1.1 Introduction to heterocyclic compounds:

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous. Heterocyclic aromatic compounds are widely distributed pollutants in soil, air, sediments, surface water and groundwater, as well as in animal and plant tissues.\textsuperscript{1a} They may be of natural origin (e.g. alkaloids), but high environmental concentrations mainly result from human activities.

Heterocyclic compounds constitute the largest and most varied family of organic compounds. Many heterocyclic compounds are the source of important life saving drugs. Quinine is a traditional anti malarial drug isolated from bark of \textit{Chincona tree}. They are also widely used in pharmaceuticals and agricultural field. Hence, heterocyclic chemistry is an evergreen branch of organic chemistry attracting not only synthetic organic chemists but also the bio-organic, agro and medicinal chemists. Consequently, development of new, efficient and useful methods for the synthesis of biologically important heterocyclic compounds is still in demand. In this prospective, versatile synthons like dithioesters, oxodithiesters find recognition in synthesis of variety of five and six membered heterocyclic compounds. They have been recognized as precursors. Their rich chemistry and the ease availability make them attractive synthons to heterocyclic compounds. Benzene fused, five-membered heterocycles compounds have been the subject of sustained interest\textsuperscript{1–3} because they are useful reactants for organic synthesis.\textsuperscript{4} There are many experimental results for
benzopyrrole, benzofuran, benzo-thiophene, and their corresponding isomers\textsuperscript{5–9} (Fig. 1). Benzopyrrole and isobenzopyrrole have similar chemical properties and stability. However, benzofuran and iso-benzofuran present different stabilities. The existence of isobenzofuran has been clearly demonstrated,\textsuperscript{5,8} but this compound is unstable in solution and it reacts rapidly with dienophiles to give the corresponding Diels–Alder products.\textsuperscript{9} This reactivity has been used in many synthetic applications. Some authors have referred to this compound as ‘the most reactive isolated diene for cycloaddition purposes’.\textsuperscript{10} In contrast, benzofuran is very stable and can be obtained with several synthetic methods.\textsuperscript{7} For the two benzothiophenes, it was reported that isobenzothiophene is more reactive than benzothiophene.\textsuperscript{11}

![Fused heterocyclic compounds](image)

**Figure-1:** Fused heterocyclic compounds

In particular, industrialized areas, such as creosote contaminated sites, represent important sources of tar oil pollutants.\textsuperscript{12–13} Creosote represents a complex mixture of over 10,000 single organic substances which are formed by thermal processes related to coal and fossil fuels. Beside technical and chemical processes that involve tar oil, heterocyclic compounds are also present in dyestuff\textsuperscript{15} pesticides and pharmaceuticals.\textsuperscript{16–17} The higher polarity and water solubility of the heterocyclic substances is based on the substitution of one carbon atom by nitrogen, sulfur or oxygen (NSO-HET).\textsuperscript{18} These chemical properties lead to increase of bioavailability and as compared to the homologous polycyclic aromatic hydrocarbons (PAH).
1.2 Synthetic Approaches to dithioesters and its applications.

Dithioesters are promising starting materials in the preparation of many heterocycles, because of their relatively stable and conveniently available diverse methods of preparation. Dithioesters are also used as chain transfer agents in RAFT process of polymerization.

The synthesis of dithioesters were described during 1902 by J. Houben and L. Kesselkaul, using Grignard method. Since then several methods of its synthesis and reactions were developed. The work in this thesis makes use exclusively of aromatic dithioesters that contain a dithiobenzoate moiety. An overview is presented here detailing the most recent and frequently applied synthetic pathways to dithioesters and its applications in building heterocyclic compounds.

1.2.1 Synthesis of dithioesters from aromatic mono-, di- and tri-halidemethylates.

The first synthesis of a dithiocarboxylate was reported by Fleischer. He prepared dithiobenzoic acid 2 from benzal chloride 1 and potassium hydrosulfide in ethanol and water, which yielded traces of the acid as a red oil upon the addition of hydrochloric acid (Scheme 1).

Scheme 1: Synthesis of dithiobenzoic acid from benzal chloride and potassium hydrosulfide

Later, Wood J. H. and his coworkers explained that, potassium sulfide present as an impurity in potassium hydrosulfide reacts with benzal chloride to form thiobenzoaldehyde. The unstable thiobenzoaldehyde, depending on the reaction
conditions, can undergo the Cannizzaro reaction to yield potassium dithiobenzoate along with the other products.\textsuperscript{21}

Also benzotrichloride was converted to potassium dithiobenzoate by slow addition to a suspension of potassium sulfide in boiling methanol.\textsuperscript{22} In another method aromatic mono-halidemethylates were treated with elemental sulfur and alkali alkoxides leading to multiple dithiocarboxylates moieties.\textsuperscript{23}

1.2.2 Synthesis of dithioesters via thioacylation

Thioacylation is nothing but the nucleophilic displacement at the thiocarbonyl carbon by a sulfur nucleophile. In the preparation of dithioesters, thiols and alkali thiolates are converted to dithioesters from respective thioacyl halides, thioacyl anhydride and thio ketenes by thioacylation. Mayer R. and Scheithauer S. synthesized alkyl and aryl dithioesters by thioacylation of thiols \textsuperscript{4} in alkaline medium with thioacyl halides in high yields (Scheme 2).\textsuperscript{24}

![Scheme-2: Synthesis of dithioesters from thioacylation.]

1.2.3 Oxidative sulfuration

Sulfuration provides a large substrate scope for the synthesis of dithioesters and dithiocarboxylic acid. Bost R. W and Shealy Otis L. accomplished the conversion of aldehydes \textsuperscript{6} to corresponding dithiocarboxylic acids \textsuperscript{7} using ammonium polysulphide (Scheme 3).\textsuperscript{25}

![Scheme-3: Conversion of dithiocarboxylic acids from aldehydes.]
Jensen K.A. and Pedersen C. have discussed three different routes for the preparation of carboxymethyl dithioates 12 which involves sulfuration process in detail. They opine that thiohydrolysis of S-carboxymethylthiopiperidium bromides 10, prepared from thiopiperidines 9 and bromoacetic acid 8 is a generally applicable method (Scheme 4).^2^6

![Scheme 4](attachment:image.png)

**Scheme-4:** Preparation of carboxymethyl dithioates from bromoacetic acid.

1.2.4 Friedel-Crafts type reactions.

An alternative route to (substituted) dithiobenzoate esters is reported by Viola et al. In their approach, a reaction of thiophosgene 13 and thiol forms a reactive chlorodithio formic acid ester 15, which, under Friedel-Crafts conditions, adds to activated arenes in high yields^2^7. (Scheme 5).^2^7

![Scheme 5](attachment:image.png)

**Scheme-5:** Synthesis of chlorodithioformic acid ester from thiophosgene.

Trimethyl silyl methyl dithiobenzoate 19 has been prepared from benzene. George,^2^8 who described a one-pot synthesis from a mixture of benzene, carbon disulfide and (chloromethyl)methyl dichlorosilane 18 (Scheme 6).
Scheme-6: Synthesis of trimethyl silyl methyl dithiobenzoates from benzene.

1.2.5 Sulfur organo-phosphorous catalyzed preparation of dithioesters.

Earlier literatures suggest that, sulfur organo-phosphorus reagent, like Lawesson’s reagent catalyzed the esterification of carboxylic acids and thiols to obtained dithioesters in high yields.\textsuperscript{29-30}

Brian C. B.\textsuperscript{31} and his team reported the reaction of carboxylic acids 20 with a variety of thiols or alcohols in the presence of phosphorus pentasulfide ($P \textsubscript{4}S_{10}$) as a catalyst (20–40 mol%), which proceeded effectively to afford the corresponding dithiocarboxylic esters in high yields (Scheme 7).

\[
\text{COOH} + \underset{\text{or}}{\text{R}_2\text{S}^-\text{H}} \xrightarrow{P \textsubscript{4}S_{10}} \text{S}^-\text{S}^-\text{R}_2
\]

Scheme-7: Synthesis of dithioesters from thiols or alcohols.

An early report for the use of Grignard reagents was by Houben.\textsuperscript{32} Wherein, arylmagnesium halides were reacted with carbon disulfide in dry ether producing the magnesium halide of the corresponding dithioacid. These reactive species were transformed directly into a dithioester 24 by addition of a suitable alkyl halide or alkyl sulfate (Scheme 8).\textsuperscript{33}

\[
\text{MgX} + \text{CS}_2 \xrightarrow{\text{dry ether}} \text{S}^-\text{SH} \xrightarrow{\text{R'Y}} \text{S}^-\text{S}^-\text{R}'
\]

Scheme-8: Synthesis of dithioesters from Grignard reagents
1.3 Reactions of dithioesters

Comprehensive reviews on the synthesis and reactivity of dithioesters have been published. Owing to their simple methods of preparation and flexible substitution patterns, they have been used to generate libraries of heterocycles. The presence of the thioalkyl group, which behaves as a good leaving group enhances the binding action during nucleophilic attack.

1.3.1 Redox reactions of dithioesters

Oxidation of dithiocarboxylates \( 25 \) with benzene selenic anhydride \( 26 \) furnishes thiol esters \( 27 \) as the products (Scheme 9).

![Scheme 9: Oxidation of dithiocarboxylates with benzene selenic anhydride.](image)

The electrochemical oxidation of ACDA and its nickel(II) complex, shows the ring formation between two di-thio groups is with the elimination of one sulphur atom via two electron processes and a two-electron transfer process by releasing a proton.\(^{35}\) Kistenbrugger L.\(^{36}\) and Mischke P.\(^{37}\) have reported electro-reduction of alkyl dithiobenzoates in the presence of alkylating agents, wherein thioacetal \( 80 \) formed as major products in good yield.

1.3.2 Synthesis of thioamides.

The successive addition of amines to the Grignard reagent, formed by carbon disulfide and alkyl halide, mediated by TFMST or triflic anhydride, was presented by Katritzky, Alan R et al as an effective and general route to thioamides \( 30 \). Francesco Babudri and his co-workers have reported similar method with a little
modification, wherein the reaction is mediated by transition metal catalyst, NiCl$_2$ (dppe) (Scheme 10).$^{38-39}$

![Scheme 10: Synthesis of thioamides from Grignard reagents](image)

1.3.3 Synthesis of heterocyclic compounds from dithioesters.

The presence of the thioalkyl group, which behaves as a good leaving group in dithioesters, may enhance the binding activity during nucleophilic attack. Some heterocyclization reactions of this type of dithioester with dielectrophiles, particularly when there is acidic hydrogen, may lead to sulfur-containing heterocycles. In fact, the literature reveals exclusive work on sulfur containing synthons like trithiocarbonates, dithiocarbamates and dithioesters like methyl dithioester, $\alpha$-enolic dithioester, $\beta$-oxodithioester, and ketene dithioacetals, N-S-acetals or S,S-acetals have been reported by Ila H, Junjappa H, Ashokan C.V. and Maya Shankar Singh. Quite a few elegant approaches are reported in the literature to the synthesis of thiopyrans, among them en route dithioester is reported by M. S. Singh and his team. Wherein, they report a new method for the regioselective synthesis of 2$H$-thiopyrans 34 from $\beta$-allyl-$\beta$-hydroxy dithioesters through a cascade dehydrative intramolecular annulation sequence mediated by BF$_3$.Et$_2$O at room temperature (Scheme 51).$^{40-42}$

Synthesis of 4,5-disubstituted thiazoles by the reaction of active methylene isocyanides with methyl dithiocarboxylates has been reported by, Lingaraju, G. S. et al.\textsuperscript{43} This procedure was extended to various aryl and heteroaryl substituted methyl dithioesters and substituted isocyanides to afford a library of thiazoles 37 with yields of 84–95\% (Scheme12).

\[
\begin{align*}
\text{R}_1\text{S}^- + \text{R}_2\text{N}^+\text{C}^- & \xrightarrow{\text{NaH, DMF}, 0 \degree\text{C-RT}} \text{R}_1\text{R}_2\text{S}\text{N}^- \\
35 & \quad 36 \quad 37
\end{align*}
\]

Scheme-12: Synthesis of 4,5-disubstituted thiazoles

Quiroga \textit{et al.} reported addition-cyclization of dimethyl N-(alkylimino) dithiocarbonates 38 with dithioesters to yield thiazoles 39 (Scheme13).\textsuperscript{44}

\[
\begin{align*}
\text{R}_1\text{N}^-\text{S}^- + 1. \text{t-BuOK/THF} & \xrightarrow{2. \text{R}_2\text{CS}_2\text{Me}} \text{R}_1\text{R}_2\text{S}^-\text{N}^- \\
38 & \quad 39
\end{align*}
\]

Scheme-13: Synthesis of thiazoles from dimethyl N-(alkylimino) dithiocarbonates.

Cycloaddition and dipolar cycloaddition reactions of methyl dithioesters have been explored a lot as they lead to heterocycles of various ring sizes. For an instance, the photocycloaddition of arylazirines 40 in benzene with an internal water-cooled mercury arc lamp in the presence of an equimolar amount of methyl dithioester produced a mixture of two thiazolines 41 and 42, but in poor yields (Scheme14).\textsuperscript{45}
Scheme 14: Photocycloaddition of arylazines to thiazolines.

An efficient route for the synthesis of substituted 2-thiobenzamidomethylindole derivatives was reported by Bernath et al.\textsuperscript{[46]} which involved the Hugerschoff reactions of thiobenzamides \textsuperscript{[44]} with phenyltrimethylammonium tribromide to provide 2-arylthiazino[5,6-\textit{b}]indoles \textsuperscript{[45]} in moderate to good yields. The reactions of aminomethylindole in dichloromethane at room temperature with substituted methyl dithiobenzoates furnished thiobenzamides. Bernath and co-workers\textsuperscript{[47]} reported a similar route for altered indole moieties \textsuperscript{[102]} which furnished 2-arylthiazino[6,5-\textit{b}]indole derivatives \textsuperscript{[48]} as analogues of the phytoalexin cyclobrassinin (Scheme 15).

Scheme 15: Synthesis of substituted 2-thiobenzamidomethylindole from dithioesters.

Recent literature on reactions of dithioester reveals the growing number of diverse heterocycles with increasing substrate scope and more facile strategies of synthesis. Implicatively, Maya Shankar Singh\textsuperscript{[48]} and his team have proposed the straightforward synthesis of diverse 4,5-disubstituted 1,2,3-thiadiazoles \textsuperscript{[53]} from \textit{a}-
enolic dithioesters via nitrosation/reduction/ diazotization/ Wolff cyclization sequence in one-pot through the formation of cascade 1–2 (N–S) and 3–4 (C–N) bonds (Scheme 16).

**Scheme-16:** Synthesis of diverse 4,5-disubstituted 1,2,3-thiadiazoles from α-enolic dithioesters

Ila H. et al\(^9\) have reported a new class of potentially useful three-carbon 1,3-bielectrophile novel 3-carbon 1,3-bis(het)aryl-monothio-substituted 1,3-diketones 54 and corresponding 3-methylthio-1,3-bis(het)aryl-2-propenones 53a accessed from (het)aryldithioesters 53b. Monothio 1,3-diketones 54 and β-alkylthioenones 55 were treated with hydroxylamine hydrochloride in two different condition (i) in the presence of sodium acetate/acetic acid (pH 2.2) in refluxing ethanol/benzene to give 3,5-bis(het)arylisoxazoles 56; (ii) in the presence of barium hydroxide by refluxing in ethanol gave 3,5-bis-(het)arylisoxazoles 56 with complementary region-selectivity in high yields (Scheme17).\(^{50-51}\)
Scheme-17: Synthesis of 3,5-bis-(het)arylisoxazoles from 1,3 diketones.

1.3.4 Miscellaneous Reactions

The latest inclusion in the chemistry of synthesis of dithioester via Grignard reaction is the development a facile indium (0)-mediated regioselective alkylation protocol for α-enolic ester/dithioester 57 systems that proceeds through a Csp$^3$–S/O cross coupling reaction of alkyl indium reagents, allyl halides and α-enolic esters/dithioesters (Scheme18). \(^{58}\)

\[
\begin{align*}
\text{Scheme- 18: Inidium (0) catalysed regioselective alkylation of for α-enolic dithioesters} \\
\text{Halawa A. H.}^{51}\text{ has accounted for the interaction of alkyl dithioester 57 with} \\
\text{hydrazonyl halides 58 in ethanol containing triethylamine at reflux temperature to} \\
furnish 1,3,4-thiadiazole}
\end{align*}
\]
derivatives 63. The initial condensation of 2-acetyl-5-bromo benzofuran 60 with methyl hydrazinecarbodithioate and thiosemicarbazide 63 in ethanol at reflux temperature afforded product (Scheme19).

Scheme-19: condensation of 2-acetyl-5-bromo benzofuran with methyl hydrazinecarbodithioate and thiosemicarbazide.

1.4.0 Benzothiophenes:

Among bicyclic heteroaromatic compounds, benzo[b]thiophene52 and its substituted derivatives occupy a unique place in organic chemistry. This class of compounds has been known for a long time since their isolation from coal tar distillates. Several synthetic methodologies have been developed in the intervening years. On the other hand, the practical applications of benzothiophenes, especially as pharmaceutical agents, pale when compared with their nitrogen cousins, i.e. indole alkaloids. However, growing interests in this area, especially those of medicinal applications, have rekindled research activities in this venerable field. This review will focus on the most recent developments in the synthesis and medicinal applications of benzo[b]thiophenes. Selected reactions unique to benzothiophene, that offer previously unmet synthetic needs will also be discussed. For a systematic coverage of this heterocycle, including its chemical reactivity’s and physical properties, reviews that appeared in the last decade53-55 and earlier are available56-58.
Fig-2: Examples of natural products containing benzo[\(b\)]thiophenes core structures.

Although alkylated benzo[\(b\)]thiophenes account for a large portion of the sulfur content in coal tar distillates and crude petroleum, their origin has not been clearly elucidated and their presence in these products has largely been regarded as a nuisance to product quality. The isolation of pure benzothiophene derivatives from these sources posed a considerable technical challenge as many close analogs with similar physical characteristics often coexist. While there was some earlier interest of thioindigo as a dye, the commercial availability of benzo[\(b\)]thiophene and its derivatives has so far been very limited. Whereas indole plays a key role in protein chemistry as part of the essential amino acid L-tryptophan, and numerous natural products of important bio-logical activities containing that heterocycle have been identified, synthesized and commercialized. There is a relative scarcity of benzo[\(b\)]thiophene-containing compounds which are isolated from living organisms.\(^{54-56}\)

However, the recent discovery of a novel class of antitumor and antimicrobial compounds from the latrunculia sponge species of Newzeland is likely to elevate the interest level of benzothiophene in the natural products arena, as represented by a hexahydrobenzothiophene, The benzothiophene moiety is better manifested in another member of the marine natural product family as the dihydro derivative (\(-\))-makaluvamine F.

In the last two decades, benzothiophene has increasingly been recognized as a pharmacophore that offers advantages including superior chemical and
pharmacological stability, low intrinsic toxicity, and, most importantly, a rich chemistry that enables medicinal chemists to explore molecular diversity in a rapid fashion using tools that have been developed concurrently and are recently gaining popularity, such as transition metal catalyzed carbon-carbon, and carbon-hetero bond formation and combinatorial chemistry.

A large body of work related to benzothiophenes emerged with the development and introduction of three new chemical entities (NCE) containing this heterocycle as pharmaceuticals in recent years. Raloxifene is a selective estrogen receptor modulator (SERM) that mimics the beneficial effects of estrogen in the skeletal and the cardiovascular systems, while lacking certain unpleasant side effects linked with traditional estrogen replacement therapies in reproductive tissues.

![Chemical Structures](image)

**Figure-3:** Examples of drugs containing benzo[b]thiophenes core structure

This drug has been approved in the US and Europe for the prevention of osteoporosis in postmenopausal women. Zileutin 5-lipoxygenase inhibitor has been approved and is on the market for anti-inflammatory indications. Sertaconale has recently been introduced to the market as a broad spectrum antifungal reagent.
1.4.1 C-S Bond formation in Benzothiophene.

There are two possible modes of cyclization via the formation of an aryl-sulfur bond to construct the thiophene ring. One involves an electrophilic sulfur species attacking the phenyl ring. The other requires an activated leaving group on the recipient carbon of the phenyl ring being displaced by a sulfur nucleophile. The latter mode of reaction has not received much attention, primarily for the reason that such aromatic nucleophilic substitution (SNA) would require a highly activated aryl halide, a thioenolate anion, photochemical activation, and/or transition metal catalysis. The preparation of these cyclization precursors may be time and effort consuming. Cyclization through the intermediacy of electrophilic sulfur, on the other hand, does not require a predisposed leaving group other than a proton at the C-8 position. The transient sulfur cation, however, is unstable and could not be easily isolated. In most cases the reaction is limited to forming benzothiophenes with an electron withdrawing group such as cyano or carboxylate at the 2-position and, more critically, the lack of such groups on the benzene ring.\textsuperscript{62-64}

\textbf{Scheme-20:} Synthesis of benzothiophenes by insertion of sulfur
1.4.2. Different approaches for the synthesis of benzothiophenes

Among recent syntheses, the most common approach for benzo[b]thiophenes involves intramolecular \(5\)-\(endo\)-\(dig\) cyclization of \(\alpha\)-alkynyl arylthioethers or their surrogates, employing electrophilic reagents such as iodine, bromine, NBS, PhSCl, or PhSeCl. The methodology has also been extended to transition-metal-catalyzed cyclization of these analogues, such as Pd, Cu, or gold-catalyzed anulations.2-

Substituted benzothiophenes have also been accessed via tandem intra- molecular palladium- or copper-catalyzed S-vinylation and an intermolecular cross-coupling reaction of \(\alpha\)-(gem-dibromovinyl)-thiophenols. The crucial bond-forming event in these reactions is intramolecular attack of the nucleophilic sulfur atom on the activated C–C multiple bond, leading to the formation of the S(1)–C(2) bond of the benzothiophene core. These reactions, although selective and an efficient, however, require prior synthesis of difficult to access pre functionalized thiophenol precursors.

Recently, copper-catalyzed (or Pd-catalyzed) double thiolation of \(\alpha\)-(2-
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halovinyl)halobenzenes or 2-bromoalkynylbenzenes with metal sulfides or its surrogates, leading to 2-substituted benzo[\(b\)]thiophenes, has also been reported.\(^{65-68}\)

1.4.3 Recent reported literature for the synthesis of benzothiophenes.

Zhao et al reported a ligand-free Pd(OAc)\(_2\) was found to catalyze very efficiently the direct C2-arylation of benzothiophene derivatives under low catalyst concentration.\(^68\)

![Scheme-22: Palladium-catalyzed direct arylation of benzothiophene derivatives with (hetero) aryl bromides.](image)

Siang-en Syu and et al reported new types of highly functional benzothiophenes via intramolecular Wittig reaction with the corresponding ester, thioester and amide functionalities. The key intermediate, phosphorous ylide presumably result from the addition of Bu\(_3\)P toward aldehyde followed by acylation and deprotonation.\(^{69-72}\)

![Scheme-23: Synthesis of highly functionalized benzothiophenes.](image)
Christopher and et al reported a tandem catalytic reaction of a gem-dihalovinyl thiophenol system in which an intramolecular $S$-vinylation is paired with an intramolecular C-C bond forming reaction to yield 2-substituted benzothiophenes.\textsuperscript{73}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {Br\hspace{1cm}Br};
\node (b) at (2,0) {R-B(OH)$_2$};
\node (c) at (4,0) {PdCl$_2$ (3 mol\%)};
\node (d) at (6,0) {SPhos (3 mol\%)};
\node (e) at (8,0) {K$_3$PO$_4$/Et$_3$N (3 eq)};
\node (f) at (9,0) {dioxane, 110 $^\circ$C};
\node (g) at (11,0) {$\text{SH}$};
\node (h) at (13,0) {$R$};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\draw[->] (e) -- (f);
\draw[->] (f) -- (g);
\draw[->] (g) -- (h);
\end{tikzpicture}
\end{center}

\textbf{Scheme-24:} Synthesis of benzothiophenes from gem-dihalovinyl thiophenes

M. Jacubert and et al reported a synthesis of 2-aryl benzothiophenes from $o$-substituted arylalkynes with PTSA in EtOH.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{Ph=CH$_2$}};
\node (b) at (2,0) {\text{Ph=CH$_2$}};
\node (c) at (4,0) {X};
\node (d) at (6,0) {R$_1$};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\end{tikzpicture}
\end{center}

\textbf{X} = \text{S, O}

\textbf{Scheme-25:} Synthesis of benzothiophenes form $o$-aryl substituted arylalkynes.

Kazunori and et al reported a rhodium-catalyzed $o$-alkenylation of phenyl sulfoxides using alkene as substituent through sulfoxide group directed C-H bond cleavage to produce the corresponding $o$-alkenylphenyl sulfoxides. The products readily undergo interrupted Pummer cyclization as well as reduction to afford benzothiophenes and $o$-alkylphenyl sulfides.
Scheme-26: Reaction of phenyl sulfoxide with alkene to afford benzothiophenes.

1.5.0 Benzothiazines:

Benzothiazines are six membered cyclic compounds containing sulfur and nitrogen atoms at 1,2, 1,3 & 1,4 positions. In connection with the chemical peculiarities of this class of heterocycles and in connection with the fact that numerous logically active compounds have been found in the benzothiazine series, the research on this heterocyclic system has been undergoing extremely intensive development in the last decades.

Thiazine ring fused with the benzene ring system is commonly known as benzothiazine. Thienothiazine, pyridothiazine and benzothiazine ring systems are well known due to their medicinal activities. Their oxides as benzothiazine dioxides have gained much attraction in various fields of applied chemistry. Theoretically possible dioxides are benzothiazine-1,1-dioxide, and benzothiazine-2,2-dioxide as shown below.
Benzothiazine derivatives have extensively been studied in different areas of chemistry including the pharmaceutical and other chemical industries. With respect to biological applications, these derivatives are found potent anti-inflammatory, analgesic, anti-pyretic, anti-microbial, anti-viral, herbicidal, fungicidal, anticancer, anti-diabetic, anti-hypertensive and anti-oxidant agents. These derivatives have also been reported as synthetic intermediates for other drugs, as stabilizers in rubber vulcanization, corrosion inhibitors, and fading preventers. Besides the above applications these have been found useful during organ operations, activate metabolism, reduce gastrointestinal toxicity, be active as histamine receptor antagonist and have been synthesized with the aim to exhibit the high vaso relaxant potency as potassium channel openers (K$_2$CO$_3$).

1.5.1 Methods for the synthesis of 1,3-Benzothiazines:

$1H$-1,3-Benzothiazines only substituted compounds are obtained from dehydrobenzothiazinone through its silver derivatives are known. Their structure was proved by hydrolysis which leads to 2-(alkylthio)benzamides and benzaldehyde.\(^{74}\)

![Scheme 27: Synthesis of 1,3 benzothiazines from dehydrobenzothiazinone.](image)

Condensation of $N$-(hydroxymethyl)formamide and 3,4-dimethoxythiophene in the presence of phosphorous oxychloride is also known for 1,3-benzothiazine\(^{75-76}\).
Scheme 28: Synthesis of 1,3-benothiazines from N-(hydroxymethyl)formamide.

2H-1,3-Benzothiazinedervatives were first obtained by thermolysis of 2-(arylthio)axazol-573

Scheme-29: Synthesis of benzothiazines from 2-(arylthio)axazol-5.

2,4,4-Trisubstituted 4H-1,3-benothiazines are formed by the reaction of aromatic nitriles in the presence of mineral acids.77-78

Scheme-30: Synthesis of 2,4,4-trisubstituted 4H-1,3-benothiazines from aromatic nitriles.
1.5.2 Reactions of 1,3-benzothiazine derivatives with substituted acetyl chlorides

Cycloaddition reactions of 6,7-dimethoxy-2H-1,3-benzothiazine was reacted with the acid chloride in the presence of triethylamine, the product were the β-lactum derivatives. The heating of β-lactum with hydrogen chloride in ethanol led to cleavage of the β-lactum ring to yield compounds of β-amino-ester type.

Scheme-31: Synthesis of β-amino-ester from 6,7-dimethoxy-2H-1,3-benzothiazine

The reaction of 4-methyl-6,7-dimethoxy-2H-1,3-benzothiazines and the acid chloride gave under similar conditions, the enamides in good yield.

Scheme-32: Synthesis of enamides from 4-methyl-6,7-dimethoxy-2H-1,3-benzothiazines.

1.6.0 Introduction to oxadiazoles

Oxadiazoles are five-membered hetero aromatic rings containing two carbons, two nitrogens, and one oxygen atom, and they exist in different regioisomeric forms. Oxadiazoles are frequently occurring motifs in drugs like molecules, and they are often used with the intention of being bioisosteric replacements for ester and amide functionalities. Oxadiazoles are of considerable interest in different areas of medicinal
and pesticide chemistry and also polymer and material science. The level of interest is clearly shown, as over the past 10 years the number of patent applications containing oxadiazole rings has increased considerably (100%), to a total of 686. Within drug discovery and development, a number of compounds containing an oxadiazole moiety are in late stage clinical trials, including zibotentan as an anticancer agent\textsuperscript{108} and ataluren for the treatment of cystic fibrosis\textsuperscript{109} So far, one oxadiazole containing compound, raltegravir,\textsuperscript{110} an antiretroviral drug for the treatment of HIV infection, has been launched onto the marketplace. It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes,\textsuperscript{111} obesity,\textsuperscript{112} inflammation,\textsuperscript{113} cancer,\textsuperscript{114} and infection.\textsuperscript{115}

![Figure 8: Bioactive oxadiazoles](image)

**1.6.1 Introduction to 1,2,4-oxadiazoles:**

Among many heteroaromatic rings present, fused [1, 2, 4]-oxadiazoles are also ubiquitous feature of many pharmaceutical products. Compounds having five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or furodiazoles in the older literature. The oxadiazoles are classified into four different groups, depending on the position of nitrogen and oxygen atoms in the ring. These are 1:2:3-oxadiazole, 1:2:5 oxadiazole, 1:2:4 oxadiazole and 1:3:4 oxadiazole as shown in (Table 1). [1, 2, 3]-oxadiazole: This ring system has been supposed to exist in the (aliphatic) diazo-oxide. The importance of the [1,2,3]-oxadiazole ring system lies in the stabilization offered in the derivatives, in higher oxidation states.
these are known as sydnones and sydnonimines. Among the 1,2,3-oxadiazole derivatives two compounds received much attention in tests for biological activity. Both are sydnonimics: Molsidomine (A) and Sydnocarb (B). It is reported that Molsidomine has long–term effect in vasodilatation and diminishes the work of the heart in cases of ischemic heart disease. It acts like nitroglycerine in treating angina pectoris. Sydnocarb acts on the central nervous system and has been used as a psycho stimulant, as a CNS stimulant to motor activities. Many other sydnones and sydnonimines have been tested for anti-inflammatory, anti-tumor, antibacterial, analgesic and antipyretic activity.

**Table-1: Types of oxadiazoles:**

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</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image2" alt="Structure 2" /></td>
<td><img src="image3" alt="Structure 3" /></td>
<td><img src="image4" alt="Structure 4" /></td>
</tr>
<tr>
<td>1:2:3oxadiazole (A)</td>
<td>1:2:5oxadiazole (B)</td>
<td>1:2:4oxadiazole (C)</td>
<td>1:3:4oxadiazole (D)</td>
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**1.6.2 General methods for the synthesis of [1,2,4]-oxadiazoles:**

Two general methods of synthesizing 1, 2, 4-oxadiazoles can be pictured as joining of the skeletons as shown below. The carbon C-5 in B can be in oxidation state +4, +3 or +2 to give oxadiazoles or the reduced ring oxadiazolines. The SP² carbon at C-3 is commonly in an amidoxime or an iminoether. The fragments C and D may be triple bonds as shown, undergoes 1,3-dipolar cycloaddition to form 1,2,4-oxadiazoles. These two methods of ring formation comprise at least 95 % of the successful syntheses of [1,2,4]-oxadiazole compounds.
1.6.3 Synthesis of 1,2,4-oxadiazoles from amidoximes with acid derivatives

Oxadiazoles 120 can be synthesized by reacting amidoxime 117 with a suitably activated acid derivative 118 such as ester or acid chloride or anhydride or orthoester to obtain intermediate 119 which under different experimental conditions yields compound 120.

![Chemical structure](image)

Scheme 33: Synthesis of 1,2,4-oxadiazoles from amidoximes with acid derivatives.

1.6.4 Synthesis of 1,2,4 oxadiazoles from amidoximes with amide derivatives

Synthesis of oxadiazole by heating an amide with an amidoxime salt is practical since separation and recovery are simple.

![Chemical structure](image)

Scheme 34: Synthesis of 1,2,4-oxadiazoles from amidoximes with amides

1.6.5 Recent reported literature for the synthesis of 1,2,4-oxadiazoles:

John K. Augustine and et al reported a PTSA-ZnCl$_2$ to be an efficient and mild catalyst for the synthesis of 3,5-disubstituted -1,2,4-oxadiazoles from amidoxime and organic nitriles.$^{116}$

![Chemical structure](image)
**Scheme-35:** Synthesis of 3,5-disubstituted -1,2,4-oxadiazoles from amidoxime and organic nitriles

Barros and *et al* reported a synthesis of 3-(aryl)-5-(n-pentyl)-1,2,4-oxadiazoles by treatment of arylamidoximes with ethylhexanoate for 8 min under microwave irradiation using carbonate as base in solvent-free condition.

![Chemical structure](image)

**Scheme-36:** Synthesis of 3-(aryl)-5-(n-pentyl)-1,2,4-oxadiazoles from aryl amidoximes.

Shivaji Kandre and *et al* reported a 3,5-substituted 1,2,4-oxadiazoles from amidoximes and substituted benzoyl cyanide under microwave irradiation.

![Chemical structure](image)

**Scheme-37:** Synthesis of 1,2,4-oxadiazoles from amidoxime with benzoyl cyanide

Zakeri and *et al* reported a reaction of aryl nitriles with hydroxylamine using acetic acid as a catalyst followed by subsequent addition of crotonoyl chloride to the intermediate amidoxime represents a straightforward one-pot access to new 1,2,4-oxadiazole synthesis under mild conditions.
Scheme-38: Synthesis of 1,2,4-oxadiazoles from nitriles and acid chlorides.

Kenley, *et al* have reported that the substituted amidoximes 138 were undergoes cyclodehydration to the 3-substituted 5-methyl-[1,2,4]-oxadiazole 139 by refluxing in acetic anhydride.

Scheme-39: Synthesis of 1,2,4-oxadiazoles from acetic anhydride.

Alan Katritzky, *et al*.117 have reported the synthesis of [1,2,4]-oxadiazoles 141 derived from chiral alpha amino acid esters in 70-94 % yield.

Scheme-40: Synthesis of 1,2,4-oxadiazoles from α-amino acid esters.
1.7. References:


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