Iron(III) Phthalocyanine-Chloride-Catalyzed Synthesis of Sulfones from Sulfonylhydrazones

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Iron(III) Phthalocyanine-Chloride-Catalyzed Synthesis of Sulfones from Sulfonylhydrazones

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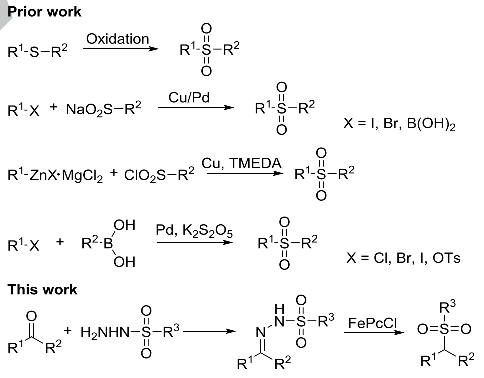
ABSTRACT

In this study, sulfones are synthesized from sulfonylhydrazones catalyzed by iron(III) phthalocyanine chloride. This reaction offers broad substrate scope, occurs under mild conditions, utilized readily available reactants, and forms products in good-to-high yields. Crossover experiments reveal that the reaction occurs via an intramolecular process, which is possibly different from other studies reported previously. The method provides a novel, simple, and promising strategy for synthesizing functionalized sulfones in the research field of sulfur chemistry.

Keywords:
Iron(III) phthalocyanine chloride
Sulfones
Sulfonylhydrazones

Sulfones are ubiquitous bioactive molecules,[1] which are commonly found in several pharmaceutical[2] and agrochemical compounds.[3] They are also widely applied as important intermediates in organic synthesis[4] and polymeric compounds.[5] Despite their widespread use in these areas, methods commonly employed for their preparation typically involve either the oxidation of sulfides[6] or the alkylation/arylation of sulfinate salts (Scheme 1).[7] Besides, in recent years, some other methods have also been developed, such as the use organometallic reagents[8] as well as SO_2 and its surrogates.[9] However, these methods generally have limitations in that oxidation methods are often incompatible with sensitive functional groups found in complex organic substrates and that the commercial availability of sulfonate salts is limited. Hence, it is imperative to develop a simple, convenient, and generally applicable protocol for synthesizing sulfones.



Scheme 1. Methods for the Preparation of Sulfones

Sulfonylhydrazones are versatile synthetic intermediates, which have been used as a source for the in situ synthesis of diazo compounds in different transition-metal-catalyzed reactions,[10] such as XH (X = C, N, O) insertion reactions,[11] cyclopropanation,[12] epoxidation,[13] and aziridination.[14] Recently, Barluenga and co-workers have reported the metal-free coupling of tosylhydrazones with boronic acids[15] or hydroxyl compounds,[16] which has significantly improved the application of sulfonylhydrazones. To our delight, when tosylhydrazones were heated in the presence of iron(III) phthalocyanine chloride and base, the corresponding sulfones were obtained in high yields. Although Che and co-workers have previously reported the same reaction by using a Ru-based catalyst,[17] their observations were not satisfactory, and very poor product yields were observed with a limited substrate scope. However, recently, a similar transformation promoted by Cu salts[18] and Fe salts[19] has been reported. However, these transformations are not satisfactory; furthermore, either lower yields are obtained, or the reaction requires a strong base. Herein, we report a practical iron(III) phthalocyanine-chloride-catalyzed synthesis of sulfones from sulfonylhydrazones (Scheme 1). Furthermore, we describe a novel mechanism for their synthesis.

First, the decomposition of tosylhydrazone **1a**, which was derived from acetophenone and tosylhydrazide, was chosen as a model system for optimizing the reaction conditions, and various catalysts, bases, solvents, and temperatures were then screened (Table 1). Initially, we chose iron(III) phthalocyanine chloride as the catalyst, K_2CO_3 as the base in 1,4-dioxane at 100 °C for 2 h, and the desired product **2a** was obtained in 43% yield (Table 1, entry 1). Next, the temperature of the reaction was changed, and

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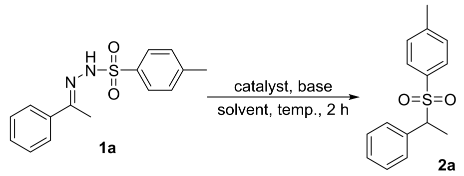
∗ Corresponding author. Tel.: +86-29-88302687; e-mail: zhaojunlong327@163.com the chemical yield dramatically increased to 93% when the reaction temperature was lowered to 80 °C (Table 1, entry 2). However, with further decrease in the temperature, the yields also decreased (Table 1, entries 3 and 4). Only a trace amount of target product **2a** was observed in the absence of either iron(III) phthalocyanine chloride (entry 5) or base (entry 6). Thus, both iron salt and base are crucial for this transformation. A range of bases such as Na_2CO_3, K_3PO_4, and Et_3N were then screened, and K_2CO_3 was found to be the most suitable base (Table 1, entries 7–9). The use of some alternative solvents (CH_3CN, EtOH, THF, and DMF, entries 10–13, respectively) and iron salts ($FeCl_3$, Fe_2O_3, and $Fe(NO_3)_3$, entries 14–16, respectively) also led to decreased yields or even no reaction. Finally, even with an increased amount of catalyst, the yield did not improve (Table 1, entry 17).

Table 1
Optimization of the Reaction Conditions[a]

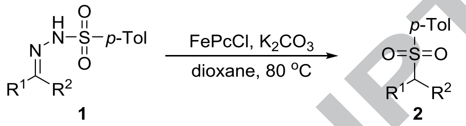


entry	catalyst	base	solvent	yield [b] (%)
1[c]	FePcCl	K_2CO_3	1,4-dioxane	43
2	FePcCl	K_2CO_3	1,4-dioxane	93
3[d]	FePcCl	K_2CO_3	1,4-dioxane	0
4[e]	FePcCl	K_2CO_3	1,4-dioxane	26
5	----	K_2CO_3	1,4-dioxane	trace
6	FePcCl	----	1,4-dioxane	trace
7	FePcCl	Na_2CO_3	1,4-dioxane	22
8	FePcCl	K_3PO_4	1,4-dioxane	46
9	FePcCl	Et_3N	1,4-dioxane	trace
10	FePcCl	K_2CO_3	CH_3CN	15
11	FePcCl	K_2CO_3	EtOH	trace
12[f]	FePcCl	K_2CO_3	THF	13
13[g]	FePcCl	K_2CO_3	DMF	28
14	$FeCl_3$	K_2CO_3	1,4-dioxane	trace
15	Fe_2O_3	K_2CO_3	1,4-dioxane	0
16	$Fe(NO_3)_3$	K_2CO_3	1,4-dioxane	0
17[h]	FePcCl	K_2CO_3	1,4-dioxane	89

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (1 mol%), base (2 equiv), and solvent (4 mL) at 80 °C for 2 h.
[b] Isolated yield.
[c] 100 °C.
[d] Room temperature.
[e] 60 °C.
[f] 70 °C.
[g] 110 °C.
[h] Catalyst (2 mol%)

With the optimized reaction conditions, the scope of the reaction was investigated (Table 2). Various carbonyl compounds were investigated for this reaction. Tosylhydrazone substrates were prepared by the reaction between carbonyl compounds, such as aldehydes and ketones containing aromatic or heteroaromatic substituents, and tosylhydrazide. This method was confirmed to be general and efficient for preparing sulfones. From the results obtained, the presence of electron-withdrawing or -donating groups on the aromatic rings does not affect the reaction, and they are conveniently transformed to their corresponding sulfones in excellent yields.

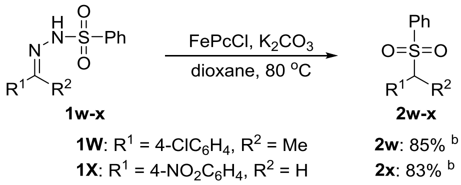
Table 2
Decomposition of Tosylhydrazones Derived from Various Carbonyl Compounds[a]



entry	R1	R2	T (h)	yield [b] (%)
1	**1a**, C_6H_5	Me	2	**2a**, 93
2	**1b**, 3-$MeOC_6H_4$	Me	3	**2b**, 85
3	**1c**, 4-ClC_6H_4	Me	3	**2c**, 86
4	**1d**, 4-$MeOC_6H_4$	Me	6	**2d**, 87
5	**1e**, 2-Nap	Me	3	**2e**, 82
6	**1f**, C_6H_5	*i*-Pr	3	**2f**, 83
7	**1g**, C_6H_5	H	1	**2g**, 89
8	**1h**, 4-$NO_2C_6H_4$	H	2	**2h**, 89
9	**1i**, 4-ClC_6H_4	H	3	**2i**, 96
10	**1j**, 4-MeC_6H_4	H	2	**2j**, 83
11	**1k**, 4-$MeOC_6H_4$	H	2	**2k**, 95
12	**1l**, 4-$(CH_3)_2NC_6H_4$	H	3	**2l**, 82
13	**1m**, 4-OHC_6H_4	H	3	**2m**, 85
14	**1n**, 4-FC_6H_4	H	2	**2n**, 87
15	**1o**, 2-FC_6H_4	H	2	**2o**, 89
16	**1p**, 2-$MeOC_6H_4$	H	2	**2p**, 95
17	**1q**, 3-$NO_2C_6H_4$	H	3	**2q**, 89
18	**1r**, 2,4-diClC_6H_4	H	3	**2r**, 94
19	**1s**, 2-MeO-4-OHC_6H_4	H	6	**2s**, 87
20	**1t**, 2-Thienyl	H	3	**2t**, 87
21	**1u**, 2-Furanyl	H	3	**2u**, 93
22	**1v**, 5-Me-2-Furanyl	H	3	**2v**, 91

[a] Reaction conditions: The reaction was conducted using **1** (0.5 mmol), FePcCl (1 mol%), and K_2CO_3 (2 equiv) in dioxane (4 mL) at 80 °C.
[b] Isolated yield.

Further, we substituted tosylhydrazide with benzenesulfonyl hydrazide, which could afford the corresponding sulfones in high yields (Scheme 2).



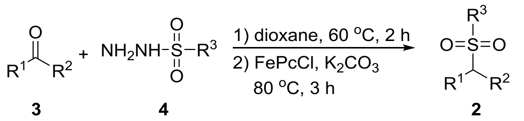
[a] Reaction conditions: The reaction was conducted using **1** (0.5 mmol), FePcCl (1 mol%), and K_2CO_3 (2 equiv) in dioxane (4 mL) at 80 °C for 3 h.
[b] Isolated yield.

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

Sulfonylhydrazones can be readily prepared by mixing sulfonyl hydrazides with the corresponding aldehydes or ketones. Hence, we investigated whether the reaction could be directly conducted in one pot from carbonyl compounds without the isolation of intermediate sulfonylhydrazones. To our delight, positive results were observed. After heating carbonyl compound **3** and sulfonyl hydrazide **4** for 2 h at 60 °C, followed by the addition of base and catalyst FePcCl, the mixture was heated at 80 °C for another 3 h. Product sulfones **2** were obtained with similar yields, but without the need to isolate the intermediate sulfonylhydrazones. Table 3 shows selected examples.

Table 3

One-Pot Synthesis of Sulfones from Carbonyl Compounds with Sulfonyl Hydrazides[a]

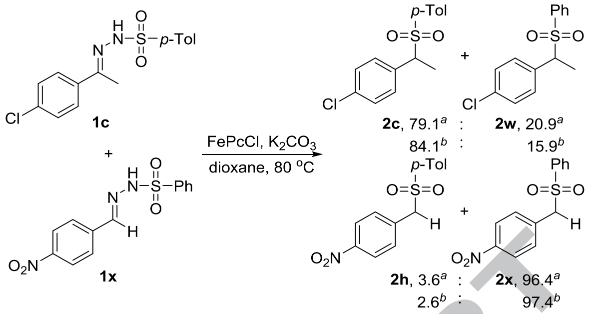


entry	R^1	R^2	R^3	yield [b] (%)
1	**1a**, C_6H_5	Me	4-Tol	**2a**, 91
2	**1c**, 4-ClC_6H_4	Me	4-Tol	**2c**, 82
3	**1h**, 4-$NO_2C_6H_4$	H	4-Tol	**2h**, 84
4	**1k**, 4-$MeOC_6H_4$	H	4-Tol	**2k**, 90
5	**1u**, 2-Furanyl	H	4-Tol	**2u**, 92
6	**1w**, 4-ClC_6H_4	Me	Ph	**2v**, 83

[a] Reaction conditions: 1) **3** (0.5 mmol), **4** (1.05 equiv), and 1,4-dioxane (4 mL), 60 °C, 2 h; 2) FePcCl (1 mol%) and K_2CO_3 (2 equiv) at 80 °C for 3 h.

[b] Isolated yield.

N-tosylhydrazones are well known to undergo thermal decomposition via the Bamford–Stevens reaction in the presence of base, generating diazo compounds; this reaction occurs via a carbine intermediate to finally form elimination and dimerization compounds.[20] To obtain additional proof for this mechanistic proposal and to eliminate the possibility of intramolecular nitrogen extrusion, we conducted a crossover experiment by using two sulfonylhydrazones. Thus, tosylhydrazone **1c**, derived from 1-(4-chlorophenyl)ethan-1-one, and benzene sulfonyl hydrazone **1x**, derived from 4-nitrobenzaldehyde, were used in the established procedure (Scheme 3). The reaction afforded four combinations of carbonyl and sulfonyl fragments. These four products were not formed in equimolar amounts, and the corresponding sulfone produced by a hydrazone accounted for the majority of the product (Scheme 3, conditions a). Hence, we speculate that this is an intramolecular process in the presence of iron(III) phthalocyanine chloride, rather than an intermolecular process as has been previously proposed.[18,19] For confirming this hypothesis, we decided to increase the amount of solvent for decreasing the contact between the two hydrazones (Scheme 3, conditions b). We were pleasantly surprised to observe a slight increase in the yield of sulfone with the corresponding hydrazone. This result confirms our hypothesis, and the process occurs via an intramolecular pathway and not via intermolecular extrusion.

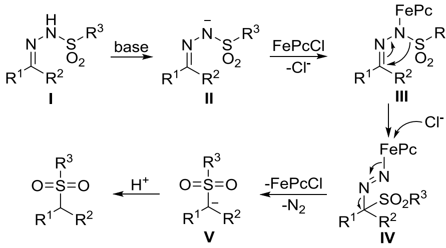


[a] Reaction conditions: **1c** (0.5 mmol), **1x** (0.5 mmol), FePcCl (2 mol%), K_2CO_3 (4 equiv), and dioxane (8 mL) at 80 °C for 3 h.

[b] Reaction conditions: **1c** (0.5 mmol), **1x** (0.5 mmol), FePcCl (2 mol%), K_2CO_3 (4 equiv), and dioxane (40 mL) at 80 °C for 3 h.

Scheme 3. Study of the Pathway of the Iron(III) Phthalocyanine-Chloride-Catalyzed Synthesis of Sulfones by a Crossover Experiment.

Scheme 4 shows the supposed reaction mechanism. First, hydrazone salt **II** was formed in the presence of base from hydrazone **I**. Subsequently, in the presence of Fe(III)PcCl, **II** combined with Fe(III)PcCl and formed compound **III**. Compound **IV** was formed by the intramolecular migration of compound **III**. Compound **V** was then formed by the loss of the catalyst and release of nitrogen from compound **IV**. The final product was formed by proton exchange.



Scheme 4. Proposed mechanism

In conclusion, we developed a simple, efficient method for synthesizing sulfones. The reaction used sulfonylhydrazones, which were easily prepared from carbonyl compounds, to provide corresponding target products in good-to-excellent yields. In addition, we proposed a new reaction mechanism for this transformation. Further applications of this methodology are currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:.

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Graphical Abstract

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Iron(III) Phthalocyanine-Chloride-Catalyzed Synthesis of Sulfones from Sulfonylhydrazones

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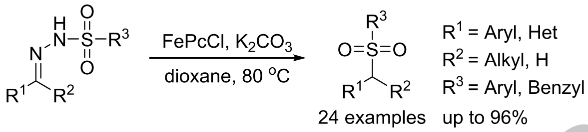

Highlights

Mild conditions
Readily available reactants
Good-to-high yields
New reaction mechanism