Synthesis of unsymmetrical disulfides via the cross-dehydrogenation of thiols

Shangfeng Ren¹, Nianhua Luo², Kunming Liu¹ and Jin-Biao Liu¹

Abstract
Organosulfur compounds with unsymmetrical S–S bonds are usually called unsymmetrical disulfides and are widely used in the biological, medicinal, and chemical fields. Their versatility has guided the development of various new methods for the synthesis of disulfides. In recent years, the synthesis of disulfides by cross-dehydrogenation of thiols has attracted much attention due to its high atomic economy. Herein, this review summarizes progress toward the synthesis of unsymmetrical disulfides under chemical oxidation, electrooxidation, or photocatalysis by cross-dehydrogenation of thiols.

Keywords
unsymmetrical disulfides, oxidation, cross-dehydrogenation, thiols, S–S bonds

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Introduction
Disulfides exist in many biologically active natural products¹–² and are widely employed in the pharmaceutical industry,³–⁷ materials sciences,⁸ and so on. Unsymmetrical disulfides have attracted significant attention because of their role in stabilizing protein structures⁹ and for their promising use in the clinical application of tumor therapies.¹⁰,¹¹ Thus effective methods for the construction of unsymmetrical disulfides are increasingly important.

A number of methods have been reported for the construction of unsymmetrical disulfides. For example, thiocyanates,¹²,¹³ alkyl halides,¹⁴,¹⁵ and thioacetates¹⁶,¹⁷ can be used as sulfur sources to build disulfide bonds. However, these methods often rely on more complicated processes. The method of synthesizing unsymmetrical disulfides by employing commercially available thiols is relatively simple and has high atom economy. The synthesis of unsymmetrical disulfides predominantly includes nucleophilic substitution of the thiol¹⁸–²⁶ and exchange with a disulfide bond.²⁷–³¹ Another method relies on an oxidative dehydrogenation coupling reaction of S–H/S–H bonds. The former two methods require pre-functionalization of the thiol and multi-step reactions. This makes the study of the latter method more attractive. This review therefore focuses on the synthesis of unsymmetrical disulfides via the oxidative cross-dehydrogenation of thiols.

Oxidative cross-dehydrogenation of thiols
Sodium tellurite as the oxidant
Sodium tellurite is commonly used in organic synthesis. In 1991, Suzuki et al.³² reported that sodium tellurite, under phase-transfer conditions, allows for the synthesis of unsymmetrical disulfides via thiols with high selectivity...
under mild conditions (Scheme 1). Under their reported reaction conditions, sodium tellurite is used as an oxidant and can instantly oxidize aryl thiols and benzyl thiols to their corresponding disulfides. The oxidation of primary thiols and secondary thiols is slow, while tertiary thiols are unreactive. Suzuki’s group explored the limitations of the reaction and found that the outstanding ability of sodium tellurite to distinguish between thiol types is reflected by an efficient one-step synthesis of a number of unsymmetrical disulfides. For example, when a 9:10 mixture of benzyl thiol and tert-butyl thiol is reacted with Na₂TeO₃ in the presence of tetrabutylammonium hydroxide under biphasic conditions for 36 h, benzyl tert-butyl disulfide (3a) is obtained in 97% yield; the reaction of thiophenol and tert-butyl thiol gave 3b in only 74% yield under the same reaction conditions. The reactivity of various thiols is of the order: benzyl thiol > primary thiol > secondary thiol > tertiary thiol. This also helps to explain the various steps in the reaction of unsymmetrical disulfides: first, the more reactive thiol forms a symmetrical disulfide through coupling, and then the less reactive thiol gradually reacts with the symmetrical disulfide to give the unsymmetrical product. Since many sensitive functional groups are inert to sodium tellurite, including amino, hydroxy, azo, hydrazino, phenol, sulfide, disulfide bonds, sulfoxide, aldehyde, olefin bonds, and acetylene bonds, the substrate scope is limited. Despite these shortcomings, Na₂TeO₃ has proven to be an ideal oxidant for oxidative thiol cross-coupling reactions.

**Iodine as the oxidant or mediator**

N-Iodosuccinimide (NIS) can also act as a catalyst in the synthesis of unsymmetrical disulfides. In 2014, Yuan et al. synthesized unsymmetrical aryl tertiary alkyl disulfides. In this reaction, 2-mercaptobenzothiazole 4a and tert-butyl thiol 5a were reacted in the presence of tert-butyl hydroperoxide (TBHP) as the oxidant and NIS as the catalyst over 1 h to give 6a in 89% yield. The reaction conditions are amenable to a wide range of substrates. Sulfhydryl heterocycles, including benzothiazoles, imidazoles, tetrazoles, 1,3,4-dithiazoles, and six-membered heterocycles containing sulfhydryl groups, showed good selectivity, with yields ranging from 75% to 90% (Scheme 2). Mercaptopyridine, pyrazine, and pyrimidine are also suitable under the reaction conditions, but the corresponding products were obtained in lower yields (75%). Secondary alkyl thiols could also be used in place of tertiary alkyl thiols to obtain 6d. Unfortunately, the
cross-coupling product \(6c\) from 4-fluorophenylthiophenol was obtained in only a 44% yield under these conditions. Yuan et al. also proposed a reasonable mechanism for this reaction. First, aryl thiol \(4a\) is oxidized in the presence of THBP and the NIS catalyst to give dimer \(4b\). Next, there are two possible pathways: a nucleophilic reaction between tert-butyl thiol \(5a\) and dimer \(4b\) may give product \(6a\). An alternative pathway is the reaction of a tert-butyl thiol radical with dimer \(4b\). This methodology represents an effective atom economical selective S–H/S–H cross-coupling reaction for the synthesis of unsymmetrical disulfides.

Water plays an important role in many organic reactions.\(^3^4,^3^5\) In 2019, Parida et al.\(^3^6\) reported the use of iodine as a catalyst and 4-dimethylaminopyridine (DMAP)/water as a reaction promoter, in order to synthesize unsymmetrical organic disulfides in EtOH-H\(_2\)O (2:1) as the solvent via an umpolung method (Scheme 3). This methodology is suitable for the synthesis of unsymmetrical diaryl disulfides (9a and 9b), dialkyl disulfide (9c), and aryl-alkyl disulfide (9d). The electron-rich thiophenol could be easily oxidized to form the intermediate \(10\). Then, another relatively inert thiol attacks \(10\) and results in a high selectivity of the cross-coupling reaction.

**Trichloroisocyanuric acid as the oxidant**

Trichloroisocyanuric acid (TCCA) is often used as a chlorinating agent and oxidizing agent in synthesis.\(^3^7\) In 2016, Yang et al.\(^3^8\) used TCCA as the oxidant to construct unsymmetrical disulfides under mild conditions. Unsymmetrical aromatic-aromatic disulfides and aromatic-aliphatic disulfides can be obtained in good yields with a reaction time of only 5 min. A reasonable mechanism has been proposed as shown in Scheme 4. After adding TCCA to the thiol, two sulfur intermediates \(11a\) and \(11b\) may be produced. Both intermediates can react with the second thiol to form unsymmetrical disulfides (12). The well selectivity of this method was achieved by the sequential addition of the thiols.

**\(H_2O_2\) as the oxidant**

\(H_2O_2\) is an ideal reagent in green chemistry. Hydrogen peroxide often acts as an oxidant in the synthesis of disulfides. In 1996, Marchand-Brynaert et al.\(^3^9\) reported the coupling of cysteamine and 3-mercaptopropionic acid using hydrogen peroxide as the oxidant for the synthesis of unsymmetrical disulfide 14 (Scheme 5).

**2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant**

Choosing the appropriate oxidant is important for the preparation of unsymmetrical disulfides via the oxidative S–H/S–H cross-coupling method. After investigating many oxidants (such as DDQ, ammonium cerium nitrate, pyridinium chlorochromate (PCC), potassium ferricyanide, and manganese acetate), in 2011, Vandavasi et al.\(^4^0\) disclosed DDQ as an oxidant to efficiently synthesize unsymmetrical disulfides (Scheme 6). Under the optimum conditions consisting of dichloromethane as the solvent, a reaction temperature of 0 °C and a short reaction time of 5 min, the desired products 17 could be obtained in good yields. The reaction conditions tolerate thiols (15 and 16) containing hydroxy, carboxy, halogen, methoxy and methyl groups. All of these unsymmetrical products come from the thiophenols or mercaptans with large structural differences. It can be speculated that the structural differences lead to the cross-coupling of the thiols, though the authors did not reveal the mechanism in their work.

In 2013, inspired by Wang, Smith et al.\(^4^1\) envisaged employing DDQ for the synthesis of unsymmetrical glycosyl disulfides. Seven unsymmetrical glycosyl disulfides have been synthesized directly from the corresponding
Scheme 4. Synthesis of unsymmetrical disulfides with TCCA as the catalyst.

Scheme 5. Synthesis of unsymmetrical disulfide 14 with H₂O₂ as the oxidant.

Scheme 6. Synthesis of unsymmetrical disulfides 17 with DDQ as the oxidant.
glycosyl thiols by oxidation with DDQ (Scheme 7). The coupling of α-thiols and β-thiols proceeded smoothly, giving the moderate yields (32%–78%) of the cross-coupling products. The homo-coupling of thiols was also obtained, and the mechanism of the reaction was not revealed in their work.

**DMSO as the oxidant**

In 2012, Miller et al. used dithiol as a substrate and DMSO as a mild oxidant to synthesize an unsymmetrical disulfide peptide. However, the yield of the reaction was low (20% of the theoretical yield) (Scheme 8).
Diethyl azodicarboxylate as the oxidant

Diethyl azodicarboxylate (DEAD) can also be used as an oxidant for thiol couplings for the synthesis of unsymmetrical glycosyl disulfides. Various aromatic and heterocyclic thiols were reacted with a number of acetylated thiosugars (1-thiogalactose, mannose, rhamnose and glucose). Reaction with DEAD as the oxidant proceeds through intermediate 20a, which reacts with the thiol to give a disulfide sugar as the target product 22 (Scheme 9). The high selectivity of this method was also realized by the sequential addition of the thiols.

O$_2$ as the oxidant

Oxygen is cheap and readily available, and it is environmentally friendly. In 2017, Dou et al. synthesized unsymmetrical disulfides via the catalytic aerobic oxidation of thiol cobalt phthalocyanine (Scheme 10). The products resulting from the cross-coupling of two electron-rich aromatic thiols can be obtained in yields of 91%–94%. Aromatic thiols can also react with aliphatic thiols, providing higher yields of the corresponding products. For example, the yield of 25c formed by the reaction of p-methylphenylthiol with cyclohexanethiol is 97%. Since thiol
favored homo-coupling, 5 equiv. of 24 was necessary for the yield of the major cross-coupling product.

In 2019, Song et al. demonstrated a novel K₂CO₃ catalyzed aerobic oxidative cross-coupling of thiols for the preparation of unsymmetrical disulfides \(28\) (Scheme 11). In the K₂CO₃/O₂ system, O₂ was employed as the oxidant, and the reactivity of these thiols follows the order \(\text{Ar-SH} \gg \text{ArCH₂-SH} > \text{alkyl-SH} \gg \text{tBu-SH}\). A possible mechanism has been proposed. The highly reactive aryl thiol \(26a\) reacts with K₂CO₃ to form ArSK. ArS⁻ then loses an electron to generate ArS \(26b\) oxidized by O₂. Radical \(26b\) then undergoes coupling to form a symmetrical disulfide. Finally, the symmetric disulfide couples with the less active alkyl thiol to form an unsymmetrical disulfide.

**Electro-oxidative cross-dehydrogenation of thiols**

In 2018, Lei et al. developed a novel S–H/S–H electrooxidation cross-coupling of aryl mercaptan with alkyl mercaptan, resulting in hydrogen evolution, to prepare unsymmetrical disulfides (Scheme 12). The ratio of aryl
mercaptop to alkyl mercaptan was 1:1, and various heterocyclic mercaptans and thiophenols were suitable substrates for this transformation. In the control experiments, when using dimer 30c to replace 30a, the desired product was detected only in trace amounts (Scheme 12ii). However, a good reaction yield was obtained when using dimer 29c as the replacement for 29a (Scheme 12iii). Therefore, they speculated that the key intermediate dimer 29c was formed more easily and determined the high selectivity of the reaction. A proposed mechanism of electro-oxidative S-H/S-H cross-coupling was depicted. First, thiol 29a and 30a are oxidized at the anode to form free radical 29b and 30b. Then, two free radicals couple to give the final product 31a. Meanwhile, the free radicals can dimerize to form the side product symmetrical disulfide. The symmetrical disulfide receives an electron at the cathode to generate the radical anion which then decomposes to generate the corresponding radical and the anion.

Photocatalyzed cross-dehydrogenation of thiols

Photocatalytic oxidation is another green and effective method for the synthesis of unsymmetrical disulfides in the absence of extra oxidants. Dethe et al. developed and used tris(2-phenylpyridine)iridium (Ir(ppy)3) as a photocatalyst to dehydrogenate mercaptan to the corresponding unsymmetrical disulfide. This methodology can generate high yields with a photocatalyst loading of only 0.5 mol% under white LED light, and has good functional group tolerance (nitro, methoxy, ester and carboxyl functionalities are all tolerated). Scheme 13 shows a reasonable mechanism for the reaction. First, Ir(ppy)3 is excited by visible light to produce Ir(III)*. Ir(III)* gains electrons from R1SH/R2SH which is reduced to Ir(II), and at the same time R1SH/R2SH loses protons to form R1S/R2S. These radicals are replaced by a second thiol to form disulfide radical anions 32a or 34a. Ir(ppy)3II loses electrons to form the disulfide and Ir(III). An alternative pathway involves replacement of the generated symmetrical disulfide R1S-R1 by a nucleophilic free radical R2S to give the unsymmetrical disulfide 34. In order to improve the yield of the cross-coupling product 34, 2 equiv. of 33 was employed. This studies show that photocatalytic dehydrogenation is a green and effective strategy for the synthesis of disulfides.

Conclusion and future prospects

In the past decades, many novel strategies for the synthesis of various unsymmetrical disulfides via the cross-dehydrogenation of thiols have been developed. These unsymmetrical disulfides are important precursors of promising compounds for use in the pharmaceutical industry and materials field. Although numerous effective methods for the synthesis of unsymmetrical disulfides have been established, more environmentally green, simpler, and efficient
strategies for the construction of unsymmetrical disulfides are still necessary. In particular, it is highly desirable to find alternative sulfur sources\textsuperscript{48,49} to help broaden the substrate scope.

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**ORCID iD**

Jin-Biao Liu  
https://orcid.org/0000-0002-5038-6541

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