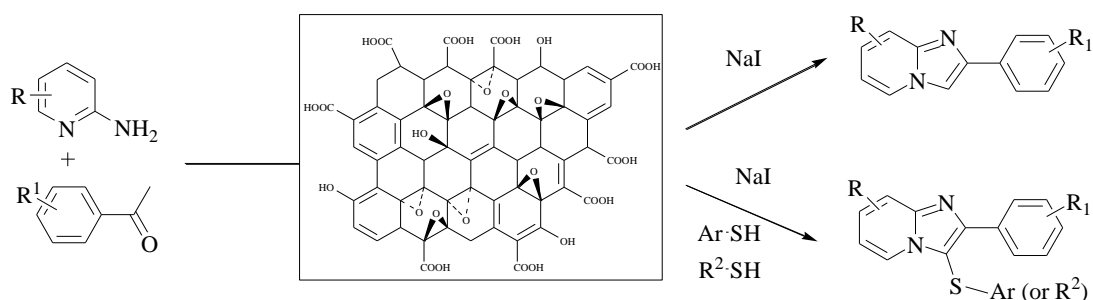


ABSTRACT

The research work embodied in the thesis entitled “**Solid-Phase Synthesis of Libraries of Heterocyclic Molecules and further Functionalization by Cross-Coupling Reactions**” was initiated in December, 2011, intending primarily to develop new reaction methodologies using the advent of solid-phase techniques and catalysis. The major focus was given on pursuing green chemistry guidelines and towards synthesis of heterocyclic small molecules of biological interests. The thesis has been divided into six chapters.

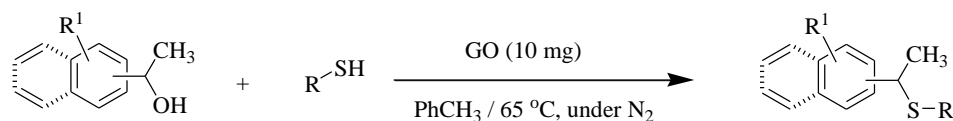
In the first chapter (**Chapter I**), a brief review on the importance of various heterocyclic small molecules, which are ubiquitous in nature as well as of immense biological activities, is given. Then a short preamble on the green chemistry principles is presented. Finally, some recent solid-surface-promoted syntheses of heterocyclic scaffolds are discussed with special emphasis on the use of two materials viz. mesoporous silica and carbonaceous graphene oxide (GO). In this dissertation, these two specific materials are used in developing diverse reactions leading to the synthesis of various heterocycles and hetero-atom containing molecules. The use of GO as metal-free catalyst is a growing area of recent interest, and the works presented in **Chapter II & III** represent unique examples of diverse reactivity of the carbonaceous and renewable material GO to afford complex molecules.

The **Chapter II** describes a new method for selective and expedient synthesis of biologically important motifs imidazo[1,2-*a*]pyridines, and 3-sulfenylimidazo[1,2-*a*]pyridines via one-pot multi-component reactions (MCR) with the aid of graphene oxide (GO) as the 'carbocatalyst'. Diversity in small heterocyclic molecular synthesis has been demonstrated with tolerance of broad range of functional groups establishing the generality of the reaction as well as demonstrating preparation of libraries of potential pharmacophores. The reactions are believed to proceed via selective and tandem reactions in the presence of GO and NaI (as the additive) and a plausible mechanism involving Ortoleva-King type intermediate has been proposed. The catalyst GO is found to be easily recoverable and recyclable with appreciable conversions for several runs. The major important facet of this reaction, which makes it unique, is the utilization of green carbocatalyst GO instead of traditional metal catalysts keeping the whole process environment friendly.



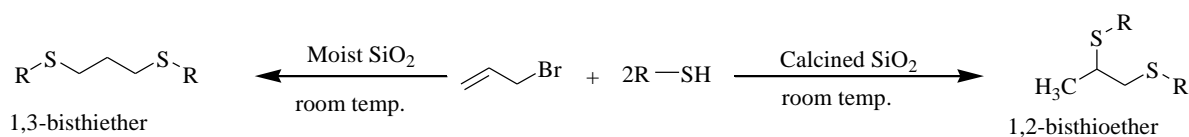
[The work has been published: S. Kundu and B. Basu, *RSC Adv.*, 2015, 5, 50178]

Chapter III delineates an efficient and mild one-pot graphene oxide (GO)-catalyzed sequential dehydration-regioselective hydrothiolation from a mixture of *sec.* aryl alcohols and thiols. The catalyst can be reused for five runs tested with significant conversions. Recent reports from Bielawski and subsequently from other groups have revealed an intriguing new direction for metal-free catalytic use of GO in organic reactions. GO-catalyzed oxidation of benzyl alcohols and oxidative dimerization of thiols to disulfide are reported recently. The present work, however, demonstrates the control use of GO under ambient conditions could lead to diverse reactions and synthesis of new chemical entities.



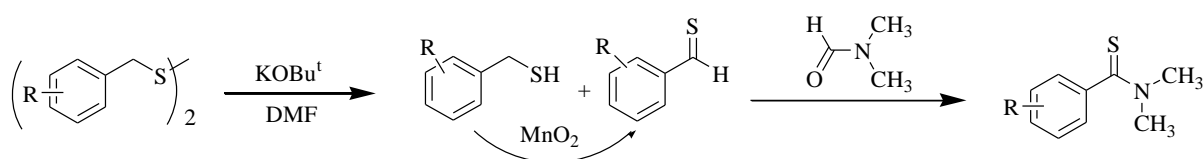
[The work has been published: B. Basu, S. Kundu, D. Sengupta, *RSC Adv.*, 2013, 3, 22130]

In **Chapter IV**, development of silica-promoted highly selective synthesis of 1,2- or 1,3-dithioethers via solvent-free one-pot tandem reactions of an allyl bromide with excess thiol at room temperature is described. The choice of silica, either pre-calcined or moist with water, exhibits notable regioselectivity in the formation of dithioethers. The sequential reactions in one-pot protocols are robust, neutral, metal-free and notably selective with a broad range of substrates. Plausible mechanistic routes leading to regioselective formation of 1,2- or 1,3-dithioethers are believed to occur in two-step reactions, viz. (i) formation of allyl sulfane and (ii) selective addition of thiol to olefinic bond either in Markovnikov or anti-Markovnikov fashion. The proposed mechanism has been evidenced by several approaches including insertion of deuterium while the silica is moistened with D₂O instead of H₂O.



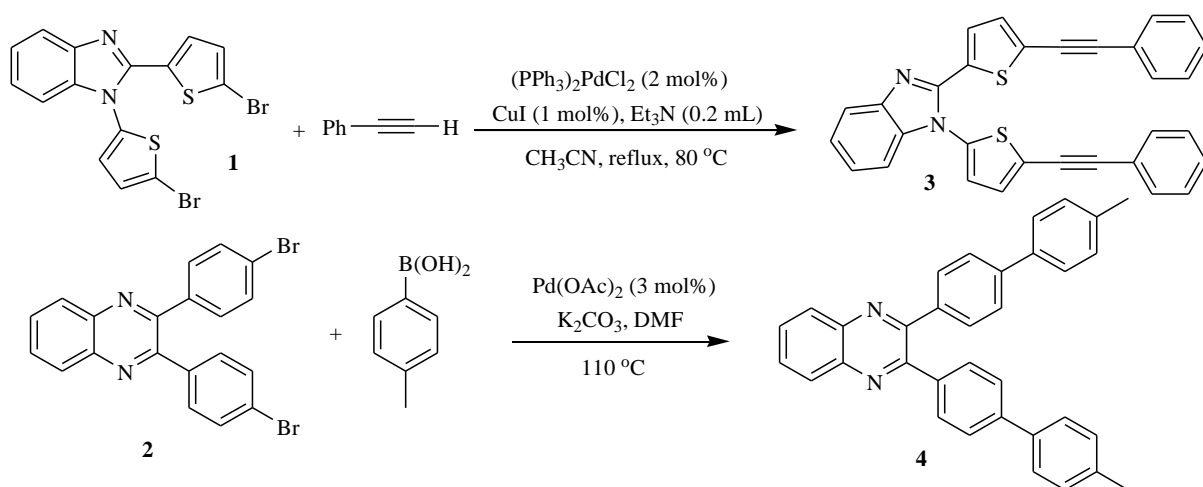
[The work has been published: S. Kundu, B. Roy, B. Basu, *Beil. J. Org. Chem.*, 2014, 10, 26]

The **Chapter V** represents an unprecedented reaction of *N,N*-dimethylformamide (DMF) with 'transient' aryl thiobenzaldehydes, derived from diaryl disulfides under basic conditions. The unique role of DMF has been generalized to constitute a simple method for the synthesis of *N,N*-dimethyl aryl thioamides. The structure of thiobenzamide was confirmed by single crystal X-ray and a plausible mechanism for this transformation is discussed. The reaction possibly proceeds with the formation KNMe_2 and subsequent attack at the thiocarbonyl carbon. Aryl thioamides are important class of compounds, and the present study involving inexpensive DMF could not only replace the common Willgerodt-Kindler (WK) reaction but also spur diverse reactions its uses beyond as a solvent.



[The work has been published: B. Basu and S. Kundu, *New J. Chem.* 2014, 38, 3367]

The **Chapter VI** depicts an overview on various approaches towards functionalization of heterocyclic small molecules via C–C cross-couplings such as Mizoroki-Heck, Suzuki-Miyaura, Sonogashira reactions etc. The present study is however of exploratory nature, and two different C–C cross-coupling reactions have been studied: (i) Pd-catalyzed Sonogashira reaction between benzimidazole-based scaffold bearing two bromide functions (**1**) to couple with phenyl acetylene, and (ii) Pd-catalyzed Suzuki-Miyaura reaction between quinoxaline-based (**2**) scaffold possessing two bromide groups to couple with *p*-tolyl boronic acid. Both bis-coupled products (**3** and **4**) are characterized by their NMR spectral data and future scopes for such approaches are discussed.



PREFACE

Heterocyclic compounds constitute the largest classical division of organic chemistry and are of immense importance in biological, pharmaceutical and industrial fields. They are ubiquitous in nature and conquer almost every part of a developed human society from vitamins, antibiotics, alkaloids, carbohydrates and other natural products to pesticides, dyestuffs, textiles, lubricants, paints, food and nutrition. Their synthesis and functionalization have remained a vast area of research from many decades.

Over the last two decades, organic synthesis has taken a major turn towards developing reaction conditions that are environment-friendly, sustainable and amenable to industries. Recent developments have replaced with the traditional synthetic routes by the greener, safer and economically more viable methodologies. In this context, solid-surface promoted reactions, heterogeneous catalysis, use of focused microwaves, metal-free, solvent-free and room temperature reactions are some of the major points of interest to the synthetic chemists. While different porous inorganic oxides often facilitate various organic reactions and are considered favourable to promote eco-friendly chemical processes, organic polymers are also utilized as supports for mediating organic reactions and for the immobilization of metal nanoparticles for further use. In the recent years, metal organic frameworks (MOFs) and carbonaceous materials like graphene (G), graphene oxide (GO) and reduced graphene oxide (rGO) are proven to be extremely useful for diverse purposes. The present works primarily include organic reactions catalyzed by GO as well as selective reaction mediated over inexpensive and commercially available silica. Both materials are easily recoverable and reusable for several runs without any significant drop in their catalytic activity or yield of the product(s) and change in their morphology and functionality. Some of their utilizations have been demonstrated in the present dissertation, which consists of six chapters including the first chapter delineating a brief introduction on the background literature review. During this investigation, new observation like the use of *N,N*-dimethylformamide (DMF) as a source of *N,N*-dimethyl group ($-NMe_2$) has been established as a practical method for making aryl thioamides.

Catalytic activity of GO has been explored in **Chapter II** towards the green synthesis of pharmacophore imidazo[1,2-*a*]pyridines and further one-pot sulfenylation to 3-sulfenylimidazo[1,2-*a*]pyridines in three-component reaction. The GO-catalyzed multi-component tandem reactions and application to important pharmaceutically active scaffolds

are hitherto unknown and reported for the first time. Further applications of this sustainable and easily available carbonaceous material are expected to come out in the synthesis of diverse complex molecules of importance in pharmaceutical chemistry and material sciences. Another application of GO as 'carbocatalyst' in one-pot sequential dehydration-hydrothiolation of *sec.* aryl alcohols to the selective formation of Markovnikov adduct has been described in **Chapter III**. Graphene-based materials (GO) as 'carbocatalyst' is a recent field of interest. Metal-free catalysis under mild conditions is indeed promising and expected to reveal a host of new catalytic applications. Utilization of silica as an efficient catalyst for one-pot solvent-free regioselective tandem synthesis of 1,2- or 1,3-dithioethers constitutes the **Chapter IV**. Diverse reactivity of silica in the formation of vicinal or 1,3-dithioethers is likely to spur not only adopting the procedures for selective dithioether preparation but also to attract more new applications. Further application of this diverse reactivity is underway in this laboratory. A new process of amidation of 'transient' thiobenzaldehyde, resulting from disulfides in the presence of base, by using *N,N*-dimethylformamide (DMF) as both solvent and reagent has been established in **Chapter V**. Aryl thioamides are important class of compounds and their classical synthesis includes Willgerodt-Kindler (WK) reaction. The present study involving inexpensive DMF could not only replace the common WK reaction that requires harsh conditions but also spur diverse reactions with the aid of DMF beyond its uses as a solvent. Finally, the **Chapter VI** deals with some pharmaceutically important scaffolds and their further functionalization via C–C cross-coupling reaction. Although the last chapter is partly of exploratory nature, the results are indicative of further scope and would be developed in future studies.