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Non-Aqueous Reduction of Aromatic Sulfonyl Chlorides to Thiols Using a Dichlorodimethylsilane-Zinc-Dimethylacetamide System

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Abstract: *A new and efficient method for the non-aqueous reduction of sulfonyl chlorides to affored the corresponding thiols by use of a dichlorodimethylsilane-zinc-dimethylacetamide system was successfully developed. Various aromatic thiols were prepared in high yield by easy operation. Continuous reactions with the above reduction using the prepared thiol were also demonstrated.*

Organic sulfur compounds are widespread in numerous natural products and widely used as various artificial chemicals. Especially, aromatic thiols are often employed as fundamental starting material for the synthesis of a variety of useful compounds such as optical materials, agricultural chemicals, medicines, and so on. Of numerous methods for the preparation of thiols developed and used,[1] the reduction of sulfonyl chlorides[2] is one of the most useful and facile processes. These traditional reductions are generally carried out by the combined use of zinc metal and aqueous acid, and usually give the desired thiols in good yield.[3] However, these aqueous reduction conditions prevent continuous reactions using the obtained thiol without isolation. In this communication, we would like to report a new and facile method for the non-aqueous and high-yielding reduction of various aromatic sulfonyl chlorides to the corresponding thiols by use of dichlorodimethylsilane-zinc-dimethylacetamide as a new and effective reduction system.

In general, oxidative addition of zinc metal to sulfonyl chlorides is difficult in non-polar organic solvents because of their low reactivities. Further, reduction of arylsulfonyl chlorides to the corresponding arylsulfinic acid with zinc metal was achieved under aqueous reflux conditions.[4] On the other hand, it is known that the Vilsmeyer-type iminium salt was easily generated by mixing of sulfuryl chloride or aryl sulfonyl chloride with dimethyformamide at room temperature.[5] The reactive iminium salt in turn is able to accept various nucleophiles to give the sulfonylation product in good yield.[6] Therefore, this type of sulfonylated iminium-ion intermediate was expected for a easily reducible species on the sulfur atom.

In the first place, the effect of the addition of dimethylformamide was examined by the reduction of 1-naphthalenesulfonyl chloride with zinc metal as a model. In the presence of a stoichiometric amount of dimethylformamide(DMF), 1-naphthalenesulfonyl chloride smoothly reacted with zinc metal in 1,2-dichloroethane (1,2-DCE) and gave the corresponding sulfinic acid in high yield (Scheme 1).

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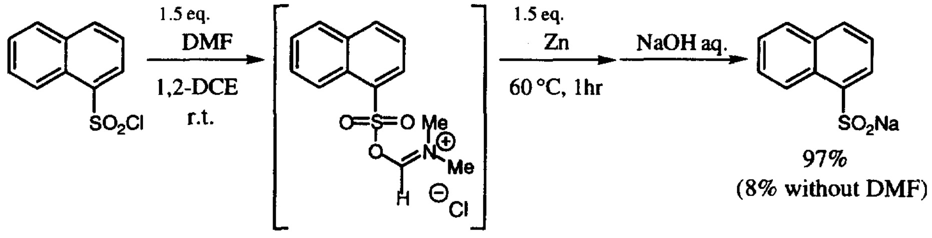
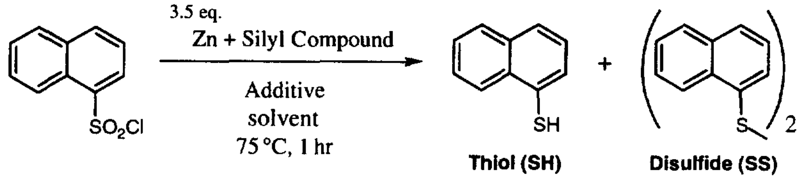


Scheme 1. Effect of DMF on the Reduction of Sulfonyl Chloride to Sulfinic Acid

On the other hand, sulfinic acid was obtained only in 8% yield without the addition of dimethylformamide under the same conditions. Thus, it became clear that the oxidative addition of zinc metal with sulfonyl chloride, the initial step of the reduction, was effectively promoted by the formation of an iminium-ion intermediate. Therefore, further steps for the deoxygenative reduction of intermediary sulfinic acid to the desired thiol were then studied.

A combined use of zinc metal with silyl halide such as a chlorotrimethylsilane-zinc system has been reported as a good reagent for the deoxygenative reduction such as for sulfoxide[7] and so on.[8] Although the system is quite ineffective for the reduction of sulfonyl chlorides to thiols (Table 1, Entries 1 and 2), the reactivity was dramatically improved by the addition of dimethylformamide (Table 1, Entry 3).

Table 1. Reduction of 1-Naphthalenesulfonyl Chloride



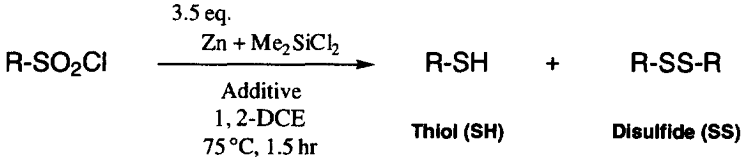
Entry	Silyl Compound (eq.)	Additive (eq.)	Solvent	Yield / %	
				SH	SS
1	Me_3SiCl (5.0)	None	THF	0	trace
2	Me_3SiCl (5.0)	None	1,2-DCE	0	trace
3	Me_3SiCl (5.0)	DMF (3.0)	1,2-DCE	74	6
4	Me_2SiCl_2 (3.0)	DMF (3.0)	1,2-DCE	83	4
5	Me_2SiCl_2 (2.5)	DMA (3.0)	1,2-DCE	69	4
6	Me_2SiCl_2 (3.0)	DMA (3.0)	1,2-DCE	89	2
7	Me_2SiCl_2 (3.5)	DMA (3.0)	1,2-DCE	**95**	**trace**
8	Me_2SiCl_2 (3.5)	DMA (2.0)	1,2-DCE	40	39
9	Me_2SiCl_2 (3.5)	DMA (1.0)	1,2-DCE	0	72

1,2-DCE = 1,2-Dichloroethane

In addition, the yield of thiol was significantly improved when dichlorodimethylsilane was used instead of chlorotrimethylsilane (Table 1, Entry 4). Further optimization of the reaction conditions was carried out (Table 1, Entries 5-9). The superior effect of dimethylacetamide was clearly demonstrated and a decrease in the amount of dimethylacetamide caused a significant lowering of the yield of thiol.

Several examples of the present reduction of various aromatic sulfonyl chlorides are demonstrated in Table 2. In every case, the desired thiol was selectively obtained in high yield. A reduction of 4-methoxybenzenesulfonyl chloride gave a mixture of the desired 4-methoxybenzenethiol and bis(4-methoxyphenyl)disulfide when dimethylacetamide was used as the additive. This result is probably due to influence of an electrodonative methoxy group on the aromatic ring. Interestingly, this lowering of the selectivity was completely recovered by use of 1,3-dimethylimidazolidin-2-one (DMI) instead of dimethylacetamide. This improved reaction condition was also effective for the synthesis of 3,4-dimethoxybenzenethiol having a more electron-rich aromatic ring.

Table 2. Reduction of Various Sulfonyl Chlorides



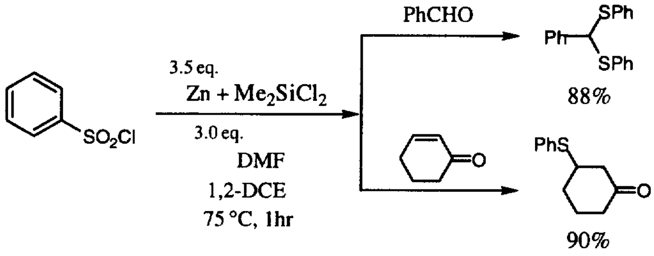
$$\text{R-SO}_2\text{Cl} \xrightarrow[\substack{\text{Additive} \\ \text{1,2-DCE} \\ 75\,^\circ\text{C, 1.5 hr}}]{\substack{3.5\text{ eq.} \\ \text{Zn + Me}_2\text{SiCl}_2}} \underset{\textbf{Thiol (SH)}}{\text{R-SH}} + \underset{\textbf{Disulfide (SS)}}{\text{R-SS-R}}$$

Entry	R	Additive (eq.)	Yield / % SH	Yield / % SS	SH/SS
1	C_6H_5	DMA (3.0)	**95**	**trace**	**>99/1**
2	$4\text{-}CH_3C_6H_4$	DMA (3.0)	**96**	**trace**	**>99/1**
3	$2,4\text{-}(CH_3)_2C_6H_3$	DMA (3.0)	**95**	**trace**	**>99/1**
4	1-Naphthyl	DMA (3.0)	**95**	**trace**	**>99/1**
5	$3\text{-}CF_3C_6H_4$	DMA (3.0)	**93**	**trace**	**>99/1**
6	$4\text{-}ClC_6H_4$	DMA (3.0)	**96**	**trace**	**>99/1**
7	$4\text{-}CH_3SC_6H_4$	DMA (3.0)	**97**	**trace**	**>99/1**
8[a]	$4\text{-}CH_3OC_6H_4$	DMA (3.0)	47	48	50/50
9[a]	$4\text{-}CH_3OC_6H_4$	DMF (3.0)	13	72	15/85
10[a]	$4\text{-}CH_3OC_6H_4$	DMI (3.0)	**95**	**trace**	**>99/1**
11[a]	$3,4\text{-}(CH_3O)_2C_6H_4$	DMI (3.0)	**96**	**trace**	**>99/1**

[a] The reaction was carried out at 80 °C.

Typical experimental procedure is as follows: To a stirred suspension of zinc powder (57.2 mg, 0.875 mmol) and dichlorodimethylsilane (0.113 g, 0.875 mmol) in 1,2-dichloroethane (2.0 ml) was successively added the mixed solution of 1-naphthalenesulfonyl chloride (56.7 mg, 0.250 mmol) and dimethylacetamide (65.3 mg, 0.750 mmol) in 1,2-dichloroethane (2.0 ml). The mixture was stirred for 1h at 75°C, then the zinc powder alomost disappeared. After the solution was filtered and evaporated, methanol (2.0 ml) was added to the residue and then evaporated, each two times. Further purification of the residue (preparative TLC, silica gel) gave the desired 1-naphthalenethiol (38.1 mg) in 95% yield.

This non-aqueous reduction has a great advantage which had not yet been accomplished by the previously reported reduction condition. Various sulfenyl compounds could be readily obtained by a one-pot procedure without isolation and purification of the resulting thiols. For example, dithioacetalization of aldehydes and 1,4-addition with α,β-unsaturated ketone were efficiently carried out in good yields (Scheme 2). These reactions would be promoted by zinc chloride as a Lewis acid catalyst which was formed during the reduction process.



Scheme 2. One-pot Facile Synthesis of Sulfenyl Compounds

Thus, a new and efficient method for the non-aqueous reduction of aromatic sulfonyl chlorides to afford the corresponding thiols in high yield was successfully developed. It is noted that this new reduction system has great advantages over the conventional methods in its efficiency and easy operation. In addition, one-pot and facile sulfenylation starting from non-volatile and non-stench aromatic sulfonyl chlorides is expected to be widely applicable for the synthesis of various useful organosulfur compounds.

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