Synthesis of Heterocyclic Compounds Containing Sulphur

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Abstract

Compounds that containing benzothiazole nucleus have several biological activities. So, new benzothiazole derivatives were synthesized by introducing many heterocyclic systems such as pyrazole, quinoxaline, indolinone and isatin to 2-mercaptobenzothiazole (2) and 2-hydrazinobenzothiazole (87). Also, some acyclonucleosides, hydrazones and hydrazides derivatives linked to benzothiazole were prepared. A study of the US on some of the synthetic approaches were investigated. The assigned structures were based on microanalysis and spectral analysis (IR, $^1$H NMR, $^{13}$C NMR). Some selected compounds were studied for their antimicrobial and antiviral activities.
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Chapter I

Introduction

The attention of the organic chemists has been directed towards the field of heterocyclic chemistry, because their valuable utilities in the synthesis of variety of biologically active derivatives. Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic entities exist in many natural products and chemotherapeutic agents. Their attachment to sugar molecules either as thioglycoside or nucleoside analogues, plays an important role in vital biological processes as well as in the synthetic organic chemistry.

Recent trends in organic synthesis utilize a non-conventional technique such as ultrasound US (sonochemistry), which has proved to have many advantages. Thus, the introductory part in this thesis will deal with the role of ultrasound in assisting organic synthesis and selected aspects of benzothiazols as well as acyclonucleosides.

Benzothiazole derivatives represent an extensive group of heterocyclic compounds that possess interesting biological activities, such as antitumor,\(^1\)\(^,\)\(^2\) antimicrobial,\(^3\) anthelmintic,\(^4\) antileshmanial,\(^5\) anticonvulsant,\(^6\) anti-inflammatory,\(^7\) and anti-human rhinovirus (HRV) activities.\(^8\)

The benzothiazole ring (1) is present in various marine or terrestrial natural compounds that have useful biological activities.\(^9\)
2-Mercaptobenzothiazole (MBT) (2) is an interesting bicyclic heteroatomic molecule known as important accelerator for the vulcanization of unsaturated elastomers. It has been widely used in the manufacture of tyres, rubber shose and other rubber articles.\(^{(10,11,12)}\) It plays a role in analytical chemistry as a reagent for cadmium, as well as for the determination of copper, lead, bismuth, silver, mercury, thallium, gold, platinum, and iridium.\(^{(13)}\) Also, The 2-mercaptobenzothiazole ring has been found to be useful for developing an external chemotherapeutic and industrial fungicide.\(^{(14)}\) Moreover, 2-thiosubstituted derivatives of mercaptobenzothiazole have many applications based on their wide spectrum of biological activity; such as antifungal, antibacterial, and antitumor activities.\(^{(15,16)}\) Moreover, some derivatives have antioxidant and radioprotective effects.\(^{(17)}\) This good activity of thiol derivatives of benzothiazole shows that the hypothesis of a direct link between thiol function and an aromatic ring was a good one. The thiol catches the radical and then, the aromatic ring permits the trapping of this radical.\(^{(17)}\) 2-Mercaptobenzothiazole derivatives were also found to be useful in the leather industry\(^{(18,19)}\) and as intermediates in the synthesis of cyanine dyes.\(^{(20)}\)
1.1 Ultrasound Assisted Organic Synthesis (UAOS)

High-power ultrasound can generate cavitation within a liquid that providing a source of energy which can be used to enhance a wide range of chemical processes. Sonochemistry concentrates on the applications in organic synthesis where, ultrasound seems to provide a distinct alternative to other, more traditional, techniques of improving reaction rates and product yields. It has also provided, in some cases, new synthetic pathways.

1.1.1 Role of US in the synthesis of S-alkylation of 2-mercaptobenzothiazoles

A series of 2-alkylthio derivatives of benzothiazole 5 were synthesized by selective S-alkylation of compound 3 with alkyl halides 4 (bromides and iodides) by US irradiation under mild conditions at rt. in short time (1-5 min). The reaction was found to be generally applicable to thiol derivatives with different substituents in the aromatic nucleus and various alkyl halides (bromides and iodides) and gives high to excellent yields of products with high purity. N-diisopropylethylamine was used as a base in order to avoid the formation of N-alkylated products. It is known as a sterically hindered Hünig’s base and affords only a proton separation. Also, three solvent systems were investigated: acetone, water and mixtures of glycerol and water in different proportions (Scheme 1).
1.1.2 Role of US in the synthesis of 2-arylbenzothiazoles using Cu(OAc)$_2$/MCM-41 as a solid acid catalyst

2-Arylbenzothiazoles are important class of compounds owing to their potent utility as antitumor (23) and anticancer (24) agents. These compounds also exhibit nonlinear optical (25) and luminescent (26)/fluorescent (27) properties and are therefore being used in designing sensor molecules of specific interest (28).

A simple efficient and practical approach for the synthesis of 2-arylbenzothiazoles 8 without solvent under US irradiation was described (28). The synthesis of these compounds was done by the reaction of o-aminothiophenol (6) with different aldehydes 7 in the presence of a catalytic amount of MCM-41-supported Cu(OAc)$_2$ as a heterogeneous catalyst (28) (Scheme 2). The main advantages of this procedure are: short reaction times, easy and quick isolation of the products, reusability of the catalyst and excellent yields (28).
1.2. Functionalized 2-Mercaptobenzothiazole (MBT)

One of the most interesting properties of 2-mercaptobenzothiazole (2) is the existence of thiol (I) and thione (II) tautomeric forms (Figure 1.1). The tautomeric equilibrium of 2-mercaptobenzothiazole (2) has been point in controversy for many authors.\textsuperscript{(29-34)} Most authors have proposed the thione form (benzothiazoline-2-thione) to be prevailing species by evidence of IR and Raman spectroscopy.\textsuperscript{(29-31,34)} The existence of thiol form has also been discussed.\textsuperscript{(33)} This molecule is associated by hydrogen bonding into a dimer structure (III) (Figure 1.2) where two mercaptobenzothiazole molecules in thione form are connected with linear N-H−S hydrogen bonds resulted by mutual proton transfer.\textsuperscript{(29-34)}

The existence of 2-mercaptobenzothiazole (2) in the thiol and thione tautomeric forms explains its capacity for forming derivatives substituted at the sulfur or the nitrogen atoms.\textsuperscript{(35)}
Figure 1.1 2-Mercaptobenzothiazole in thiol (I) and thione form (II).

Figure 1.2 2-Mercaptobenzothiazole dimer.

1.2.1 Synthesis of 2-mercaptobenzothiazole

2-Mercaptobenzothiazole (2) was prepared industrially using Kelly method by the reaction of aniline (9), CS$_2$ and sulfur at elevated pressure and temperature.$^{(36)}$ Furthermore, 2-mercaptobenzothiazole (2) was synthesized by the reaction of $o$-haloaniline 10 with potassium $O$-ethyl dithiocarbonate in DMF or with CS$_2$ in the presence of NaOH or KOH $^{(37)}$ (Scheme 3).

![Scheme 3](image)

On the other hand, one pot synthesis of 2-mercaptobenzothiazole (2) was achieved $^{(38)}$, by heating $o$-nitrochlorobenzene (11) with an aqueous solution of
NaHS, while passing into the mixture a stream of H₂S previously saturated with CS₂ (Scheme 4).

![Scheme 4](image)

1.2.2 Reactions of 2-mercaptobenzothiazoles

1.2.2.1 2-Mercaptobenzothiazole as a good leaving group

The most well-known procedures to make amides and thioamides are the reactions between amines and acyl halides, or between amines and thioacyl halides. The synthesis for a variety of phenylamides, thiobenzamides and various carbamates by adopting 2-mercaptobenzothiazole (2) as a good leaving group moiety was reported.\(^\text{39,40}\)

The phenomenon of the acyl group rearrangement between derivatives of 2-mercaptobenzothiazole (A and B) was also reported.\(^\text{41}\) Both acyl derivatives of 2-mercaptobenzothiazole have demonstrated that they can be used in the facile synthesis of other alkylamides (alkyl, methyl, benzyl, cinnamyl) and benzylthioamide.

The reaction of 2-mercaptobenzothiazole (2) with various acyl chlorides 13 in the presence of Et₃N at rt. gave the corresponding acylating reagent S-acyl-2-benzothiazole thioester (derivative A) along with 3-acylbenzothiazoline-2-thione (derivative B) quantitatively.\(^\text{41}\) Starting with either form of the 2-mercaptobenzothiazole acyl derivative (S-acyl or N-acyl), acyl group rearrangement occurred to
achieve a certain ratio of mixture under either reflux conditions or rt. (Scheme 5). The ratio of $S$-acyl and $N$-acyl derivatives was very similar regardless of the R substituent of acyl group except cinnamoyl group.\textsuperscript{(41)}

\begin{align*}
\text{Scheme 5}
\end{align*}

The fact that the $S$-acyl derivative was the dominant species indicates that sulfur containing anion is more stable and stronger nucleophile owing to d-orbital delocalization of sulphur compared to the nucleophilic properties of the nitrogen containing anion. Interestingly, when 2-mercaptobenzothiazole (2) was reacted with thiobenzoyl chloride, it formed only the $S$-acyl derivative, $S$-thiobenzoyl-2-benzo-thiazole thioester.\textsuperscript{(41)} The mixture of $S$-acyl derivative and $N$-acyl derivative
underwent reaction with various amines to give amides quantitatively in very high yield.\(^{(41)}\)

The mechanism of acyl group rearrangement between \(N\)-acyl and \(S\)-acyl derivatives was predicted as shown in Scheme 6. The lone pair of electrons on the \(N\) or \(S\) are positioned close enough to attack the carbonyl group carbon. In addition, the aminoalcohol, which has a hydroxyl group and amine group within one molecule, reacted with \(S\)-acyl / \(N\)-acyl derivatives cleanly, without protection of the OH group, to give the corresponding amide with hydroxyl group intact.\(^{(41)}\) In most cases, the reaction occurred at rt. Sometimes it needs a reflux condition depending on which amine is used.\(^{(41)}\)

![Scheme 6](image)

(A) \(S\)-acylderivative

(B) \(N\)-acylderivative

1.2.2.2 Condensation of 2-mercaptobenzothiazole with carbohydrates

The thiazole nucleus, as well as carbohydrates, are important classes of compounds found in many natural and synthetic products with a wide range of biological activities. Due to the importance of the thiazole nucleus and carbohydrate derivatives as potential antimicrobial agents, a series of 2-mercaptobenzothiazole (MBT) derivatives 16, 19 and 22 were prepared\(^{(42)}\) by the coupling of 2-mercaptobenzo-thiazole (2) with 6-iodo-1,2,3,4-diisopropylidene-\(\alpha\)-D-galactopyranose (15), 2,3,4,5-diisopropylidene-\(\alpha\)-D-fructo-pyranosylidode\(^{(43,44)}\) (18) and 6-mesy1-1-methyl-\(\alpha\)-D-glucopyranoside\(^{(45)}\) (21), respectively, in presence of
NaH in DMF at 120°C. Hydrolysis of 16 and 19 by trifluoroacetic acid in THF gave the corresponding compounds 17 and 20, respectively (Scheme 7).

Important biological processes are carried out by carbohydrate processing enzymes and in particular by glycosides.\(^{(46-48)}\) That is why, a modified nitrogen and sulfur glycosylation reaction involving benzothiazole nucleoside bases with furanose and pyranose sugars were reported.\(^{(49)}\) A series of nitrogen glycosylated and their sulfur analogues bearing benzothiazole bases were synthesized.\(^{(49)}\)

The silylation of the nucleoside bases 23 was accomplished with bis(trimethylsilyl) acetamide (BSA) in anhydrous MeCN, and furnished the trimethylsilylated derivatives 24; these derivatives were condensed \(^{(50)}\) with 1,2,3,5-
tetra-\(O\)-acetyl-\(\beta\)-D-ribofuranose (25) in the presence of TMSOTf as a catalyst. The nucleoside 26 was isolated by chromatography.\(^{51}\) Removal of the acetyl groups from the glycon moiety of compound 26 with 16\% \(\text{NH}_3/\text{MeOH}\) solution at rt., furnished 3-(\(\beta\)-D-ribofuranosyl)-2-thiobenzothiazole (27).\(^{51}\) The nucleoside 28 was purified by chromatography and then deblocking with 16\% \(\text{NH}_3/\text{MeOH}\) solution, furnished 29 \(^{49}\) (Scheme 8).

\[
\text{Scheme 8}
\]

When compound 23a was reacted with NaH in anhydrous MeCN followed by the addition of 2,3,4,6-tetra-\(O\)-acetyl-\(\beta\)-D-glucopyranosyl bromide (30), the 3-(2',3',4',6'-tetra-\(O\)-acetyl-\(\beta\)-D-glucopyranosyl)-2-thiobenzothiazole (31) \(^{52}\) and 2-(2',3',4',6'-...
tetra-O-acetyl-β-D-glucopyranosyl)-2-thiobenzothiazole (32a) were obtained, respectively.\(^{(52)}\) Similarly, the treatment of compound 23b with 30 under the same conditions afforded 6-methoxy-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-2-thiobenzothiazole (32b). Deprotection of 32 with saturated 16\% \(\text{NH}_3/\text{MeOH}\) solution at rt. furnished the corresponding free nucleosides 33\(^{(49)}\) (Scheme 9).

\[ R \begin{array}{c} \text{SH} \end{array} \rightarrow \begin{array}{c} \text{AcO} \end{array} \]

\[ \text{i) NaH, MeCN} \]

\[ \text{ii) AcO} \]

\[ 31 \]

\[ 30 \]

\[ 32 (a,b) \]

\[ 33 (a,b) \]

\[ \begin{array}{c} \text{HO} \\ \text{OH} \\ \text{OH} \end{array} \rightarrow \begin{array}{c} \text{AcO} \end{array} \]

\[ \begin{array}{c} \text{HO} \\ \text{OH} \end{array} \]

\[ 16\% \text{NH}_3/\text{MeOH} \]

\[ a: R = \text{H}; b: R = \text{OMe} \]

\textbf{Scheme 9}

\subsection{1.2.2.3 Reaction of 2-mercaptobenzothiazole with anacardic acid derivatives to obtain cyclooxygenase inhibitors}

The synthesis of new class of cyclooxygenase inhibitors (compounds 38a and 38b) from anacardic acid (34) were designed\(^{(53)}\) which belongs to 2-mercaptobenzothiazole (2).
Compounds \(38a\) and \(38b\) were synthesised from anacardic acid (2-hydroxy-6-[(8Z,11Z)-pentadeca-8,11,14-trienyl])benzoic acid (34). Saturated anacardic acid 35 was obtained by hydrogenation of the ene mixture of anacardic acid (34). It was converted to dialkylated compound 36 by reacting with dimethyl sulfate/diethyl sulfate in acetone. Dialkylated anacardic acid 36 was reduced to the corresponding alcohol 37 by treatment with LAH in THF and then converted to the chloro compound by reacting with SOCl\(_2\) in CH\(_2\)Cl\(_2\). The resultant chloro compound was condensed with 2-mercaptobenzothiazole (2) in CH\(_2\)Cl\(_2\) solution containing 20% aqueous NaOH and \((C_4H_9)_4N^+Br^-\) as phase transfer catalyst to obtain (53) compounds \(38a\) and \(38b\) (Scheme 10).

There are two types of cyclooxygenase enzymes, COX-1 and COX-2. COX-1 is a constitutive enzyme, produced in many tissues such as the kidney and the gastrointestinal tract, while COX-2 is inducible and is expressed during inflammation at a site of injury.\(^{54-56}\) Prostaglandins made by COX-1 enzyme are protective prostaglandins, the presence of which leads to normal renal function in the kidneys,\(^{57}\) whereas, prostaglandins made by COX-2 cause inflammation. Therefore complete inhibition of COX-1 is not preferred and drugs that inhibit the COX-2 enzyme are better anti-inflammatory agents.\(^{58}\)
Compound 38b has selective COX-2 inhibition effect more than 470-fold compared with COX-1 and thus it is a good anti-inflammatory agent.\(^{(53)}\)

\[
\begin{align*}
\text{OH} & \quad \text{COOH} \\
\text{R}_2\text{SO}_4 & \quad \text{K}_2\text{CO}_3, \quad \text{K}_2\text{CO}_3, \quad \text{K}_2\text{CO}_3, \\
\text{35} & \quad \text{36} \\
\end{align*}
\]

\[
\begin{align*}
\text{LAH} & \quad \text{THF} \\
\text{36} & \quad \text{37} \\
\end{align*}
\]

\[
\begin{align*}
\text{MBT} & \quad \text{SO}_2\text{Cl}_2, \quad \text{CH}_2\text{Cl}_2 \\
\text{20}\%\text{NaOH}, \quad (\text{C}_4\text{H}_9)_2\text{N}^+\text{Br}^- & \quad \text{38} \\
\end{align*}
\]

\[
\begin{align*}
\text{a: } & \text{R= Me; b: } \text{R= Et} \\
\end{align*}
\]

**Scheme 10**

**1.2.2.4 Synthesis of 4-oxo-thiazolidines derived from 2-mercaptobenzothiazole**

4-Thiazolidinones are known for versatile pharmacological activities such as hypnotic,\(^{(59)}\) anesthetic\(^{(60)}\) and antifungal\(^{(61)}\) activities. Incorporation of the 4-oxo-thiazolidine moiety into 2-mercaptobenzothiazole (2) scaffold has been found to enhance its activity.\(^{(62)}\) So, an efficient and extremely fast procedure for the synthesis of 4-thiazolidinones 42 by the reaction of arylidene-[(2-benzoazolyl-thio)-acetamidyl] 41 with thioglycolic acid in DMF in the presence of a catalytic amount of anhydrous ZnCl\(_2\) under microwave irradiation (MWI) was reported. A considerable increase in the reaction rate has been observed with better yield in MW technique\(^{(63)}\) (Scheme 11).

Alkylation of 2-mercaptobenzothiazole (2) with ethyl chloroacetate in dry acetone gave ethyl-2-(benzothiazolylthio)-acetate (39).\(^{(64)}\) The compound 39 on aminolysis
with hydrazine hydrate in EtOH yielded [2-(benzothiazolylthio)-acetyl]-hydrazine (40). Compound 40 underwent condensation with different aldehydes to afford the arylidene-[2-(benzothiazolylthio)]acetamides 41. These intermediates on reaction with thioglycollic acid yielded five membered sulfur-containing heterocyclic derivatives 2-(aryl)-3-[2-(benzothiazolylthio)]-4-oxo-thiazolidines 42 (Scheme 11). These compounds 42 have antibacterial and antifungal activities. (63)

![Scheme 11](image)

Furthermore, the alkylation of compound 2 with chloroacetyl chloride yielded 2-(chloroacetyl)-2-mercaptobenzothiazole (43), which on treatment with hydrazine-hydrate yielded 1-hydrazinoacetyl-2-mercaptobenzothiazole (44). Condensation of compound 44 with various aromatic aldehydes yielded 2-[α-(arylidine hydrazino)-acetyl]-2-mercaptobenzothiazole 45. Reaction of compound 45 with thioglycolic acid
underwent dehydrative annulation to afforded 2-(aryl)-3-[(acylamino)-1,3-thiazolidin-4-ones]-2-mercaptobenzothiazole 46 which on application on Knoevenagel reaction with various aldehydes gave 2-{5-arylidine-2-aryl-3-(acylamino)-1,3-thiazolidin-4-ones]}-2-mercaptobenzothiazole 47 (Scheme 12). Some of 46 and 47 derivatives have antimicrobial and antiinflammatory activities. 

\[
\begin{align*}
\text{Scheme 12}
\end{align*}
\]

1.2.2.5 Synthesis of 2-mercaptobenzothiazole derivatives with two benzothiazole fragments

2-Mercaptobenzothiazole derivatives which include two benzothiazole fragments were produced by nucleophilic substitution and condensation reaction using various functional derivatives (chlorine derivatives, amines, thiols, aldehydes, ketones and others) of benzothiazole.
The reaction between the equimolar amounts of 2-mercaptobenzothiazole (2) and 2-chlorobenzothiazole (48) in DMF at 80-90°C afforded di(2-benzothiazolyl)sulfide\(^{67,68}\) (49). Moreover, 2-(2-thioxo-3-benzothiazolinyl)benzothiazole (50) was obtained by fusion of 2 with 48 at 190-230°C in addition to the sulfide 49 \(^{69}\) (Scheme 13).

![Scheme 13](image)

The reactions of the sodium salt of 2-mercaptobenzothiazole 51 with 2,5-dichlorobenzothiazole (52) in DMF or compound 48 with 5-chloro-2-mercaptobenzothiazole (53) in i-PrOH lead to the same reaction products, the sulfide 49, di(5-chloro-2-benzothiazolyl) sulfide (54), and 2-(2-benzothiazolythio)-5-chlorobenzothiazole (55) in different proportions\(^{68}\) (Scheme 14).

Moreover, benzothiazoline-2-thione (56) was reacted with (CH\(_2\)=CHO)\(_3\)P and (ClCH\(_2\)CH\(_2\)O)\(_2\)POH \(^{66}\) (Scheme 16). When it is heated (70°C) with (CH\(_2\)=CHO)\(_3\)P in toluene the only product is 1,1-di(2-thioxo-3-benzothiazolinyl)ethane (58), which formed by the addition of the thione 56 to the intermediate 3-vinylbenzothiazoline-2-thione (57).\(^{66}\) On the other hand, from the reaction of the thione 56 with (ClCH\(_2\)CH\(_2\)O)\(_2\)POH, the two isomeric compounds 1-(2-benzothiazolythio)-2-(2-
thiooxo-3-benzothiazolinyl)ethane (59) and 1,2-di(2-benzothiazolylthio)ethane (60) were obtained, respectively\(^{(66)}\) (Scheme 15).

Scheme 14

Scheme 15
Consequently, the reaction of 2-mercaptobenzothiazole (2) with oxalyl chloride in benzene leads to the formation of bis(2-thioxo-3-benzothiazolinyl)carbonyl (61) together with the sulfide (66) 49 (Scheme 16).

![Scheme 16](image)

1.2.2.6 Synthesis of 2-mercaptobenzothiazole derivatives containing heterocyclic substituents

In recent decades, there has been constant interest in the chemistry of benzothiazoles containing heterocyclic fragments as substituents. Among compounds of this type, substances with high and varied biological activity and a wide spectrum of practical qualities have been found. These kinds of compounds were produced by nucleophilic substitution and condensation reaction or by cyclization reaction (66).

Alkylation of 2-mercaptobenzothiazole (2) with 5-aryl-3-chloromethyl-1,3,4-oxa(thia)diazoline-2-thiones 62 in an alcoholic solution of alkali gave 5-aryl-3-(2-benzothiazolylthiomethyl)-1,3,4-oxa(thia)diazoline-2-thiones (66) 63 (Scheme 17).

![Scheme 17](image)
The structure of the heterocyclic reagents (particularly the capacity for tautomerism) and reaction conditions affect the direction of the reactions and frequently leads to the formation of a mixture of compounds. 3-(2-Benzothiazolyl)-N-methylimidazoline-2-thione (65) can be obtained by fusion (66) of 2-chlorobenzothiazole (48) with 2-mercapto-N-methylimidazole (64), while 2-(2-benzothiazolylthio)-1-methyl-imidazole (66) was formed during the reaction in DMF in the presence of NaH (66) (Scheme 19). Furthermore, reaction of compound 48 with 2-mercapto-4,5-dimethylthiazole (67) in boiling xylene gave di(2-benzothiazolyl) sulfide (49) in significant amounts in addition to the expected reaction product 2-(2-benzothiazolylthio)-4,5-dimethylthiazole (68) (66) (Scheme 18).

![Scheme 18](image)

Moreover, 6-[(1-methylamino)-5-R²-tetrazolyl]-2-(R¹-thio)benzothiazoles 71 were obtained by the Mannich reaction from 6-amino-2-(R¹-thio)benzothiazoles 69, 5-R²-tetrazoles 70, and 34% formaldehyde in EtOH (66) (Scheme 19).
Condensation of the hydrochloride of the imidic ester (70,71) 72 with ethylenediamine, N-substituted ethylenediamines, α-amino alcohols, and 2-aminoethanethiol in absolute MeOH leads to 2-(2-benzothiazolythiomethyl)-1-R-Δ²-imidazolines 73, 2-(2-benzothiazolythiomethyl)-5-R¹-Δ²-oxazolines 74, and 2-(2-benzothiazolythiomethyl)-Δ²-thiazolines 75, respectively (Scheme 20).

Scheme 19

![Scheme 19](image)

**Scheme 20**

![Scheme 20](image)

R¹ = Alk (C₁ - C₉), CH₂=CHCH₂, PhCH₂
R² = Ph, 4-O₂NC₆H₄, 3,4-Cl₂C₆H₃

R = H, Bu, C₁₂H₂₅, NCCH₂CH₂, PhCH₂, 4-HO-3,5-(t-Bu)₂C₆H₃(CH₂)₃, 2-thienylmethyl
R¹ = H, CH₃
When the \(N^1\)-phenyl- and \(N^1\)-(3,5-dichloro-2-pyridyl)amidrazones of (2-benzothiazolylthio)acetic acid (76a) and (76b) are heated with acid chlorides in toluene or DMF, 1-phenyl- and 1-(3,5-dichloro-2-pyridyl)-3-(2-benzothiazolylthio-methyl)-5-R\(^1\)-1H-1,2,4-triazoles 78 were obtained.\(^{(66,70)}\) The reaction of \(N\)-acyl(2-benzothiazolylthio)acetimidic esters 77 with phenyl- or 3,5-dichloro-2-pyridyl-hydrazine in absolute MeOH also leads to compound 78\(^{(66,70)}\) (Scheme 21).

\[
\begin{align*}
\text{SCHEME 21} & \\
\text{1.2.2.7 Synthesis of 2-mercaptobenzothiazole analogues of clofibrlic acid} & \\
\text{2-Mercaptobenzothiazole analogues of clofibrlic acid (79) with a benzothiazole} & \\
\text{instead of benzene ring and with a thioisobutyrate side-chain were synthesized.}^{(72)} & \\
\text{Compounds 81 were readily obtained by the reaction of ethyl 2-bromoiso-} & \\
\text{butyrate (80) with sodium salts of 2-mercaptobenzothiazoles, in refluxing EtOH. The} & \\
\text{esters 81 were hydrolyzed in presence of KOH to give the acids}^{(72)} & \\
\text{82 (Scheme 22).} &
\end{align*}
\]
2-[(5-Chloro-1,3-benzothiazol-2-yl)thio]-2-methylpropanoic acid (82b) revealed a
dose-dependent antiplatelet activity.\(^{(72)}\)

![Chemical structure 79]

\[
\text{BrO} \quad \xrightarrow{\text{EtOH}} \quad \text{KOH} \quad \text{EtOH}
\]

\[
\text{80} \quad \text{81} \quad \text{82}
\]

a: X=H  
b: X=Cl

**Scheme 22**

### 1.2.2.8 Unusual difluoromethylation of 2-mercaptobenzothiazole

Difluoromethylation of 2-mercaptobenzothiazole (2) by reacting with chlorodifluoromethane and solid KOH in DMF gave 2-difluoromethylthiobenzothiazole (83)\(^{(73)}\) in addition to N-difluoromethylbenzothiazole-2-thione (84) (Scheme 23).

![Chemical structures 2, 83, and 84]
1.2.2.9 Synthesis of some benzothiazol-2-thione salts

2-Thioxobenzothiazolidin-3-yl-methanol (85) was obtained by the reaction of benzothiazole-2-thione (56) with formalin, which is alkylated by sulfoalkyl halides or propan-1,3-sulfone in the presence of KOH to form salts of the (2-thioxobenzothiazolidin-3-yl-methoxy) alkanesulfonic acids 86 (35) (Scheme 24).

\[
\text{Scheme 24}
\]

1.3. Functionalized 2-Hydrazinobenzothiazole (HBT)

The crystal structure of 2-hydrazinobenzothiazole (HBT) (87) is stabilized by two intermolecular hydrogen bonded interactions (Figure 1.3). (74)
1.3.1 Synthesis of 2-hydrazinobenzothiazole

2-Hydrazinobenzothiazole (87) was prepared from the reaction of 2-mercapto-
benzothiazole (2) with hydrazine hydrate by heating directly as \( \text{H}_2\text{S} \) was librated (Scheme 25). Also, it can be obtained from the reaction of compound 2 with
hydrazine hydrate in MeOH under reflux and without solvent under MWI for
1 min. (76)

![Scheme 25](image)

When gaseous chlorine was bubbled through 2-mercapto benzothiazole (2)
suspended in chloroform and water, it yielded 2-chlorobenzothiazole (48). The
reaction of compound 48 with hydrazine hydrate gave 2-hydrizinobenzothiazole (77) (87) (Scheme 26).

\[
\begin{align*}
\text{2} & \xrightarrow{\text{Cl}_2, \text{CHCl}_3} \text{48} & \xrightarrow{\text{N}_2\text{H}_4} \text{87}
\end{align*}
\]

Scheme 26

On the other hand, compound 87 obtained from the reaction of 2-amino benzothiazole (88) with hydrazine hydrate by “exchange amination” which is used to the exchange of one amino group for another. (78) The reaction of 2-aminobenzothiazole (88) with a hydrazine-hydrazine hydrochloride mixture in ethylene glycol solution affords the corresponding 2-hydrizinobenzothiazole (87) in excellent yield (Scheme 27). (79)

\[
\begin{align*}
\text{88} & \xrightarrow{\text{N}_2\text{H}_4 / \text{N}_2\text{H}_4\text{HCl}, \text{HOCH}_2\text{CH}_2\text{OH}} \text{87}
\end{align*}
\]

Scheme 27

1.3.2 Reactions of 2-hydrizinobenzothiazole

1.3.2.1 Condensation reaction

2-Hydrizinobenzothiazole (87) undergoes condensation reaction with various aldehydes to obtain benzothiazol-2-yl hydrazones (89) (Scheme 29). The benzothiazol-2-yl-hydrazones with heteryl substituents like pyridyl, furyl and thieryl have antifungal activity. (77) Also, compound 87 was condensed with cyclohexanone.
and cyclopentanone as a carbonyl compounds to afford cycloalkanone (80) 90 (Scheme 28).

Moreover, compound 87 on condensation with various substituted aromatic aldehydes yielded compounds 91 which on reaction with chloroacetyl chloride in the presence of Et$_3$N afforded 4-substituted aryl-3-chloro-2-oxazetidine-2-iminobenzothiazoles 92 (Scheme 29). The later compounds were also obtained by using MWI to give higher yields and shorter time than conventional methods. Most of these derivatives have antibacterial and antifungal activities and it has been observed that among the substituents present on the phenyl ring, halo derivatives were found to be the highly active in the series. (76)
Alternatively, the derivatives 94 were synthesized by condensation of 2-hyrazino-6-methylbenzothiazole (93a) and 2-hyrazino-6-fluorobenzothiazole (93b) with different substituted acetophenones in presence of AcOH \(^{(81,82)}\) (Scheme 30). Some of these compounds showed good antimicrobial activity \(^{(81)}\) and anti-bacterial activity.\(^{(82)}\)

Scheme 30

2-(3-Pyridyl)-5-(4-methylphenyl)-1,3,4-oxadiazoled (96) underwent condensation reaction with substituted 2-hyrazinobenzothiazoles 95 in dry pyridine resulted to
3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-substitutedbenzothiazol-2-amino)-4H-1,2,4-triazoles \(^{(83)}\) \(97\) (Scheme 31). These compounds have antimicrobial and antituberculosis activity. The antibacterial data indicates that the analogs with halogen, methyl and nitro substituents emerged as promising antimicrobials.\(^{(83)}\)

![Chemical structure](attachment:image.png)

\(R = 6\)-F, 6-Br, 6-NO\(_2\), 6-CH\(_3\), 6-OCH\(_3\), 6-Cl, 4-CH\(_3\), 4-NO\(_2\), 5-Cl, 6-Cl, 4-Cl

**Scheme 31**

### 1.3.2.2 Cyclization reactions

Formic acid reacted with 2-hydrazinobenzothiazole \((87)\) to form 1,2,4-triazolo[4,3-\(b\)]benzothiazole \(^{(35)}\) \(98\) (Scheme 32). Moreover, compound \(87\) reacted with \(\text{CS}_2\) in presence of KOH to produce s-triazolo[4,3-\(b\)]benzothiazole-3-thiol \((99)\) (Scheme 32). Reynolds pointed out that it might have a double-bonded sulfur \(^{(84)}\) in \(100\) rather than a mercapto group as in \(99\) (Scheme 32).

Mannich and double Mannich reaction were performed.\(^{(84)}\) A suspension of 1,2,4-triazolo[4,3-\(b\)]benzothiazole-3-thiol \((100)\) in EtOH and formaldehyde was stirred, then appropriate p-toluidine, phenylenediamine or benzidine was added to afford 2-p-toludinomethyl-3-thion-1,2,4-triazolo[4,3-\(b\)]benzothiazole \((101)\), \(N,N^{'}\)-bis(2-methylene-1,2,4-triazolo[4,3-\(b\)]benzothiazol-3-thione)-phenylenediamine \((102)\) and \(N,N^{'}\)-bis(2-methylene-1,2,4-triazolo[4,3-\(b\)]benzothiazol-3-thione)-diaminobiphenyl \((103)\), respectively \(^{(84)}\) (Scheme 33).
Furthermore, a series of 3,5-diaryl-1-benzothiazolopyrazoline derivatives 105 were synthesized by the reaction of appropriately substituted chalcones 104 (as α,β-unsaturated ketones) and 2-hydrazinobenzothiazole (87) in EtOH (Scheme 34). The synthesized 3,5-diaryl-1-benzothiazolopyrazoline derivatives 105 have been
subjected to *in vitro* antimicrobial activity against various plant and human pathogenic bacteria and fungi.\(^{85}\)

The condensation of 2-hydrazino-6-R-benzothiazoles 106 with 1-R\(^1\)-3-R\(^2\)-1,3-butanediones in EtOH in the presence of catalytic amounts of AcOH \(^{69,86}\) or conc. HCl \(^{66}\) takes place regioselectively with the formation of 1-(6-R-2-benzothiazolyl)-3-methyl-4-R\(^2\)-5-R\(^1\)-pyrazoles 107 (Scheme 35).

The reaction of the hydrazines 106 with 2,4-dioxopentanoic ester in EtOH in the presence of catalytic amounts of conc. HCl gives a mixture of regioisomers: 5-methyl-3-pyrazolecarboxylic (108) and 3-methyl-5-pyrazolecarboxylic esters 109 \(^{66}\) (Scheme 36).
Scheme 36

When equimolar amounts of the hydrazines 106 are kept in EtOH at 20°C with 1,1,1-trifluoropentadi-2,5-one, 5-hydroxy-3-methyl-5-trifluoromethyl-Δ²-pyrazolines 110 were formed. The products are converted by treatment with an alcoholic solution of HCl into the corresponding pyrazoles (66) 111 (Scheme 37).

Scheme 37

Furthermore, the reaction of equimolar amounts of the hydrazines 106 and β-oxobutyraldehyde dimethyl acetal in EtOH at 20°C leads to the formation of the hydrazones 112, which undergo cyclization to 1-(6-R-2-benzothiazolyl)-3-methyl-pyrazoles 113 when boiled in EtOH in the presence of conc. HCl (66). At the same time the regioisomeric 5-methylpyrazoles 114 are formed together with the
pyrazoles 113 when the reagents are boiled in EtOH in the presence of conc. HCl (Scheme 38). (66)

\[
\text{R} = \text{H, CH}_3, \text{Cl, CH}_2\text{O}
\]

**Scheme 38**

Moreover, the reaction of the hydrazines 106 with the hydrochlorides of \(\beta\)-dimethylaminopropiophenones leads to the formation of 3-aryl-1-(6-R-2-benzo-thiazolyl)-\(\Delta^2\)-pyrazolines (66) 115, while boiling with aroylacetonitriles in EtOH in the presence of AcOH leads to the formation of 5-amino-3-aryl-1-(6-R-2-benzo-thiazolyl)pyrazoles (66) 116 (Scheme 39).
On the other hand, when the reaction of the hydrazines 106 were reacted with acetoacetic ester in the presence of conc. HCl, the 1-(6-R-2-benzothiazolyl)-3-methyl-4-R\(^1\)-pyrazol-5-ones 117 were obtained\(^{66,86}\) (Scheme 40). 1-(6-R-2-benzothiazolyl)-3,4-dimethylpyran[2,3-c]pyrazol-6(1H)-ones 118 were obtained when equimolar amounts of the respective 5-pyrazolones 117 (R\(^1\) = H) and acetoacetic ester are heated\(^{66}\) (Scheme 40).

**Scheme 39**

**Scheme 40**
Condensation of the hydrazines 106 with 2-hydroxymethylenecyclohexanone in EtOH in the presence of conc. HCl leads to the isomeric tetrahydroindazoles 1-(6-R-2-benzothiazolyl)-4,5,6,7-tetrahydro-1H-indazoles 119 and 2-(6-R-2-benzothiazolyl)-4,5,6,7-tetrahydro-2H-indazoles 120 (Scheme 41).

The reaction of equimolar amounts of the hydrazines 106 and 2-propionylindane-1,3-dione in EtOH gives the hydrazones 121, which undergo cyclization to 1-(6-R-2-benzothiazolyl)-3-ethylindeno[1,2-c]pyrazol-4-ones 122 when boiled in AcOH (Scheme 42).
1.4 Objectives of the Work

Considerable attention has been paid in the chemistry of mercapto and hydrazino benzothiazole derivatives and their conversion into nitrogen containing heterocycles. Various heterocyclic rings were taken as a ground to constitute large series of biologically active compounds. Thus, the incorporation of nucleoside or sugar moieties on a heterocyclic system becomes a subject of current interest because of their potential uses as pharmaceutical and therapeutic agents. In this respect we report herein the introduction of many heterocyclic systems such as pyrazole, quinoxaline, indolinone and isatin to 2-mercaptobenzothiazole (2) and 2-hydrazino-benzothiazole (87) and their conversion to regioselective alkylation and acetylation. Also, the synthesis of several derivatives that obtained from the resulting compounds were investigated. Synthesis of some acyclonucleosides, hydrazone and hydrazide derivatives linked to benzothiazole ring were reported in this work.

The utility of ultrasound (US) irradiation as a non-conventional energy has advantages as the significant rate-enhancements, higher product yields and greater selectivity of some organic reactions.

The work of this thesis can be divided into five sections as follows:

5. Biological activities.
تحضير مركبات حلقيّة غير متجانسة تحتوي على الكبريت

سوسن عزام سليم نورالدين

المستخلص

تتميز المركبات المحتوية على حلقة البنزوثيازول بأن لها العديد من الأنشطة البيولوجية التي تستجيب لاحتياج الباحثين. وعليه تم تحضير مشتقات مختلفة تحتوي على البنزوثيازول وذلك إدخال العديد من المركبات الحلقيّة غير المتجانسة مثل البيرازول والكينوكزالين والإندولينون والإيزاتين إلى 2- ميركبتوبنزوثيازول (2) و 2- هيدرازينوبنزوثيازول (87). كذلك تم تحضير العديد من المشتقات المحتوية على النيوكليوسيديات المفتوحة والهيدرازون والهيدرازيد المرتبطة بحلقة البنزوثيازول. كما استخدمت تقنية الأشعة فوق الصوتية لتحضير بعض المركبات لوجود العديد من الأبحاث المتقدمة. وتصل إلى توفير الوقت وتحسين نسبة النتائج عند استخدام هذه الطريقة إضافة إلى نقاء النواتج كما تم مقارنتها بما تم تحضيره بالطرق التقليدية. وقد تم إثبات التركيب الكيميائي للمركبات المحضرة بدراسة أطيافها المختلفة مثل طيف الرنين النووي المغناطيسي للبروتون والكربون وطيف الأشعة تحت الحمراء والتحليل الكمي للعناصر. كذلك تم دراسة النشاط المضاد لبعض أنواع البكتيريا والفطريات والفيروسات على بعض المركبات المحضرة ووجد أن لبعضها نشاط مثبط لبعض أنواع البكتيريا والفطريات.