ABSTRACT OF THE THESIS

Investigation embodied in this thesis entitled “Studies directed towards the synthesis of dithiocarbamates and its application in organic synthesis” divided into four chapters, which are as follows:

Chapter I:

Introduction, synthesis of dithiocarbamates and its application

Introduction chapter deals with the important features of dithiocarbamates and its synthesis.

A dithiocarbamate is a functional group in organic chemistry. It is the analogue of carbamate in which both oxygen atoms are replaced by sulfur atoms (figure 1). Organic dithiocarbamates are valuable synthetic intermediates. They also exhibit valuable biological effects, including anticancer, antibacterial and antifungal activity. Dithiocarbamic acid ester represents a new kind of compound with a novel structure, significant anticancer activity and very low toxicity.

![General formula of the dithiocarbamate](image)

Figure 1: General formula of the dithiocarbamate

Dithiocarbamates have received considerable attention due to their numerous biological activities and their pivotal role in agriculture and as linkers in solid phase organic synthesis. They are also used in the rubber industry as vulcanization accelerators and in controlled radical polymerization techniques. Because they have a
strong metal binding capacity, they can also act as inhibitors of enzymes and have a profound effect on biological systems. Dithiocarbamates are also widely used in medicinal chemistry and have found application in the treatment of cancer (figure 2). Furthermore, dithiocarbamates are versatile classes of ligands with the ability to stabilize transition metals in a wide range of oxidation states.

![Sulforamate and RWJ-025856](image)

Figure 2: Structures of dithiocarbamates with anti-cancer activity

Recently, Brassinin (figure 3), a dithiocarbamate isolated from cabbage, was reported to have anticancer activity, and its structural modification led to the design and synthesis of a potential cancer chemopreventive agent (4-methanesulfinyl-butyl)-dithiocarbamic acid methyl ester (Sulforamate).

![Brassinin](image)

Figure 3: Structure of Brassinin

This chapter also depicts a comprehensive survey of literature on the synthesis of various dithiocarbamate derivatives and their
application. General methods for their synthesis involve the reaction of an amine with costly and toxic reagents, such as thiophosgene. However, there are several disadvantages to these methods: many isothiocyanates are hazardous and tedious to prepare and display poor long-term stability with the formation of side products such as urethane in alcoholic media.

Here we have developed an efficient, novel, and simple procedure for the direct synthesis of dithiocarbamates employing amines, CS$_2$, and alkyl halides, in one-pot, without the use of any catalyst in aqueous condition (Scheme 1).

![Scheme 1](image)

**Chapter II:**

**Dithiocarbamate and DBU-promoted amide bond formation under microwave condition**

Second chapter dithiocarbamate and DBU promoted synthesis of $N$-phenyl amides under microwave condition has been discussed.

The amide bond is among the most common chemical function present in natural or synthetic organic molecules. The amide functionality is a common feature in small or complex synthetic or
natural molecules. An in-depth analysis of the comprehensive medicinal chemistry database revealed that the carboxamide group appears in more than 25% of known drugs. This can be expected, since carboxamides are neutral, are stable and have both hydrogen-bond accepting and donating properties.

The stable amide bond is not only common in naturally occurring materials like peptides and proteins but is also found in many synthetic substances. This makes the amide function important to synthetic chemists especially in peptides and lactam synthesis, in which the formation of amide bond is crucial. Some derivatives of amides exhibit biological properties such as anticancer, antihistamine, antifungal, and antibacterial. Recently, it has been observed that many potent kinase inhibitors contain N-aryl amide bonds and this kind of bond plays a crucial role for enzyme inhibition as observed in the cases of Imatinib and ZM-447439 (figure 4). In connection with a drug discovery program, we needed an efficient route to the synthesis of various N-phenyl amides.

Figure 4: Kinase inhibitor with N-phenyl amide bond
In the last decade, microwaves (MWs) have been used to simplify and improve reaction conditions for many classic organic reactions. Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, and easier workup matching with green chemistry protocols.

The condensation reaction between isocyanates and carboxylic acids is a well-known method for practical synthesis of \(N\)-substituted amides. The major drawback of these reactions is the use of toxic isocyanate. Apart from handling these toxic agents, the synthesis of isocyanates requires handling of highly toxic phosgene. Moreover, the disadvantage with isocyanates is that they are unstable if stored for a longer period. Herein, we report a highly efficient microwave-assisted one-pot synthesis of amides using various substituted acids and substituted dithiocarbamates (Scheme 2).

![Scheme 2](image)

**Chapter III:**

Dithiocarbamate and CuO promoted one-pot synthesis of 2-(\(N\)-substituted)-aminobenzimidazoles and related heterocycles

In this chapter dithiocarbamate promoted synthesis of 2-(\(N\)-substituted)-aminobenzimidazoles has been discussed.
Of the wide variety of heterocyclic systems known till today, the nitrogen heterocycles are of great importance as they are present in nucleic acids, vitamins, proteins and biologically molecular systems. Benzimidazole is one amongst such important nitrogen heterocycles since several of its derivatives have pharmacological properties and have been marked as commercial products.

2-Substituted benzimidazole particularly 2-(N-Substituted)-aminobenzimidazoles are widely used structural motifs in medicinal chemistry as well as in drug discovery and can be found in a number of biologically active molecules. Several compounds from this class have been used as anticancer, antihistamine and antiviral agents. Some examples of pharmaceutical interest are shown below (figure 5).

![Figure 5: Biologically active 2-amino benzimidazole class of compounds](image)

Therefore, an efficient practical method for the synthesis of a diverse collection of 2-aminobenzimidazoles would be of great value for drug discovery. Several synthetic methodologies have been reported in the literature for the synthesis of 2-aminobenzimidazoles. Most involve formation of thioureas using isothiocyanates followed by
cyclodesulfurization using desulfurizing agents such as mercury(II) oxide, mercury(II) chloride, copper(I) chloride, methyl iodide, tosyl chloride, dicyclohexylcarbodiimide (DCC) and PS-carbodiimide (figure 6).

![Figure 6: Cyclodesulfurization](image)

Herein, we report a highly efficient copper (II) oxide mediated one-pot synthesis of 2-(N-Substituted)-aminobenzimidazoles using various substituted diamines and substituted dithiocarbamates. We also investigated this methodology with respect to different diamines and dithiocarbamates (Scheme 3). The reaction gave good yields with both electron-withdrawing groups and electron-donating groups. This procedure could also be applied to other diamine moieties, providing quinazolines.

![Scheme 3](image)

In connection with a drug discovery program, we recently required an efficient synthetic protocol into the new class of trisubstituted purines known as Aurora-A Kinase inhibitors. To synthesize this class of compounds we applied this methodology
(Scheme 4). Thus, condensation of 2,4,5-trisubstituted pyrimidines with dithiocarbamates in the presence of CuO (0.2 equiv) and K$_2$CO$_3$ in DMF at 60 °C for 2 h furnished the desired substituted purines in good yields.

![Scheme 4]

**Chapter IV:**

**Dithiocarbamate promoted practical synthesis of N-aryl-2-aminobenzazoles**

In this chapter dithiocarbamate promoted synthesis of N-aryl-2-aminobenzazoles has been discussed.

Benzo-1,3-diazoles are a biologically important class of molecules and are widely used as pharmaceutical agent. Interestingly, during the structure activity relationship (SAR) studies it was observed that change of the structure of substituent group at C-2 position commonly results the change of its bioactivity. 2-Substituted benzoxazoles particularly N-aryl-2-aminobenzoxazole derivatives have been or are currently under investigation for the treatment of a wide variety of disorders such as HIV, neurodegeneration and inflammatory diseases (figure 7). Moreover 2-aminobenzoxazoles have also been reported as VEGFR inhibitors hence are particularly important in
hyper proliferative diseases such as cancer and rheumatoid arthritis. The 2-aminobenzothiazole compounds mostly were synthesized as kinase inhibitor recently. For example, the investigations of 2-amino benzothiazole as a key pharmacore led to investigational new drugs such as the p56lck inhibitor, p38α MAP kinase inhibitor. Also 2-aminobenzothiazole moiety selectively targeting T-and B-cell lymphomas has been reported (figure 7).

Figure 7: Several N-substituted-2-aminobenzothiazole derivatives reported as biologically active compounds and pharmaceutical products.

Therefore, an efficient practical method for the synthesis of a diverse collection of N-aryl-2-aminobenzazoles would be of great value for drug discovery.

Following our studies towards the development of a new route for the synthesis of organic compounds, our interest remains in dithiocarbamate mediated reactions. We were particularly interested
in the synthesis of $N$-aryl-2-aminobenzoxazoles and $N$-aryl-2-aminobenzothiazoles via a method suitable for large scale preparations as well as not requiring toxic starting materials or reagents. Herein, we report an efficient one pot synthesis of $N$-aryl-2-aminobenzazoles by using o-aminophenol or o-aminothiophenol and substituted dithiocarbamate at room temperature with high yields (Scheme 5).

**Scheme 5**

Having demonstrated the generality of this reaction in between o-aminophenol /o-aminothiophenol and different dithiocarbamates, we further explored the possibility in synthesizing novel 4-aminoquinazoline class of compounds as aurora kinase-A inhibitor. For this purpose 4-chloroquinazoline derivatives (4) was synthesized and treated with various $N$-aryl-2-aminobenzoxazoles/$N$-aryl-2-aminobenzothiazoles (3) to yield 4-aminoquinazoline derivatives (5) (Scheme 6).
**Scheme 6**

1. $\text{H}_2\text{N}_X R \xrightarrow{\text{K}_2\text{CO}_3/\text{DMF}} 80-82\% \xrightarrow{\text{EtOH}} 88-90\%$

2. $\text{NO}_2$ $\text{H}_{2\text{N}}$ $X = \text{C, N}$

3. $Y = \text{O, S}$

4. $R = \text{H, Cl}$

5. $Z = \text{O, NMe}$