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 $H_2O_2/POCl_3$ or $H_2O_2/ZrCl_4$ System for Synthesing of Sulfonyl chlorides, and its Derivatives

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March 2012

Acknowledgments

I would like to express my heartful thanks to ***Prof. Mohammad Mehdi Khodaei*** and ***Dr. Kiumars Bahrami*** the major directors of the thesis, for their supervision, constructive guidance, excellent suggestion and great disposing efforts. Deep acknowledgments are offered to ***Dr. Farzad Nikpour*** for her grateful providing with any help. I also like to thank ***Dr. Ebrahim Soleimani*** for his excellent guidance.

I extend thanks to ***Dr. Mohsen Irandoust, Mr. Hiva Daraei*** *and* ***Mrs. Ronak Sabouri*** for running the NMR spectra.

I am grateful to all Ph.D Students (***Mr. Ehsan Nazari, Mr. Peyman Fattahpour, Mr. Davood Kordestani Mr. majid hashemi, Mr. Mojtaba Beygzadeh,fardin naal, Mr. Mehdi Sheykh Arabi***) and M.Sc. Students in organic research laboratory for providing a friendly environment during my stay in the research laboratory.

I am grateful to all of ***my dear friends in inorganic Chemistry*** for providing a friendly environment during my stay in the research laboratory.

Finally, I am forever indebted to ***my dear family***, especially amirali (***lovely my boy)*** for their unconditional love , moral support and patience throughout this work.

j.abbasi, desamber2012

Abstract

This thesis has been carried out in six parts:

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

H_2O_2-$POCl_3$ 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 H_2O_2-$POCl_3$ under mild conditions

The H_2O_2-$POCl_3$ 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 H_2O_2-$ZrCl_4$

A facile and efficient method for synthesizing sulfonic esters was developed using a H_2O_2-$ZrCl_4$ reagent system. A wide range of sulfonic esters were synthesized in excellent yields and short reaction times.

5. Direct Conversion of Thiols to Sulfonyl azids with H_2O_2-$POCl_3$ reagent system

A one-pot process for preparing sulfonyl azides was developed by treating thiol and disulfide compounds with H_2O_2-$POCl_3$ 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 azids with H_2O_2/$ZrCl_4$ reagent system

A simple and convenient method for the synthesis of sulfonylazides utilizing H_2O_2/$ZrCl_4$ 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 amides[1] 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 SO_2Cl 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.

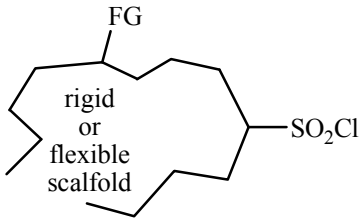


Figure 1.1

A successful literature example of the sulfonamide-containing linkers utilization in drug design is the development of potent Human b3 Adrenergic Receptor Agonists shown in Fig 1.2.[3]

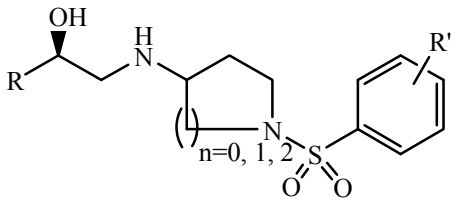


Figure 1.2

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

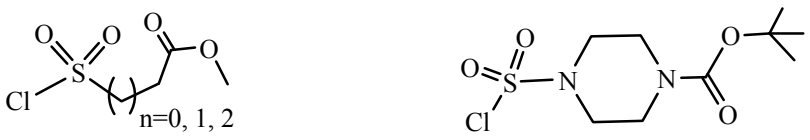


Figure 1.3

Conformationally constrained linkers (Fig. 1.4):

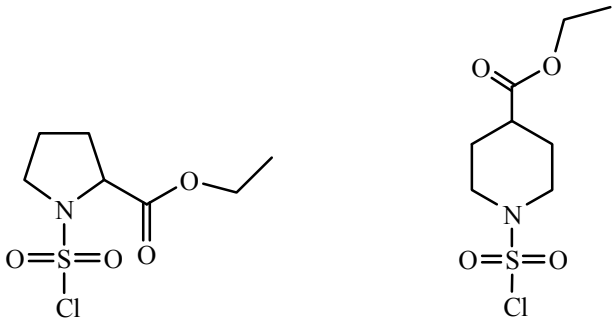


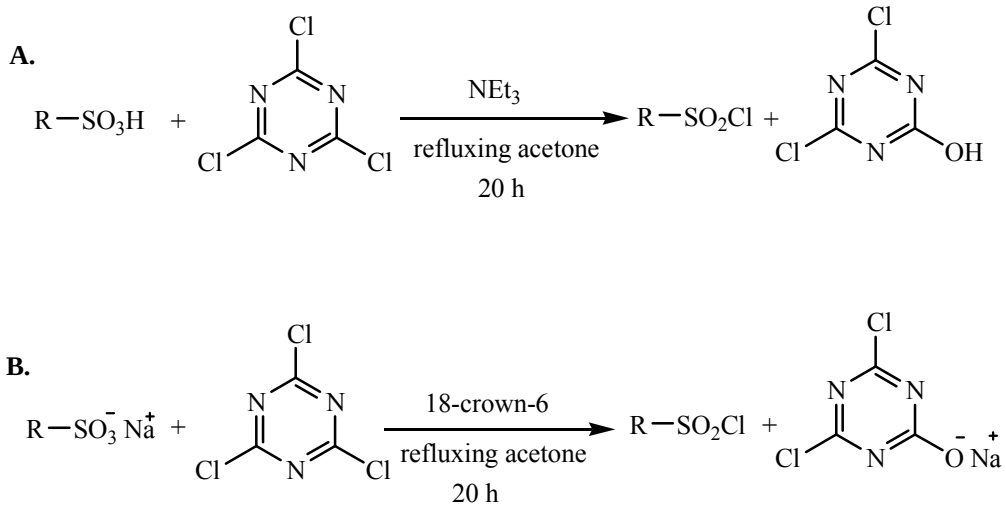
Figure 1.4

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 sulfonylcholorides. We present here several methods for obtaining sulfonylcholoride compounds.

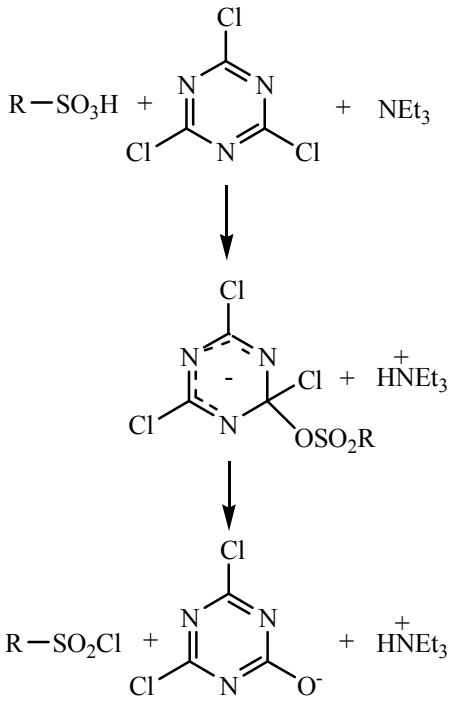
1.1.1.1. TCT

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

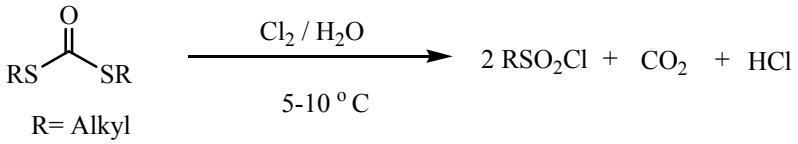
A likely mechanism for this reaction is presented in Scheme 1.2. Nucleophilic attack of the sulfonic acid anion on trichloro-s-triazine gives a delocalized carbanion, which yields the sulfonyl chloride and insoluble dichlorohydroxy-s-triazine.



Scheme 1.2

1.1.1.2. Cl_2-H_2O

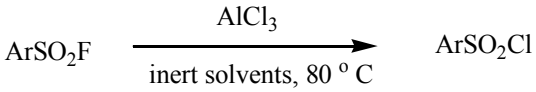
Barbero M. et al.[5] reported alkanesulfonyl chlorides in 93-100% yields, can be synthesized by aqueous chlorination of ready accessible S,S-dialkyl dithiocarbonates (Scheme 1.3).



Scheme 1.3

1.1.1.3. $AlCl_3$

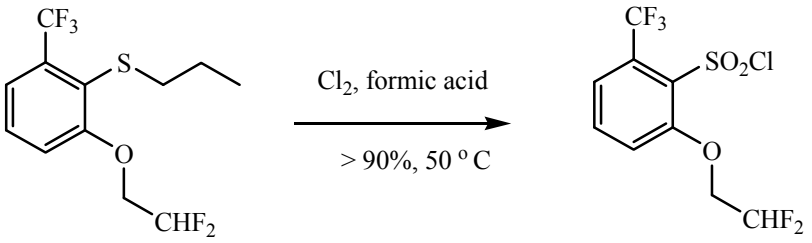
Norris T. et al.[6] showed that conversion of sulfonyl fluorides to sulfonyl chlorides can be carried out by dissolving or suspending the arenesulfonyl fluoride in boiling 1,2-dichloroethane followed by treatment with a 1-4 mole excess of anhydrous aluminium chloride (Scheme 1.4).



Scheme 1.4

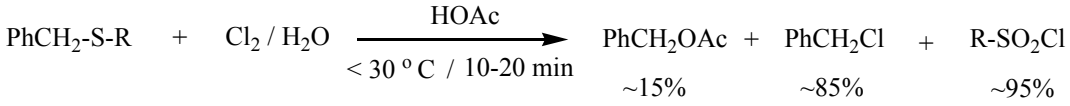
1.1.1.4. Cl_2

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).



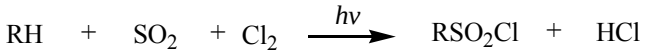
Scheme 1.5

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

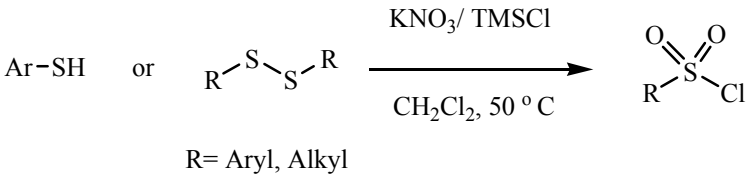
Another method for the preparation of sulfonyl chloride reported by *Reed C. F. et al.*[9] In this method photochemical oxidative chlorination of paraffins and cycloparaffins is done by sulfur dioxide and chlorine under irradiation with ultraviolet light (Scheme 1.7).



Scheme 1.7

1.1.1.5. KNO_3-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).

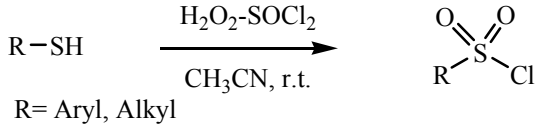


Scheme 1.8

1.1.1.6. H_2O_2-$SOCl_2$

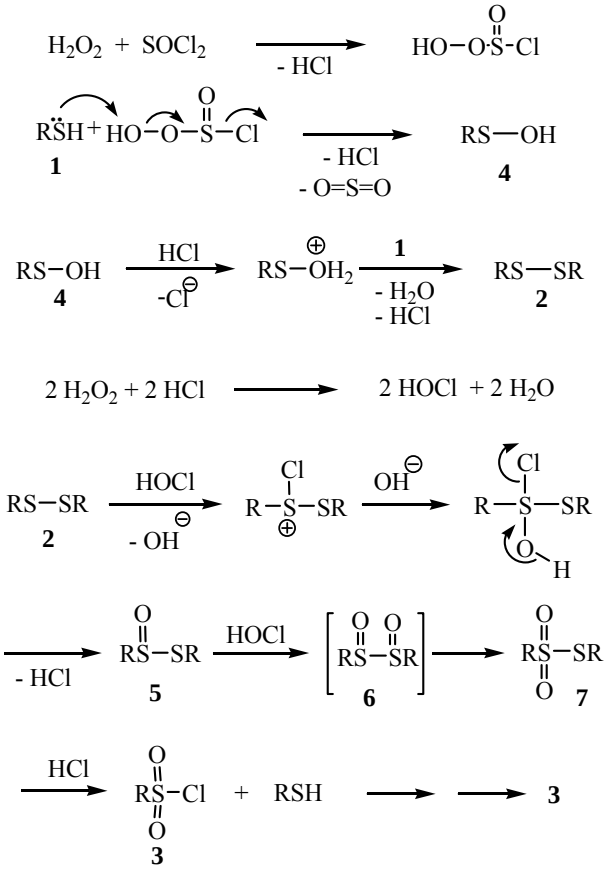
Recently, *Bahrami K. et al.*[11] reported the oxidative chlorination of thiol derivatives to the corresponding sulfonyl chlorides using H_2O_2-$SOCl_2$ as a valuable reagent system. All

desired sulfonyl chlorides were generated in excellent yield while the reaction times were significantly reduced (Scheme 1.9).



Scheme 1.9

The possible mechanism for this transformation is shown in Scheme 1.10. It is acceptable to assume that the nucleophilic attack of H_2O_2 on $SOCl_2$ makes oxygen atoms more electrophilic. Therefore, the mechanism proceeds through hydroxylation of thiol (**1**) leads to the formation of sulfenic acid (**4**), which gives the corresponding symmetric disulfide (**2**). Then the successive oxidation of both sulfur atoms of the disulfide molecule by hypochlorous acid produces the intermediate (**6**) that undergoes rapid isomerization to the thiosulfonate (**7**), which can easily furnish sulfonyl chloride (**3**). Conversion of **6** to **7** has been well documented and recognized.[12]



Scheme 1.10