Shiraz University
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Ph.D. Dissertation in Organic Chemistry

NEW APPROACHES TO C-S BOND FORMATION USING THIOLIC AND NON-THIOLIC PRECURSORS

By
MOHAMMAD ABBASI

Supervised by
Professor Habib Firouzabadi

JULY 2009

IN THE NAME of GOD

In the Name of God

DECLARATION

Hereby, Mohammad Abbasi (832781) student of Organic Chemistry College of Sciences certify that this thesis results from my own research and whenever I have utilized other sources, I have clearly reference them. I also declare that the research and the title of my thesis are novel and I promise, without the permission from the university, the results never be published or bring to someone else. The copyright of this thesis is the property of Shiraz University.

Name and Surname: Mohammad Abbasi

Date and Signature: 9-19-2009 M. Abbasi

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THESIS

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EVALUTED AND APPROVED BY THESIS COMMITTEE AS: EXCELLENT

H. Firouzabadi, Ph.D., Prof. of Chemistry (Chairman)

N. Iranpoor, Ph.D., Prof. of Chemistry

A. A. Jarrahpour, Ph.D., Assoc. Prof. of Chemistry

P. Salehi, Ph.D., Prof. of Chemistry (Shahid Beheshti University)

JULY 2009

Dedicated to:

My Family Specially My Dear Son,

Ali Reza

On the Occasion of His 4th Birthday

And

My Teachers

Prof. Habib Firouzabadi & Prof. Nasser Iranpoor

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ABSTRACT

New approaches to C-S bond formation using thiolic and non-thiolic precursors

BY:

Mohammad Abbasi

In this thesis we have introduced two odorless, one-pot methods for preparing thia-Michael adducts from non-thiolic precursors. In one procedure, thia-Michael adducts are prepared from alkyl halides, thiourea and Michael acceptors in SDS micellar media. In this method, α,β-unsaturated ketones, esters, nitriles and amides successfully produced the corresponding thia-Michael adducts in good to excellent yields.

In the second method, polyethylene glycol (PEG 200) is employed as another green media for direct preparation of thia-Michael adducts from non-thiolic precursors under mild conditions. In this protocol, a mixture of an alkyl halide (primary, secondary, tertiary, allylic or benzylic), thiourea, a conjugated olefin (ketones, esters, nitriles) and sodium carbonate in wet PEG 200 cleanly produced the related thia-Michael adducts in good to excellent yields.

We have also developed two odorless methods for the preparation of disufides from non-thiolic precursors. In the first, disulfides are produced in SDS micellar media from their corresponding primary, benzylic or allylic halides using thiourea, MnO_2 and a base ($NaHCO_3$ or Na_2CO_3) in good to excellent yields. By the second method, wet PEG 200 is used as a media for direct conversion of alkyl halides to disulfides. In this method, primary, secondary, tertiary, allylic, and benzylic halides were efficiently converted to their corresponding symmetrical disulfides by the use of thiourea, MnO_2 and Na_2CO_3 in high yields at 30-35 ˚C.

In addition, a catalyst-free procedure for large-scale addition of thioacids to a variety of electron-deficient olefins under solvent-free conditions at room temperature is also developed.

We have also developed two new mild procedures for regioselective addition of thioacids to epoxides in the presence of silica gel. In the first method, thioacids are added to epoxides in the presence of small portions of silica gel under solvent-free conditions to produce the corresponding β-hydroxy thioesters in good to excellnt yields. However, it has been found that the resulted β-hydroxy thioesters in treatment with silica gel were partially rearranged to their corresponding β-mercapto ester isomers *via* an acyl transfer process. Accordingly, we have developed another method for one-pot and selective preparation of β-mercapto esters from the reaction of thioacids with epoxides in the presence of silica gel.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

DMF	N,N-Dimethylformamide
HMDS	Hexamethyldisilazane
SDS	Sodium dodecyl sulfate
GC	Gas chromatography
TLC	Tin layer chromatography
EtOAc	Ethyl acetate
THF	Tetrahydrofuran
Bu	Butyl
Me	Methyl
Et	Ethyl
i-Pr	*iso* Propyl

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

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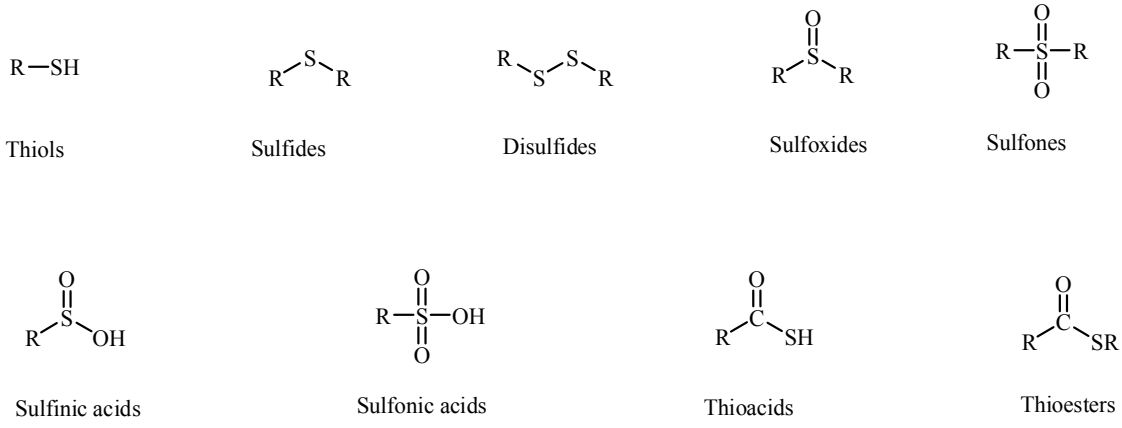
1.1. Introduction

Organosulfur compounds are molecules which contain at least one sulfur atom in their molecular structures and are found extensively in nature. Fossil fuels, coal, petroleum, and natural gas, which are derived from ancient organisms, necessarily contain organosulfur compounds. Sulfur-containing molecules can be found in all living organisms (such as: biotin, ligands in bio-inorganic complexes and amino acids) which play important roles in catabolism and anabolism reactions. Thus, they are essential part of life. These compounds have found wide applications in agriculture, medicine, and industry as insecticide, fungicide, emulsifier, and etc.

Important organosulfur compounds can be classified in several groups, including thiols (mercaptans), sulfides (thioethers), sulfoxides, sulfones, thioesters, thioacids, sulfonic and sulfinic acids and their derivatives and also disulfides (Scheme 1.1).



Scheme 1.1

Synthetically, carbon-sulfur bond formation is the essence of organic sulfur synthesis and provides the foundation of generating more complicated organo-sulfur compounds from simpler molecules such as thiols.[1]

1.2. Thiols

Thiols are among the simplest classes of the organosulfur compounds playing important part in many chemical transformations. This is primarily due to the presence of a sulfur atom, a reactive center of variable valency, and also the S-H bond whose rupture can result in generation of thiyl radicals, thiolate anions, and sulfenyl cations operating as relatively stable and highly reactive intermediates. Thiols also play important role in many biochemical processes. For instance, cysteine is a component of proteins that operate in the biochemical redox processes and in the capture of free radicals.[2] The presence of this amino acid rest ensures formation of disulfide bridges fixing the conformation of proteins and polypeptides by building up a cystine fragment. The cystamine enters into disulfide exchange with the newly synthesized proteins containing thiol groups.[3] Glutathione tripeptide with a thiol group is present in a relatively high concentration in the intercellular space of the living organisms.[4] It preserves the thiol groups in proteins, destroys peroxides and free radicals, and performs the coenzyme function. Glutathione espermidine takes part in the growth control and in metabolism of nucleic acids.[5] The coenzyme A (COA-SH) containing an active mercapto group catalyzes acyl groups transfer in the biosynthesis of fatty acids and biotin.[6] Certain dithiols, in particular, dihydrolipoic acid, take part in the photosynthesis and the metabolism in mitochondria.[7,8] The conversion of the green form of sulfomyoglobin into the red form is believed[9] to result from transformation of a thioepoxy group into a thiol one. The natural occurrence of thiols is relatively rare due to their ready oxidation to disulfides. Thiols naturally form mostly as