

Recent Developments in Disulfide Bond Formation

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Abstract: This review summarizes the recent developments of disulfide bond formation with a variety of reagents. The scope and limitations of the presented methods are discussed. The syntheses of unsymmetrical disulfides are highlighted in order to present the most versatile achievements.

- 1 Introduction
- 2 Preparation of Disulfides
 - 2.1 By Oxidation of Thiols
 - 2.2 By Reductive Coupling of Sulfonyl Chlorides
 - 2.3 By Reaction with Sulfur Monochloride
 - 2.4 By Radical Cyclization of Substituted Aminothiourethane Derivatives
 - 2.5 Using 1-Chlorobenzotriazole
 - 2.6 From Elemental Sulfur
 - 2.7 From Organophosphorus Sulfonyl Bromide
 - 2.8 From *N*-Trifluoroacetyl Arenesulfenamides
 - 2.9 Using Phase-Transfer Catalysis
 - 2.10 From a Thiol–Disulfide Exchange Reaction
 - 2.11 From Thiocyanates
 - 2.12 From 2-(Trimethylsilyl)ethyl Sulfides
 - 2.13 From Thiosulfonates and Thiosulfates
 - 2.14 From Thioesters
 - 2.15 By Disulfide Exchange Reactions
 - 2.16 From Tetrathiomolybdate
 - 2.17 By Miscellaneous Reactions
- 3 Conclusions

Key words: disulfides, thiols, synthesis, symmetrical disulfides, unsymmetrical disulfides

1 Introduction

Modern methods for the formation of disulfide bonds are required for the synthesis of many biologically active compounds involved in chemical and biological processes.¹ There are many biologically active peptides and peptide mimetics that possess unsymmetrical disulfide bonds.² Disulfides are used for the preparation of self-assembled monolayers³ and monolayer-protected clusters with versatile properties.⁴ Several unsymmetrically substituted aromatic donor–acceptor disulfides have been analyzed for their second-order nonlinear optical properties. These compounds exhibited moderately high first hyperpolarizability with excellent transparency in the visible region.⁵ This class of molecules has potential applications in optical data processing and communication. Compounds containing a disulfide linkage have been used for the prep-

aration of dynamic combinatorial libraries,⁶ catenanes,⁷ macrocycles,⁸ [5]carceplexes,⁹ dendrimers,¹⁰ rotaxanes and micelles.¹¹ These examples demonstrate the wide applications of disulfides and show that the synthesis of disulfide bonds is a pivotal transformation in modern research.¹² The current review is intended to summarize achievements in the last decade.

2 Preparation of Disulfides

A comprehensive survey of this area is not possible within the constraints of this review. Therefore, this section combines coverage of examples of classical methods of disulfide formation with an introduction to the most important methods of disulfide synthesis that have been developed in the last decade.

2.1 By Oxidation of Thiols

Perhaps the most common method for the preparation of disulfides is the oxidation of the appropriate thiols. The ease of oxidation usually decreases from aromatic thiols, through primary and secondary to tertiary. Mixed disulfides may be prepared using this method, although a mixture of disulfide products is then expected. However, when sufficient structural differences exist between the two thiols present, such as in the oxidation of benzylthiol in the presence of *tert*-butylthiol,¹³ then the unsymmetrical disulfide can become the major product. The most frequently used oxidizing agents are presented below.

2.1.1 Aerial Oxidation

Aerial oxidation of thiols **1** to disulfides **2** is quite facile in most cases; however, tertiary alkanethiols have been found to be quite resistant. The reaction of thiols with oxygen or air is sensitive to the presence of catalyst. The successful syntheses were catalyzed by iron,¹⁴ manganese,¹⁵ or cobalt salts supported on silica gel¹⁶ (Scheme 1), trichlorooxyvanadium,¹⁷ cesium fluoride–Celite,¹⁸ silica chloride¹⁹ (Scheme 2), anhydrous potassium phosphate,²⁰ and hydrotalcite clay.²¹

Both aliphatic and aromatic thiols **1** can be oxidized under aerial conditions. Silica chloride appeared to be a highly efficient and selective heterogeneous catalyst for the rapid conversion of various thiols into disulfides (Scheme 2).

The yields of symmetrical disulfides **2** are very high, and in some cases cyclic bis-disulfides **4** can also be obtained