

In The Name of God



Razi University

**Faculty of Chemistry
Department of Organic Chemistry**

Ph. D. Thesis

Title of Thesis

**Application of SDS as Micellar Nanoreactor and $\text{H}_2\text{O}_2/\text{POCl}_3$ or
 $\text{H}_2\text{O}_2/\text{ZrCl}_4$ System for Synthesing of Sulfonyl chlorides, and its
Derivatives**

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Abstract

This thesis has been carried out in six parts:

1. Direct conversion of thiols and disulfides to sulfonyl Chlorides and sulfonic acids

$\text{H}_2\text{O}_2\text{-POCl}_3$ is found to be a reactive reagent system for the direct oxidative chlorination of thiol and disulfide derivatives to the desired sulfonyl chlorides in SDS micellar solution in aqueous media. The oxidation of thiols and disulfides to sulfonic acids with this system is also reported. The SDS surfactant micelles (SDS micelle diameter about 4 nm) act as nanoreactors to induce better solubilization of thiols and disulfides. In most cases these reactions are highly selective, simple, and clean, affording products in excellent yields and high purity.

2. A novel practical synthesis of sulfonamids from thiol derivatives

Hydrogen peroxide in the presence of phosphoryl chloride is a very efficient reagent for the direct oxidation conversion of thiol and disulfide to the corresponding sulfonyl chlorides with high purity through oxidative chlorination. Excellent yields, very short reaction times, avoiding harsh reagents under mild reaction conditions are the main advantages of this method.

3. A simple and efficient method for sulfonylation of phenols with $\text{H}_2\text{O}_2\text{-POCl}_3$ under mild conditions

The $\text{H}_2\text{O}_2\text{-POCl}_3$ reagent system has been used as a new and efficient reagent for conversion of thiol and disulfide compounds to sulfonic esters. The protocol offers several advantages such as excellent yields of products, extremely fast reaction, and operation at room temperature. Furthermore, the reagent system is very easy to handle, environmentally safe and economical.

4. Direct Conversion of Thiols to Sulfonicesters with $\text{H}_2\text{O}_2\text{-ZrCl}_4$

A facile and efficient method for synthesizing sulfonic esters was developed using a $\text{H}_2\text{O}_2\text{-ZrCl}_4$ reagent system. A wide range of sulfonic esters were synthesized in excellent yields and short reaction times.

5. Direct Conversion of Thiols to Sulfonyl azides with H₂O₂-POCl₃ reagent system

A one-pot process for preparing sulfonyl azides was developed by treating thiol and disulfide compounds with H₂O₂-POCl₃ reagent system, and sodium azide at room temperature. A wide range of sulfonyl azides was synthesized in excellent yields under mild conditions. Excellent yields, short reaction time, easy and quick isolation of the products, environmentally safe, and excellent chemoselectivity are main advantages of this procedure.

6. Direct Conversion of Thiols to Sulfonyl azides with H₂O₂/ZrCl₄ reagent system

A simple and convenient method for the synthesis of sulfonylazides utilizing H₂O₂/ZrCl₄ has been established. The protocol offers several advantages such as excellent yields of products, extremely fast reaction, and operation at room temperature. Most importantly, the reagent system is very easy to handle, environmentally safe and economical.

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Chapter One

Introduction

1.1. Sulfonyl chlorides

Sulfonyl chlorides are an important class of compounds widely utilized as reagents or intermediates in organic synthesis drug chemistry. They are widely used for the preparation of amides¹ and esters.² Functionalized sulfonyl chlorides form one of the most attractive classes of the linkers. These compounds have general formula shown in Fig 1.1, where FG – a functional group possessing orthogonal reactivity to the SO₂Cl group. The latter can be used first to attach a fragment to the scaffold by formation of sulfonamide or sulfonate, and then the second fragment can be linked, employing the group FG.

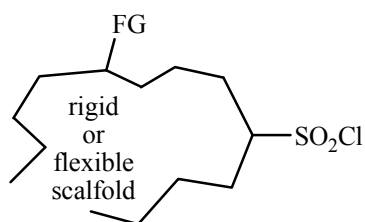


Figure 1.1

A successful literature example of the sulfonamide-containing linkers utilization in drug design is the development of potent Human β_3 Adrenergic Receptor Agonists shown in Fig 1.2.³

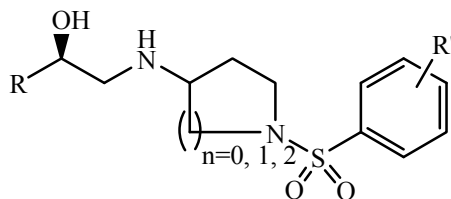


Figure 1.2

Some examples of sulfonylchloride linkers are shown below. Conformationally flexible linkers (Fig 1.3):



Figure 1.3

Conformationally constrained linkers (Fig. 1.4):

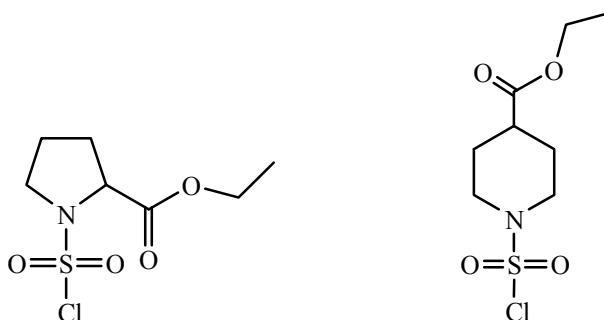


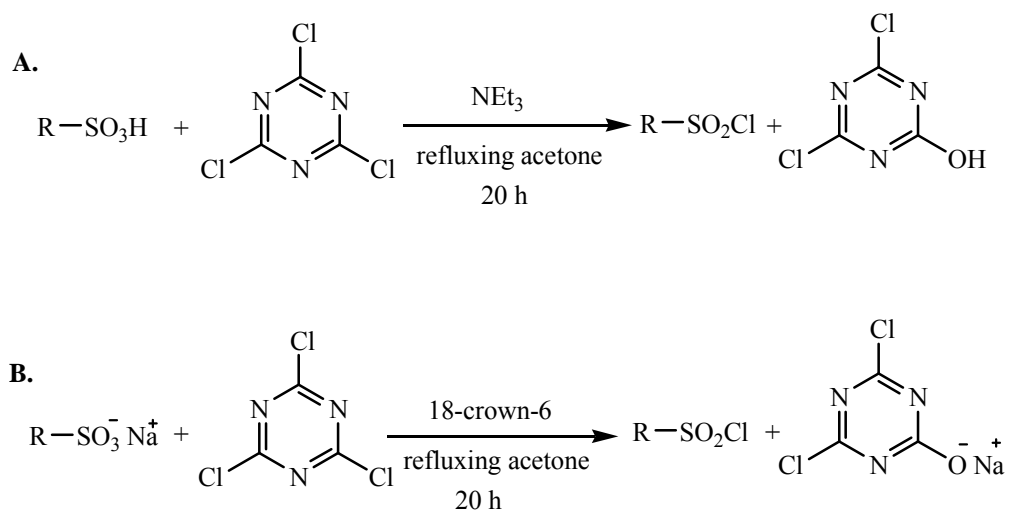
Figure 1.4

1.1.1. Synthesis of sulfonyl chlorides

Due to the broad applicability of sulfonyl chlorides, it is desirable to find general and effective methods for their synthesis. There are many ways to prepare sulfonylchlorides. We present here several methods for obtaining sulfonylchloride compounds.

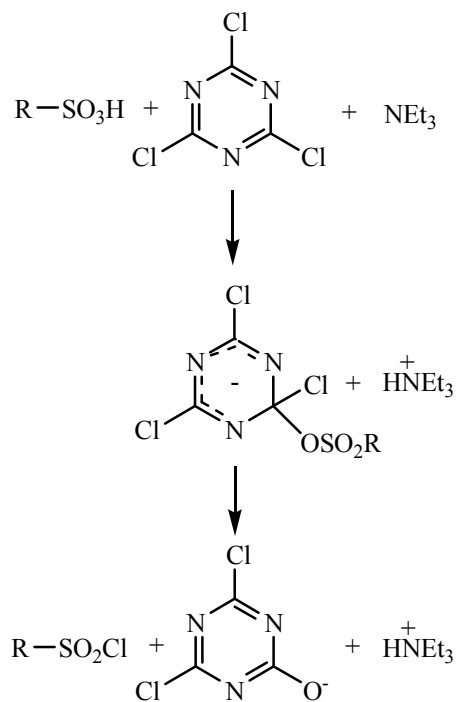
1.1.1.1. TCT

*Blotny G.*⁴ developed a new approach to sulfonyl chlorides synthesis utilizing sulfonic acids and 2,4,6-trichloro-1,3,5-triazine (TCT) in reflux acetone under neutral conditions (Scheme 1.1).



Scheme 1.1

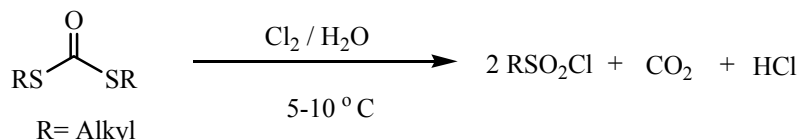
A likely mechanism for this reaction is presented in Scheme 1.2. Nucleophilic attack of the sulfonic acid anion on trichloro-s-triazine gives a delocalized carbanion, which yields the sulfonyl chloride and insoluble dichlorohydroxy-s-triazine.



Scheme 1.2

1.1.1.2. Cl₂-H₂O

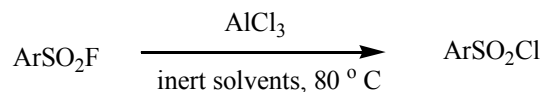
*Barbero M. et al.*⁵ reported alkanesulfonyl chlorides in 93-100% yields, can be synthesized by aqueous chlorination of readily accessible S,S-dialkyl dithiocarbonates (Scheme 1.3).



Scheme 1.3

1.1.1.3. AlCl₃

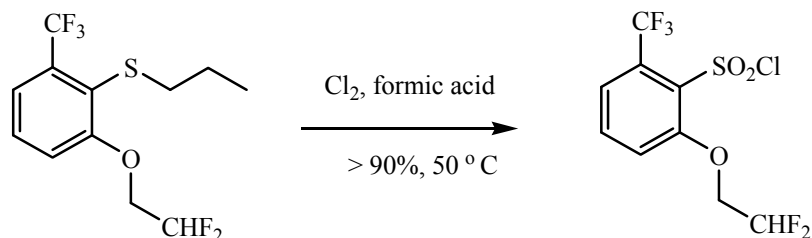
*Norris T. et al.*⁶ showed that conversion of sulfonyl fluorides to sulfonyl chlorides can be carried out by dissolving or suspending the arenesulfonyl fluoride in boiling 1,2-dichloroethane followed by treatment with a 1-4 mole excess of anhydrous aluminium chloride (Scheme 1.4).



Scheme 1.4

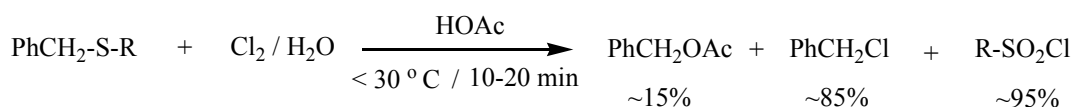
1.1.1.4. Cl₂

*Wang C. et al.*⁷ showed that chlorine gas and formic acid as solvent is another method for conversion of aryl sulfides to sulfonyl chlorides (Scheme 1.5).



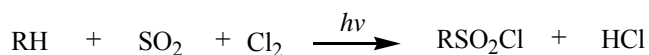
Scheme 1.5

Also, *Langler R. F.*⁸ synthesized sulfonyl chlorides yields by reaction of benzylic sulfides with molecular chlorine in aqueous acetic acid (Scheme 1.6).



Scheme 1.6

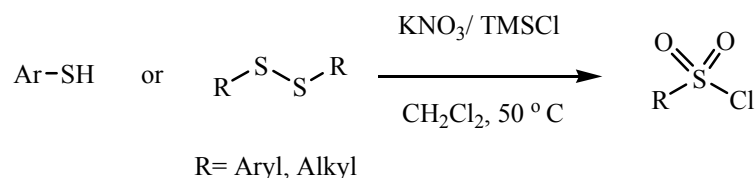
Another method for the preparation of sulfonyl chloride reported by *Reed C. F. et al.*⁹ In this method photochemical oxidative chlorination of paraffins and cycloparaffins is done by sulfur dioxide and chlorine under irradiation with ultraviolet light (Scheme 1.7).



Scheme 1.7

1.1.1.5. KNO₃-TMSCl

Another method for preparing sulfonyl chlorides is direct oxidative chlorination of thiol and disulfide derivatives. *Olah G. A. et al.*¹⁰ showed that a mixture of nitrate salt and chlorotrimethylsilane is a mild and efficient reagent for the direct oxidative chlorination of thiols and disulfides to the corresponding sulfonyl chlorides. In most cases these reactions are highly selective, simple, and clean, affording products in high yield and purity (Scheme 1.8).



Scheme 1.8

1.1.1.6. H₂O₂-SOCl₂

Recently, *Bahrami K. et al.*¹¹ reported the oxidative chlorination of thiol derivatives to the corresponding sulfonyl chlorides using H₂O₂-SOCl₂ as a valuable reagent system. All

