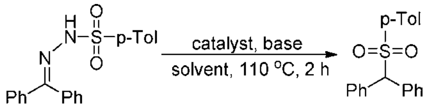


panations,[8] epoxidations,[9] and aziridinations.[10] Recently, Valdés and co-workers have reported metal-free coupling of tosylhydrazones with boronic acids[11] or hydroxylic compounds,[12] which significantly improved the application of sulfonyl hydrazones.

As early as 1952, Bamford and Stevens described that thermal decomposition of tosylhydrazones under basic media gave rise to diazo compounds, which went through a carbene intermediate to elimination and dimerization compounds (Bamford−Stevens reaction).[13] To our delight, we observed the formation of corresponding sulfones in good yields when tosyl hydrazones were heated in the presence of copper salt and base. Although pyrolysis[14] and photolysis[15] of tosyl hydrazones have been reported to obtain sulfones, these results were not satisfactory, and very poor yields were observed with limited substrate scope. Che and co-workers have reported that sulfones were formed as byproducts in ruthenium(II) porphyrin-catalyzed cyclopropanation of alkenes with tosylhydrazones.[16] Nevertheless, only some special substrates can provide sulfones, and precious metal Ru was used. In recent years, copper salts as economical metal compounds led to remarkable progress in the development of catalytic methodology.[17] Drawing from recent experiences in the field of copper-catalyzed diazo metallocarbene reactions,[18] we herein disclose a Cu-catalyzed decomposition of sulfonyl hydrazone (Scheme 1). A wide variety of sulfones were obtained in moderate to good yields.

First, the decomposition of tosyl hydrazone **1a**, which was derived from benzophenone, was chosen as a model system for optimization of the reaction conditions (Table 1). Initially, copper(I) iodide was used as copper source, and a variety of ligands, bases, and solvents were then screened. Reactions were inhibited to some extent after the addition of ligand (proline, bipyridine, or TMEDA, entries 2−4). CuI alone gave the best results, in which the yield was up to 84% (entry 5). Only a trace amount of target product **2a** was observed in the absence of either copper salt or base (entries 1 and 6). Thus, both copper salt and base are crucial for this transformation. Increase of the basicity of basic salts led to a harsh decrease of yields. When NaOMe and KO^{t}Bu were used as bases, decreased yields of 46% and trace were obtained, respectively (entries 7 and 8). The employment of some alternate solvents (DMSO and toluene, entries 9 and 10) and copper salts (Cu(II) acetate and Cu(II) chloride,

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	catalyst	base	solvent	yield[b] (%)
1		K$_2$CO$_3$	dioxane	trace
2	CuI/Pro	K$_2$CO$_3$	dioxane	83
3	CuI/bpy	K$_2$CO$_3$	dioxane	75
4	CuI/TMEDA	K$_2$CO$_3$	dioxane	78
5	CuI	K$_2$CO$_3$	dioxane	84
6	CuI		dioxane	trace
7	CuI	NaOMe	dioxane	46
8	CuI	KO^{t}Bu	dioxane	trace
9	CuI	K$_2$CO$_3$	DMSO	14
10	CuI	K$_2$CO$_3$	toluene	47
11	Cu(OAc)$_2$. H$_2$O	K$_2$CO$_3$	dioxane	63
12	CuCl$_2$	K$_2$CO$_3$	dioxane	55
13[c]	CuI	K$_2$CO$_3$	dioxane	36
14[d]	CuI	K$_2$CO$_3$	dioxane	84

[a] Reaction conditions: **1a** (0.3 mmol), [Cu] (20 mol %), ligand (20 mol %), base (2 equiv), solvent (2 mL), 110 °C, 2 h, under air. [b] Isolated yields. [c] 80 °C. [d] Under N$_2$.

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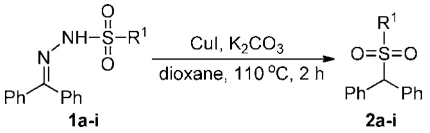
entries 11 and 12) also led to dereased yields. The chemical yield was dramatically decreased to only 36% when the reaction temperature was lowered to 80 °C (entry 13). The reaction was also carried out under nitrogen atmosphere, and same yield was found, indicating that oxygen is not necessary for this reaction (entry 14).

Under optimized conditions, studies on the development of substrate scope were then carried out. Various substituted sulfonyl hydrazones, which were prepared from benzophenone and relative sulfonyl hydrazides, were used as substrates. Table 2 summarizes the results. This method was proven to be general and efficient to prepare aryl and alkyl sulfones. Sulfonyl hydrazones derived from both electron-rich (entries 1 and 2) or electron-deficient (entries 5 and 6) sulfonyl hydrazides could afford the corresponding sulfones in good yields. It is worth mentioning that alkyl sulfones could also be produced from the corresponding sulfonyl hydrazones in moderate to good yields (entries 7−9).

Table 2. Decomposition of Sulfonylhydrazones Prepared from Benzophenone with Relative Sulfonyl Hydrazides[a]

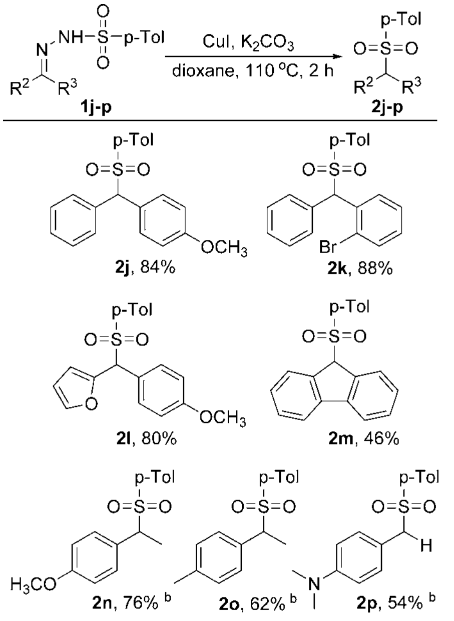


entry	R^1	1	2	yield[b] (%)
1	4-Tol	**1a**	**2a**	84
2	4-MeO-C_6H_4	**1b**	**2b**	77
3	Ph	**1c**	**2c**	80
4	2-Nap	**1d**	**2d**	75
5	4-NO_2−C_6H_4	**1e**	**2e**	80
6	4-Br-C_6H_4	**1f**	**2f**	84
7	Bn	**1g**	**2g**	90
8	Me	**1h**	**2h**	60
9	n-Bu	**1i**	**2i**	85

[a] Reaction conditions: **1** (0.3 mmol), CuI (20 mol %), K_2CO_3 (2 equiv), dioxane 2 mL. [b] Isolated yields.

Further, various carbonyl compounds were investigated for this type of reaction. These carbonyl compounds, including aldehydes and ketones with aromatic or heteroaromatic substituents, were used to prepare tosyl hydrazone substrates with tosyl hydrazide. These tosyl hydrazones **1j−p** could give target sulfones through the same reaction with moderate to good yields (Scheme 2). Tosyl hydrazone derivatives of diaryl ketones gave sulfone products with better yields than those derived from other carbonyl compounds. We speculated that this result might be ascribed to the more stable metallocarbene intermediates. Product **2m** was formed in lower yield, probably due to its rigid structure that was unfavorable to the transformation. Various benzaldehydes with electron-deficient or electron-donating substitutents were also investigated. Relative products were obtained in poor to moderate yields (data not shown), and electron-donating substituents could facilitate the reaction (**2p**).

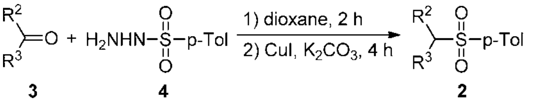
Scheme 2. Decomposition of Tosylhydrazones Derived from Various Carbonyl Compounds[a]



[a] Reaction conditions:**1** (0.3 mmol), CuI (20 mol %), K_2CO_3 (2 equiv), dioxane (2 mL), all yields given are isolated yields. [b] 4 h reaction time was needed.

As sulfonyl hydrazones could be simply prepared by mixing relative sulfonyl hydrazides and the carbonyl compounds, we investigated whether the reaction could be carried out in a one-pot fashion directly from carbonyl compounds without the isolation of sulfonyl hydrazone intermediates. We were pleased to achieve positive results. After heating the carbonyl compound **3** and sulfonyl hydrazide **4** for 2 h at 110 °C, we added the base and catalyst CuI, and then the mixture was heated for another 4 h. The product sulfone **2** was isolated with a slight decrease in the yield (Scheme 3).[19]

Scheme 3. One-Pot Synthesis of Sulfones from Carbonyl Compounds



R^2 = 4-$(CH_3)_2N$-C_6H_4, R^3 = H, 50%
R^2 = 4-CH_3O-C_6H_4, R^3 = CH_3, 62%

Scheme 4 showed the supposed reaction mechanism. First, diazo compound **III** and sulfinate salt **IV** were formed by decomposition of the hydrazone salt **II**. Subsequently, in the presence of copper salt, **III** released nitrogen and led to metallocarbene **V**. For the gemini nucleophile **IV**, we

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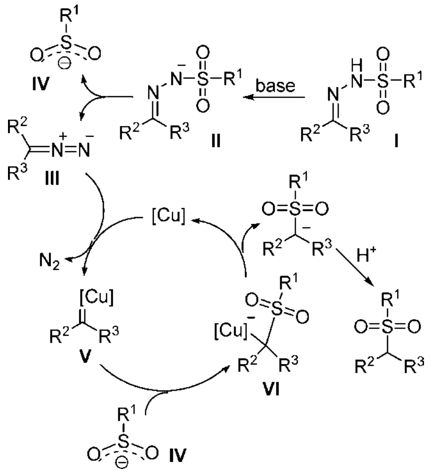
(19) Diarylketones were also tested. As the sulfonyl hydrazones derived from diaryl ketones were more difficult to prepare, the results were not satisfactory.

Scheme 4. Possible Reaction Mechanism



considered that the sulfur would act as the attack atom because of its higher nucleophilicity compared to that of oxygen, so intermediate **VI** could be formed directly. The final product was then formed through loss of copper and proton exchange.

In conclusion, we have developed a simple and efficient method for the synthesis of sulfones. The reaction used sulfonyl hydrazones, which were easily prepared from carbonyl compounds, to provide corresponding target products in moderate to good yields. Further applications of this methodology are now in progress.

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Supporting Information Available: General experimental procedures and spectroscopic data (^{1}H NMR and ^{13}C NMR) for the corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

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