Formation of Carbon-Sulfur Bonds with Sp^2 and Sp^3-Carbons Under Metal and Metal-Free Conditions

Thesis submitted in partial fulfillment for the

Award of Degree

Doctor of Philosophy

by

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Year of Submission
2024

CHAPTER-6

Summary and Conclusions

6.1 Summary and Conclusions

The thesis entitled "**Formation of Carbon-Sulfur Bonds with *Sp*^{2} and *Sp*^{3}-Carbons Under Metal and Metal-Free Conditions**" presented new methods for the formation of C-S bond with ***Sp*^{2}** and ***Sp*^{3}**-carbons. The contents of the thesis have been organized into six chapters including the current one.

Chapter 1 provides a comprehensive overview of organosulfur compounds, applications, numerous types of C-S bond-forming reactions, etc., **(Figure 6.1).** In addition, the main objectives of the thesis work have been addressed in this chapter.

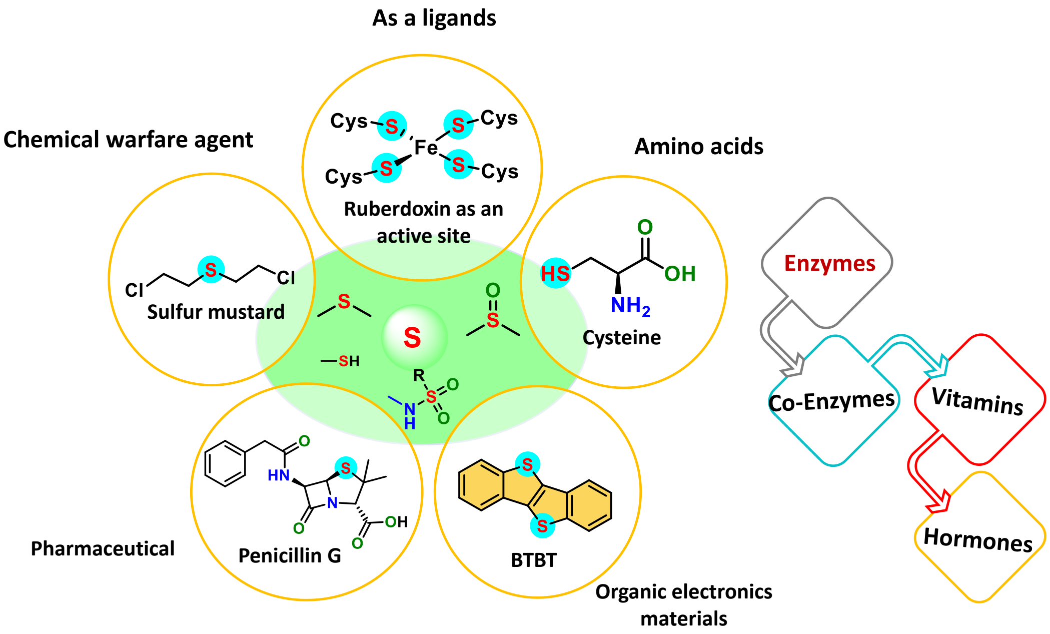
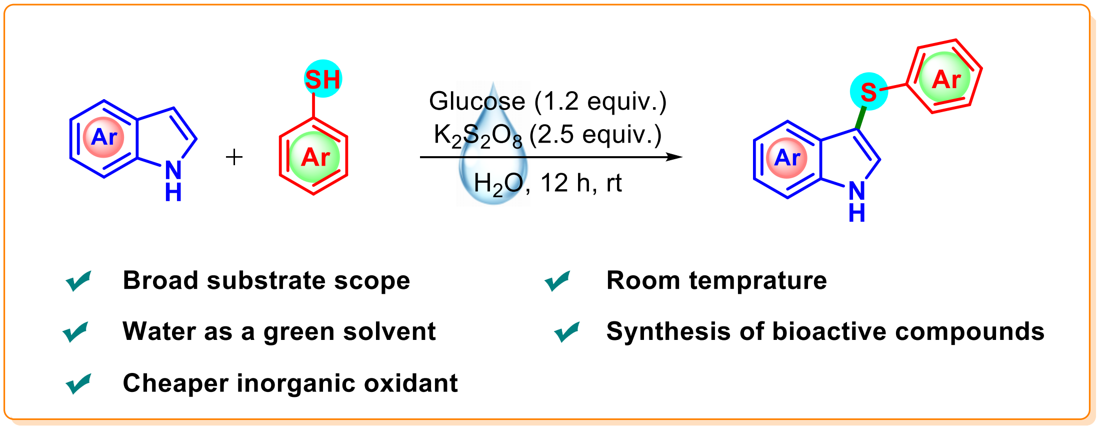


Figure 6.1 Importance of organosulfur compounds.

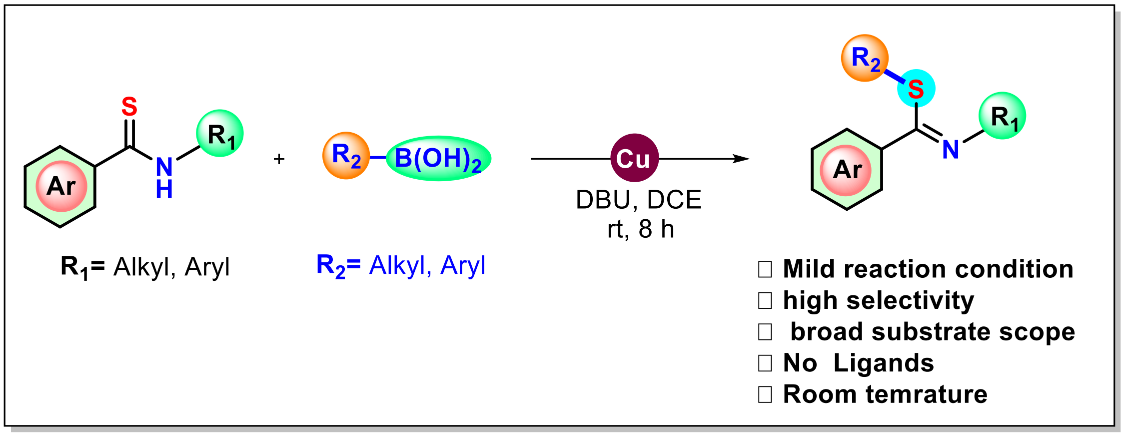
Chapter 2 described the potassium persulfate-glucose mediated synthesis of (3)-S-arylthioindoles from indole and thiophenols in water **(Scheme 6.1).** Indole structure motifs are commonly found in various natural products, bioactive molecules, drugs, agrochemicals, and materials. Hence, developing efficient synthetic approaches to construct functionalized indoles received significant attention in organic synthesis and medicinal chemistry. Among the different derivatives of indoles, synthesis of (3)-*S*-arylthioindoles (i.e. 3-sulfenylindoles) received considerable interest in medicinal chemistry due to their broad spectrum of biological activities, including anti-cancer, anti-HIV, antiallergic, antiviral and antibacterial activities. Synthesis of 3-(*S*)-arylthioindoles has been achieved through direct C-H functionalization of indole with various sulfenylating agents, such as aryl thiols, sulfonium salts, sulfenyl halides, sulfinates, sulfonyl hydrazides and disulfides. Nevertheless, most of these existing methods suffer from the use of high reaction temperatures, hazardous solvents, expensive thiol surrogates, longer reaction times, etc.



Scheme 6.1 Pictorial presentation of chapter-2.

Within this framework, we developed a green and practical method for synthesizing 3-(*S*)-aryl thioindoles from indole and thiophenol in water. The reaction was promoted by $K_2S_2O_8$ in the presence of glucose at room temperature and gave good to excellent yields. Broad substrate scope, functional group tolerance, and metal-free conditions are important advantages of the developed methodology.

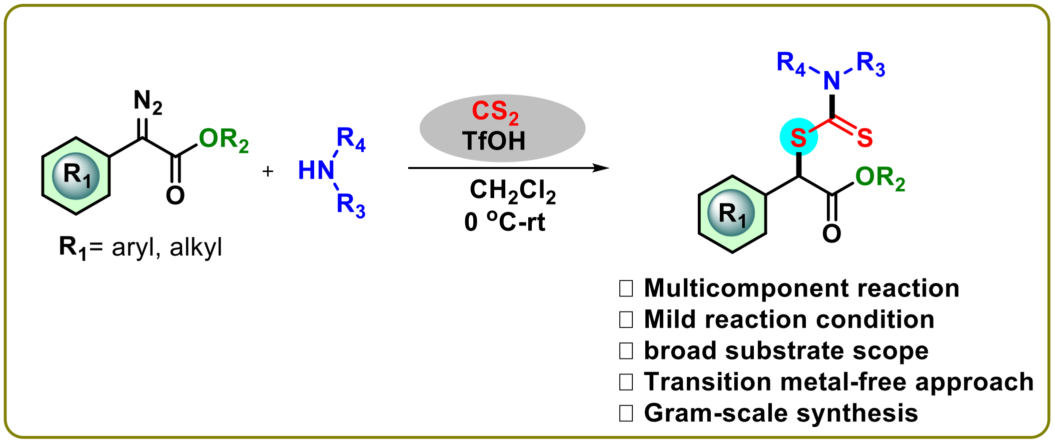
Chapter 3 explored the method for the synthesis of functionalized thioimidates from thioamides and boronic acids via copper-catalyzed cross-coupling reaction **(Scheme 6.2).** Among the different organosulfur compounds, thioamides play important roles in synthetic organic chemistry and medicinal chemistry. On the other hand, thioamides undergo various types of reactions and provide biologically relevant molecules and heterocycles. The reaction of thioamides with carbon electrophiles provides thioimidates, one of the important scaffolds in organic synthesis and drug discovery. In peptide synthesis, thioimidates have been well explored as a protecting group for thioamides. Synthesis of S-alkyl thioimidates is simple and can be achieved from thioamides and alkyl halides in the presence of a base. However, the synthesis of S-aryl thioimidates is relatively difficult. Besides different approaches, the S-arylation of thioamides is considered as a straightforward approach for synthesizing S-aryl thioimidates. There are few reports available for synthesizing S-aryl thioimidates from thioamides. Each of the methods has its own advantages and disadvantages in terms of reaction conditions, substrate scope, safety, high temperature, chemoselectivity, high boiling point solvents, etc.



Scheme 6.2 Pictorial presentation of chapter-3.

In this context, under mild conditions, we explored the highly selective approach for synthesizing functionalized thioimidates from thioamides and arylboronic acids via copper-catalyzed cross-coupling reaction. The reaction occurs at room temperature and in an open-air atmosphere. Broad substrate scope, a wide range of functional groups tolerance, and high selectivity are the key features of this methodology, affording good yield to the corresponding thioimidates. In addition, this approach allows for the synthesis of both s-aryl thioimidates and S-alkyl thioimidates.

Chapter 4 focused on the synthesis of functionalized S-benzyl dithiocarbamates from diazo-compound via multi-component reactions with carbon disulfide and secondary amines**(Scheme 6.3).** Diazo compounds are important synthons in organic chemistry, and they have been widely used as carbene precursors to construct various biologically active molecules. Among the different types of diazo compounds, α-aryl α-diazo esters are relatively stable, and they are well-explored in many organic transformations, including nucleophilic insertion reactions with a variety of nucleophiles. Over the past few decades, the importance of dithiocarbamate compounds has grown significantly due to their diverse applications in different fields. Organic dithiocarbamates display antioxidant, antibacterial, antifungal, anticancer and anti-alzheimer activities. S-benzyl dithiocarbamates are typically synthesized from benzyl halides through a multicomponent reaction with carbon disulfide and amines. Nevertheless, methyl arenes, aryl alcohols, and aldehydes were also used as precursors for the preparation of *S*-benzyl dithiocarbamates.

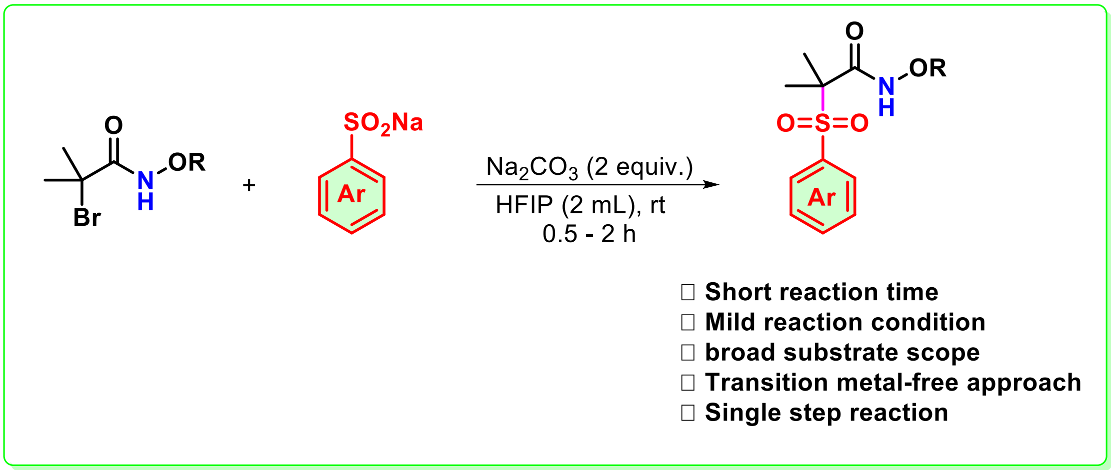


Scheme 6.3 Pictorial presentation of chapte- 4.

This report highlights a straightforward and efficient method that has successfully used triflic acid to synthesize various functionalized *S*-benzyl dithiocarbamates from α-aryl diazo esters via a multicomponent reaction involving carbon disulfide and amines. The reactions occur at room temperature and give the desired dithiocarbamates in good yields.

Broad substrate scope and easy operations are the important features of the reaction methodology.

Chapter 5 discussed the synthesis of α-arylsulfone propanamide from arylsulfinates with α-halohydroxamates under mild conditions**(Scheme 6.4).** Sulfones are an important class of organosulfur compounds used as precursors and intermediates in organic synthesis. Sulfones have been named “chemical chameleons” or “pluripotent” due to their versatile chemical properties and reactivity. Besides the synthetic applications, sulfones have found applications in different fields, including pharmaceuticals, agrochemicals, and functional materials. Due to their high importance, considerable attention has been given to developing methods for synthesizing sulfones. Sulfones are typically synthesized from sulfides via oxidation reactions using various oxidants including peroxides. Alternatively, Friedel-Crafts-type reactions with sulfonyl chlorides have been used for the construction of aryl sulfones. Besides these traditional methods, i) the reaction of sulfinic acid salts with carbon electrophiles,[10] ii) the addition of sulfonyl radicals to alkenes or alkynes, iii) fixation of sulfur dioxide, etc., provides aryl, alkyl, and aryl-alkyl mixed sulfones. α-Halohydroxamates are important precursors in organic synthesis. The treatment of α-halohydroxamates with base in fluorinated solvents provides azaoxyallyl cations, a transient reactive species. which is used as intermediates to synthesize various biologically relevant nitrogen-containing heterocycles. Further, the insertion of different nucleophiles with azaoxyallyl cations provides sterically hindered amines, sulfides, ethers, etc., under different reaction conditions.



Scheme 6.5 Pictorial presentation of chapter-5.

Here, the synthesis of α-aryl sulfone propanamide from arylsulfinates with α-halohydroxamates under mild reaction conditions was explored. The reactions proceed at room temperature and in the presence of a base. Broad substrate scope and good functional group tolerance with good to excellent yield to the corresponding α-aryl sulfone propanamide are the key features of the current methodology. Moreover, single-step synthesis and short reaction time got more attention in organic synthesis.

The methods presented in the thesis are simple and efficient in terms of reaction conditions and yield. The utilization of harmless reagents, practicable strategies, and high yields make these approaches more appealing in the field of organic synthesis. Therefore, the created methodologies will have extensive applications in the field of organic synthesis.