DIVERSE REACTIONS OF α/β-MERCAPTOALKANOIC ACIDS: IN THE SYNTHESSES OF CONDENSED FUSED POLYCYCLIC HETEROCYCLES

(dedicated to late Dr. KALLAM ANJI REDDY)

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Abstract: This review describes the reactions of α/β-mercaptoalkanoic acids as building blocks for the synthesis of polyfunctional heterocycles with pharmacological interest. Annelated heterocycles have been prepared by the cyclocondensation reaction of α/β-mercaptoalkanoic acids with carbonyl function. This reaction takes place by nucleophilic addition, followed by cyclisation with elimination of water. The main objective of this survey is to provide a comprehensive account of the reactions of α/β-mercaptoalkanoic acids with carbonyl function, β-halovinylaldehydes, α-haloesters, hetero/aromatic halides, α-halonitriles, imines in building various heterocycles and examining their potential in developing better chemotherapeutic agents.

Keywords: 2-mercaptoacetic acid, β-mercaptopropanoic acid, cyclocondensation, spiro heterocycles.

1. INTRODUCTION

Voluminous literature on the utility of α/β-mercaptoalkanoic acids (1a-e), esters as a versatile synthron in the preparation of condensed fused heterocycles has appeared in recent times. In spite of the fact that there appeared in literature reviews on reactions of these reagents (1a-e) with aldimines, β-halovinylaldehydes, a detailed account on the reactions with carbonyl group and other functionalities like α-haloesters, hetero/aromatic halides, α-halonitriles, imines, olefin, hydroxyl functional groups, is not reported till date. This necessitated us to review and highlight the current reactions in the field of polycyclic heterocycles.

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The present review is divided into 4 sections based on the nature of heterocycles formed or employed or the type of reaction used.

1. Spiroheterocycles
2. Heterocycles based on S_N-Ar mechanism
3. Conjugate addition to olefinic bonds
4. Miscellaneous

2. SPIROHETEROCYCLES

Spiro heterocyclic compounds are of interest in synthetic organic chemistry. Indeed, the presence of spiro carbon atom induces a relative steric strain and allows thermal, base or acid promoted rearrangement of these products. Thus they yield new and often unexpected heterocycles. 

The cycloaddition between dipolarophiles bearing an exocyclic carbon-carbon double bond and appropriate 1,3-dipole is one of the best methods for the synthesis of bicyclic spiro compounds. The other method is the cyclocondensation of aldimines with bifunctional nucleophiles such as \( \alpha/\beta \)-mercaptocarboxylic acids. Recent literature reports revealed the synthesis of some spiro heterocycles that have activity as herbicides and pesticides.

2.1. Spiro thioxa-4-one derivative

Pelter et al. \(^{12}\) reported the synthesis of spirooxathiolanones (3) by the reaction of mercaptosuccinic acid and cyclohexanone (2) in toluene under azeotropic removal of water using \( p \)-toluenesulfonic acid as a catalyst in 80 \% yield (Eq.1).

\[
\begin{align*}
2 & \xrightarrow{(i), \text{1d}} 3 \\
(\text{i}) & \text{p-TSA, toluene}
\end{align*}
\]

\[(\text{Eq.1})\]

2.2. Spiro-oxathiolanones

The synthesis of optically active \( \alpha \)-substituted thioglycolic acids has been reported by Liu and Chen \(^{13}\) in recent years, which involves a self-reproduction of chirality from an optically active \( \alpha \)-monosubstituted thioglycolic acid \(^{14}\) or reaction of thiolates with an optically active \( \alpha \)-hetero substituted acetic acid. \(^{15}\) When a benzene solution containing R-(+) -camphor (4) and 2-mercaptoacetic acid 1a in the presence of catalytic amount of \( p \)-toluenesulfonic acid was refluxed for 120 hours, two optically active oxathiolanones 5a and 5b were obtained \(^{16}\) in a ratio 5.6 to 1 with a total yield of 95\% (conversion 52\%).
The preferential formation of 1,3-oxathiolan-5-one 5b would be predicted by an \textit{endo} attack on carbonyl carbon of camphor by the more nucleophilic sulfur atom of the 2-mercaptoacetic acid, followed by lactonization. The major oxathiolanone 5a was deprotonated with lithium diisopropylamide in THF at -78 °C and alkylated with a variety of alkyl halides to yield monoalkylated products 6, 7 with excellent diastereoselectivity. The predicted stereochemistry of ketalization and alkylation were in agreement with X-ray crystallography result (Scheme 1).

2.3. Spiro [fluoren-oxathiolan]-one and Spiro [anthracen-oxathiolan]-one

![Diagram](https://via.placeholder.com/150)

Spiro derivatives exhibit interesting photochromic properties, biological activity and optical activity.\(^{17}\) Thiazolidinones are known for their bactericidal, fungicidal, anti-inflammatory activity.\(^{18}\) Hozien and Wareth\(^{19}\) reported the synthesis of spirotetrahydrothiochromeno-1,2,3-selena/thiadiazoles much emphasis has been placed on the synthesis of heterocyclic compounds resembling a steroidal moiety because of the interest in their chemical and physical properties.\(^{20}\) The gem-
ester functionality of 2, 6-dimethyl-4-oxocyclohexan-1,1-dicarboxylates was found to be a useful one for the development of spiro-pyrimidine-triones, pyrazolidinediones and isoxazolidinediones. Bhaskara Reddy and Ramana Reddy reported the synthesis of spiro-pyrimidine-triones having 1, 2, 3-selena/thiadiazole group in a rigid framework. The condensation of 15 and 16 with 2-mercaptoacetic acid 1a and β-mercaptopropanoic acid 1b in the presence of p-toluenesulfonic acid in benzene resulted in the corresponding thioacids which, on cyclodehydration with phosphorous pentoxide, led to the formation of tricyclic ketones. The semicarbazones of the tricyclic ketones by oxidative cyclization with SeO2 and Hurd-Mori reaction process with SOCl2 furnished 6,8-diarylspiro[5,6,7,8-tetrahydrobenzo[4,5]thieno[3,2-d][1,2,3]selena/thiadiazole-7,5'-[hexahydropyrimidine]2,4''-triones (29/33), 7,4'-[tetrahydroisoxazole]-3,5'-diones (30/34) and 7,9-diaryl spiro [hexahydropyrimidine-5,8- (6,7,8,9-tetrahydro-4 H-thiochromene)[4,3-d][1,2,3] selena / thiadiazoles]-2,4,6-triones (31 /35) and [tetrahydro-isoxazole-4,8'-(6',7',8',9'-tetrahydro-4'H-thiochromene)[4,3,-d] [1,2,3] selena/thiadizole]-3,5-diones (32/36) (Scheme 3).

\[ \text{Scheme 3} \]

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2.5. Spiro-pyrazolidinedione-dithietano-thiazolidinone
The 3,5-pyrazolidinediones have gained increasing importance in recent years owing to the medical use of 4-butyl-1,2-diphenyl-3,5-pyrazolinedione (butazolidin) in the treatment of rheumatoid arthritis. Khodairy reported the synthesis of fused spiro heterocyclic compounds containing a pyrazole moiety using PTC technique. 4,4-dibromo-1-phenyl-pyrazolinedione (38) was treated with CS$_2$ and active methylenes namely ethyl cyanoacetate under PTC conditions to afford the corresponding dithietane derivative 39. The reaction of dithietane 39 in pyridine with 2-mercaptoacetic acid gave the spiro derivatives of thiazolidinone 40 in 56% yield (Scheme 4).

![Scheme 4](image)

2.6. Spiro-coumarylideno-thiophenones
α,β-unsaturated nitriles are versatile reagents extensively utilized in heterocyclic synthesis. Coumarin derivatives are known for their physiological, anti-bacterial and antifungal properties. Abdel Ghany et al. reported the synthesis of spiro heterocyclic systems attached to coumarin nucleus by the addition of bidentates to 2-coumarylidene malononitrile derivatives. The reaction of thiocoumarin 41 with malononitrile in refluxing ethanol in presence of triethylamine as a catalyst gave 2-coumarylidemalononitrile 42 in 83-86% yield. The reaction of compounds 42a, b with mercaptoacetic acid 1a in refluxing pyridine gave the corresponding spiro thiophen-3-one derivatives 43a,b. The postulated mechanism involves addition of the mercapto group on the ethylene bond followed by cyclization via elimination of water molecule to afford the spiro compound (Scheme 5).

![Scheme 5](image)

2.7. Spiro 1,3-oxathiolane
Development of organic solid state reaction has emerged as frontier area of research in synthetic organic chemistry. The reactions are especially appealing because they have certain advantages, such as high efficiency, selectivity, mild reaction conditions, and environmental acceptability. This approach has been widely used in a variety of organic reactions. The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole, spirooxathiolane heterocycles have made them attractive synthetic targets.
Dandia et al. have reported the synthesis of spiro 1, 3-oxathiolanes containing different alicyclic / heterocyclic moieties (48-53). Cyclocondensation was performed using excess molar ratio of α/β-mercaptoalkanoic acids 1a-c with carbonyl compounds such as cyclopentanone 44, cyclohexanone 45, substituted indoles 46,47, by the solid state reaction at room temperature in 2-3 min after grinding the two reactants in agate mortar. The method was extended to reaction of aromatic aldehydes 52/ ketones 530 giving 2-(substitutedaryl)-4-methyl-1,3-oxathiolane derivatives (54-55). This cyclocondensation reaction is a two step reaction. The first step involves nucleophilic attack of thiol group on carbon-oxygen double bond of carbonyl group giving the intermediate hydroxyl alkylthio acids (A & B) which on elimination of water gave the products (48-55) (Scheme 6).

3. HETEROCYCLES BASED ON S_N AR MECHANISM (ADDITION-ELIMINATION PATH)

The chemistry of α/β-mercaptoalkanoic acids thus far has always been the subject of intense research efforts. Undoubtedly this is due to their synthetic potential and numerous applications associated with their chemistry. As a consequence, α/β-mercaptoalkanoic acids and their esters
have enjoyed a similar pronounced attention. Here we would like to report the reactions between \( \alpha/\beta \)-mercaptoalcanoic acids and other reactive intermediates such as \( \beta \)-halovinylaldehydes,\(^{43-46}\) \( \alpha \)-haloesters,\(^{47}\) hetero/aromatic halides,\(^{48}\) \( \alpha \)-halonitriles, imines which involves the formation of C-S bond by nucleophilic substitution followed by addition-elimination path\(^{49,50}\) resulting in the formation of condensed five, six or seven member heterocycles. Derivatives prepared in this fashion relate to patents or experiments to develop potent heterocycles aiming at agrochemicals or drugs.

Johnson \textit{et al.}\(^{51}\) has reported the synthesis of 5,6-dihydro-7,1,4,2-oxathiazepin-7-one (57) by the reaction of hydroximoyl chloride (56) with \( \beta \)-mercaptopropionic acid 1b, followed by cyclisation with DCC (Eq.2).

![Chemical structure of 57](image)

**Eq. 2**

### 3.1. Oxathiolanones

Imidoyl chlorides combine the properties of both acid chlorides and azomethines. They are reactive and versatile chemical agents that have found wide application in organic synthesis and in the study of chemical reactivity.\(^{52}\) Trifluoroacetimidoyl chlorides are regarded as promising new building blocks for the synthesis of functionalized fluorine-containing compounds.\(^{53}\)

![Chemical structures of oxathiolanones](image)

**Fig. 1**

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**Scheme 7**

The derivatives of 1,3-oxathiolanones have applications as fungicides, herbicides, growth regulators\(^{54}\) (Figure 1a, b). Onys’ko \textit{et al.}\(^{55}\) reported the synthesis of oxathiolanones, based on accessible fluoroacetimidoyl chlorides, activated by \( N \)-acyl-\( O \)-\( N \)-sulfonyl substituents. Heterocyclization of imidoyl chlorides 58 with \( \alpha \)-mercaptocarboxylic acids 1a, 1c in benzene affords the corresponding oxathiolanones 60 in high yields. The unusually facile transformation of 58 to 60 most likely results from the highly electrophilic nature of imines 58 and from a beneficial five membered ring formation. It is quite possible that substitution of the chlorine atom by the thio-function is accompanied by far intramolecular ring closure of immonium salts of type 59. The remarkable ease of heterocyclization can be explained by the high electrophilicity of the iminium C-atom (59) and the geometrically favorable location of the reactive centers\(^{56}\) (Scheme 7).
3.2. 2-Benzothiopyran and 3-Benzothiepin Derivatives

Ipriflavone (7-isopropoxyisoflavone) 61 enhanced bone-like tissue formation in vitro due to stimulation of differentiation of rat bone marrow stromal cells into osteoblasts. 57 2-Benzothiopyran-1-carboxamide derivatives were found to increase cellular alkaline phosphatase (ALP) activity, in cultures of rat bone marrow stromal cells. Oda and co-workers 58 reported the synthesis of 2-benzothiopyran-1-carboxamide derivatives (70) and the ring expanded 3-benzothiepin-2-carboxamide derivatives (71) starting from α-haloesters (62, 63) as described in scheme 8.

The sulfides 64, 65 were prepared by coupling of 62 or 63 with α-mercaptocarboxylic acids in the presence of a base. The sulfides (64, 65) were converted into acyl chlorides and cyclised by intramolecular Friedel-Crafts reaction to give esters (66, 67), which were then hydrolysed to provide carboxylic acids (68, 69). The amides (70, 71) were prepared by coupling reaction of 68 or 69 with amines 59 (R2NH2). The intramolecular cyclization of the sulfides 64, 65 gave a mixture of cis and trans products 66, 67, which were treated with alkoxide to afford the more stable trans form as a single product (Scheme 8).

The synthesized compounds 70a-h, 71a-h were screened for biological activity. The ALP activity of these 3-benzothiepin derivatives bearing a 4-(dialkoxyphosphoryl methyl) phenyl group on the 2-carboxamide moiety such as 71f and 71h exhibited significant improvements of activity compared to ipriflavone. The effect of compounds (10⁻⁵ M) on ALP activity in the culture of rat bone marrow stromal cell line MC3T3-E1 was evaluated according to the method.
of Maniatopoulos et al. and expressed as the ratio value compared to the control group \( (n = 5-10) \). This study revealed that \( 71h \) enhanced the effect of bone morphogenic protein.

3.3. 2-[Mercapto(cyano)methylene]-1, 2, 3, 4-tetrahydroquinazolin-4-ones
Quinazolin-4-ones have received considerable attention in the literature of pharmaceutical chemistry. Fleischer et al. reported the synthesis of substituted 2[mercapto(cyano)methylene]-1,2,3,4-tetrahydroquinazolin-4-ones 74 as a part of program aimed at the development of potent \( N \)-methyl-D-aspartic acid antagonists. The reaction of Quinazolinones (72) and \( N \)-bromosuccinimide in acetonitrile at room temperature gave the bromoquinazolinones (73) in 73% yield. The reaction of 73 with thiolactic acid 1c in methanol gave mercaptoquinazolinone derivative 74 in 18% yield (Scheme 9).

3.4. 3,4-Dihydro-2H-1,4-benzthiazine / 1,5-benzthiepine derivatives

![Scheme 9]

![Scheme 10]
Selective 5-HT₃ receptor antagonists exhibit potent antagonism of chemotherapy or radiation-induced emesis in humans, ondansetron, granisetron and azasetron (Fig. 2a-c) have already been marketed for this indication. Kuroita and co-workers reported the synthesis of benzthiazine-8-carboxamide and benzthiepine-9-carboxamide derivatives. Commercially available 2,5-dichloro-3-nitrobenzoic acid was converted into ethyl 2,5-dichloro-3-nitrobenzoate (75) by reaction with ethanol as per the methodology described by Spreklov's. Thioethers 76a and 76b were prepared by coupling of 75 with mercapto acids 1a, b respectively. The nitro group of 76a was reduced with iron powder under a neutral condition of aqueous ammonium chloride, followed by spontaneous cyclization to afford 77a with a desired ring system. Compound 76b was reduced by the use of iron powder without spontaneous cyclization and cyclization with an acid catalyst provided 77b. The amides 77a, 77b were reduced to the amines 78a,b in presence of sodium borohydride, boron trifluoride etherate and tetrahydrofuran by the Merkel’s method of selective reduction of an amide in the presence of an ester moiety. Compounds 78a and 78b were methylated at the 5-position with iodomethane in the presence of K₂CO₃, followed by hydrolysis with base to afford carboxylic acids 79a and 79b respectively. Compounds 79a and 79b were coupled with 3-amino-1-azabicyclo[2.2.2]octane to give 80a and 80b respectively (Scheme 10).

### 3.5. Thienoquinolines

The reaction of 3-formyl-2-chloroquinolines (81a-d) with 2-mercaptoacetic acid in the presence of sodium hydroxide in absolute ethanol afforded a mixture of uncyclised [3-formylquinolin-2-yl]thioacetic acid (82a-d) in 60-70% yield and cyclised thieno[2,3-b]quinoline-2-carboxylic acids (83a-d) in a 30-40% yield respectively. The uncyclised compounds 82a-d on refluxing with POCl₃ in various alcoholic media gave [(3-formylquinolin-2-yl)thio]acetates 84a-l in 68-82% yield. Cyclisation of quinolinylthioacetates 84a-l under reflux conditions in DMF gave thieno[2,3-b]quinoline derivatives 85a-l in 70-85 % yield (Scheme 11).
3.6. 3-Thienoquinolinyl-thienoquinolinones

![Scheme 11]

Thienoquinolines are effective antipyretic, analgesic and anti-inflammatory agents and also useful as herbicides and insecticides. Few methods are known for the synthesis of angularly fused thienoquinolinones in the literature. Gupta and Darbarwar reported facile synthesis of thienoquinolines. 4-Chloro-1-substitutedquinolin-2(1H)-one were reacted with mercaptoacids, in dry methanol in the presence of anhydrous K$_2$CO$_3$ and triethylamine under reflux conditions afforded 2-[1,2-dihydro-2-oxo-4-quinolinthio]-acetic/propionic acids in 90-96% yield. The cyclodehydration of in polyphosphoric acid at 175-180 °C afforded 3-hydroxythieno[3,2-c]quinoline-1-substituted-4-(5H)-ones in 62-70 % yield. The compounds undergo aldol type condensation in aqueous acid medium resulting in the formation of 3-hydroxy-2-[4,5-dihydro-4-oxo-thieno[3,2-c]quinolin-3-yl]thieno[3,2-c]quinolin-4(5H)-ones in 67-69 % yield (Scheme 12).

3.7. Thiazino/thiazepinoquinolinecarboxylic acids

Synthetic fluoroquinolones [e.g. ciprofloxacin (Fig. 3a)] represent a successful achievement towards the design and development of potent antiinfective drugs. 1,4-benzothiazines derivatives are reported as excellent inhibitors of Nickel peptide deformylase (Ni-PDF) (Fig. 3b) and showed improved antibacterial potency. 2,3-dihydro-1,5-benzothiazepine-4(5H)-one derivatives, diltiazem (Fig. 3c) are of significant interest synthetically and pharmacologically. Huniti et al. reported the synthesis of hybrid tricyclic system encompassing the structural features of both “fluoroquinoline” (rings A, B) and dihydro-1,4-benzothiazine/thiazepine-4-one (rings B,C). The reaction of 2,4-dichloro-5-fluoro-3-nitrobenzoyl chloride with ethyl 3-(N,N-dimethylamine)acrylate following the reported procedure gave ethyl ester (92). The acid-catalysed hydrolysis of (93) gave 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxa-1,4-dihydroquinoline-3-carboxylic acid (94). The reaction between 7-Chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (94) and α/β-mercapto acids (1a-d), in aqueous acetone containing triethylamine afforded the corresponding acyclic precursors in 77-91 % yield (Scheme 13). This reaction follows a nucleophile aromatic substitution ‘SN Ar’ (addition-elimination) path and is facilitated by the presence of the electron withdrawing C(6)-fluoro-, C(4)-keto and C(8)-nitro groups. Reduction of the 8-nitro compound with sodium dithionite in aqueous potassium carbonate gave the respective 8-amino derivative. The intermediate 8-amino derivatives underwent lactamization upon heating with polyphosphoric acid (PPA) at 140-150 °C afforded the corresponding annulated products (97) in 68-75 % yield. The authors have reported the synthesis of pyrido[3’,2’:4,5]thieno[2,3-b][1,4] thiazines (99a-c) in 74-84 % yield utilizing 2-
chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carbo-xylic acid 97 as common synthon by adopting the same methodology as discussed in the above scheme (Scheme 48). The compounds 96a-d and 99a-c were tested using 10 uM concentration against the panel of 60 human cancer cell lines used by the National Cancer Institute (NCI, USA). The more affected cell line was IGROVI (from ovarian cancer). The % growth inhibition at 10 uM was 76%, 64%, 65% and 88% for compounds 96a, 96c and 99a, 99c respectively.

3.8. Benzothiazepines

Existing treatments for type II diabetes include insulin and modified insulins, insulin secretagogues (sulfonylureas and metiglinides), insulin sensitizers (thiazolidinediones and biguanides) and blockers of glucose uptake (acarbose and pramlintide). Compounds from different structural classes, such as CGP37157 [1,4-benzothiazepin-2-one] [Fig. 4], diltiazem [1,5-benzothiazepin-2-one] and prenylamine and fendiline (both phenylalkylamines), have been reported to inhibit mitochondrial sodium-calcium exchanger (mNCE) activity. The synthesis of benzothiazepinones described by Hirai et al. requires 5 steps starting from 2-aminobenzophenones. Pei and co-workers reported the synthesis of benzothiazepinones in two steps by 5-alkylation and cyclization. Benzhydrol 100a was allowed to react with 3-mercaptopropionic acid in trifluoroacetic acid to give thioacid derivatives 101. Cyclization of 101 using ethylene dichloride, diethylamine, 4-dimethylaminopyridine and bis(2-oxo-3oxazolidinyl)phosphonic chloride yielded the corresponding lactams 102 in 98% yield. The
compounds 102a-d were evaluated for their ability to inhibit m-NCE function, where in the exchanger-mediated Na\(^{+}\)/Ca\(^{2+}\) translocation in mitochondria in permeabilised cells was monitored by using a Ca\(^{2+}\) sensing fluorescence based assay. The 1,4-benzothiazepinone exhibited an IC\(_{50}\) of 1.4 µM which was comparable to the reported literature value of 0.4 µM. Substituents on the 5-phenyl ring appeared to be crucial for m-NCE activity. The 1,5-benzothiazocinone 101a exhibited an IC\(_{50}\) of 12.6 µM for m-NCE which indicates the potential of this lead as a drug candidate (Scheme 14).

3.9. 2-Arylmethyl isoidol-1-ones
Tetracyclic systems, as in Figure 5 incorporating an isoidole moiety with its nitrogen atom as one of the two junction atoms are widely expanded. The isoidololo [1,2-b] [3] benzazepine (n = 2, m = 0, X = CH\(_2\), ring D = benzene; Fig. 5) belonging to the aporhoeadane alkaloid series is one example.\(^{97}\) Pigeon and Decroix \(^{98, 99}\) reported the synthesis of substituted isoidolones 104a-e could be the precursors for the synthesis of tetracyclic isoidolobenzothiazoline 105 (X = S, n+m = 3). Hydroxylactam 100 103a-e [n = 0, 1; Ar = Ph, thien-2 (3)-yl] reacted with 2-mercaptoacetic acid 1a under the acidic conditions gave the substitution products 104a-e in 81-94% yield via a N-acyliminium ion. The acid derivative 104a was treated with thionly chloride under reflux conditions of DCM for 2 hrs and the resulting acid chloride in presence of aluminium chloride as a catalyst at -5 °C gave the cyclic ketone (105) in 62 % yield (Scheme 15).

3.10. Dihydropyrrolo-thiazole-3,5-dione
Pramiracetam (CI-879) compound Fig. 6a, was discovered to reverse electro-convulsive shock (ECS) induced amnesia in rodents and was found to possess cognition-enhancing activity in other paradigms.\(^{101}\) The dihydro-1H-pyrrolizine-3,5 (2H,6H)-diones (Figure 6b) have shown the reversal effects of ECS in mice over an extraordinarily broad dose range.\(^{102}\) Butler \textit{et al.} \(^{103}\) reported the synthesis of cyclic imides of pyrrolidone derivatives. 5-Ethoxy-2-pyrrolidinone 106
on reaction with mercaptoacids 1a,b at 70 °C for 24 h gave the 2/3-[5-oxo-(2-
pyrrolidinyl)thio]acetic/propanionic acids (107a,b) in 70-76 % yield. The reaction of thio acids (107a,b) with Ac$_2$O in acetic acid medium gave Dihydropyrrolo[2,1-b]thiazole-3,5 (2H, 6H)-
dione 108a and Dihydro-2H-pyrrolo[2,1-b][1,3]thiazole-4,6(3H,7H)-dione 108b in 45-58 %
yield (Scheme 16).

![Scheme 16](image_url)

4. CONJUGATE ADDITION TO OLEFINIC BOND
Carbon sulfur bond formation by conjugate addition of mercapto acids to α, β-unsaturated
 carbonyl compounds has versatile applications in chemistry and biology as it plays critical roles
(i) in biosynthesis, \(^{105}\) (ii) protection of the olefinic double bond of conjugated enones, \(^{106}\) (iii) synthesis of bioactive compounds, \(^{107}\) (iv) homoenolate anion equivalents \(^{108}\) and (v) generation of
β-acylvinyl cation. \(^{109}\) The present review aims to highlight the application mercaptoacids in this
field.

4.1. 3-(1-pyrrolidinyl)thiophenes

![Scheme 17](image_url)

Substituted 3-(1-pyrrolidinyl)-thiophenes undergo [2+2] cycloaddition reactions with
dimethylacetylene dicarboxylate in a polar solvent to give thieno [3,2-b]pyrrolizines. Reinoudt
et al. \(^{110}\) has reported the synthesis of alkyl- and aryl-substituted 3-(1-pyrrolidinyl)-thiophenes in
four steps. The initial step is the addition of mercaptaoacid 1a to α, β-unsaturated acid (109)
in presence of triethylamine in 1,4-dioxane under reflux conditions and it gave the substituted 3-
[(carboxymethyl)thio]propanoic acids 110a-d in 70-90% yield. Ring closure of the dicarboxylic
acid 110a-d in presence of acetic anhydride and lithium acetate as a catalyst at 120 °C afforded
the substituted 4-oxotetrahydrothiophenes (111a-d) in 60-83 % yield. Condensation of the cyclic
thioketones (111a-d) with pyrrolidine in presence of p-toluenesulfonic acid under azeotropic
removal of water gave pyrrolidinyl-2,3-dihydrothiophenes (112a-d) in 77-80 % yield. The
aromatization of the enamine (112a-d) in disopentyl disulfide medium \(^{111}\) at 200-250 °C
following the methodology of Buiter et al. \(^{112}\) gave 3-(1-Pyrrolidinyl)-thiophenes 113a-d in 14-
27 % overall yield (Scheme 17).
4.2. Long chain thioethers

![Chemical structure](image)

**Scheme 18**

Thioethers have been described as lubricants, additives, coatings, rubber substitutes and as intermediates for the preparation of wetting agents and detergents. Thioethers are also capable of increasing thermal stability of polymers and rubbers. Osman et al. have reported the synthesis of sulfurated ethers of olefinic fatty acids. Methyl 4-o xo-trans-2-hexadecenoate (114a) and 9, 12-dioxo-trans-10-octadecenoic acid (114b) were reacted with mercaptoacetic acid (1a) and 3-mercapto propionic acid (1b) in benzene medium under reflux conditions to afford branched chain thioethers 115a-d in 92-98 % yield. The addition products are of isomeric type in both cases (Scheme 18).

4.3. Telomerization Process

![Chemical structure](image)

**Scheme 19**

3-Mercaptopropionic acid (3-MPA) is known as a versatile bifunctional chain transfer reagent in the telemerization of short oligomers for biotechnology application. The dialkyl propenamide (116) undergoes telomerization process in presence of 3- mercaptopropionic acid, AIBN in methanol medium. AIBN is used as initiator to transform the thiol into radical and the isolated polymer (117) contains a single specific functional end group because of the high transfer activity of the 3-MPA. By the variation of the conc. of 3-MPA, the telomer length (117) is easily adjusted to a convenient molecular average weight (2000-2500 g/mol). Structures with a lower critical solution temperature are often used for bioconjugates (Scheme 19).

4.4. Dihydrochalcones

The Claisen-Schmidt condensation of substituted acetophenone (118), with substituted benzaldehyde (119), or furfural (120) in presence of sodium hydroxide and ethanol medium at room temperature gave chalcone derivative (121, 122) in 69-97 % yield. Ceylan et al. and Albert Levai have reported the reaction of chalcones (121, 122) with 2-mercaptoacetic acid1a
or 3-mercaptopropionic acid 1b in mild conditions. The Michael reaction of chalcones with mercapto acids occurs in presence of t-BuOK (6 mmol) at room temperature without solvent in a short reaction time of 3-hours to give the desired 1,4-addition products (123a-l; 124a-j). All the compounds showed antifungal activity. The dihydrochalcones 123a, e was an especially active against Aspergillus niger, Trichophyton mentagrophytes, Micosporum gypseum and Epidermophyton floccosum strains (Scheme 20).

![Chemical structure](image)

**Scheme 20**

<table>
<thead>
<tr>
<th>123 X</th>
<th>Ar'</th>
<th>n</th>
<th>Y %</th>
<th>124 X</th>
<th>Ar'</th>
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<td>1</td>
<td>74</td>
<td>b</td>
<td>3-MeO</td>
<td>Furan-2-y</td>
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</tr>
<tr>
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<td>4-ClC₆H₄</td>
<td>1</td>
<td>90</td>
<td>c</td>
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<td>1</td>
</tr>
<tr>
<td>d H</td>
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<td>83</td>
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<tr>
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<td>2</td>
<td>87</td>
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<td>4-Cl</td>
<td>Furan-2-y</td>
<td>1</td>
</tr>
<tr>
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<td>58</td>
<td>l</td>
<td>2-OH</td>
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<td>1</td>
</tr>
</tbody>
</table>

4.5. Tripodal Thio Ethers

1,3,5-triacyrloyl hexahydro-1,3,5-triazine (TAT) is an inexpensive stable symmetrical synthon and is used extensively for the synthesis of tripodal thioethers compounds which are of value as chelating ligands, and in nanoparticle assembly. Son et al. have reported the facile synthesis of functionalised tripodal thioether from ionic thiol-ene reactions of TAT. TAT (125) was reacted with 3-mercaptopropionic acid in presence of potassium bicarbonate and methanol to give the thioether 126 in 63 % yield. The triazine ring exists in the chair confirmation with the three ‘arms’ pointing out toward the same side of the ring to create a bowl-like cavity, due to combination of intra- and intermolecular hydrogen bonding, the extended structure consists of a linear chain of dimeric capsules in which triazine rings constitute the ends of capsule (Scheme 21).

![Chemical structure](image)

**Scheme 21**

126
4.6. Thiopyrano-benzopyrano-4, 5-diones

\[
\begin{align*}
\text{(i) pyridine; (ii) PPA; (iii) AcOH, 30 \% H_2O_2} \\
129 (a) & \text{ R = H, X = S (50\%); (b) R = H, X = SO_2 (55\%); (c) R = MeO, X = S (60\%)} \\
& \text{(d) R = MeO, X = SO_2 (45\%); (e) R = EtO, X = S (50\%); (f) R = EtO, X = SO_2 (68\%)}
\end{align*}
\]

Scheme 22

Merchant et al. \cite{133} have reported the reaction of 3-bromocoumarin derivatives 127 with β-mercaptopropionic acid in excess of pyridine under reflux conditions for 4-5-hours to yield the corresponding coumarinomercaptopropionic acids 128 in 50-60\% yield. The reaction has occurred at ‘4’ position instead of the expected ‘3’ position. The coumarinomercapto-propionic acids (128) were cyclised to the corresponding 2\(H\), 4\(H\), 5\(H\), 3, 2, (c)-1-benzopyrano-4,5-diones in 50-60\% yield. The above diones were oxidized with 30 \% H_2O_2 in acetic acid at room temperature to yield appropriate sulfones (129) in 45-58\% yield (Scheme 22).

4.7. Naphtho-bis-1,4-oxathiin-2,7-diones

A number of benzoquinones, naphthoquinones were reported to exhibit antifungal activity. \cite{134} Tandon et al. \cite{135-140} have reported the reaction of 1,4-naphthoquinones (130) \cite{141,142} with mercapto acids (1a-c) in ethanol at room temperature gave the S-(1,4-naphthoquinon-2-yl)mercapto acids (131a-i) in 40-80\% yield. The reaction of 1,4-naphtha-quinones 130 with two equivalents of 2-mercaptoacetic acid 1a, thiolactic acid 1c, however gave the tetracyclic oxathiin-diones (135a,b) in about 30-65\% yield. The mechanism of formation of (135a,b) from (130) and mercaptoalkanoic acids (1a, 1c) is shown in (Scheme 23).

The first step involves the addition of the anion of (1a, 1c) to form 131, which disproportionate to the corresponding S-(1,4-naphthoquin-2-yl) mercaptoalkanoic acid (132). Compound 132a, b, undergo further reaction with another molecule of (1a, 1c) to give 133a, 133b. The latter aromatises to the dihydro form (134a, b) leading to facile dehydration resulting in the formation of 135a, b. The preferential formation of 133b to give 134b may be due to the higher nucleophilicity of the sulfide anion of the thiolactic acid (1c) than 2-mercaptoacetic acid (1a)

Moreover, the side chain in 133b and 134b may exist only in folded or cisoid confirmation to facilitate the formation of 135b. The steric control observed during the formation of 135b in preference to 135a facilitated intramolecular cyclodehydration of 134b. The uncyclised acid (132a) S-(1,4-naphthoquinon-2-yl)mercapto acetic acid on cyclisation with PPA at 100 °C afforded 2,3,4,9-tetrahydronaphtho[2,3,-b]thiophene-3,4,9-trione 136 in 25\% yield (Scheme 23).

The evaluation of antifungal properties of compounds 259a-i was conducted against various strains of pathogenic fungi, for example C. albicans, C. neoformans, S. Schenckii, T. mentagrophytes, M. cannis and A. tumifaciens according to the method of Dhar et al., \cite{144} The promising inhibitory effect of 1,4-naphthoquinones containing a sulfur atom attached to carboxylic group 132h was pronounced against a number of fungi. MIC value of this compound was 3.12 \(\mu g/mL\) against C. albicans, T. mentagrophytes and M. cannis, where as it holds 1.56 \(\mu g/mL\) MIC value against C. neoformans and 25.0 \(\mu g/mL\) against A. tumifaciens. The activity of this compound against all the fungi is more when compared with amphotericin B and miconazole.
Naphthaquinone based oligonucleotides are known to sensitize the selective oxidation of thymine and serve as the basis for in-vivo application of specific modification of DNA. 

Rokita & Chatterjee reported the condensation reaction of 3-mercaptopropionic acid with 5-methyl-1,4-naphthoquinone (137) in 70 % ethanol at 4 °C to provide a convenient method for attaching a sequence-directing oligonucleotide. The products of this reaction, two inseperable regioisomers (138) were carried together throughout the sequence. Treatment of this acid
(138) with N-hydroxysuccinimide in presence of 1-ethyl-3-[3-(dimethylamino) propyl] carbodiimide yielded the activated succinimidyl ester 139. This was subsequently used to acylate a hexamethylenamine linking arm that was coupled to the 5’-terminus of an oligonucleotide 15 bases in length. The oligonucleotide with linker (140) preparation is based on standard procedure of solid-phase phosphoramidite chemistry (Scheme 24).

4.9. Brefeldin A sulfide Derivative
Brefeldin A is a macrolide antibiotic first isolated from the fungus *Penicillium decumbens*. Brefeldin A possesses a number of interesting biological properties of potential therapeutic interest, including antitumor and antiviral effects. However, the potential clinical use of Brefeldin A is severely limited by its undesirable pharmacokinetic properties including negligible bioavailability after oral administration and rapid clearance from blood plasma after intravenous administration. To make Brefeldin A prodrug water soluble compounds Argade et al. reported the synthesis of sulfide derivatives of Brefeldin A by Michael addition of thiols to the α, β-unsaturated lactone system present in 141. Brefeldin A was reacted with mercaptoacetic acid in aqueous methanol in the presence of Proton Sponge [1,8-(bisdimethylamino)naphthalene] to give thiol addition product 142. The reaction occurred readily and was found to be highly diastereoselective. The R configuration at C-3 in these products was assigned on the basis of the X-ray. The sulfide 142 was oxidized to sulfoxide 143 by oxidation with m-chloroperbenzoic acid in chloroform in 68% yield. The greater solubility of Brefeldin A (thioether) 143 (40 mg/mL) when compared to Brefeldin A (141) (2.8 mg/mL) indicates its potential for better formulation (Scheme 25).

**Scheme 25**

5. MISCELLANEOUS HETEROCYCLES

5.1. Dithianonanedioic acids
5-(2-dodecylphenyl)-4,6-dithianonanedioic acid (Fig. 7a, SK&F 102081) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid (Fig. 7b, SK&F 102922) prototypes of a class of selective leukotriene antagonists having improved potency and an increased duration of action. Perchonock et al. have reported the synthesis of alkynyl- and arylidithiaalkanedioic acids (“dithioacetals”) for evaluation of leukotriene antagonist activity. The disubstituted aryls (144) were alkylated with appropriate alkyl halides in presence of n-butyl lithium, tetrahydro, di-isopropylamine to give corresponding 2-dodecyl/ocetyl, 5 or 6-substituted acids (145). The acids on reduction with borane followed by subsequent oxidation with pyridinium chlorochromate in DCM gave the alkoxy substituted benzaldehydes (146). Reaction of (146) with 3-mercaptopropionic acids using boron trifluoride etherate as catalyst afforded arylidithiaalkanedioic acids (147) (Scheme 26).
1,3-dithianes are well known reagents in organic synthesis. Most of the dithianes are prepared from propane-1,3-dithiol and aldehydes or ketones and therefore possess substituents at the 2-position only. Balaiah and Prema reported the synthesis of 1,3-dithianes which have substituents at other positions via condensation process. The reaction of paraformaldehyde and mercaptoacetic acid \(1a\) in presence of conc. HCl at 100 °C gave methylene dithio-diacetic acid (148), in 75-80 % yield. The oxidation of (148) with hydrogen peroxide in acetic acid at 25-30 °C gave the bis-sulfone (149) in 85 % yield. The esterification of acid 149 with alcohol gave the disulfone diester (150) in 85-90 % yield. The dimethyl or diethylmethylene-bis-sulfonyl acetate 150 was condensed with aromatic aldehydes in presence of ammonium acetate in ethanol gave the 1,3-dithiane tetraoxide (151). The six membered ring compounds were formed instead of eight membered rings because of their greater stability and ease of formation (Scheme 27).

### 5.3 Thiolactone

Nucleophilic addition of mercaptoacetic acid 1a with 2,3-epoxy-2-methylpentane (152) in chloroform under reflux conditions was reported to give a 3:4 mixture of thiolactone (153)
and the hydroxy acetate (154). The formation of hydroxy acetate was explained through (the anchimeric assisted formation of) cyclic sulfonium ion intermediate (155) (Eq. 3).

\[
\begin{align*}
152 &\xrightarrow{(i)} 1a, c, reflux \\
153 &+ 154 \\
&\text{(i) CHCl}_3, \text{reflux} \\
\end{align*}
\]

\[\text{Eq. 3}\]

5.4. 1, 4-oxathianobenzodiazepine-2-ones
The reaction of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (156) (oxazepam) with mercaptocarboxylic acids 1a,c in anhydrous benzene under reflux conditions undergoes different cyclofunctionalisation route to give [1,4]-oxathianobenzodiazepine-2-ones (159) in 85-88% yield. The reaction of tricyclic oxathia-2-ones 159 with methanol and sulfuric acid gave the N-methyl derivative (336) in 30-40% yield. The formation of compounds (159) and (161) was shown in Scheme 28. This involves an initial esterification of 3-OH to give the unstable thioester intermediate (158) which through acid promoted cyclization and subsequent elimination of water leads to the formation of (159). The reaction with HSO_4 / MeOH allows the shift of the tautomeric imine-enamine equilibrium towards the enamine form (160) allowing the N-methylation to give derivatives (161), which could also be obtained by directly reacting N-methylloxazepam 157 with mercaptocarboxylic acids 1a,c adopting the same experimental conditions described as above (Scheme 28).

\[
\begin{align*}
156 &\xrightarrow{(i)} 1a,c \\
\begin{align*}
158 &\xrightarrow{(i)} 159a, 159b \\
161a &\xrightarrow{(ii)} 161b \\
\end{align*} \\
&\text{(i) benzene, reflux; (ii) HSO}_4, \text{MeOH} \\
\end{align*}
\]

\[\text{Scheme 28}\]

5.5. 10-Membered diamide disulfide ring
Structures similar to N,N'-ethylene bis-(2-thioacetamide) are frequent precursors to complexing reagents for technetium and have been used extensively in Tc-based radioimaging work both at research and clinical levels. Maharaj et al. reported the synthesis of cyclic diamide disulfides which can be used as lipophilic, bifunctional DADS chelators for Tc radio imaging.
The 10 membered heterocycle 165 was synthesized from 2-mercaptoacetic acid and \(N,N'\)-dimethylethylene diamine in four steps in 30% overall yield (Scheme 29). Tritylation of 2-mercaptoacetic acid under Lewis acid catalysis readily afforded the 2-(Triphenylmethyl)thioacetic acid 162, which was subsequently reacted with 1,3-dicyclohexylcarbodiimide (DCC) and \(N\)-hydroxysuccinimide (NHS) to give the activated succinimidoyl ester 163. Treatment of two equivalents of 163 with \(N,N'\)-dimethyl-ethylenediamine in 1,2-dimethoxyethane, allowed for the acylation of both nitrogens and the formation of \(N,N'\)-\{Dimethyl-bis[2-(triphenylmethyl)thioacetyl]\}-ethylenediamine 164 in 76% yield. Deprotection of diamide 164 was effected with 1.1 equivalents of iodine in ethanol-acetonitrile and by maintaining high dilution conditions to preclude intermolecular disulfide formation, \textit{in situ} intramolecular oxidative cyclization readily generated the monomeric 10 membered diamide disulfide 165 in 68% yield. The choice of the \(S\)-protecting group for thioacetic acid and the method for its cleavage were crucial for the efficiency of the synthesis. The \(S\)-protection by other means as arylthioethers, hemithioacetals or thioesters requires very harsh conditions that can lead to decomposition. This cyclic diamide disulfide exists in solution as a mixture of two \(Z, Z\) and one \(Z, E\) disulfide and amide ring conformers and has been characterized by nuclear Overhauser effect (NOE), \({}^1\)H-\({}^1\)H, \({}^1\)H-\({}^{13}\)C shift correlated 2D-NMR and molecular modeling studies (Scheme 29).

\[ \text{Scheme 29} \]

5.6. Thiolactomycin analogues

Thiolactomycin (TLM, Fig. 8), an antibiotic isolated from \textit{Nocardiа sp.}, is a unique thiolactone containing molecule that exhibits potent \textit{in vitro} activity against many pathogenic bacteria and \textit{M.tuberculosis}.\textsuperscript{169} Furthermore TLM and its analogues are attractive leads for new drugs against malaria.\textsuperscript{170} Markopoulou et al.\textsuperscript{171} have reported a one pot synthesis of thiotetronic ring system based on \(C\)-acylation/cyclization reaction between the activated esters and active methylene compounds. The synthesis involves first the reaction of mercapto acids 1a, c with acetyl chloride in presence of 1,4-dioxane and triethyl amine at 0 °C to give \textit{S}-acythioglycolic acids 166,167 in 90-95 % yield. The \(N\)-hydroxy succinimide esters of \textit{S}-acyethylthioglycolic acids 168,169 were prepared in 89-90 % yield by reaction of \textit{S}-acyethylthioglycolic acids with \(N\)-hydroxysuccinimide in presence of DCC and dichloromethane. The reaction of succinimidoyl esters of \textit{S}-acyethylthioglycolic acids 168,169 and active methylene esters 170-173 and malonitrile (174) in presence of NaH, THF at 0 °C afforded either the 3-substituted thiotetronic acids 176, 177, 178, 179 or 2-aminothiophenes 180, 181, 182, 183 via an intramolecular condensation mechanism. The reaction involves the non-isolable \(C\)-acylation intermediate 175 which undergoes an \textit{in situ} cyclisation reaction resulting in the formation of highly functionalized thiophene derivatives (176-183) (Scheme 30).
5.7. 3-Hydroxythiphene-2-carboxylates

3-Thienyloxypropanolamines are known as β-adrenergic blocking agents. Lissavetzky et al. have reported the synthesis of bicyclic alkyl 3-hydroxythiphene-2-carboxylates as intermediates for the synthesis of 3-thienyloxypropanolamines by the modification of Fieselmann procedure. The condensation reaction of linear or cyclic β-ketoesters and two equivalents of 2-mercaptoacetic acid under catalysis condition of dry HCl gas bubbling in alcoholic medium at -10 °C gave a mixture of diester and triester. The isolated crude product mixture of 185 and triester 186 was subjected to cyclisation by treatment with the corresponding sodium alkoxide in alcoholic solution maintained under nitrogen atmosphere to give alkyl 3-hydroxythiphene-2-carboxylates 187a-j in 46-98 % yield (Scheme 31).

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<th>R2</th>
<th>R3</th>
<th>% Y</th>
<th></th>
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<td></td>
<td>j</td>
<td>-(CH2)2-S-</td>
<td>Me</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 31
6. CONCLUSIONS

The data presented in this review clearly demonstrate the high synthetic potential of α/β-Mercaptoalkanoic acids. Many biologically active heterocycles have been obtained based on reactions of these reagents and carbonyl compounds.

REFERENCES

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