A Facile Approach for the Synthesis of Benzothiazole from N-Protected Amino Acids

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This Dissertation is dedicated to my Parents and Siblings.

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List of Abbreviations and Symbols

AIDS	Acquired Imino Deficiency Syndrome
AMPK	AMP-activated Protein Kinase
ATP	Adenosine Tri Phosphate
BINAM	1,1′-Bis(2-Naphthylamine)
Boc	tert-Butoxycarbonyl
Bz	Benzoyl
CAN	Ceric Ammonium Nitrate
CTAB	Cetyl Trimethyl Ammonium Bromide
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMF	Di Methyl Formamide
DMSO	Dimethyl Sulfoxide
DMP	Dess–Martin Periodinane
DNA	Deoxyribo Nucleic Acid
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
FTIR	Fourier Transform Infrared Spectroscopy
GCMS	Gas Chromatography Mass Spectrometery
HIV	Human Immuno Deficiency Virus
IUPAC	International Union of Pure and Applied Chemistry
NMP	N-Methyl-2-Pyrrolidone
PEG	Poly Ethylene Glycol
PIB	Poly Iso Butylene
PIFA	Phenyl Iodine bis(trifluoroacetate)
PMP	p-Methoxyphenyl
PPA	Polyphosphoric Acid
PTSA	p-Toluene Sulphonic Acid
Rf	Retardation Factor

RNA	Ribonucleic Acid
SDS	Sodium Dodecyl Sulphate
SPC	Sulphonated Porous Carbon
TCCA	Trichloroisocyanuricacid
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-Tetramethylpiperidin-yl)oxidanyl
TLC	Thin Layer Chromatography
TMSOTf	Trimethyl Silyl Trifluoromethanesulfonate
T_3P	Propylphosphonic Anhydride

Abstract

Benzothiazole is gaining importance as a versatile nucleus in the field of Medicinal and Pharmaceutical Chemistry. The advancement in neuro imaging is in rapid progress and benzothiazoles are good imaging agents. Pittsburg compound, a benzothiazole derivative is used as imaging amyloid plaques in Alzheimer's disease. Large numbers of methods are reported in literature for benzothiazole synthesis, however, many of them suffer from limitations such as low yield, metal catalyst, expensive reagents, toxic solvents, high temperature, long reaction times and harsh reaction conditions. In present research work, benzothiazole derivatives are prepared from N-protected amino acids and 2-aminothiopenol using molecular iodine as a mild Lewis acid catalyst. Six different α-amino acids were taken that were benzoyl protected and then Boc protected to prevent side reaction.. Twelve benzothiazoles were synthesized from benzoyl and Boc protected amino acids. Yields were compared for benzoyl and Boc protected benzothiazoles and it was found that Boc protected benzothiazoles provided better yield in these reaction conditions. The synthesized compounds were characterized by physical and spectroscopic techniques like FTIR and GCMS.

Chapter 1

1.1 Introduction and Literature Survey

1.1.1 Heterocycle

Heterocycles are common structural units in marketed drugs, in medicinal chemistry targets and in the drug discovery process. Over 80 % of top small molecular drugs by US retail sales in 2010 contain at least one heterocyclic fragment in their structures [1]. Heterocycles are the largest group in the family of organic compounds. It is estimated that of the over 50 million mentioned organic compounds, approximately half are heterocyclic. Heterocyclic compounds are the compounds that contain atoms other than carbon and hydrogen in the carbon cycle such as nitrogen, oxygen or sulphur etc.

1.1.2 History

Heterocyclic chemistry has a long history going back to the early 1800s when the first description of organic compounds appeared. Some early discoveries include the characterization of morphine, the isolation of alloxan from uric acid, the synthesis of furfural from starch and sulfuric acid, the isolation of pyrrole by dry distillation of bones, the synthesis of indigo dye, the one-pot synthesis of tropanone, the isolation of chlorophyll, and the role of purines and pyrimidines in the genetic code [2].

1.1.3 Heterocyclic Chemistry

Heterocyclic chemistry is the branch of Organic chemistry that deals with the synthesis and properties of heterocyclic compounds. Heterocyclic compounds can be aromatic or non-aromatic. Two third organic compounds are heterocyclic compounds. Among the 20 million organic compounds identified by the end of second millennium, more than two third are fully or partially aromatic and approximately half are heterocyclic [3]. Of the twenty amino acids commonly found in different proteins, histidine, proline and tryptophan, are heterocyclic. Similarly, the nitrogenous bases found in DNA and RNA are heterocyclic. It is not surprising, therefore that a great deal of current research work is concerned with

methods of synthesis and properties of heterocyclic compounds [4]. Heterocyclic compounds are well known for their application in agrochemical, pharmaceutical, dyestuff and in natural products. In organic synthesis heterocycles find their uses as intermediates, chiral auxiliaries, protecting groups, ligands, solvents, reagents and as polymers. Introduction of a heteroatom in cyclic compound imparts new properties that are different from their cyclic organic analogues. Heterocycles are chemically more flexible (better intermediates) in organic synthesis and can respond to the many demands of biochemical systems [2].

1.1.4 Nomenclature for Heterocyclic Compounds

The IUPAC allows Hantzsch-Widman system of nomenclature [5] as well as common names for the heterocycles. This system of nomenclature deals with the nature of heterocycle, ring size and type of the ring whether saturated or un-saturated. Heteroatom is indicated by the prefix aza, oxa, thia etc. Ring size is suffixed with the name and mostly are derived from Latin numerals like ep from hepta, oc from octa, on from nona, and finally the ending indicates that ring is saturated or un-saturated like.

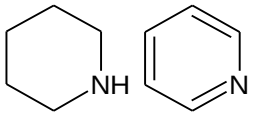


Figure 1.1: Azinane and Azine.

The substituent is given lowest possible number and heterocycle is given the least number. In case of partial unsaturation letter dihydro, tetrahydro is prefixed. In case of two or more similar hetro atoms di, tri, tetra is prefixed. If different heterocycles, then they are prefixed according to priority i.e Oxygen has gotten priority over Sulphur and Sulphur over Nitrogen. O > S > N etc.

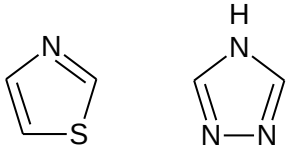


Figure 1.2: 1, 3-Thiazole and 1,2,4-Triazole.

In case of fused rings the heterocyclic ring is labelled as a, b, c on different sides like side between atom 1 and atom 2 is a, between 2 and 3 is b, etc. Heterocyclic

ring is given the parent name and the fused ring is prefixed. The prefix in such names has the ending ‘o’, *i.e.*, benzo and naptho etc. like benzo[c]thiophene.

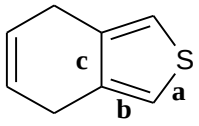


Figure 1.3: Benzo[c] thiophene.

1.1.5 Nitrogen and Sulphur Containing Heterocycles

59 % of small-molecules, U.S. FDA approved as drugs have a nitrogen heterocycle. This firmly ranks them as the most privileged and significant structures among pharmaceuticals. It is interesting to note that 4 out of 10 most commonly used nitrogen heterocycles also contain a sulfur atom [6] (cephem, thiazole, penam, and phenothiazine).

The presence of heterocycles in all kinds of organic compounds of interest is very well known. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [7]. The grounds of this interest were their biological activities and unique structures that led to several applications in different areas of pharmaceutical and agrochemical research or, more recently, in material sciences [8].

1.1.6 Benzothiazole

Benzothiazole is a nitrogen and sulphur containing heterocycle. It consists of benzene ring fused with thiazole ring. Thiazole, the simplest member is the component of thiamine (Vitamin B1), antibiotics, and is also present in the large peptides [9]. It is formed by the combination of cysteine with carbonyl group [10]. The activity of thiazole is due to the presence of nitrogen and sulphur atoms. Benzothiazole, on the other hand, are relatively rare in nature, and are found in some of the marine and terrestrial organisms. Benzothiazole is present in American cranberries [11], tail gland of red deer [12], aroma fraction of tea leaves [13], and it is present in flavor compound produced by fungi *Aspergillus clavatus* [14]. It also forms an important component of fire fly luciferin [15] and some naturally occurring antibiotics (rifamycins P and Q).

1.1.7 Nomenclature of Benzothiazole

Benzothiazole is named according to Hantzch-Widman system of nomenclature. In this system numbering starts from sulphur atom and then proceeds towards the nitrogen by shortest possible route. So, it is named 1, 3- benzothiazole. Other common names of benzothiazole are benzosulphonazole, 1-thia-3-azaindene and Benzo [d] thiazole etc.

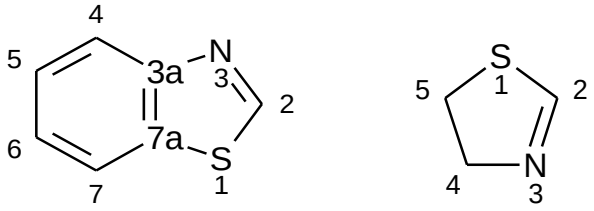


Figure 1.4: Benzothiazole and Thiazole.

Benzothiazole is biologically and chemically active moiety, due to which it shows large number of pharmaceutical and industrial applications, such as anti-cancer [16], anti-fungal[17], anti-analgesic, anti-inflammatory[18], anti-depressants[19], anti-covulsant [20], anti-viral[21], anti-diabetic[22], anti-thematic[23], anti-malarial[24] ,anti-HIV[25], anti-nociceptive[26], anti-feedant [27], anti-oxidant activity[28], appetite depressants[29], anti-tubercular[30], as cyclooxegnase inhibitors[31], lyso phosphatidic acid acyltransferase-beta inhibitors[32], Topoisomerase II inhibitors [33], protein tyrosine phosphatase-1 beta inhibitors [34], beta-glucuronidase inhibitors[35], A_2a receptor antagonist[36], Amyloid inhibitors[37], alpha glucosidase inhibitors [38]. They are also used as imaging agents [39], fluorescent materials [40], dyes [41] in leather tanning industry [42], vulcanization accelerator of rubber [43], and as thermoelectric materials [44]. Among the known heterocycles benzothiazole is the most biologically active. Benzothiazole > benzofuran > > Benzoimidazole .Changing the substituent at the 2 position alters the biological activity of benzothiazole.. Last decade has seen a rapid progress in the field of medicinal and pharmaceutical chemistry and large numbers of methods have been reported for the synthesis of benzothiazole. Some of these methods include Jacobson cyclization, condensation reactions of 2-aminothiophenol with aldehydes, acids, acid chlorides and esters etc. however some of these methods suffer from limitations such as high temperature, long reaction times, metal catalysts, low yield etc.

1.2 Literature Review

1.2.0 Synthesis of Benzothiazole

1.2.1 Hoffman Method

Benzothiazole was first time synthesized by Hoffman and coworkers [45] in 1887. In an attempt to prepare disulfhydryl derivative of thiocarbanilide by reacting CS_2 and o-aminophenol they obtained benzothiazole as a product. They also synthesized similar compounds from reaction of sodiumhydosulphide with mustard oil. Hofmann also mentioned synthesis of 2-anilinobenzothiazole from the reaction of 2-aminothiophenol and phenyl isothiocyanate.

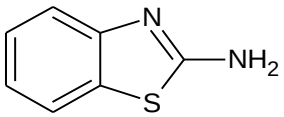
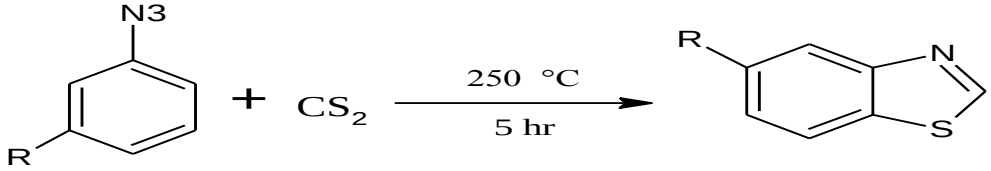


Figure 1.5: 2-Amino Benzothiazole.

1.2.2 Jacobson Cyclization

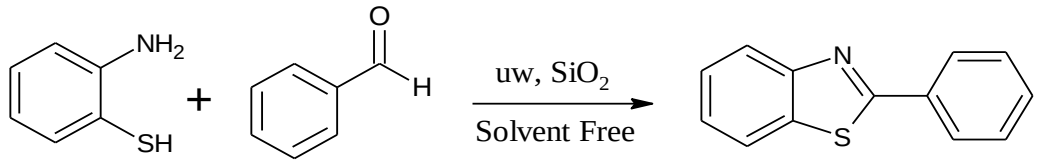
Jacobson and co-workers [46] synthesized substituted benzothiazole derivatives by reacting azobenzene with carbon disulphide in a sealed tube at 250 ^oC for 5 hours. Jacobson further reported synthesis of 2- substituted benzothiazoles by reaction of potassium ferricyanate with sodium hydroxide.



Scheme 1.1: Jacobson cyclization reaction

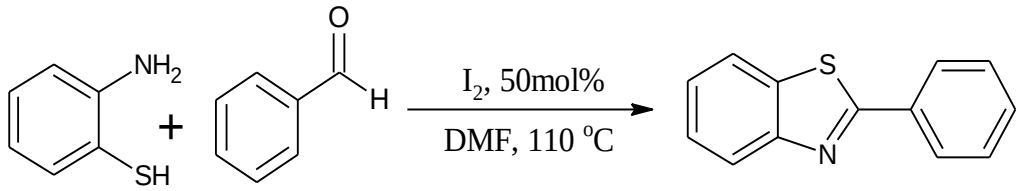
1.2.3 Condensation of 2-Aminothiophenol With Aldehydes

This is the most common method used for the synthesis of substituted benzothiazole. Mitsuo *et al.* [47] in 2004, synthesized substituted benzothiazoles by condensation of 2-aminothiophenol with aryl aldehyde in the presence of SiO_2 and microwave irradiation for 5minutes. This reaction was carried out without solvent and 73-97 % yield was obtained.



Scheme 1.2: Synthesis of 2-Substituted Benzothiazole Using SiO_2 Catalyst.

In 2006, Yan *et al.* [48] catalyzed same reaction using 50 mol% iodine as a catalyst in DMF as a solvent at 110 ^oC. The reaction was carried out with mixture of aliphatic and aromatic aldehydes.



Scheme 1.3: Synthesis of 2-Substituted Benzothiazoles Using Iodine in DMF.

Similarly, other reported reactions to synthesize the benzothiazole by using aldehydes with different catalyst, solvent and reagents are mentioned in Table 1.

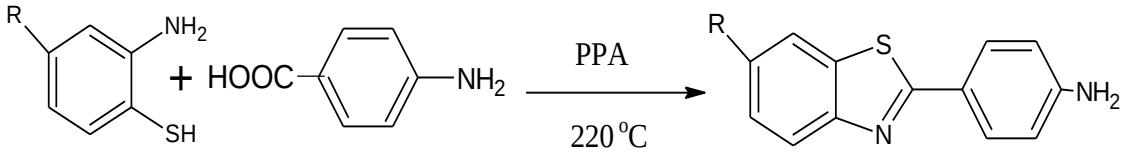
Table 1: Synthesis of Benzothiazoles from Aldehydes.

Sr No.	Solvent	Catalyst	Temperature (^oC)	Time (min)	Yield (%)	References
1	-	SiO_2	µw 600watt	5	73-97	47
2	-	I_2	MW & RT	3-20	65-95	49
3	DMF	12-15mol % I_2	100	30-60	78	48
4	H_2O	-	110	250	80-98	50
5	-	H_2O_2/CAN	50	9 – 70	92-98	51
6	Xylene	4-methoxy TEMPO (5mol %) I_2 (1atm)	100-120	150	95 –96	52
7	DCM	Baker,s yeast	RT	1440	51-84	53
8	H_2O	PTSA (10 mol %)	70	60-300	68-97	54
9	Me/THF	TCCA 1mol%	RT	120	95	55
10	Ethanol	ZnO	Reflux	60-90	93	56
11	H_2O	SDS micelles $(NH_4)_2S_2O_8$	25	22	98	57

12	PEG 400	PEG 400	RT	30-90	60-90	58
13	H_2O	CTAB 5mol%	RT	120	89-98	59
14	Toluene	Animal bone meal	110	15-960	59-96	60
15	DMF	$K_2S_2O_8$	100	120	74	61
16	EtOH	PIFA 1.05eq	MW, 80	15	59-89	62
17	Glycerol	-	RT	-	80-93	63
18	H_2O	SPC (sulphonated porous carbon)	Reflux or MW	90	90	64
19	-	Melt conditions	120-150	30-90	76-97	65

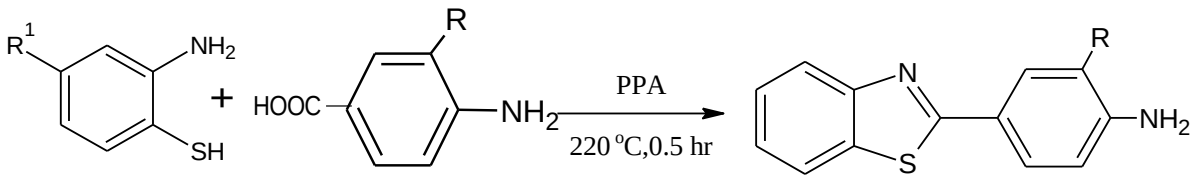
1.2.4 Condensation of 2-Aminothiophenol With Acids

Substituted benzothiazole derivatives can also be prepared by the reaction of acids with 2- aminothiophenol. In 1996, Fang Shi *et al.* [66] synthesized benzothiazole derivatives using poly phosphorous acid as a catalyst at 220 ^oC.



Scheme 1.4: Synthesis of 2-Substituted Benzothiazoles Using PPA.

In 2001, I. Hutchinson *et al*. [67] described two methods for the synthesis of fluorinated 2-(4-aminophenyl) benzothiazoles where by using previous Jacobson cyclization reactions, a mixture of Regio isomers were obtained.

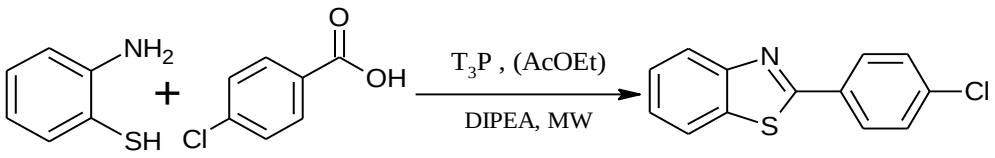


Scheme 1.5: Synthesis of Fluorine Substituted Benzothiazole from Aromatic Carboxylic Acids.

In the 2003, Fang *et al.* [68] in 2011, N.A. Almasoudi, *et al.* [69] synthesized benzothiazole from indomethacine drug and 2-amino benzathiazole using *p*-toluene

sulphonic acid and Al_2O_3 as a catalyst, reaction is completed in 20-30 min under microwave irradiation.

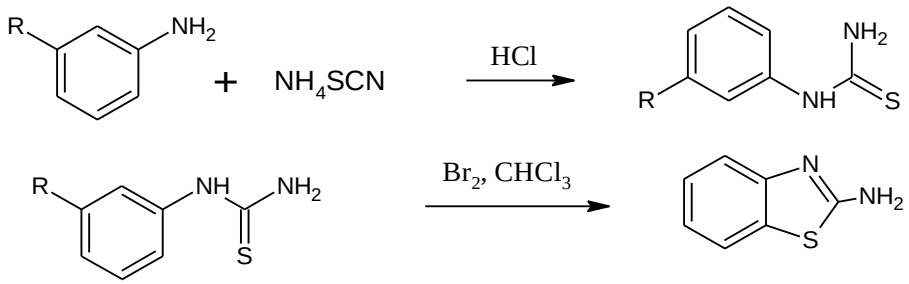
In 2012, X. wen *et al.* [70] reported synthesis of benzothiazoles, benzoxazoles and benzimidazoles. The reaction involved the cyclization of *o*-aminothiophenol, *o*-aminophenol and *o*-phenylenediamine with carboxylic acid in the presence of propylphosphonic anhydride (T_3P) under microwave irradiation. This reaction gave good yield and worked well with aliphatic, aromatic, and heteroaromatic acids. The reaction of formation of benzothiazole is shown below



Scheme 1.6: Synthesis of Benzothiazoles from Carboxylic Acid.

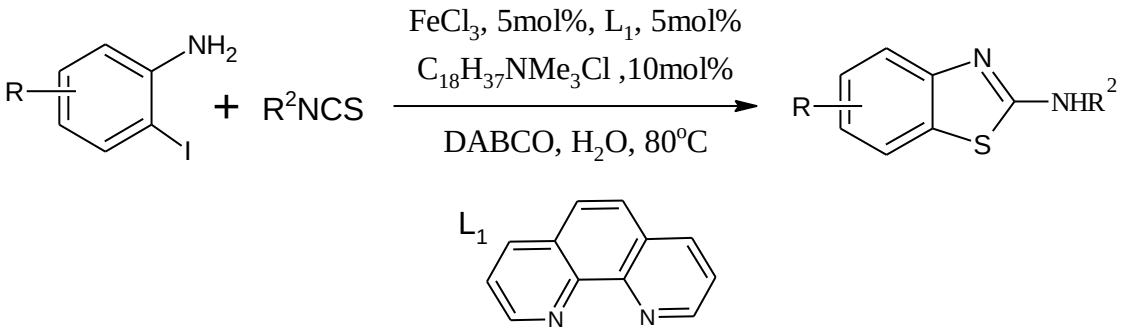
1.2.5 Reaction of Aniline With Ammonium thiocyanate

In 2009, S. Saeed *et al*. [16] synthesized amino benzothiazole as a precursor for the synthesis of isothiocyanates using aniline and ammonium thiocyanate. Both reacted in the presence of HCl and form thiourea derivative which upon further treatment with bromine was converted to amino benzothiazole in the presence of chloroform as a solvent. The reaction was completed in two steps as



Scheme 1.7: Synthesis of Benzothiazoles from Thiourea Derivatives.

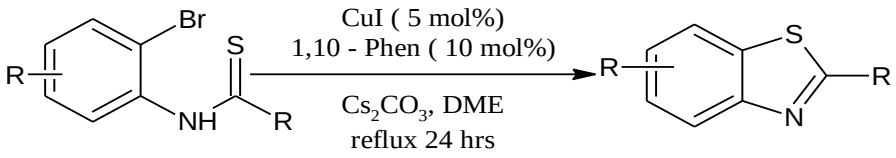
In 2010, Qiupng *et al.* [71] synthesized benzothiazoles from iodo aniline with iso-thiocyanate in water. A mixture was formed by the mixing of 2-iodo aniline, iso thiocyanate, DABCO in water and then $FeCl_3$, 1, 10-phenanthroline(L-1) and octadecyltrimethylammonium chloride (**PTC-4)** were added and the mixture was stirred at 80^oC. The product was obtained in short interval of time.



Scheme 1.8: Synthesis of Benzothiazole from Iodoaniline and Isothiocyanate.

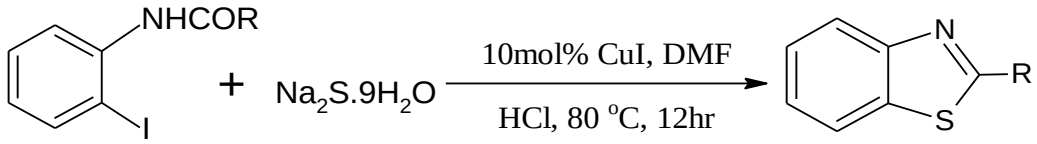
1.2.6 Metal Catalyzed Synthesis of Benzothiazole

In 2006, G. Evinder and R.A Batey [72] synthesized library of benzoxazoles and benzothiazoles using copper as a catalyst. It involved cyclization reaction of thioamide, 1,10-phenanthroline or *N*,*N*-dimethylethylenediamine, but 1,10-phenanthroline, in general, showed greater substrate tolerance as a ligand.



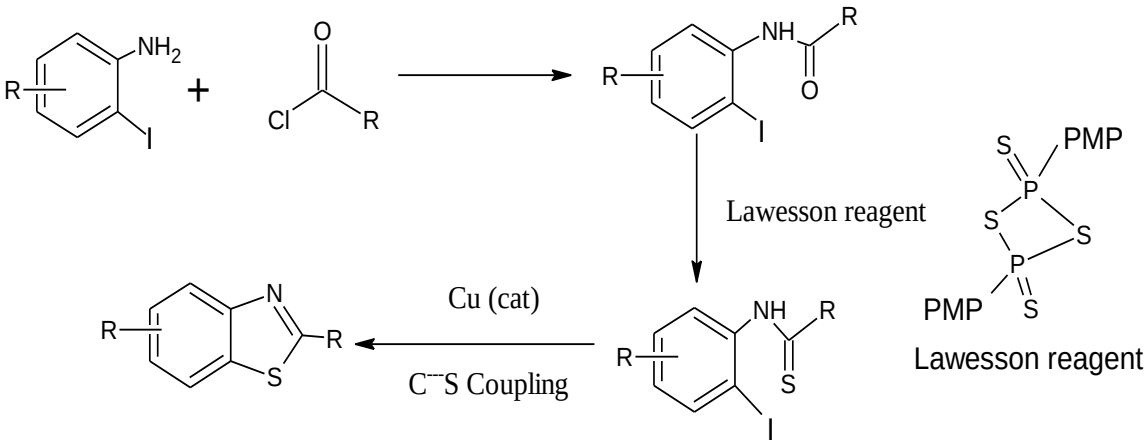
Scheme 1.9: Synthesis of Benzothiazoles from Thioamide Using CuI Catalyst.

In 2009, Dawei Ma *et. al.* [73] used copper as a catalyst to synthesize substituted benzothiazole from 2-haloanilide and metal sulphide coupling reaction. This was the first reaction in which metal sulphides were used as coupling partners for hetero arylation. CuI, *O*-iodo benzamide and Na_2S in DMF were stirred at 80 ^oC for 12hr. The reaction mixture was cooled to room temperature, HCl was added and final product was obtained after 5-10hr.



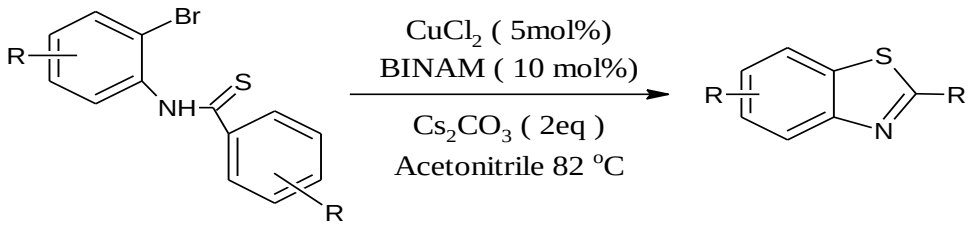
Scheme 1.10 Synthesis of Benzothiazole from 2-Haloanilide and Metal Sulphide.

In 2009, an efficient method by Ding, Qiuping *et al*. [74] was reported for the synthesis of benzothiazoles. This method involved simple steps. In the first step, 2-iodoanilines reacted with acid chlorides to give benzamides that were converted to benzothioamides in the presence of Lawesson reagent. Benzothioamides were then cyclized to benzothiazole in the presence of CuI catalyst.



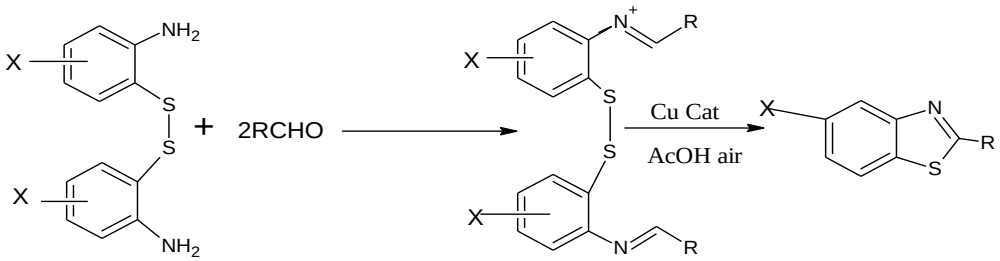
Scheme 1.11: Synthesis of Benzothiazoles from Benzamide.

Similarly, E.A. Jasser *et al*. [75] performed intramolecular cyclization reaction of N-2(chlorophenyl)benzothioamide under mild reaction conditions using Cu (II)-BINAM as a catalyst. This was the first reaction in which Cu-BINAM catalyst was used for intramolecular cyclization. Since N-2(chlorophenyl) benzothioamide was very less reactive, this method gave satisfactory yields. The reaction was carried out at 82 ^{o}C.



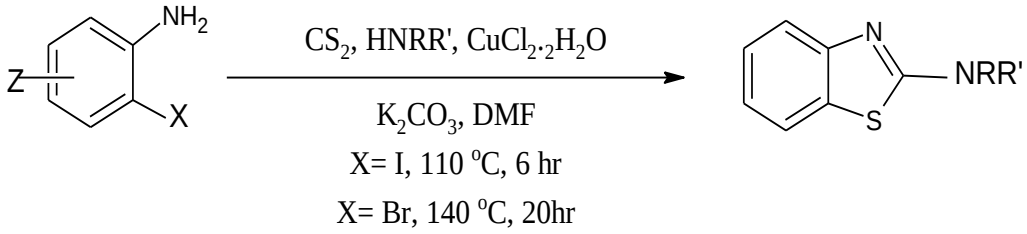
Scheme 1.12: Synthesis of Benzothiazole from N-2(Chlorophenyl)benzothioamide Using Cu-BINAM.

In the same year, J. Hyvl and J. Srogl [76] also used Cu as a catalyst for the activation of disulphides for the synthesis of benzothiazoles; Cu activated the disulphide followed by addition, activation of C-H bond of immine functionality. The reaction was carried out in acetic acid.



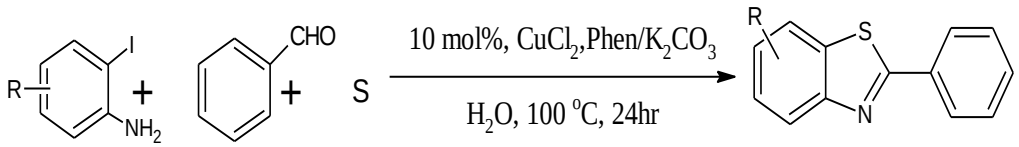
Scheme 1.13: Synthesis of Benzothiazoles from Cu Activated Disulphides and Aldehyde.

In 2011, Cu catalyzed three component domino reaction was carried out by Dawei Ma *et al.* [77]. They used dithiocarbamate salts for copper catalyzed arylation, the reaction product and 2-haloannilines reacted further to give corresponding substituted benzothiazoles. K_2SO_4 was used along with $CuCl_2$ in DMF as a solvent. The reaction was carried out at 110 ^oC for 6hr.



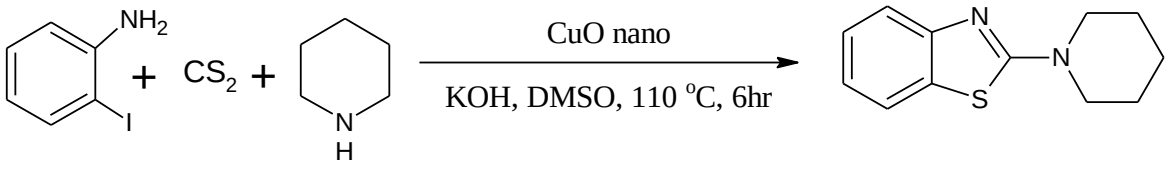
Scheme 1.14: Cu Catalyzed Three Component Domino reaction to Synthesize Benzothiazole.

In 2012, H. Deng *et al*. [78] carried out Cu catalyzed three component reaction in water for the synthesis of benzothiazoles. This was the first strategy in which sulphur as powder was used for the synthesis of benzothiazoles. Reaction involved iodoanniline aldehyde and sulphur powder and was carried out in water. Good yield, cheap catalyst and tolerance of different functional groups make this method worth mentioning.



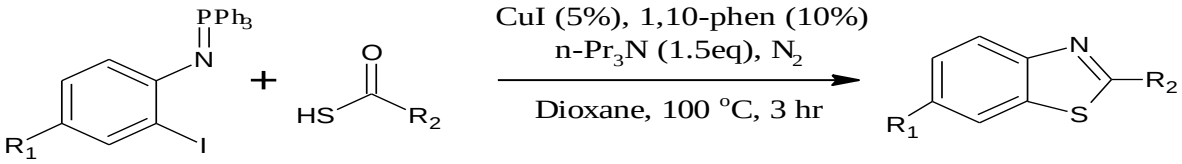
Scheme 1.15: Synthesis of Benzothiazoles From Iodoanniline Aldehyde and Sulphur Powder.

In the same year, G. Satish *et al*. [79] used CuO nano particles for the synthesis of N-substituted benzothiazoles. 2-iodoanniline, CS_2, and piperidine were mixed in the presence of CuO nano particles, KOH base and DMSO as solvent were used, reaction was heated to 110 ^oC for 6hr and 2-N substituted benzothiazoles were formed. The yield obtained was up to 80 %.



Scheme 1.16: Synthesis of Benzothiazole Catalyzed by CuO Nano Particles.

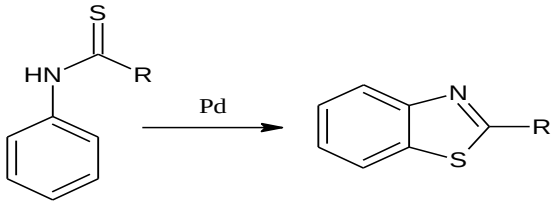
In 2013, Hui Yu *et al*. [80] used Cu as a catalyst for the synthesis of benzothiophenes and benzothiazoles. They utilized thiocarboxylic acid as coupling partner. The reaction involved C-S bond formation followed by Wittig condensation.



Scheme 1.17: Synthesis of Benzothiazoles by Wittig Condensation of Thio carboxylic Acid.

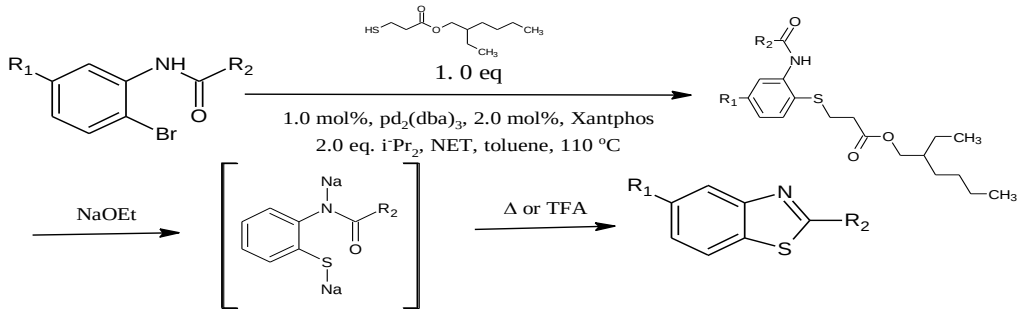
CuI and 1,10-phen, and n-Pr_3N as the base, (2-iodobenzyl) triphenylphosphonium bromide and (2-iodophenylimino) triphenylphosphorane reacted smoothly with thiocarboxylic acids to give benzo[b]thiophene and benzothiazole derivatives in good yields.

There are many examples in the literature in which Pd was used as a catalyst for the synthesis of C-N bond formation however there are fewer reports in literature where palladium is used for C-S bond formation. In 2003, C. Benedi *el al*. [81] reported synthesis of 2-substituted benzothiazoles from *o*-bromophenylthioureas and *o*-bromophenylthioamides using Pd as a catalyst. Highly hindered alkyl monophosphines proved to be the most efficient ligands.This was an intramolecular cyclization reaction the reaction is shown in equation:



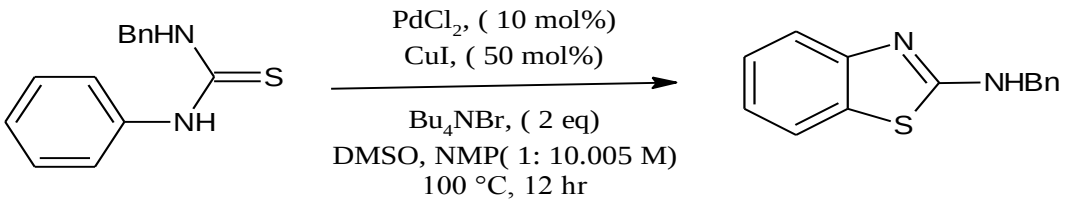
Scheme 1.18: Synthesis of Benzothiazoles from *o*-Bromophenylthioureas and *o*-Bromophenylthioamides Using Pd Catalyst.

In 2007, T. Itoh *et al*. [82] demonstrated C-S bond formation from 2-bromoannilides with sulphur source like alkyl thiolate in the presence of Pd as a catalyst. The product sulphides are converted to benzothiazoles under acidic or basic workup.



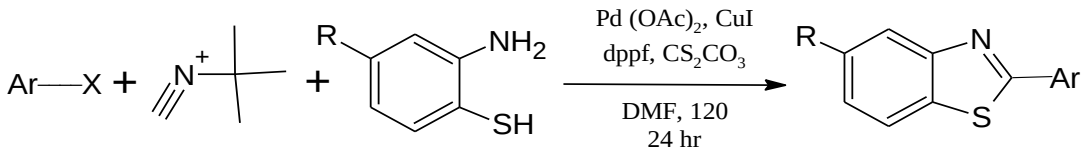
Scheme 1.19: Synthesis of Benzothiazoles from 2-Bromoannilides and Alkyl thiolates.

In 2008, Kiyofumi Inamoto *et al*. [83] used Pd as a catalyst for the synthesis of C-S intramolecular bond formation. The reaction involved thiobenzanilides, 50mol% Cu (I), 10 mol% Pd (II), and Bu_4NBr. Bu_4NBr and CuI speed up the reaction. The reaction allowed good substrate scope as well.



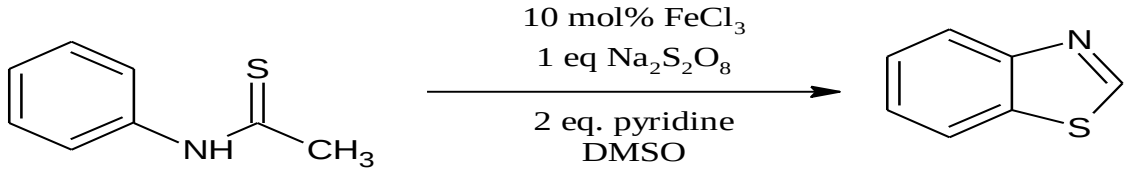
Scheme 1.20: Synthesis of Benzothiazoles from Thiobenzannilides Using Pd and Cu.

In 2013, Valentin N. Bochatay *et. al.* [84] used Pd as a catalyst for the synthesis of benzoxazoles and benzothiazoles. In case of benzothiazole formation, *t*-butyl isocyanide, thiophenol, aryl halide was mixed in the presence of Pd catalyst, CuI as a co catalyst and $CsCO_3$ as reaction accelerator was used



Scheme 1.21: Synthesis of Benzothiazoles from *t*-Butyl isocyanide, Thiophenol, Aryl halide.

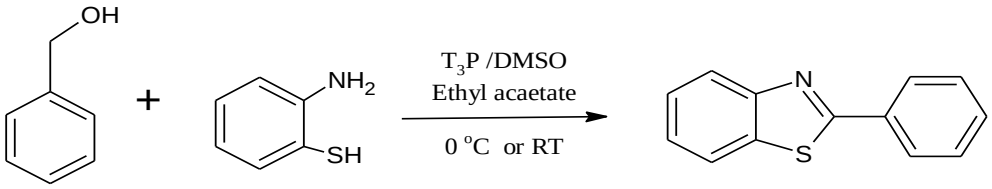
Cu and Pd catalyzed reactions are already discussed above. Fe catalyzed synthesis of benzothiazoles is also reported from benzothiamides [85]. Reaction can tolerate wide range of substrates and revealed that the reaction required the co-existence of substrate, oxidant, $FeCl_3$ and pyridine. Kinetic studies revealed that pyridine was necessary for the high selectivity of this conversion and the reaction was first order in the substrate and zero-order in oxidant $Na_2S_2O_8$.



Scheme 1.22 $FeCl_3$ Catalyzed Synthesis of Benzothiazoles.

1.2.7 Benzothiazole, Synthesis from Alcohol

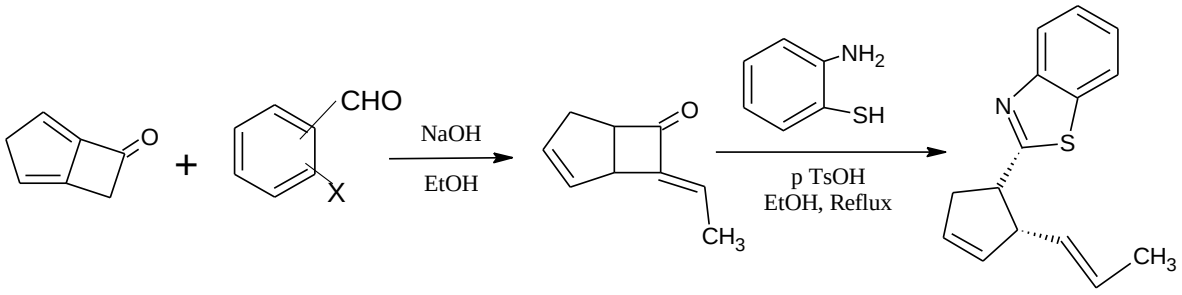
In 2011, G.M. Raghavendra *et al.* [86] synthesized benzothiazoles from alcohols and 2-Aminothiophenol using T_3P as a catalyst. The reaction took 2.5-4 hours for completion. DMSO and ethyl acetate were used as solvents. The reaction was carried out at 0 ^oC and good yield of benzothiazole was obtained.



Scheme 1.23: Synthesis of Benzothiazoles From Alcohol Using T_3P Catalyst.

1.2.8 Benzothiazole's Synthesis from Ketones

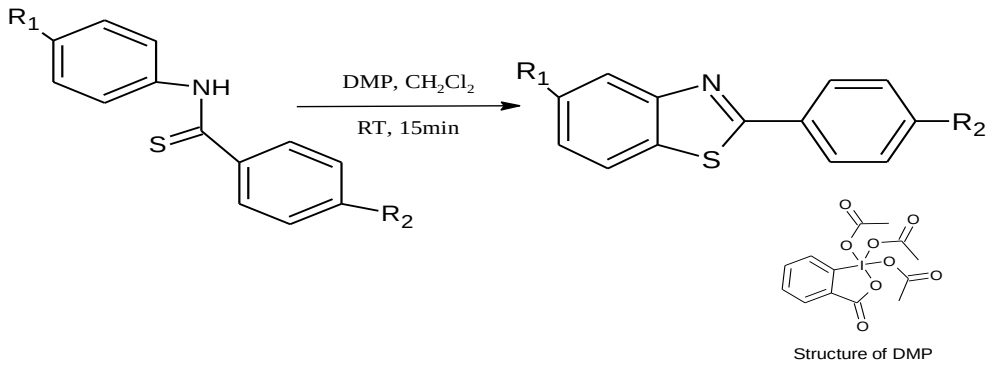
In 2012, E. Fandik [87] synthesized benzothiazole derivatives from 7-benzylidenebicyclo [3.2.0] hept-2-en-6-ones and 2-aminobenzenethiol. The reaction was carried out in the presence of *p*-TsOH (10 mol %) under reflux and the product was obtained in 93-98 % yield. This was the first reaction in which benzothiazole was synthesized by a rearrangement reaction.



Scheme 1.24: Synthesis of Benzothiazoles by Rearranment Reaction.

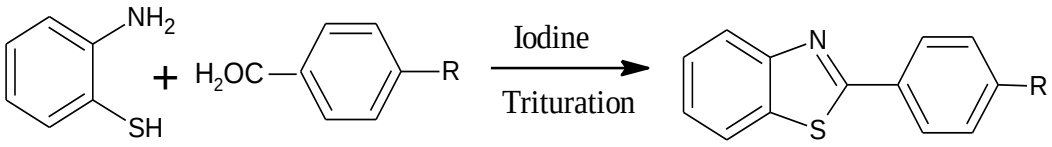
1.2.9 Iodine Catalyzed Reactions

Iodine is a good, cheap and easy substitute to metal catalysts. In 2006, D.S. Bose and M. Idrees [88] used Dess-martin periodinane as a catalyst for the synthesis of substituted benzothiazole from thioformanilides. The reaction was carried out in DMP and CH_2Cl_2 at room temperature for 15 minutes.



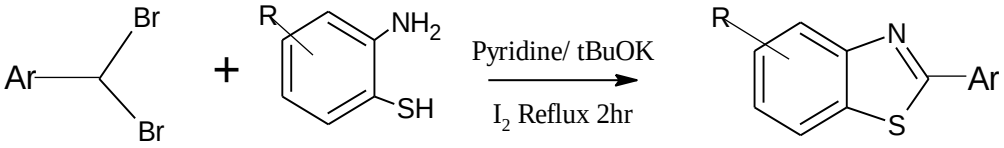
Scheme 1.25: Synthesis of Benzothiazoles From Thioformailides.

In 2007, S. D. Gupta *et al*. [89] carried out a simple reaction using benzoic acid derivatives and 2-aminothiophenol in the presence of molecular iodine as a catalyst. Trituration was carried out and product was isolated in 10 minutes.



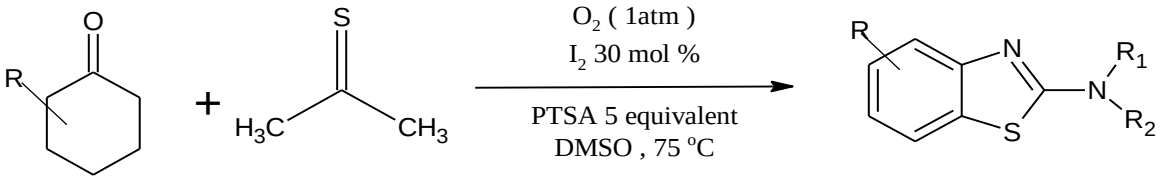
Scheme 1.26: Synthesis of Benzothiazole From Benzoic acid and Iodine Catalyst.

Similarly, a method was reported in which aldehyde and acid derivatives were replaced by geminal dibromides. 2-aryl aminothiols react with geminal di -bromide in pyridine and potassium tertiary butoxide using molecular iodine as a catalyst [90]. The reaction mixture was refluxed for 2 hrs and benzothiazoles were obtained in good to excellent yields.



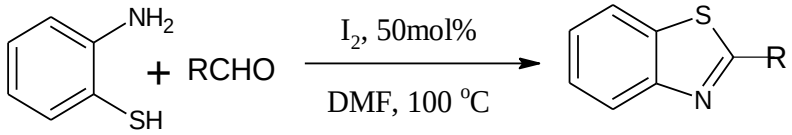
Scheme 1.27: Benzothiazole Synthesis from Germinal diBromides.

Jinwu Z. *et al*. [91] in 2013, reported a method for the synthesis of 2-aminobenzothiazoles from cyclohexanone and thiourea via oxidative cyclization. The reaction involved iodine as a catalyst and molecular oxygen as mild oxidant.



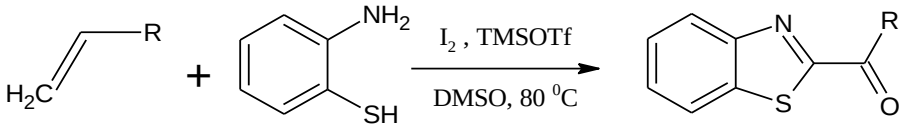
Scheme 1.28: Synthesis of Benzothiazole from Thiourea and Cyclohexanone via Oxidative Cyclization.

In 2006, Yan *et al*. [92] carried out reaction of aldehyde with 2-amino thiophenol using 50 mol % iodine as a catalyst in DMF as a solvent at 110^{o}C.



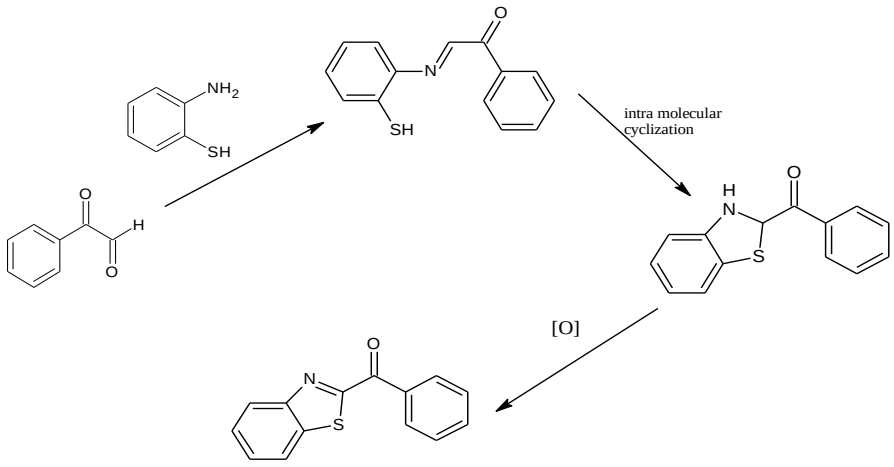
Scheme 1.29: Synthesis of Benzothiazole from Aminophenol and Aldehyde Using I_2 Catalyst.

Deshidi *et al*. [93] reported metal free iodine promoted synthesis of benzothiazoles from terminal alkenes. TMSOTf was used along with iodine in DMSO as a solvent. The reaction was carried out at 80 ^{o}C.



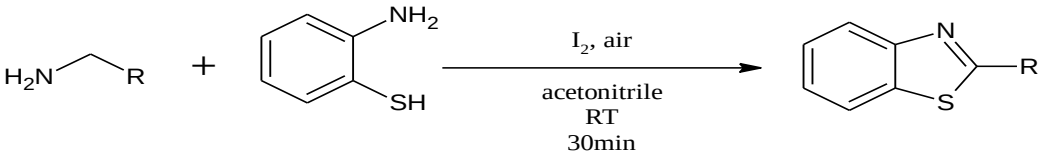
Scheme 1.30: Synthesis of Benzothiazoles From Terminal Alkenes.

The detailed mechanism of reaction is given below



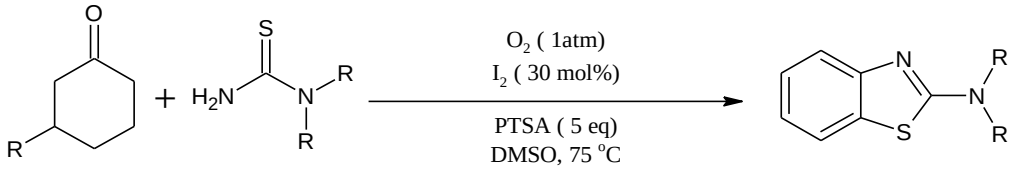
Scheme 1.31: Mechanism of the Reaction.

In 2014, Naresh *et al.* [94] synthesized benzothiazoles by molecular iodine-mediated oxidative cyclization with a new C−N and S−N bond formation at ambient temperature.



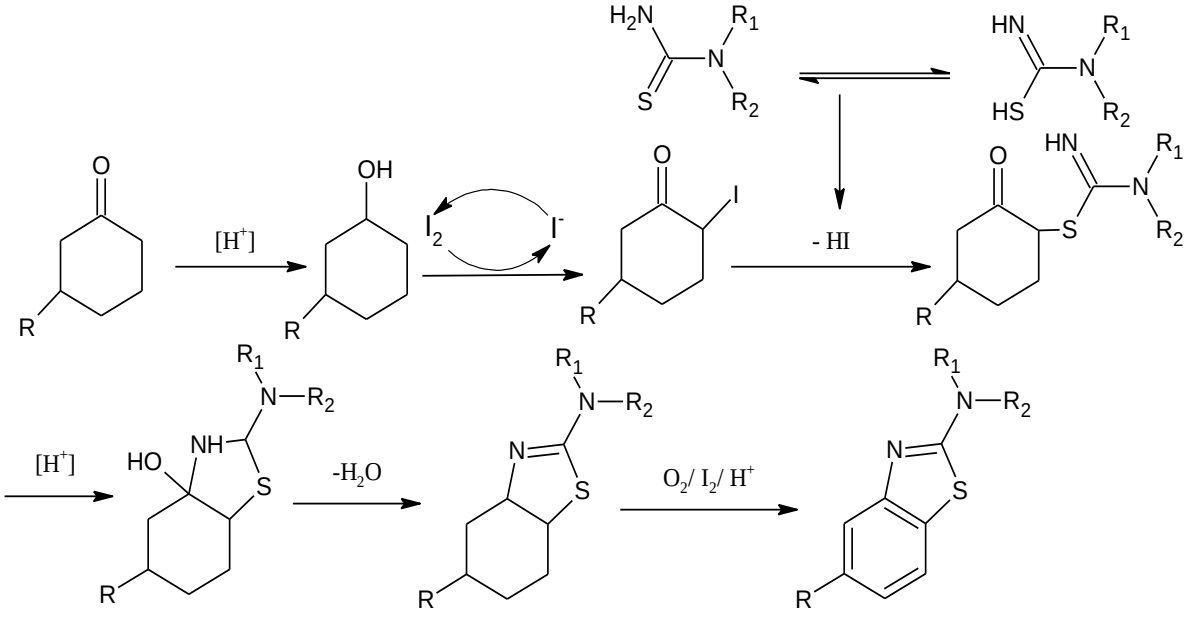
Scheme 1.32: Synthesis of Benzothiazoles by Iodine Mediated Oxidative Cyclization.

A metal-free process [95] for the synthesis of 2-aminobenzothiazoles from cyclohexanones and thioureas was carried out using catalytic iodine and molecular oxygen as the oxidant under mild conditions. Various 2-aminobenzothiazoles, 2-aminonaphtho [2,1-d]thiazoles, and aminonaphtho[1,2-d]thiazoles were prepared from this method in satisfactory yield.



Scheme 1.33: Synthesis of Benzothiazoles from Cyclohexanone and Thio -urea.

Mechanism for the synthesis of benzothiazoles is given below



Scheme 1.34: Mechanism of Benzothiazole Synthesis Using Catalytic Iodine and Molecular Oxygen.

1.3. Amino Acids

Alpha amino acids are the building blocks of complex multicellular organisms. They can exist in stereo isomeric forms, such as *dextro* and *levo*. Apart from glycine, all other amino acids can be described as mirror images, not being superimposed. Major parts of them, which are found in nature, appear to be of the L-type. That's why eukaryotic proteins are always composed of *levo* amino acids, however *dextro* ones can be found in bacterial cell walls and several peptide antibiotics. Thus, far more than three hundred kinds of amino acids have been discovered in nature. However, only 20 of them are usually found as compounds of human peptides and proteins. Molecule of an amino acid contains carboxyl (COOH) and amino (NH_2) functional groups, they generally exist in zwitter ionic form. Each amino acid contains a different side chain, also known as R group, that’s why they differ in their properties.

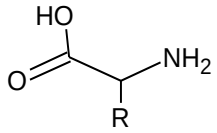


Figure 1.6: Structure of Amino Acid.

Amino acids show remarkable metabolic and regulatory versatility. They serve as important starting materials for the synthesis of a variety of molecules, regulate key metabolic pathways and processes and play a role in the health, growth, homeostasis, development, and reproduction, of organisms. This show the importance of research on amino acid biochemistry and nutrition to discover new knowledge of animal biology and solve practical problems in medicine and animal agriculture [96].

1.4 Biological Activity of Benzothiazoles

Microorganisms are the causative agents for various sorts of illness [97] like pneumonia, ameobiasis, typhoid, malaria, common cough, cold and various infections and cause some severe diseases like tuberculosis, influenza, syphilis, and AIDS etc. Since the use of antimicrobial agents have significantly reduced the danger posed by infectious diseases. The use of these antimicrobial drugs has led to a decrease in deaths from diseases that were previously widespread, untreatable and

sometimes lethal. Throughout the years, antimicrobial have saved the lives and eased the sufferings of millions of people. But today's primary concern is the emergence and spreads of microbes those are impervious to economical and effective first-line drugs. The bacterial infections which contribute most to human diseases are also those in which emerging antimicrobial resistance is generally apparent. When infections become resistant to first line drugs, treatment must be changed to second or third line drugs that are always much expensive and more harmful as well e.g. the drug needed to treat multi drug resistant form of tuberculosis are over 100 times expensive than the first line antimicrobials used to treat non-resistant forms. Most difficult circumstances of all are ailments where resistance is developing for all currently accessible drugs; current trends suggest that some ailments will have no effective therapies within the next ten years. So, there is a need to develop new drugs immediately which are effective against resistant bacteria having lesser toxicity as well as economical also. In view of the biological importance of the benzothiazole nucleus containing compound we will here discuss some important activities shown by them include:

- Antimicrobial
- Anticancer
- Amyloid imaging agents
- Anti-tuberculosis
- Anti-diabetic

1.4.1 Anti-microbial Activity

Despite various attempts to develop new structural models for the synthesis of new anti-microbial agents, benzothiazole derivatives remain as one of the most versatile class of compounds against microbes. Much research has revealed that benzothiazole derivatives as anti-microbial drugs process significant potential. In 2011, benzothiazole derivatives were tested against anti-bacterial and anti-fungal strains, and it was found that 2-(1,3-benzothiazole-2-yl)-5-(diethylamino) phenol derivatives showed excellent anti-fungal activity [98].

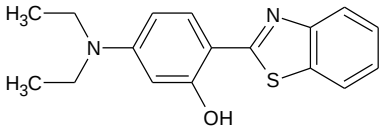


Figure 1.7: 2-(1,3-Benzothiazole-2-yl)-5-(Diethylamino) Phenol.

In 2013, Schiff bases and oxadiazole derivatives of benzothiazole derivatives are synthesized and tested for anti-bacterial and anti-fungal studies as compare to ciprofloxacin and ketoconazole as standard drugs, it was found out that following five derivatives showed excellent activity [99].

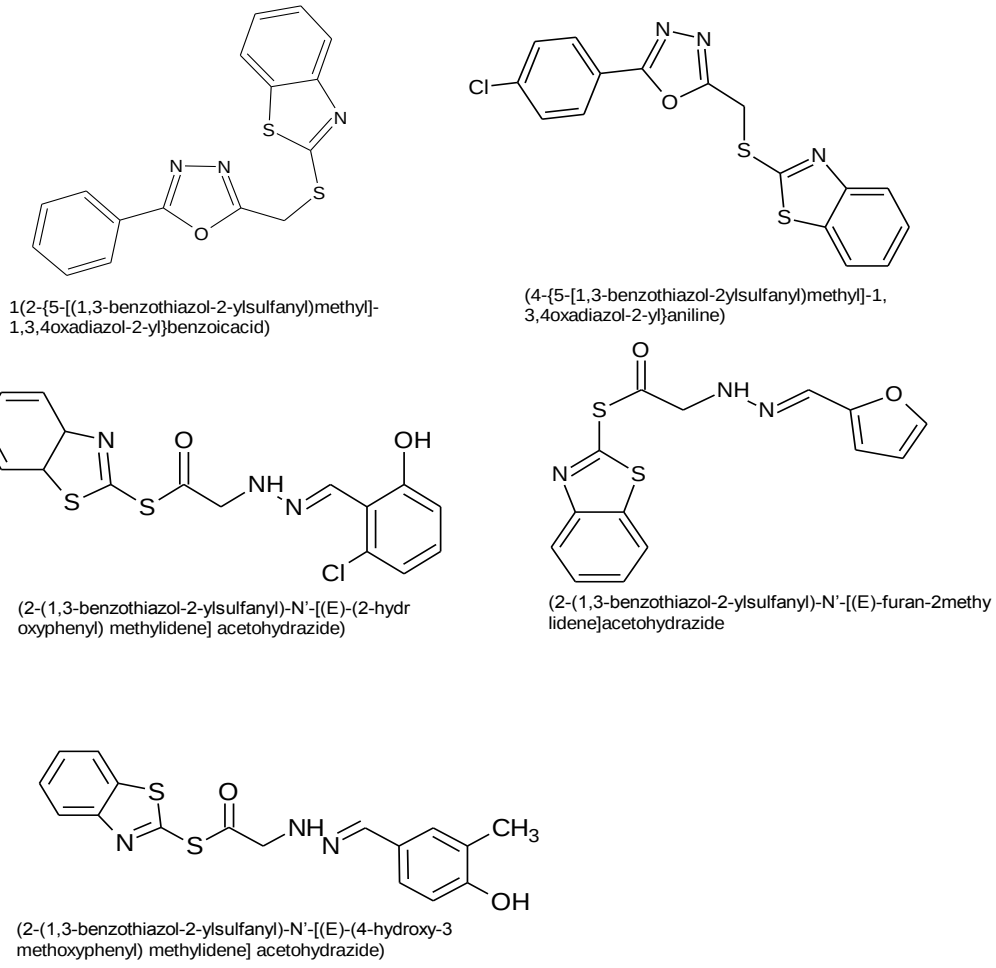


Figure 1.8: Schiff Base and Oxadiazole Derivatives of Benzothiazole.

In 2015, number of 2-amino-1,3-benzothiazole and 2-mercepto-1,3-benzothiazole were synthesized and screened for *in vitro* anti-bacterial and anti-fungal activities the 2-mercepto derivatives showed excellent anti-bacterial activity this showed that mercepto group is crucial for anti-bacterial activity. Similarly, both 2-mercepto and 2-amino groups show different anti-fungal activities depending on substitution at 6

position. The following 2-mercepto-6-chloro benzothiazole showed excellent antibacterial activity.

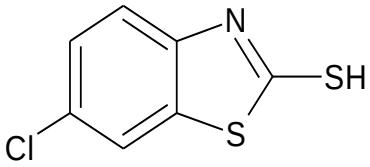


Figure 1.9: 2-Mercepto Benzothiazole.

1.4.2 Anti-cancer Activity

Benzothiazole exhibits a wide range of biological properties due to its potent biological activities. It is a versatile tool in the field of cancer treatment amongst all activities. A large number of benzothiazole derivatives show chemotherapeutic activity hence this unique molecule must act like a boon in the field of developing various synthetic anticancer agents [100]. In 1998, Bradshaw and coworkers assayed antitumor activity of 2-(4-Aminophenyl) benzothiazoles. It was seen that they showed biphasic inhibitory response against various cancer cell lines yielding IC_{50} values in nm range. Substitution of halogen and methyl groups adjacent to the amino group showed increased potency against breast cancer cell lines. Similarly, they showed greater IC_{50} values against two prostate cancer cell lines. Potency and selectivity were confirmed when compounds were examined in the National Cancer Institute's Developmental Therapeutics screen; the spectrum of activity included specific ovarian, renal, colon as well as breast carcinoma cell lines. Compared with standard anti-tumour agents evaluated in the National Cancer Institute *in vitro* cell panel, benzothiazoles revealed unique profiles of growth inhibition, suggesting a mode(s) of action shared with no known clinically active class of chemotherapeutic agents [101].

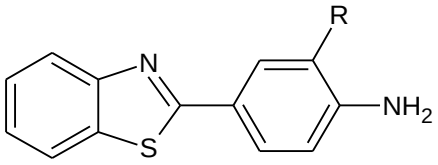


Figure 1.10: 2-(4-Aminophenyl) Benzothiazoles.

In 2002, amino acid prodrugs of antitumor 2-(4-aminophenyl) benzothiazole are synthesized due to solubility and bioavailability issues of the later one. The

synthesized drugs showed good water solubility, stability at ambient temperature and degradation to free base *in vivo*. The lysyl-amide of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole has been selected for phase-1 clinical trial [102].

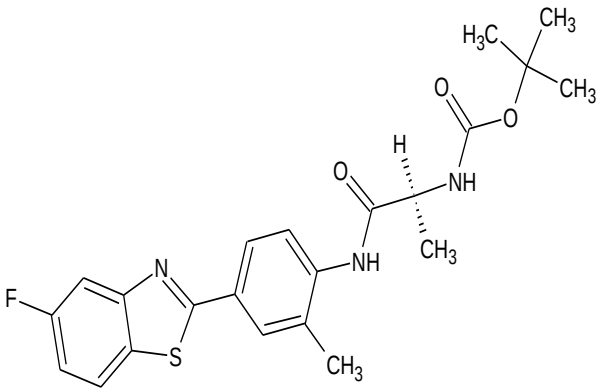


Figure 1.11: 2-(4-Amino-3-Methylphenyl)-5-Fluorobenzothiazole.

In 2005, Yoshida and coworkers synthesized 2,6-dichloro-N-[2-(cyclopropane carbonylamino)benzothiazole-6-yl] benzamide as a stable agent and exhibited excellent anti-tumor activity [103].

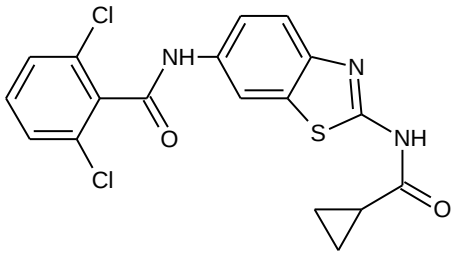


Figure 1.12: 2,6-Dichloro-N-[2-(Cyclopropanecarbonylamino) Benzothiazole-6-yl] Benzamide.

2-aryl substituted compounds were synthesized and checked for antitumor activity and were compared to standard [2-(3-bromo-4-aminophenyl) benzothiazole] against human cervical cancer cell lines. Cytotoxicity of the compounds having $N(CH_2CH_2Cl)_2$ at *para* position is more than the compounds having $-NH_2$ at para position on the phenyl ring attached to the benzothiazole. Compounds with more than one halogen atom exhibited better cytotoxic activity [104].

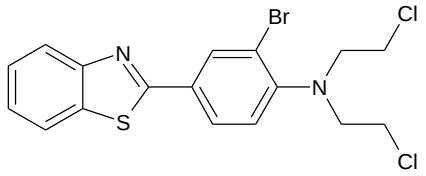


Figure 1.13: 4(1,3-Benzothiazole-2-yl)-2-Bromo-N,N-Bis(2-Chloro Ethyl)Anniline.

In 2008, S.N. Manjula and coworkers [105] synthesized 2-amino benzothiazole from optically active thiourea. The derivatives of benzothiazole that show in EAC cells IC_{50} values were in the range of 10-24 µM where as in MCF-7, Hela Cells IC_{50} values were observed in the range of 15-30 µM and 33-48 µM, respectively.

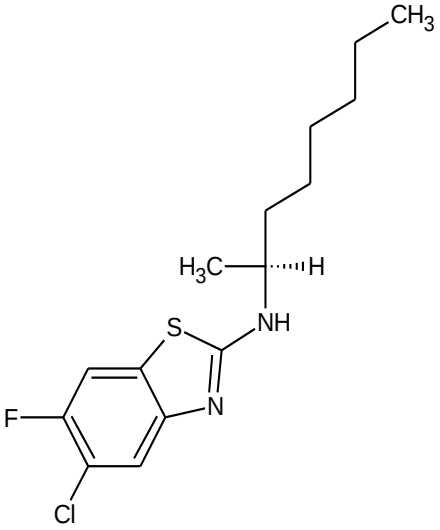


Figure 1.14: 5-Chloro-6-Fluoro-N-[(2S) Octan-2-yl]1,3-Benzothiazole-2-Amine.

1.4.3 Benzothiazole as Imaging Agent

Advancement in neuroimaging over the past few decades is in rapid progress. New and power full imaging technologies and softwares are developed. In addition to the study of normal brain function and structure such technologies also offer a greater help in studying disease related brains such as meningitis, Autism, Attention Deficit Hyperactivity Disorder (ADHD), Arteriovenous Malformation, Aphasia, Aneurysm etc. Neuro imaging makes this study easier by identification of pathognomonic proteins. Now a day imaging amyloid plaques in Alzheimer's disease is of significant interest. Benzothiazole nucleus is naturally found in fire fly luciferin and is fluorescent that's why derivatives of benzothiazoles are becoming popular as biological imaging agents for more efficient assessment of amyloid plaques in Alzheimer disease [106].

In 2003, Chester A. Mathis and coworkers [39] synthesized radiolabeled substituted 2-aryl benzothiazoles and checked amyloid binding activity. [N-methyl-11C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole or ([^{11}C]6-OH-BTA-1) was selected as the lead compound for further evaluation. Staining of AD frontal cortex tissue sections with 6-OH-BTA-1 indicated the selective binding of the compound to amyloid plaques and cerebrovascular amyloid. The encouraging *in vitro* and *in vivo* properties of [^{11}C]6-OH-BTA-1 support the choice of this derivative for further study in human subject's brain deposition.

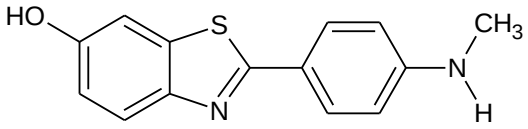


Figure 1.15: [N-Methyl-11C]2-(4′-MethylAminoPhenyl)-6-Hydroxybenzothiazole.

K. Serdons and coworkers [107] synthesized the ^{18}F labeled 2-(-4-fluoro phenyl)-1,3 Benzothiazole and checked as amyloid imaging agent as compare to Pitt's Burg compound [^{13}C] PIB. The compound showed high *invitro* amyloid binding activity. Similar studies were also carried out in mice and the compound synthesized showed good binding activity as compare to [^{13}C] PIB.

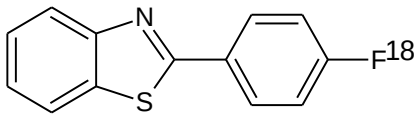


Figure 1.16 2-(-4-Fluoro Phenyl)-1,3 Benzothiazole.

Henriksen and coworkers [108] synthesized six N-^{11}C-labeled BTAs and screened for brain uptake and metabolic stability. It was found that the substitution pattern of the phenyl ring and the benzothiazole moiety has influence on the metabolic stability. The metabolic stability of the compounds in turn influences the uptake of radioactivity in brain tissue.

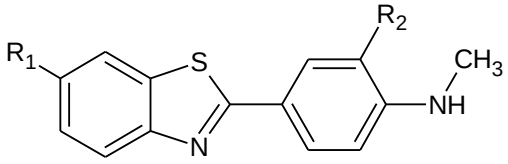


Figure 1.17: N-11C-Labeled Aminophenyl benzothiazoles Substituted with Fluorine.

1.4.4 Benzothiazole as Anti-tubercular Agent

Tuberculosis is a fatal disease caused by *Maycobacterium tuberculosis* that invades human immune system and affect lungs. Benzothiazoles are active anti -tuberculur agents. Chaitiana Mulakayala and coworkers synthesized series of benzothiazole fused with amines, 1, 2, 3- triazoles and screened for their antituberculur activity. The triazole conjugates showed good anti tuberculur and bactericidal activity [109].

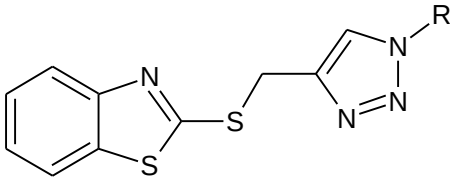


Figure 1.18: 1,2,3-Triazole Conjugates of 2-MercaptoBenzothiazole.

In 2016, Mehra and coworkers [110] studied 20,000 already used enzyme shikimate kinase inhibitors by insilico screening. It was found that 15 compounds were good inhibitors. They were then checked for *in vitro* Mtb-SK enzyme inhibition. Two compounds presented significant Mtb-SK enzyme inhibition with IC_{50} values of 10.69 ± 0.9 and 46.22 ± 1.2 μM. The best hit was then checked for the *in vitro* mode of inhibition where it came out to be an uncompetitive(binds only when enzyme substrate complex is formed) and noncompetitive (binds only to substrate) inhibitor with respect to shikimate (SKM) and ATP, respectively, suggesting its binding at an allosteric site. Both compounds are benzothiazole derivatives.

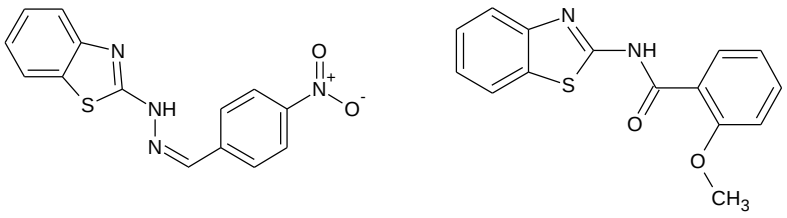


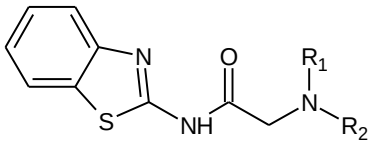
Figure 1.19: 2-[(2Z)-2-(4-Nitrobenzyliene)Hydrazinyl]1,3-Benzothiazole,

N-(1,3-Benzothiazole-2-yl)-2-Methoxy Benzamide.

1.4.5 Benzothiazole as Anti-diabetic Agent

Diabetes mellitus is one of the common metabolic disorders that results in significant morbidity and mortality. It is considered as one of the five leading causes of death in the world. Reports from the World Health Organization (WHO) indicate that diabetes mellitus is one of the major killer of our time with people in

South East Asia and Western Pacific. Heterocyclic compounds are used for antidiabetic therapy for many years. Several drugs such as sulfonylurea and biguanides are presently available to reduce hyperglycemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is crucial to overcome these problems [111]. Benzothiazole is emerging as new scaffold in drugs as antidiabetic agent. A novel series of benzothiazole derivatives were synthesized [112] and checked for *in vivo* study to investigate their hypoglycemic activity by streptozotocin-induced diabetic model in rat. These derivatives showed very good biological efficacy when compared to glibenclamide, a well-known diabetic agent. All the compounds were effective, amongst them N-(6-chlorobenzo[d]thiazol-2-yl)-2-morpholinoacetamide showed more prominent activity at 100 mg/kg.



NR_1R_2= Morphleno

Figure 1.20: N-(6-Chlorobenzo[d]thiazol-2-yl)-2-Morpholinoacetamide.

In 2013, Maltzer and coworkers [113] synthesized various substituted benzothiazole derivatives and screened for hypoglycemic (anti-hyperglycemic) activity. The ethoxybenzothiazole moiety in 2-(benzo[d]thiazol-2-ylmethylthio)-6-Ethoxybenzo[d]thiazole was found to be critical for increasing glucose transport in L6 myotubes, and for the activation of AMPK. In accordance with this observation, this moiety fits three of the pharmacological features found important for the biologic activity (Hydrophobic, aromatic, and H-bond acceptor). 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazole significantly increases the rate of glucose uptake in L6 myotubes at pharmacologically relevant concentrations (25 μM). Moreover, at 5 μM concentration increased phosphorylation of AMPK in L6 myotubes is observed.

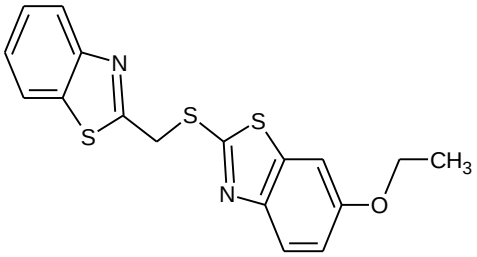


Figure 1.21: 2-(Benzo[d]thiazol-2-ylmethylthio)-6-Ethoxybenzo[d]Thiazole.

1.5 Objectives

As already mentioned, the methods discussed in literature review have their own limitations. Many of them employed metal catalysts, expensive reagents, toxic solvents, long reaction times, high temperature, low yield, costly apparatus and harsh reaction conditions. Moreover, due to increasing demand many new methods for the preparation of benzothiazole are also required. We tried to develop a method that overcomes all these limitations by using mild iodine catalyst without using any solvent and at room temperature. The reaction is completed in 20-25 minutes. We also tried to develop a reaction using N-protected amino acids for the first time to synthesize benzothiazoles.

Chapter 2

2.1 Experimental

2.1.1 Chemicals and Reagents

Glycine (≥98 %), L-Leucine (≥ 98 %), L-Proline (≥99 %), L-Valine (≥ 98 %), L-Phenyl Alanine (≥ 98 %), 2-Aminothiophenol (99%), L-Tryptophan (≥ 98.9 %), NaOH (≥ 98 %), $Na_2S_2O_3$ (≥ 98.5 %), Benzoyl Chloride (99 %), $KHSO_4$ (99 %), HCl (37 %), Iodine (≥ 99.9 %), Boc (≥ 98 %)), Na_2SO_4 anhydrous (98 %), were purchased from Sigma Aldrich, Merck and Fluka.

2.1.2 Solvents

The solvents ethanol (99.8 %), methanol (99.9 %), chloroform (99.8 %), carbon tetra chloride (99.1 %), dioxane (99.0 %), ethyl acetate (99.8 %) were purchased from Sigma Alrdich and were of analytical grade. The solvents were used as such without further purification.

2.1.3 Instruments

The compounds were weighted in electronics analytical balance ATY224, melting point was determined on melting point apparatus SMP10 and are uncorrected. Organic solvents were dried under vacuum by using Rotary evaporator R-210. TLC was observed under UV analyze lamp. FTIR was recorded in Bruker ATR FTIR spectrophotometer ranging from 4000-500 cm^{-1}. The recrystallized samples were subjected to GCMS analysis in a Perkin Elmer Clarus 600 GC coupled with 600c MS Quadpole EI (electron impact). Solvent used was $CHCl_3$ GC was performed to check the purity of samples. After confirmation of purity, mass spectrometry was carried out to confirm the products. Analytical parameters of GCMS are enlisted below:

- Column: Elite-5 (diameter 0.25 mm)
- Carrier gas: Helium
- Column flow 3mL/minute
- Solvent delay: 3minutes
- Ionization mode: EI

- Solvent delay: 3min
- Linear temperature: 290 ^{o}C
- Source temperature: 150 ^{o}C

Following steps were involved to synthesize the target compound.

1. NH_2 group protection of α-amino acid.
2. Reaction of NH_2 protected α-amino acid with 2-aminothiophenol.

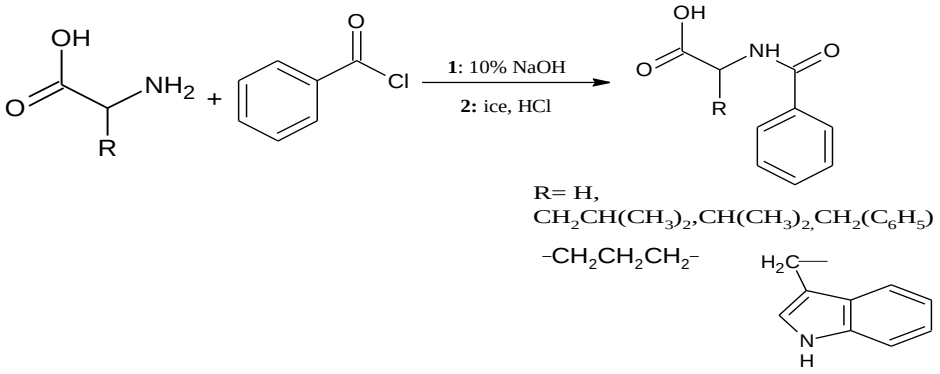
2.1.4 N-Protection of Amino Acid

i. NH_2 group protection of amino acid with benzoyl chloride.
ii. NH_2 group protection of amino acid with Boc.

The detail procedure of protection of amino acids is given below:

2.2 General Procedure for the Synthesis of N-Benzoyl Protected Amino Acids (GP1)

Amino acid 0.5g (6.66 mmol) was dissolved in 10% NaOH (0.375mL). The reaction was allowed to stir for half an hour then, benzoyl chloride 0.68 mL was added drop wise in five portions. The reaction was further allowed to stir for half an hour. The progress of the reaction was monitored by TLC. After that ice was added and carefully maintained the pH of the solution between 2-3 by addition of dilute HCl (few drops). Resultant crystals were then filtered, washed with cold water and after drying, crystals were boiled in CCl_4 for five minutes to remove excess benzoic acid if formed. The crystals were again washed with water. The product was recrystallized from methanol.



Scheme 2.1: General Scheme for the Synthesis of N-Benzoyl Protection of Amino Acids.

2.2.1 N-Benzoyl Protected Glycine (1)

The protection was carried out as mentioned in general procedure 1 (GP1). Yield = 78 %. R_f value in 1 % Methanol: Chloroform system (0.2), M.P. (179-181 ^oC), FTIR: ($\boldsymbol{v}_{max}$ cm^{-1})1760 (C=O acid), 1623 (C=O amide), 1590 (C=C aromatic), 1200 (C–NH stretch).

2.2.2 N-Benzoyl Protected L- Leucine (2)

The protection was carried out as mentioned in GP1. Yield = 82 %. R_f value in 1 % Methanol: Chloroform system (0.23), M.P. (141-144 ^oC), FTIR: ($\boldsymbol{v}_{max}$ cm^{-1})1715 (C=O acid), 1634 (C=O amide), 1600 (C=C aromatic), 1300 (C–NH stretch).

2.2.3 N-Benzoyl Protected L-Proline (3)

The protection was carried out as mentioned in GP1. Yield = 87 %. R_f value in 1 % Methanol: Chloroform system (0.45), M.P (Oily liquid), FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}) 1703 (C=O acid), 1680 (C=O amide), 1600 (C=C aromatic), 1300 (C–N stretch).

2.2.4 N-Benzoyl Protected L-Tryptophan (4)

The protection was carried out as mentioned in GP1. Yield = 80 %. as dirty yellow crystals. R_f value in 1 % Methanol: Chloroform system (0.5), M.P. (189-191 ^oC), FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}) 1710 (C=O acid), 1630 (C=O amide), 1600 (C=C aromatic), 1300 (C–N stretch).

2.2.5 N-Benzoyl Protected L-Valine (5)

The protection was carried out as mentioned in GP1. Yield = 88 %. R_f value in 1 % Methanol: Chloroform system (0.42), M.P. (129-131 ^oC), FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}) 1703 (C=O acid), 1678 (C=O amide), 1603 (C=C aromatic), 1300 (C–N stretch).

2.2.7 N-Benzoyl protected L-Phenyl alanine (6)

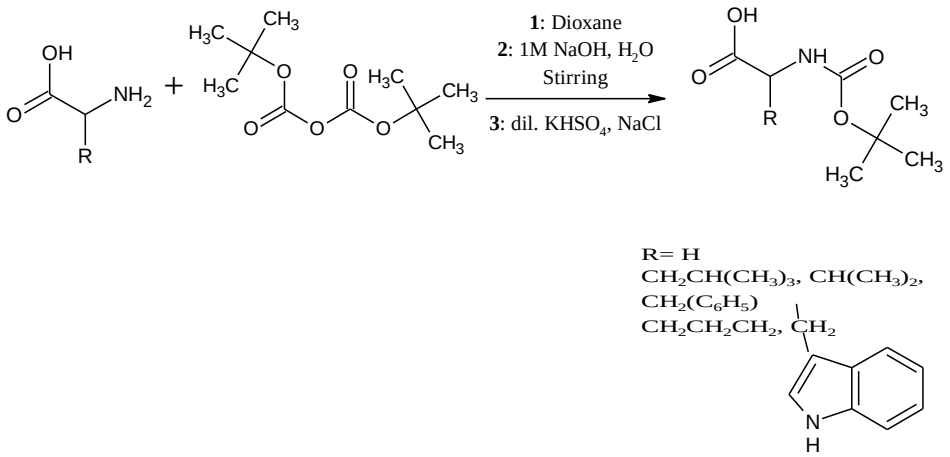
The protection was carried out as mentioned in GP1. Yield = 58 %. R_f value in 1 % Methanol: Chloroform system (0.21), M.P. (148-151 ^oC), FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}) 1717 (C=O acid), 1700 (C=O amide), 1608 (C=C aromatic), 1300 (C–N stretch).

Table: 2 Physical Data of Synthesized Compounds **1-6**.

Compd. No.	M.P. (°C)	Physical Appearance	Solvent for Recrystallization	Yield (%)
1	179-181	White crystals	Methanol	78
2	141-144	White sticky crystals	Methanol	82
3	-	Oily liquid	Methanol	87
4	129-131	Dirty yellow crystals	Methanol	80
5	126-129	White crystals	Methanol	88
6	148-151	White crystals	Methanol	58

2.3 General Procedure for the Synthesis of N-Boc Protected Amino Acids (GP2)

Amino acid (4.3g, 37.4 mmol) was first dissolved in dioxane (75 mL). After half an hour, 1M NaOH (38 mL) and H_2O (38 mL) were added. $(Boc)_2O$ (9g, 41.4 mmol) was then added in the reaction mixture and allowed to stir for an hour. The reaction mixture was concentrated under reduced pressure to about 30-40 mL. After that ice was added in reaction mixture along with small amount of ethyl acetate. Dilute $KHSO_4$ was added very carefully in reaction mixture to maintain the pH of the solution between 2-3. The product was then washed with brine, extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated under reduced pressure.



Scheme 2.2: General Scheme for The Synthesis of N-Boc Protected Amino Acids.

2.3.1 N-Boc Protected Glycine (7)

The protection was carried out as mentioned in GP2. Yield = 42 %. M.P. 80-83 ^{o}C, FTIR: (υ_{max} cm^{-1}) 1735 (C=O acid), 1670 (C=O amide), 1380 (C(CH$_3$)$_3$), 1300 (C–N stretch).

2.3.2 N-Boc Protected L-Leucine (8)

The protection was carried out as mentioned in GP2. Yield = 69 %. M.P. 102-104 ^{o}C, FTIR: **(** υ_{max} cm^{-1}) 1735 (C=O acid), 1696 (C=O amide), 1380 (C(CH$_3$)$_3$), C–N stretch (1300).

2.3.3 N-Boc Protected L-Proline (9)

The protection was carried out as mentioned in GP2. Yield = 68 %. M.P. 166-168 ^{o}C, FTIR: (υ_{max} cm^{-1})1735 (C=O acid), 1633 (C=O amide), 1300 (C-N stretch), 1424 **(**CH$_2$), 1380 (C(CH$_3$)$_3$).

2.3.4 N-Boc Protected L-Tryphtophan (10)

The protection was carried out as mentioned in GP2. Yield = 94 %. M.P. 128-131 ^{o}C, FTIR: (υ max cm^{-1}), 1717 (C=O acid), 1656 (C=O amide), 1380 (C(CH$_3$)$_3$), 1300 (C–N stretch).

2.3.4 N-Boc Protected L-Valine (11)

The protection was carried out as mentioned in GP2. Yield = 81 %. M.P. 79-81 ^{o}C, FTIR: (υ_{max} cm^{-1})1730 (C=O acid), 1678 (C=O amide), 1371 (C(CH$_3$)$_3$), 1058 (C–N stretch).

2.3.5 N-Boc Protected L-Phenyl alanine (12)

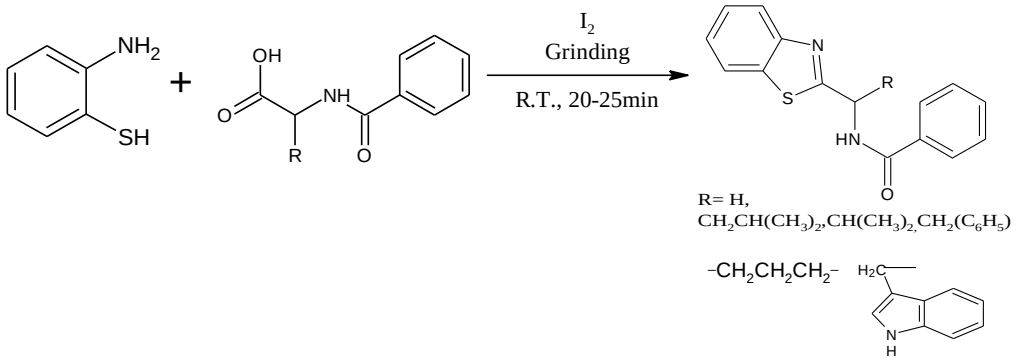
The protection was carried out as mentioned in GP2. Yield = 62 %. M.P. 86-88 ^{o}C, FTIR: (υ_{max} cm^{-1})1716 (C=O acid), 1693 (C=O amide), 1366 (C(CH$_3$)$_3$), 1049 (C–N stretch).

Table 3: Physical Data of Synthesized Compounds **7-12**.

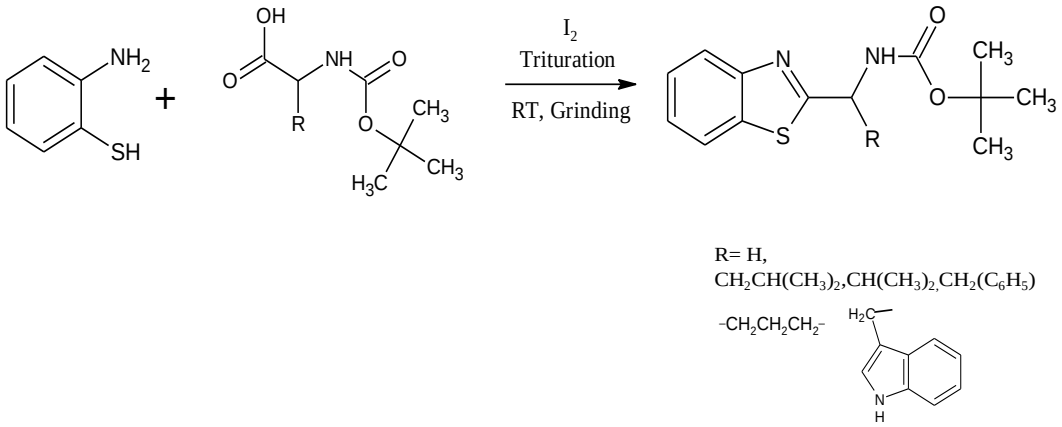
Compd. No.	M.P. (^{o}C)	Physical Appearance	Yield (%)
7	80-83	White crystals	42
8	102-104	White crystals	69
9	166-168	White crystals	68
10	128-131	White crystals	94
11	79-81	White crystals	81
12	86-88	White crystals	62

2.4 General Procedure for the Synthesis of N-Protected Amino acid Derivatives of Benzothiazoles (GP3)

The reaction was carried out as mentioned in the literature [90]. The reaction involved protected amino acid (500mg), 2.7 mmol) that reacted with 2-amino thiophenol 0.67 mL(,5.3 mmol) in the presence of iodine 223mg(, 1.8 mmol) as a catalyst. Reaction progress was monitored by TLC and was completed in 20 minutes. After the completion of reaction, product was washed with $Na_2S_2O_3$ to remove unreacted iodine. Product was recrystallized from (70:30) ethanol: water mixture for purification.



Scheme 2.3: General Scheme for the Synthesis of N-Benzoyl Protected Amino Acid Derivatives of Benzothiazoles.



Scheme 2.4: General Scheme for the Synthesis of N- Boc Protected Amino Acid Derivatives of Benzothiazoles.

2.4.1 Optimization Reaction Conditions

The reaction was optimized to check the yield of the reaction with different mmol of reactants. All the reaction conditions such as temperature, reaction time were kept constant and varied the amount of protected amino acid, 2-amino thiophenol and iodine. All the optimization conditions were developed using benzoyl glycine as a limiting reactant. Percentage yield was calculated by comparing actual yield with theoretical yield.

Table 4: Reaction Optimization Conditions.

Sr No.	Amino Acid (equiv.)	2-Aminothio phenol (equiv.)	Iodine (equiv.)	Yield (%)
1	1	1	0.5	58
2	1	1	0.25	12
3	1	1	0.75	71
4	1	1	1	72
5	1	1	1.2	69
6	1	2	0.5	55
7	1	2	0.75	77

2.4.2 Comparison of the Yields of Boc Protected and Benzoyl Protected Benzothiazoles

Yields were compared for Boc and benzoyl protected benzothiazoles under optimized reaction conditions and are mentioned below in Table 5.

Table 5: Comparison of the Yields of Boc and Benzoyl Protected Amino Acids.

Sr No.	Amino Acid	Benzoyl Protected Benzothiazoles (%)	Boc Protected Benzothiazoles (%)
1	Glycine	76	78
2	Leucine	86	96
3	Proline	91	98
4	Tryptophan	82	92
5	Valine	97	54
6	Phenyl Alanine	63	90

2.4.3 *N*-(1,3-benzothiazol-2-ylmethyl)benzamide (13)

The reaction was carried out as mentioned in GP3. Yield = 76 %. R_f value in 1 % Methanol: Chloroform system (0.7). M.P. 110-111 ^oC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1})1613 (C=O amide), 1600 (C=N stretch), 1582 (C=C aromatic), 700 (C–S). GCMS m/z(%) 268 (M^+), 191 (M^+–C_6H_5), 163 (M^+–C6H5CO), 148 (M+–C_6H_5CONH), 134 (C_7H_4NS), 108(C_6H_4S).

2.4.4 *N*-[1-(1,3-benzothiazol-2-yl)-3-methylbutyl]benzamide (14)

The reaction was carried out as mentioned in the GP 3. Yield = 86 %. R_f value in 1 % Methanol: Chloroform system (0.62). M.P. 118-119 ^oC FTIR: (ν_{max} cm^{-1}), 1703 (C=O amide), 1603 (C=N stretch), 1578 (C=C aromatic), 710 (C–S). GCMS m/z (%) 324(M^+), 247 (M^+–C_6H_5), 219(M^+–C_6H_5CO), 204(M^+–$C_6H_5CONH_2$), Second Route: 281(M^+–$CH_3CH_2CH_3$), 176(281-C_6H_5CO), 134(C_7H_4NS), 108(C_6H_4S).

2.4.5 [2-(1,3-benzothiazol-2-yl)pyrrolidin-1-yl](phenyl)methanone (15)

The reaction was carried out as mentioned in the GP3. Yield = 91 %. R_f value in 1 % Methanol : Chloroform system (0.59). M.P. 101-102 ^oC, FTIR: (ν_{max} cm^{-1}), 1680(C=O amide), 1600 (C=N stretch), 1575 (C=C aromatic), 712 (C–S), GCMS m/z (%) 308(M^+), 231(M^+–C_6H_5), 203(M^+–C_6H_5CO), 175($C_{10}H_{10}NS$), 134(C_7H_4NS), 108(C_6H_4S).

2.4.6 *N*-[1-(1,3-benzothiazol-2-yl)-2-(1*H*-indol-3-yl)ethyl]benzamide (16)

The reaction was carried out as mentioned in the GP3. Yield = 82 %. R_f value in 1 % Methanol: Chloroform system (0.69). M.P. 122-125 ^oC, FTIR: (ν_{max} cm^{-1}), 1713 (C=O amide), 1614 (C=N stretch), 1539 (C=C aromatic), 710 (C–S). GCMS m/z (%) 397(M^+), 320(M^+–C_6H_5), 292(M^+–C_6H_5CO), 277(M^+–C_6H_5CONH), 281(M^+–C_8H_6N), 267(M^+–$C_8H_6NCH_2$), 134(C_7H_4NS) .

2.4.7 *N*-[1-(1,3-benzothiazol-2-yl)-2-methylpropyl]benzamide (17)

The reaction was carried out as mentioned in the GP3. Yield = 97 %. R_f value in 1 % Methanol : Chloroform system (0.71). M.P. 96-98 ^oC, FTIR: (ν_{max} cm^{-1}), 1678 (C=O amide), 1603 (C=N stretch), 1565 (C=C aromatic), 700 (C–S). GCMS m/z (%) 310(M^+), 190(M^+–C_6H_5CO), 134(C_7H_4NS), 108(C_6H_4S).

2.4.8 *N*-[1-(1,3-benzothiazol-2-yl)-2-phenylethyl]benzamide (18)

The reaction was carried out as mentioned in the GP3. Yield = 66 %. R_f value in 1 % Methanol : Chloroform system (0.66). M.P. 144-146 ^oC, FTIR: (ν_{max} cm^{-1}) 1700 (C=O amide), 1608 (C=N stretch), 1573 (C=C aromatic), 715 (C–S). GCMS m/z (%) 358 (M^+), 281(M^+–C_6H_5), 253(M^+–C_6H_5CO), 267(M^+–$CH_2C_6H_5$), 134(C_7H_4NS).

Table 6: Physical Data of Compound 13-18.

Compd No	M.P.(ºC)	Yield (%)	Physical Appearance	Solvent for Recrystallization
13	110-111	76	Yellow rhombic crystals	(70:30) EtOH: H_2O
14	118-119	86	Yellow fine granules	(70:30) EtOH: H_2O
15	101-102	91	Bright yellow crystals	Chloroform
16	122-125	82	Dirty yellow crystals	(70:30) EtOH: H_2O
17	96-98	97	Bright yellow crystals	(70:30) EtOH: H_2O
18	144-146	66	Bright yellow crystals	(70:30) EtOH: H_2O

2.5.0 *tert*-Butyl (1,3-benzothiazol-2-ylmethyl)carbamate (19)

The reaction was carried out as mentioned in the GP3. Yield = 78 %. R_f value in 1 % Methanol : Chloroform system (0.72). M.P. 139-141 ºC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1})1600 (C=O amide), 1582 (C=N stretch), 1570 (C=C aromatic), 1308 ($C(CH_3)_3$), 1300 (C–O), 712 (C–S). GCMS m/z (%) 264(M^+), 208(MacLafferty), 164(MacLafferty 1), 148(C_8H_6NS), 134(C_7H_4NS), 108(C_6H_4S).

2.5.1 tert-Butyl [1-(1,3-benzothiazol-2-yl)-3-methylbutyl]carbamate (20)

The reaction was carried out as mentioned in the GP3. Yield = 96 %. R_f value in 1 % Methanol: Chloroform system (0.76). M.P. 90- 91 ºC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1})1735 (C=O ester), 1605 (C=N stretch), 1600 (C=C aromatic), 1298 ($C(CH_3)_3$), 1300 (C-O), 710 (C-S). GCMS m/z (%) 320(M^+), 277(M^+–$CH(CH_3)_2$), 263(M^+–$CH_2CH(CH_3)_2$) Second route, 264(MacLafferty), 220(MacLafferty 1), 204($C_{12}H_{15}NS$), 134(C_7H_4NS).

2.5.2 *tert*-Butyl 2-(1,3-benzothiazol-2-ylmethyl)pyrrolidine-1-carboxylate (21)

The reaction was carried out as mentioned in the GP3. Yield = 98 %. R_f value in 1 % Methanol : Chloroform system (0.79). M.P. 95-97 ^oC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}) 1717 (C=O ester), 1614 (C=N stretch), 1600 (C=C aromatic), 1280 ($C(CH_3)_3$), 1100 (C–O), 710 (C–S). GCMS m/z (%) 304(M^+), 248(MacLafferty), 204($C_{11}H_{12}N_2S$), 190($C_{10}H_{10}N_2S$), 134(C_7H_4NS).

2.5.3 *tert*-butyl [1-(1,3-benzothiazol-2-yl)-2-(4-hydroxyphenyl)ethyl]carbamate (22)

The reaction was carried out as mentioned in the GP3. Yield = 92 %. R_f value in 1 % Methanol: Chloroform system (0.69). M.P. 135-137 ^oC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}), 1680 (C=O ester), 1603 (C=N stretch), 1582 (C=C aromatic), 1305 (C–O), 714 (C–S). GCMS m/z (%) 393(M^+), 263(M^+–C_8H_6N), 337(MacLafferty 1), 293(MacLafferty), 134(C_7H_4NS).

2.5.4 *tert*-butyl [1-(1,3-benzothiazol-2-yl)-2-methylpropyl]carbamate (23)

The reaction was carried out as mentioned in the GP3. Yield = 54 %. R_f value in 1 % Methanol: Chloroform system (0.73). M.P. 135-137 ^oC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1})1735 (C=O ester), 1604 (C=N stretch), 1578 (C=C aromatic), 1299 ($C(CH_3)_3$), 1241 (C–O), 700 (C–S). GCMS m/z (%) 306 (M^+), 250(MacLafferty 1), 206(MacLafferty), 190($C_9H_6NS(CH_3)_3$), 134(C_7H_4NS), 108(C_6H_4S).

2.5.5 *tert*-Butyl [1-(1,3-benzothiazol-2-yl)-2-phenylethyl]carbamate (24)

The reaction was carried out as mentioned in the GP3. Yield = 90 %. R_f value in 1 % Methanol : Chloroform system (0.55). M.P. 80-82 ^oC, FTIR: ($\boldsymbol{v}_{max}$ cm^{-1}), 1693 (C=O amide), 1607 (C=N stretch), 1506 (C=C aromatic), 1366 ($C(CH_3)_3$), 1156 (C–O), 715 (C–S). GCMS m/z (%) 354 (M^+), 298 (MacaLfferty), 238 ($C_7H_4NSC_8H_8$), 134 (C_7H_4NS), 254 (MacLafferty 2), 207 (M^+–$C(CH_3)_3CH_2C_6H_5$.

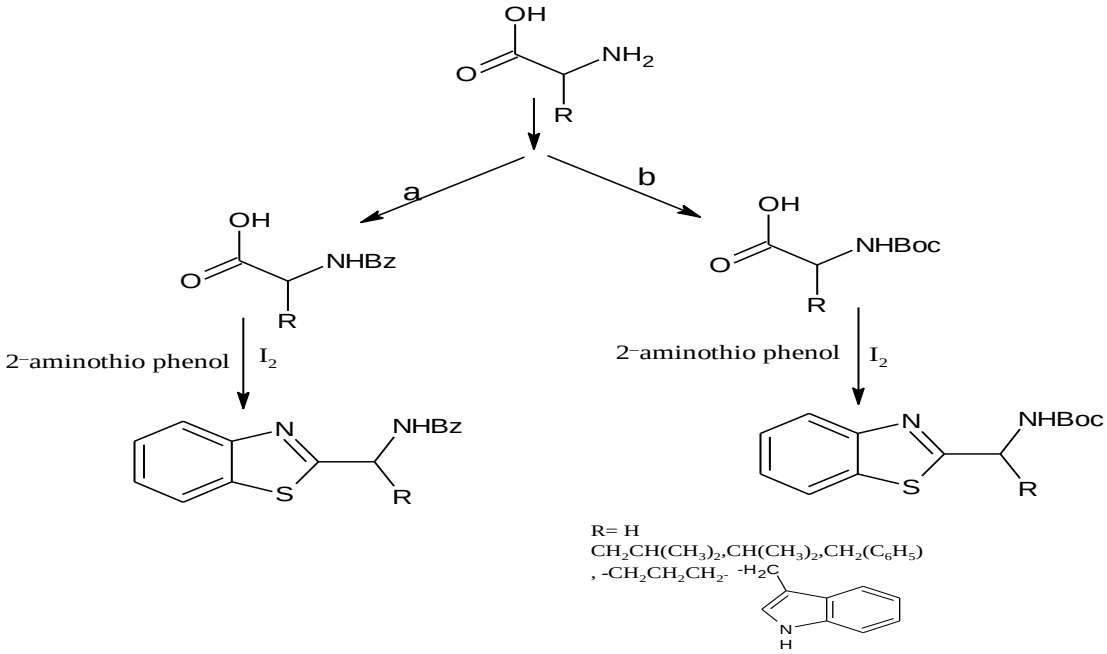
Table 7: Physical Data of Synthesized Compound 19-24.

Compd No.	M.P. (°C)	Yield (%)	Physical Appearance	Solvent for Recrystallization
19	139- 141	78	Yellow crystal	EtOH: H_2O (70:30)
20	90-91	96	Pale yellow crystals	EtOH: H_2O (70:30)
21	95 – 97	98	Bright yellow crystals	Chloroform
22	135-137	92	Dirty yellow crystals	EtOH: H_2O (70:30)
23	135-137	54	Bright yellow crystals	EtOH: H_2O (70:30)
24	80-82	90	Bright yellow crystals	EtOH: H_2O (70:30)

Chapter 3

3.1 Results and Discussion

In this chapter results of synthesized compounds and their discussion is given along with their FTIR and GCMS results as well as the synthetic strategies used to synthesize them. The reaction for the synthesis of benzothiazoles was carried out as mentioned in literature [89]. The substrate scope of the reaction was extended by using amino acids for the synthesis of benzothiazoles. The reaction is novel in the sense that up to date there is no such reaction mentioned in literature that used N-protected amino acid as a reactant for benzothiazole's synthesis using these reaction conditions. In 2013, Siva S. Panda *et al*. [114] used N-protected amino acylbenzotriazole or N-protected peptidyl benzotriazole for the synthesis of benzothiazoles and the maximum yield obtained was up to 89 %. However, in this case we obtained maximum yield of 98 % without using microwave irradiation in half reaction time as compared to their reaction. Furthermore, we used N-protected amino acids as compared to N-protected peptidal benzotriazoles. Amino acid's amino group was protected to prevent the side reaction between amino group of one amino acid and acid group of other. Two different protecting groups were used including benzoyl and Boc. Amino acid's amino group was first benzoyl protected. After that benzoyl protected amino acid was used to form benzothiazole in the second step. After the completion of reaction (monitored by TLC) products were confirmed by (M.P., FTIR, and GCMS). The reaction conditions were optimized by changing the moles of reactants and catalyst amount as mentioned in Table 4. All the reaction conditions such as temperature, reaction time were kept constant and varied the amount of protected amino acid, 2-amino thiophenol and iodine. All the optimization conditions were checked using benzoyl glycine as a reactant. The best reaction conditions (**Table 4, Entry 7**) providing greater yield were further used to synthesize benzothiazoles from other amino acids. The amino group of amino acids was then Boc protected and synthesized benzothiazoles in the similar reaction conditions as optimized for benzoyl glycine.



Scheme 3.1: A Route to Synthesize Benzothiazole From Amino Acid.

Table 4: Optimized Reaction Conditions for Benzothiazole Synthesis.

Sr No.	Amino Acid (equiv)	2-Aminothio phenol (equiv)	Iodine (equiv)	Yield (%)
1	1	1	0.5	58
2	1	1	0.25	12
3	1	1	0.75	71
4	1	1	1	72
5	1	1	1.2	69
6	1	2	0.5	55
7	1	2	0.75	77

3.2 Comparison of the Yield of Boc Protected and Benzoyl Protected Benzothiazoles

First, the optimized conditions were developed with benzoyl glycine. Then all other reactions are carried out by using other α-amino acids having side chains like aromatic and heterocyclic. These amino acids are benzoyl and Boc protected

separately [115]. Yields are compared for Boc and benzoyl protected benzothiazoles under optimized reaction conditions and are mentioned in Table 5.

Table 5: Comparison of the Yield of Benzothiazoles From Boc and Benzoyl Protected Amino Acids**.**

Compd Number	Amino Acid	Benzoyl Protected Benzothiazoles (%)	Boc Protected Benzothiazoles (%)
1	Glycine	76	78
2	Leucine	86	96
3	Proline	91	98
4	Tryptophan	82	92
5	Valine	97	54
6	Phenyl alanine	63	90

It was found that yield of Boc protected benzothiazoles was greater as compared to benzoyl counterparts. The Boc protected benzothiazoles gave better yields. It was due to milder reaction conditions in Boc protection that suited well with our reaction conditions. As Boc is acid sensitive and deprotection occurs in the case of strong acids while using iodine (soft acid) Boc was not deprotected. So iodine acted as a good catalyst by utilizing its role only in the synthesis of benzothiazole. Furthermore there are methods reported in literature where iodine as a catalyst is used for Boc protection of Amines this also supports the statement that iodine will not deprotect Boc group.

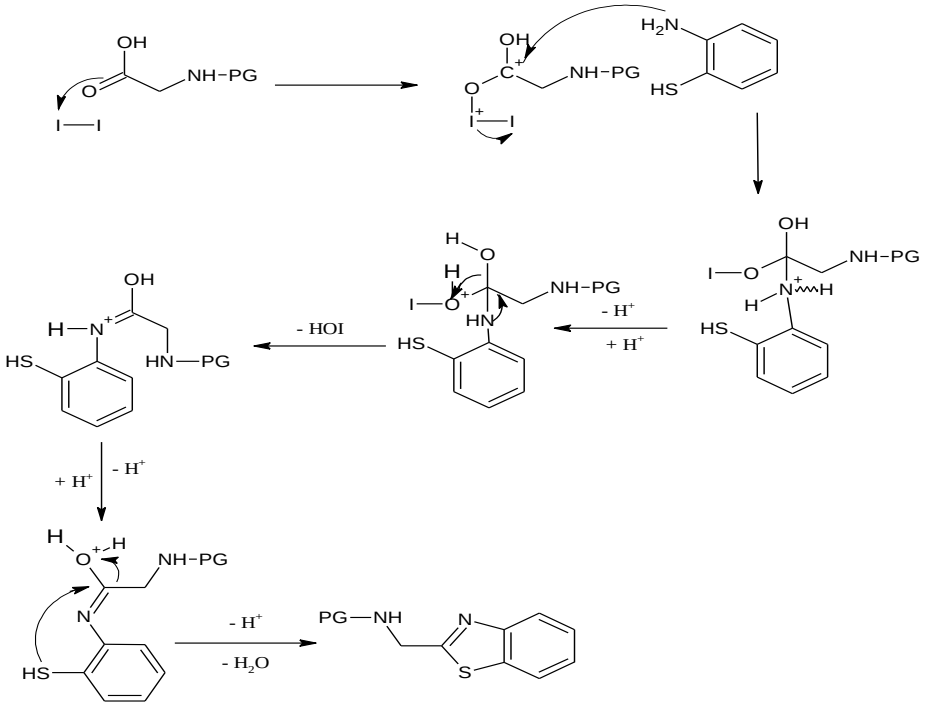
3.3 Iodine as a Mild Catalyst

Although iodine is commonly used as a disinfectant, antiseptic, as a dietary supplement and as an indicator. It has also received much attention as a versatile catalyst, able to catalyze large number of reactions. It is used in different organic reactions as a reducing agent, oxidizing agent and in cyclo condensation reactions. Iodine is also used in esterification and *trans* esterification [116], formation of hydrides from alcohols [117], in various protections of hydroxyl, amine and carbonyl groups [118] and allylation of aldehydes.Due to its mild reaction

conditions, easy availability, easy removal and low cost of iodine, it is worth using as compared to other metal catalysts.

3.4 Proposed Mechanism of the Reaction

As part of our studies for the development of novel methodology, herein we now describe a new approach for the synthesis of 2- substituted benzothiazoles in a single step, with excellent yield and shorter reaction time without the use of any costly or toxic reagent. In this reaction, iodine behaves as a Lewis acid catalyst. First, the halogen bond activation of carbonyl takes place. This makes carbonyl carbon even more electrophilic and the attack of amine electrons from 2-amnothio phenol becomes easier. This step is followed by removal of water molecule and subsequent attack of thiol functionality leading to the ring formation. The mechanism of reaction is like that of esterification and *trans* esterification and is given as under:



Scheme 3.2: Mechanism of Benzothiazole Formation.

3.5 NH_2 Protection of α-Amino acids

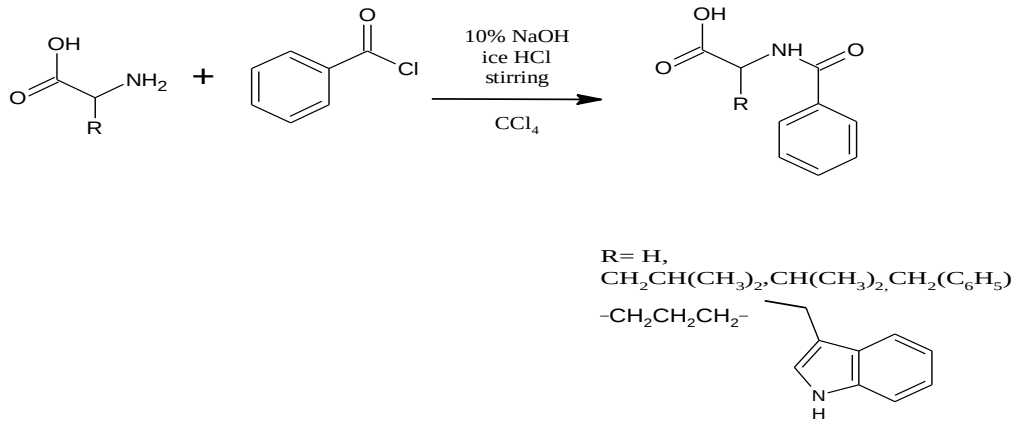
The amino group's protection of α-amino acids like glycine, L-leucine, L-tryptophan, L-proline, L-valine and L-phenyl alanine was carried out. L-Proline was the only secondary amino acid used. There are large numbers of protecting

groups mentioned in literature for the NH_2 -protection of α-amino acid but in this case benzoyl and Boc protecting groups were used. These protection schemes were used to check the compatibility of acidic iodine catalyst with these protecting groups for the synthesis of benzothiazoles.

3.5.1 Benzoyl Protected Amino acids

Amino acids were used for the synthesis of benzothiazoles. Glycine was benzoyl protected [115] and reaction progress was monitored by TLC. After the completion of reaction, FTIR of the product was taken as shown in Figure 3.1. Presence of broad OH band at 3200-3400 cm^{-1} and absence of characteristic NH_2 stretch at 3100-3500 cm^{-1} indicated that protection has successfully occurred. Furthermore, after benzoyl protection amidic carbonyl band was also observed along with acid carbonyl at 1610 cm^{-1}. The melting point of benzoyl protected glycine was than compared with reported melting point and this indicated that glycine was N-benzoyl protected. Commonly benzoyl protected glycine is also known as hippuric acid.

The general reaction scheme is given below:



Scheme 3.3: Benzoyl Protection of Amino Acids.

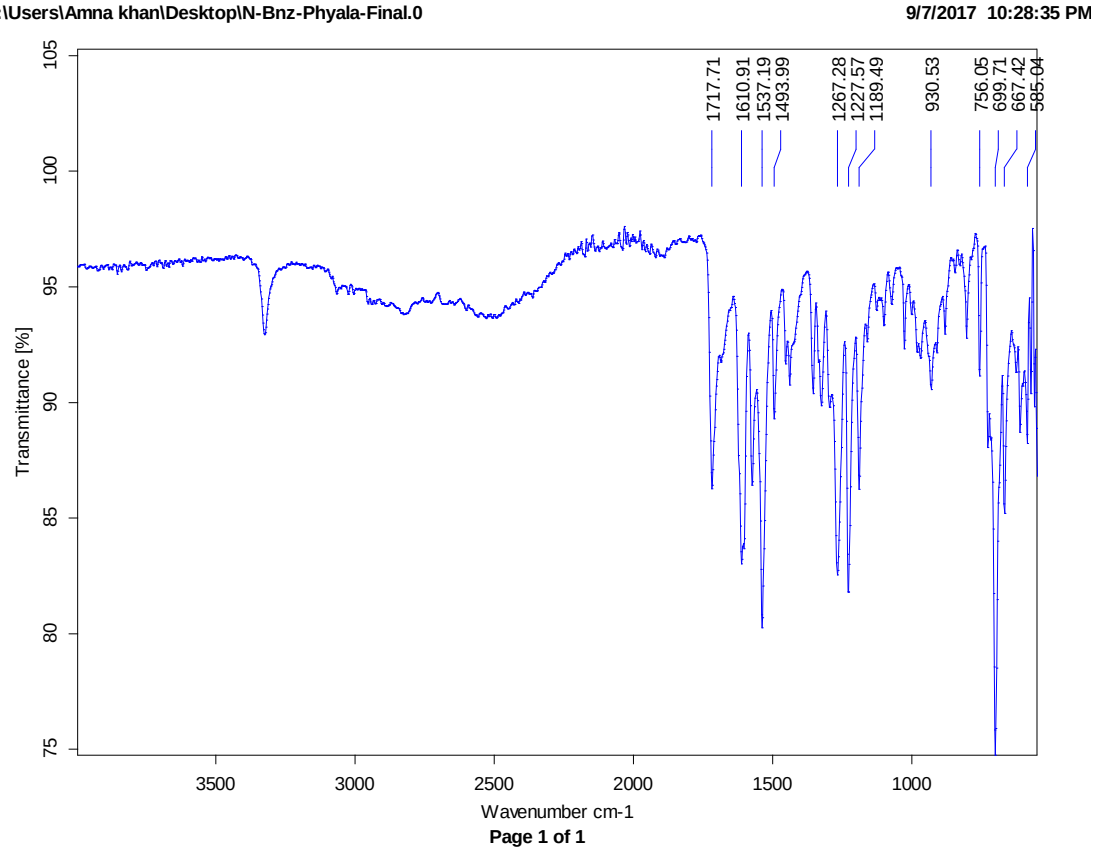
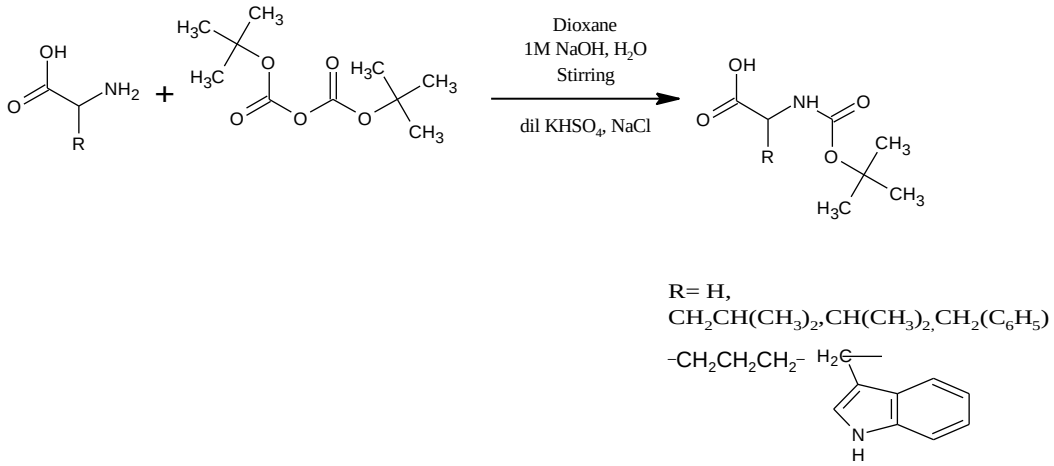


Figure 3.1: FTIR Spectrum of N-Benzoyl Protected Amino Acid.

Similarly, remaining amino acids were also benzoyl protected. Their FTIR and melting points were measured which also indicated that amino acids were protected.

3.5.2 Boc Protected Amino acids

Amino acids were also Boc protected [115]. Boc is one of the versatile protecting groups. It is used because of its mild reaction conditions to protect, easy availability and large number of methods for its easy removal. After the completion of reaction, FTIR of the product is taken as shown in Figure 2. Showing the amide carbonyl band at 1755 cm^{-1} and characteristic band of tert. butyl group due to skeletal stretching at 1372 cm^{-1}. These bands indicated the formation of products. After that melting point of Boc protected amino acid is determined and compared with reported melting points, which confirmed the formation of product. The reaction equation is given below:



Scheme 3.4: Boc Protection of Amino Acids.

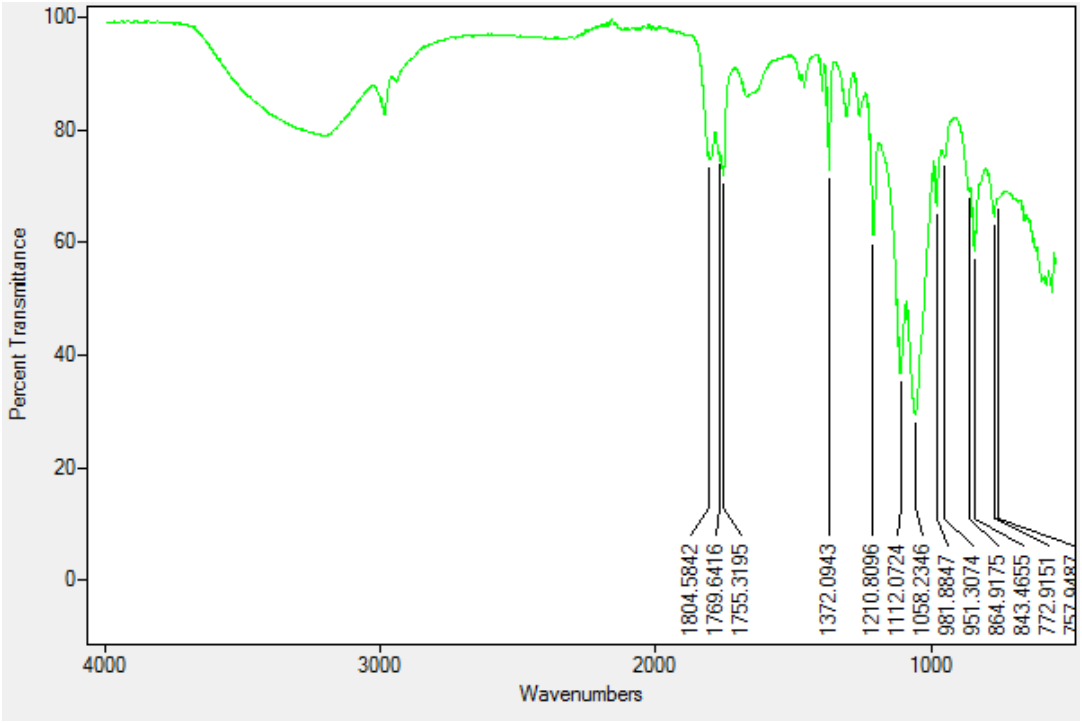


Figure 3.2: FTIR Spectrum of N-Boc Protected Amino Acid.

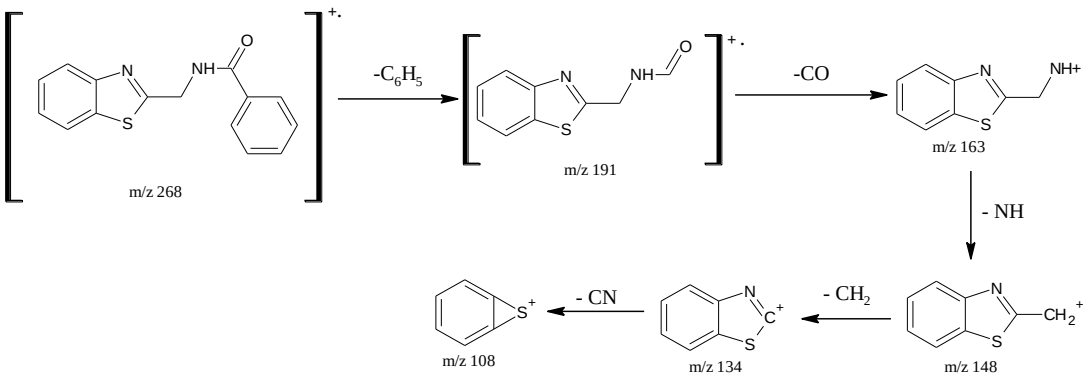
3.6 Synthesis of Benzothiazoles from Benzoyl Protected Amino acids

3.61 N-Benzoyl Glycine Benzothiazole

N-Benzoyl glycine benzothiazole was formed by same reaction as mentioned in general procedure for the synthesis of benzothiazoles. The reaction was performed under optimized reaction conditions. FTIR of the product indicated the characteristic band of C=N that mostly occurs at 1640-1690 cm^{-1} which was shifted to 1600-1614 cm^{-1} due to the conjugation of C=N electrons with the

aromatic ring. Similarly, absence of broad OH stretching at 3200-3400 cm^{-1} indicated that product is formed.

GCMS results of the product confirmed the formation of product. The peak at m/z 268 is due to molecular ion that confirms the synthesis of benzothiazole. Peaks at m/z 192, 163, 148, 134 and 108 indicate the formation of different fragments and the fragmentation pattern is given in scheme:



Scheme 3.4: Mass Fragmentation Pattern of Compound 13.

3.62 N-Benzoyl L-Leucine Benzothiazole

L-Leucine is the amino acid with branched chain. Benzoyl leucine was used to synthesize benzothiazole under optimized reaction conditions as for benzoyl glycine. FTIR of the product as shown in figure 3.3 showed characteristic band of C=N at 1605 cm^{-1} due to conjugation with the ring electrons. C-S band at 700 cm^{-1} along with absence of broad OH stretch at 3200-3400 cm^{-1} indicated the formation of product.

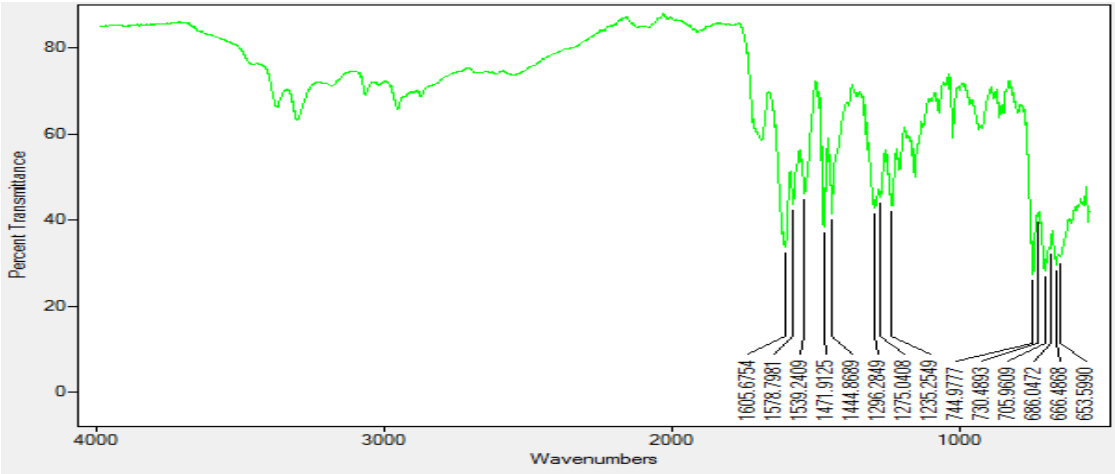
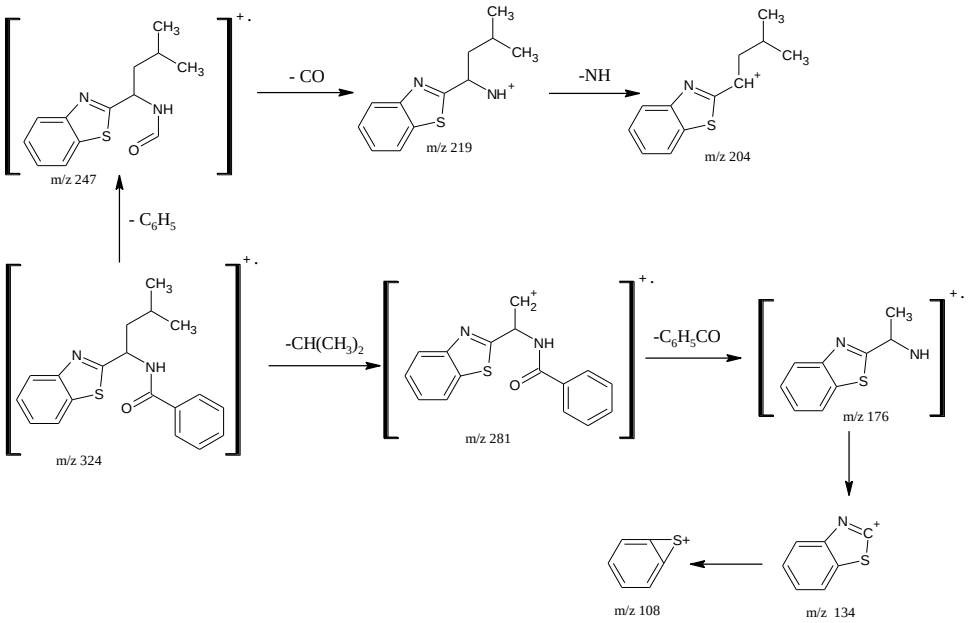


Figure 3.3: FTIR Spectrum of N-Benzoyl Leucine Benzothiazole.

After that GCMS of the product confirm the synthesis of benzothiazole. Peak at m/z 324 is due to M^+ ion, loss of phenyl ring gives peak at m/z 247 then the fragment loses CO molecule and peak at m/z 219 is observed that further under goes loss of NH giving peak at m/z 204. Peak due to loss of $CH(CH_3)_2$ was formed at m/z 281. This fragment then loses C_6H_5CO and gives peak at m/z 176. Peak at m/z 134 is due to benzothiazole ring that loses CN molecule and peak at 108 is observed.

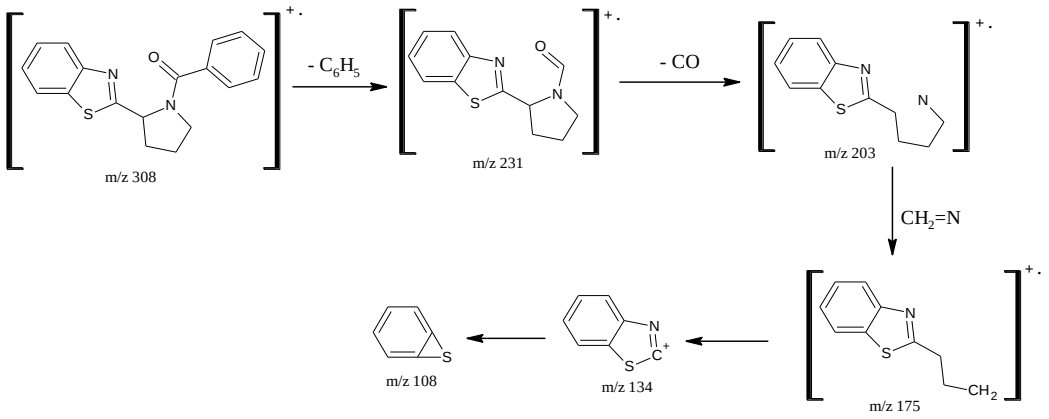


Scheme 3.5: Fragmentation Pattern of Compound 14.

3.6.3 N-Benzoyl L-Proline Benzothiazole

L-proline is the only secondary amino acid. N-benzoyl protection of proline was carried out to be utilized for benzothiazole synthesis. The unprotected acid group was then reacted with 2-aminothiophenol to form benzothiazole. Reaction progress was monitored by TLC. In FTIR spectrum the band at 1605 $cm^{-1}$and absence of broad OH stretch indicated the formation of product.

GCMS data confirms the formation of product. The peak at m/z 308 was due to M^+ ion that confirms the formation of product. M^+ ion undergo loss of phenyl ring and gives peak at m/z 231 that further undergo fragmentation by the loss of CO molecule and further the loss of NH then successive loss of CH_2 groups occurs simultaneously and their peaks occur at m/z 231, 203 and at m/z 175 respectively. Peak at m/z 135 is due to benzothiazole nucleus that undergoes loss of HCN and gives peak at 108. The fragmentation pattern is given in scheme 3.6



Scheme 3.6: Mass Fragmentation Pattern of Compound 15.

3.6.4 N-Benzoyl Tryptophan Benzothiazole

L-Tryptophan is the heterocyclic amino acid the reaction between benzoyl protected tryptophan and 2-Aminothio phenol yielded desired benzothiazole. The reaction was carried out under optimized reaction conditions. FTIR spectrum of the product indicated the formation of product as shown in Figure 3.4:

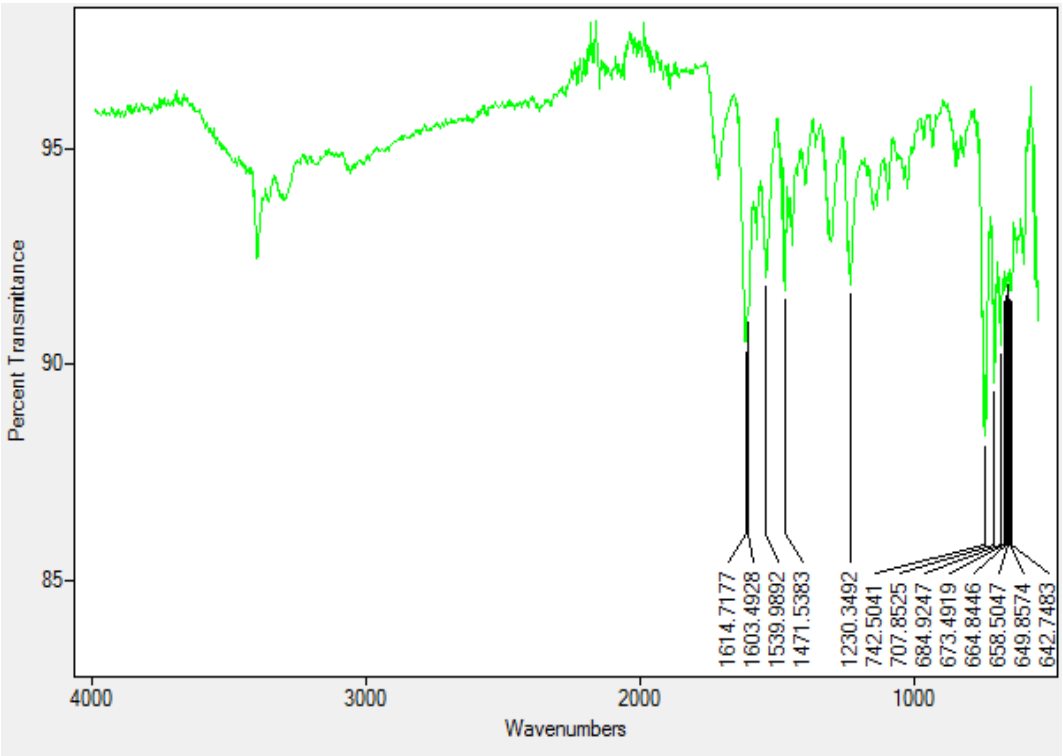
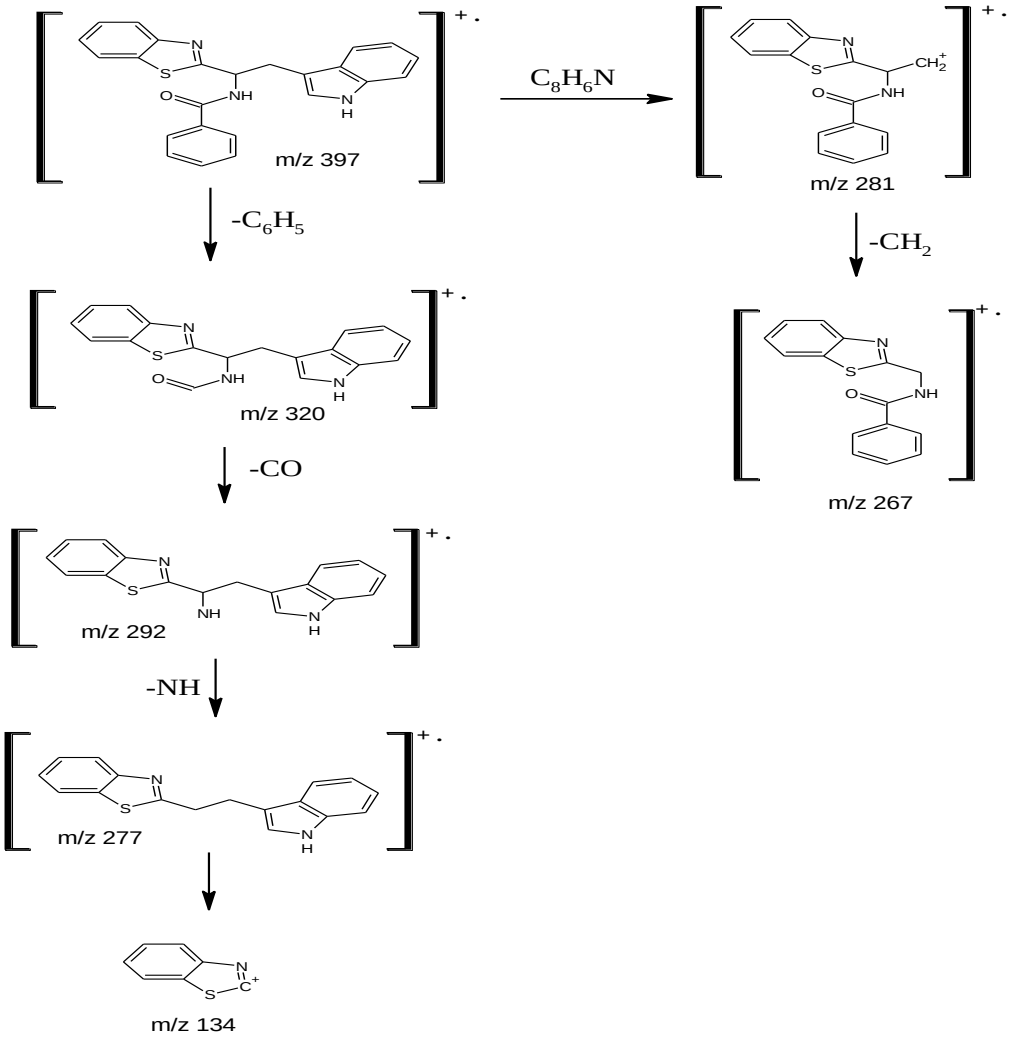


Figure 3.4: FTIR Spectrum of N-Benzoyl Tryptophan Benzothiazole.

GCMS analysis confirmed the formation of product. In MS, molecular ion peak was observed at m/z 397 that confirmed the synthesis of N-benzoyl tryptophan

benzothiazole that under goes loss of phenyl ring followed by loss of CO, NH and peaks appeared at m/z 320, 292 and 277 respectively. The second route indicated the peaks at m/z 281 by the loss of C_8H_6N functionality from M^+ ion followed by the loss of CH_2 giving peak at m/z 267. Peak at m/z 134 is due to benzothiazole nucleus. The detailed Fragmentation pattern is given in scheme 3.7:

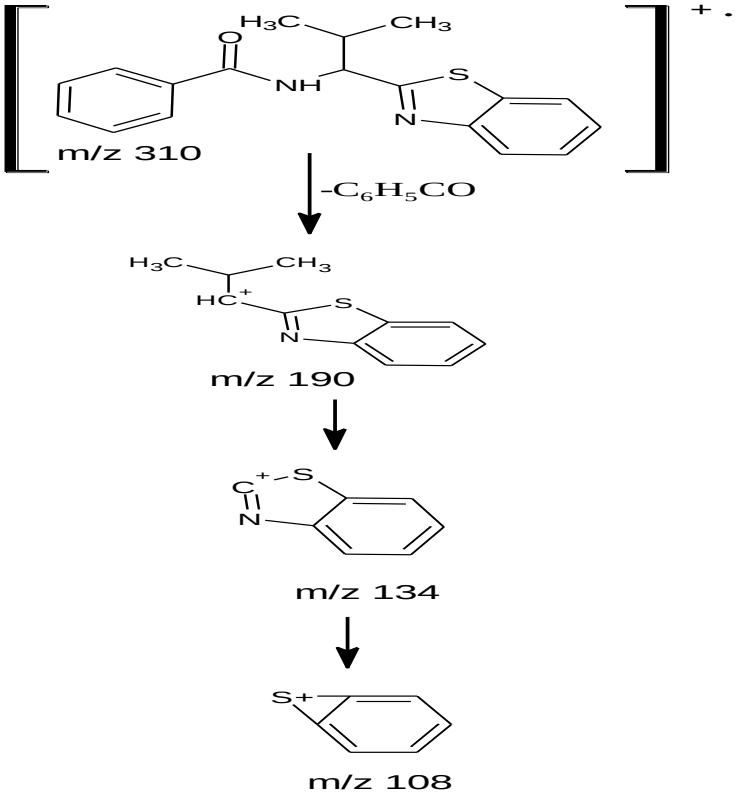


Scheme 3.7: Mass fragmentation Pattern of Compound 16

3.6.6 N-Benzoyl Valine Benzothiazole

Valine is the α-amino acid with unreactive side chain. The reaction between benzoyl protected valine and 2-aminothiophenol yielded benzothiazole. The FTIR of the product showed characteristic C=N band at 1603 cm^{-1} indicated the formation of product.

GCMS results confirmed the formation of product. The peak at m/z 310 is due to M^+ ion that loses C_6H_5CO ion and gives peak at m/z 190 which further undergoes loss of isopropyl and CHCN giving peaks at m/z 135 and 108 respectively. The fragmentation pattern is given below:



Scheme 3.8: Mass Fragmentation Pattern of Compound 17.

3.6.7 N-Benzoyl Phenyl Alanine benzothiazole

L-phenyl alanine, the amino acid with aromatic ring, was benzoyl protected and then benzoyl protected amino acid was used to synthesize benzothiazole. In figure 3.5 FTIR band at 1608 cm^{-1} was due to the C=N and absence of broad 3200-3400 cm^{-1} indicated the formation of product.

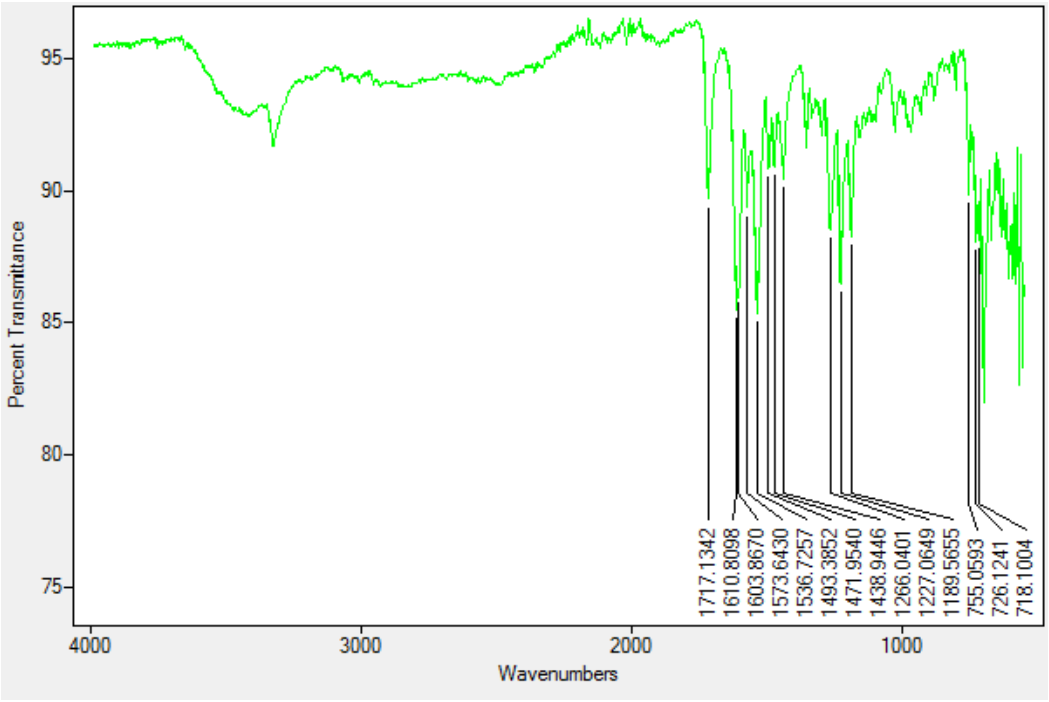
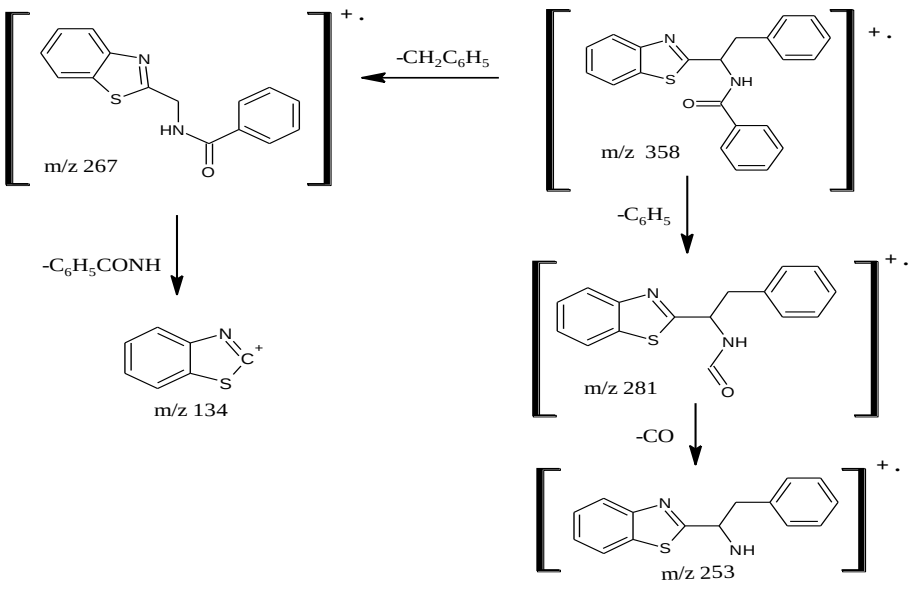


Figure 3.5: FTIR Spectrum of N-Benzoyl Phenyl Alanine Benzothiazole.

Formation of product was also confirmed by GCMS analysis. M^+ ion peak was observed at m/z 358. Loss of phenyl ring from molecular ion gave peak at m/z 281. Further loss of CO molecule from m/z 281 gave peak at m/z 253. The other fragmentation pathway was due to loss of $C_6H_5CH_2$ group from molecular ion that showed peak at m/z 267. Peak at m/z 134 was due to benzothiazole nucleus. The detailed fragmentation pathway is given below:



Scheme 3.9: Mass Fragmentation Pattern of Compound 18.

3.7 Synthesis of Benzothiazoles from Boc Protected Amino acids

3.71 N-Boc Glycine Benzothiazole

Glycine was Boc protected and then Boc glycine was used to synthesize the benzothiazole under the optimized reaction conditions. FTIR band at 1603 cm^{-1} due to C=N ,band at 1302 cm^{-1} due to tert. butyl group and absence of broad OH at 3200-3400 cm^{-1} indicated the formation of product as shown in Figure 3.6:

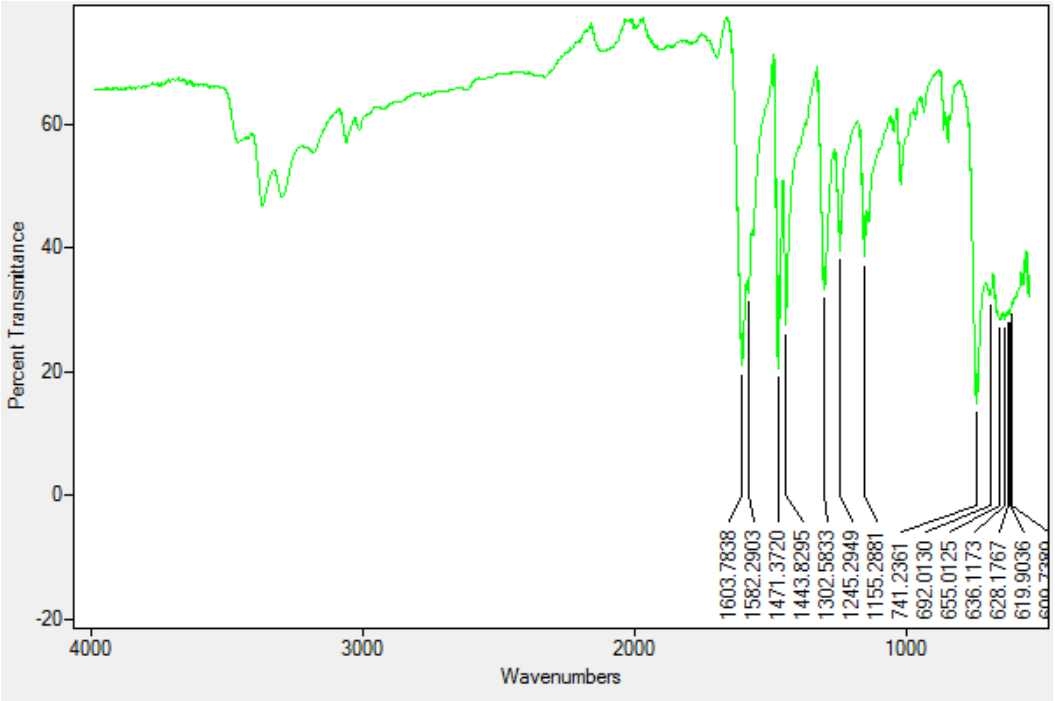
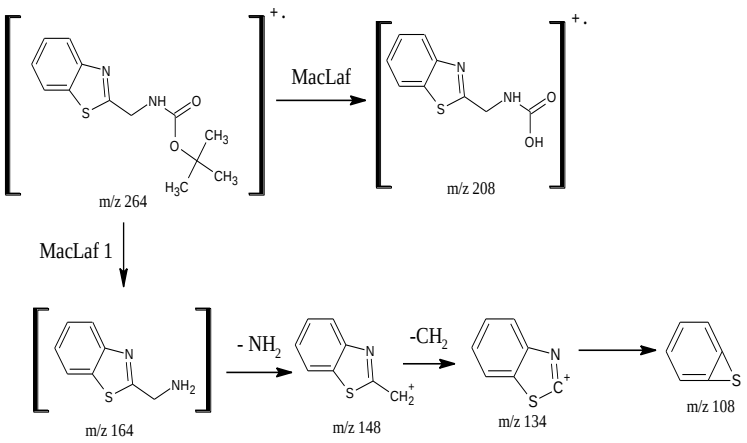


Figure 3.6: FTIR Spectrum of N-Boc Glycine Benzothiazole.

GCMS confirmed the formation of product. In GCMS a peak at m/z 264 that was due to M^+ ion. The most vulnerable ester amide bond was broken losing $C(CH_3)_3$ and CO_2 simultaneously giving peak at m/z 164 due to MacLafferty rearrangement. Similarly, peak due to second MacLaffery was found at m/z 208. The loss of NH_2 from 164 gave peak at m/z 149, while CH_2 group loss gave peak at m/z 134. Benzothiazole ion loses CN and peak appeared at 108. The detailed fragmentation path way is given in scheme:



Scheme 3.10: Mass Fragmentation Pattern of Compound 19.

3.72 N-Boc Leucine Benzothiazole

L-leucine was Boc protected and then Boc protected amino acid was further used to synthesize benzothiazole. The reaction conditions were same as optimized for benzoyl glycine. The product was obtained in good yield. The FTIR of the product showed C=N band at 1605 and tert-butyl group at 1298 cm^{-1} as shown in Figure 3.7:

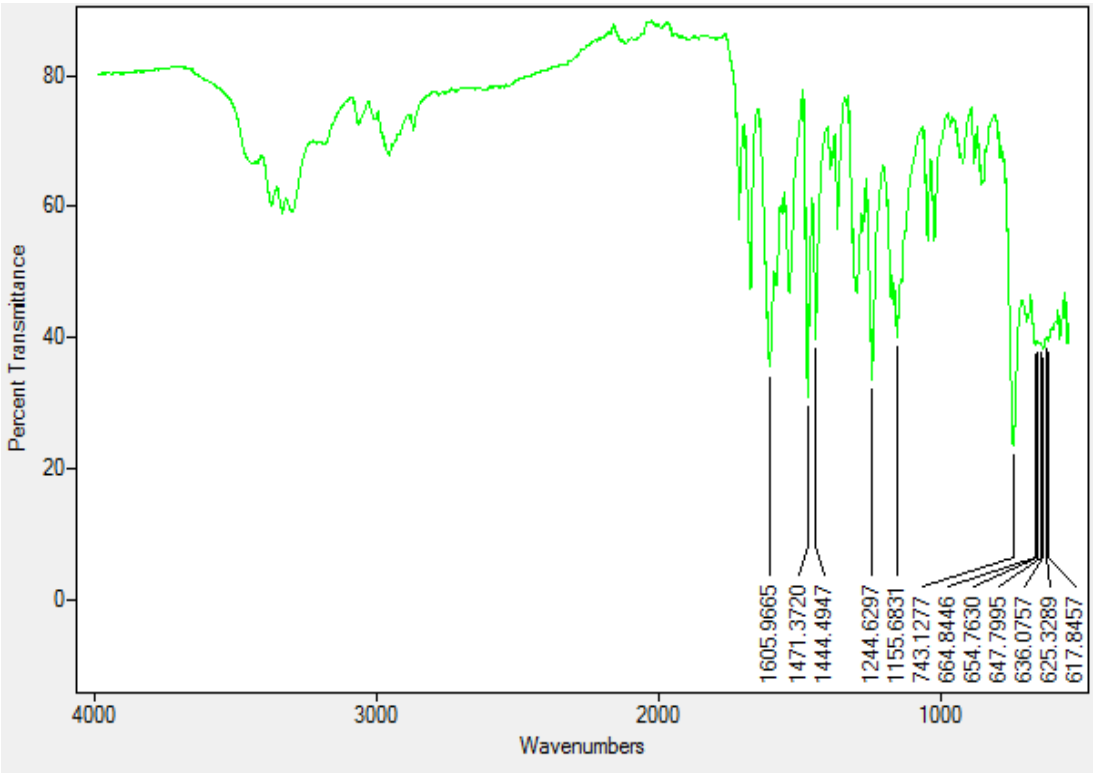
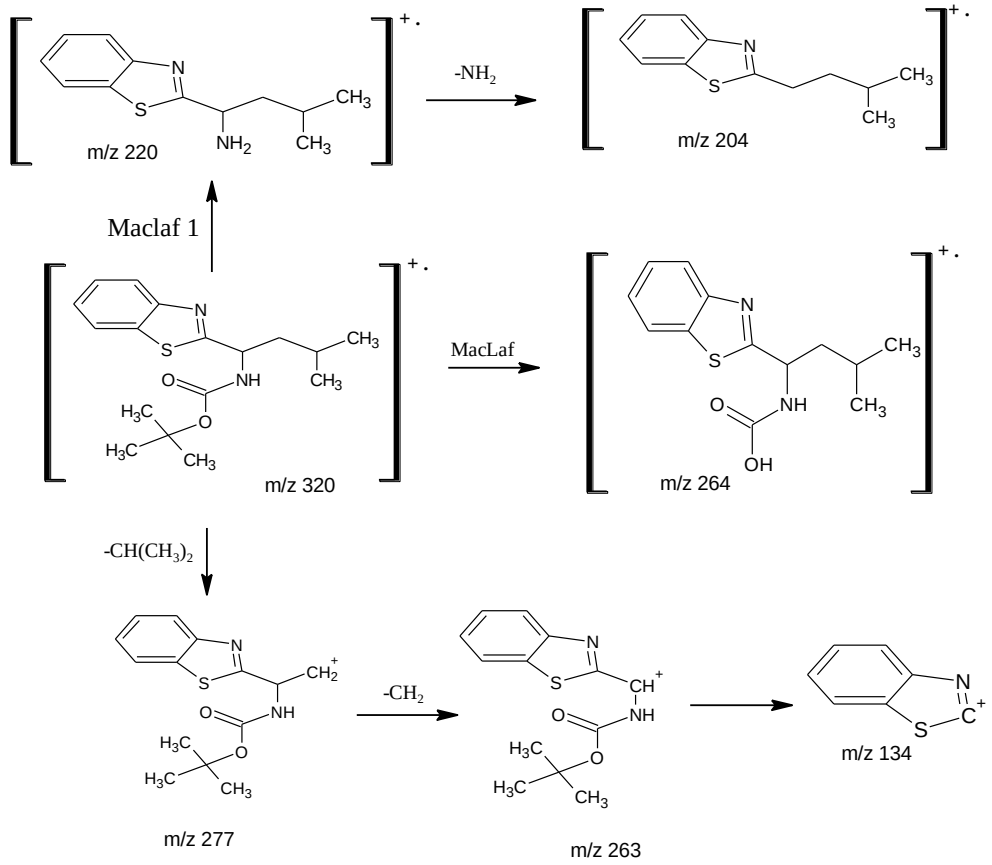


Figure 3.7: FTIR Spectrum of N-Boc Leucine Benzothiazole.

GCMS analysis of the product confirmed the synthesis of product. The peak at m/z 320 was due to M^+ ion that under goes two type of fragmentation loss of $CH(CH_3)_2$ gave peak at m/z 277 and peaks due to **McLafferty** rearrangement occurred at m/z 264 and m/z 220. Which then releases NH_2 ion and peak at m/z 204 is observed. 277 ion fragment then losses CH_2 ion and peak at m/z 263 is observed. Subsequent losses give peak at m/z 134. The detailed fragmentation scheme is given below:



Scheme 3.11: Mass Fragmentation Pattern of Compound 20.

3.73 N-Boc Proline Benzothiazole

Proline was the only secondary amino acid used. First proline was Boc protected and then Boc protected proline was further used to synthesize benzothiazole. In this case, secondary amino group has not affected the yield of the reaction. FTIR data of the product showed C=N band at 1614 cm^{-1} and band due to tert- butyl group at 1208 cm^{-1} as shown in Figure 3.8:

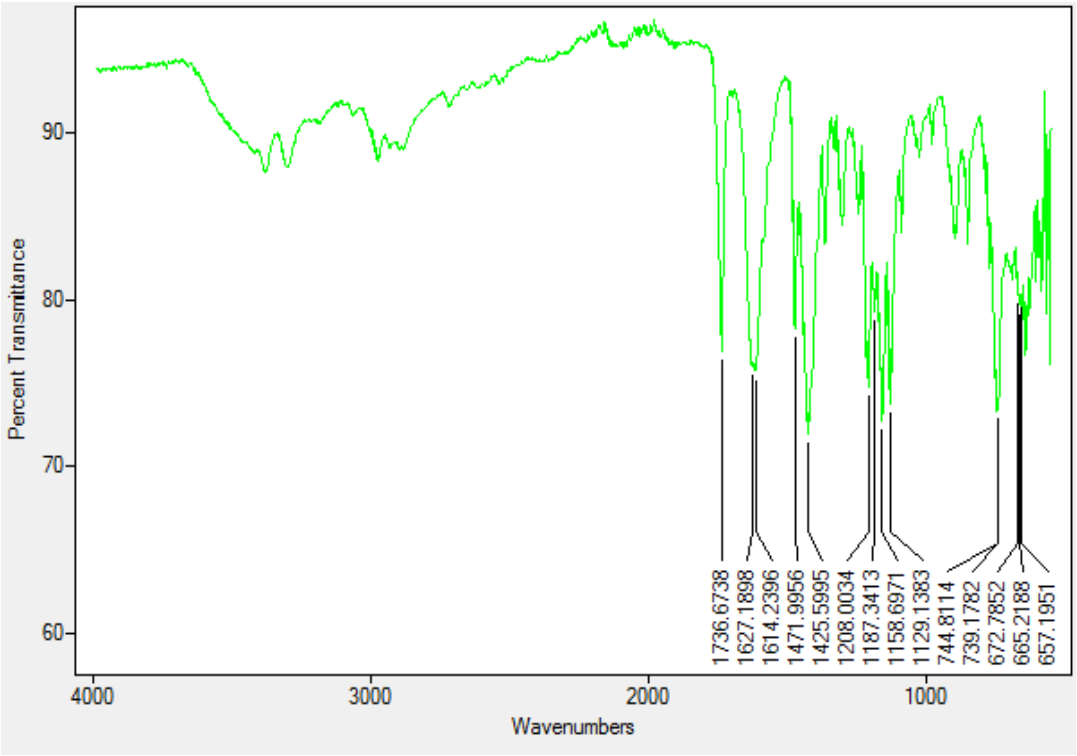
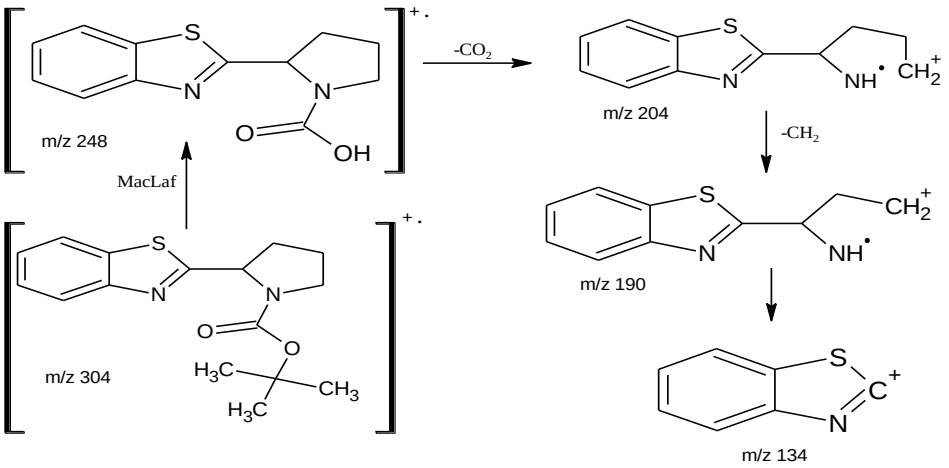


Figure 3.8: FTIR Spectrum of N-Boc Proline Benzothiazole.

GCMS confirmed the benzothiazole synthesis. The molecular ion peak at m/z 304 confirmed the formation of product. The peak at m/z 248 was due to MacLafferty rearrangement. The fragment ion then released CO_2 molecule and peak at m/z 204 was appeared. The proline ring was broken and successive loss of CH_2 groups gave peak at m/z 190 followed by loss of CH_2 and NH giving peak at m/z 149 peak at m/z 134 was due to benzothiazole nucleus. The fragmentation pattern is given below:



Scheme 3.12: Mass Fragmentation Pattern of Compound 21.

3.74 N-Boc Tryptophan Benzothiazole

L-Tryptophan is the heteroaromatic amino acid. Its Boc counterpart is used to synthesize benzothiazole as previously optimized reaction conditions. FTIR band at 1613 and 1299 cm^{-1} were due to C=N and tert. butyl group respectively that indicated the formation of productas shown in Figure 3.9:

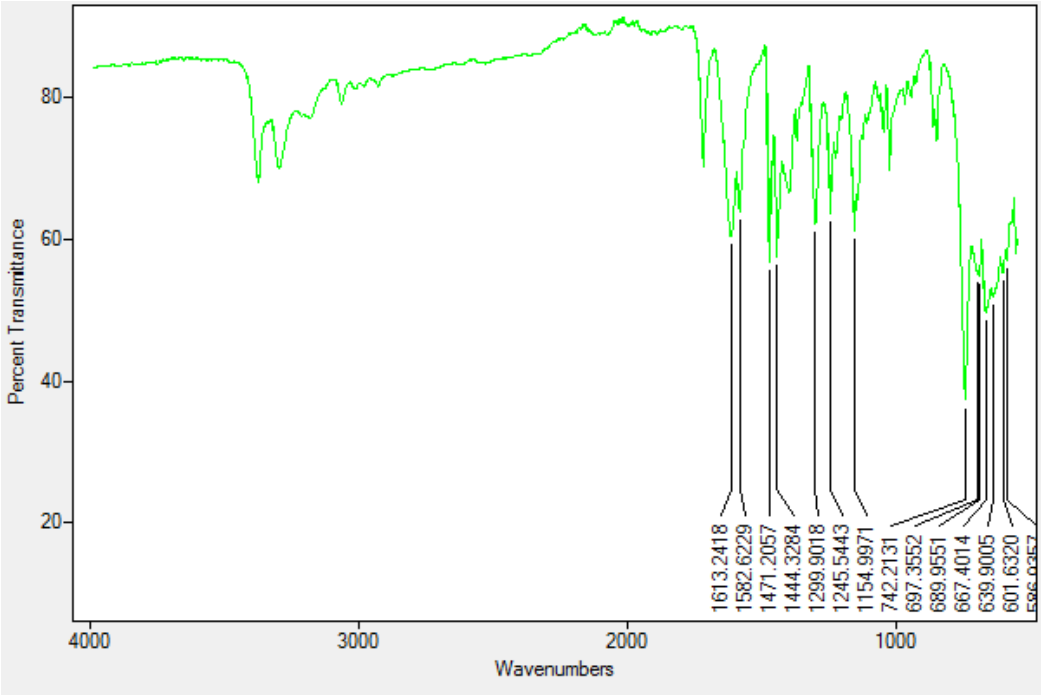
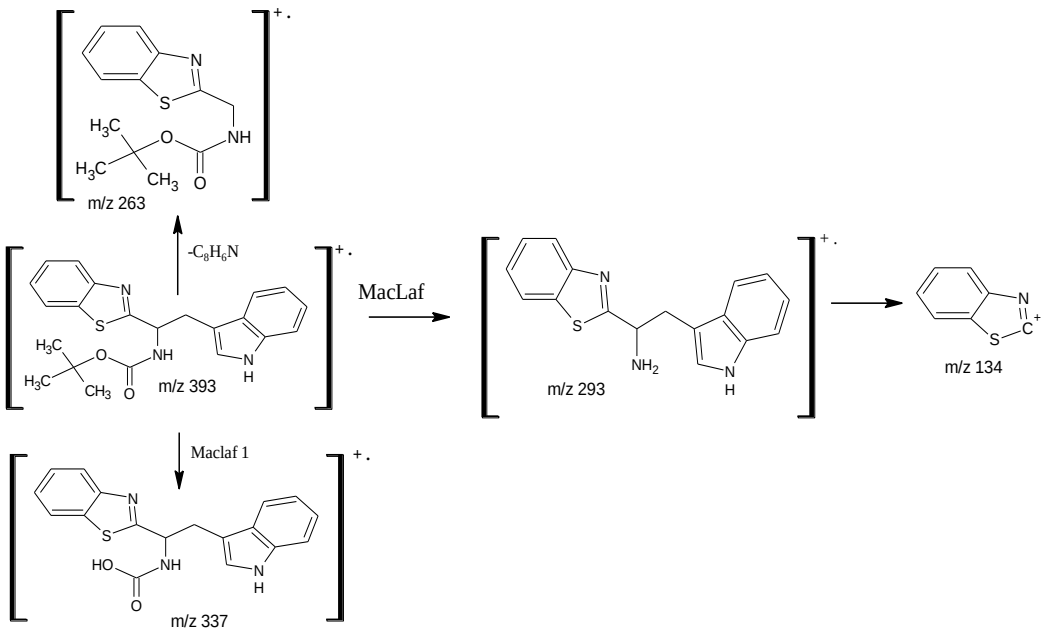


Figure 3.9: FTIR Spectrum of N-Boc Tryptophan Benzothiazole.

GCMS data confirmed Benzothiazole synthesis. The peak at m/z 393 was due to M^+ ion that loses tert. butyl group due to MacLafferty rearrangement and peak at m/z 337 was observed. Similarly, molecular ion undergoes second MacLafferty rearrangement and peak at m/z 293 was observed. The second route is in which molecular ion losses C_8H_6N fragment and peak at m/z 263 is observed. Detailed fragmentation pattern is given below:



Scheme 3.13: Mass Fragmentation Pattern Compound 22.

3.7.5 N-Boc Valine Benzothiazole

L-Valine was Boc protected and then Boc protected amino acid was used to synthesize benzothiazole. The absence of broad OH band at 3200-3400 cm^{-1} and presence of 1605 and 1298 cm^{-1} band due to C=N and tert. butyl group respectively indicated the formation of product. The Figure 4.10 confirms this:

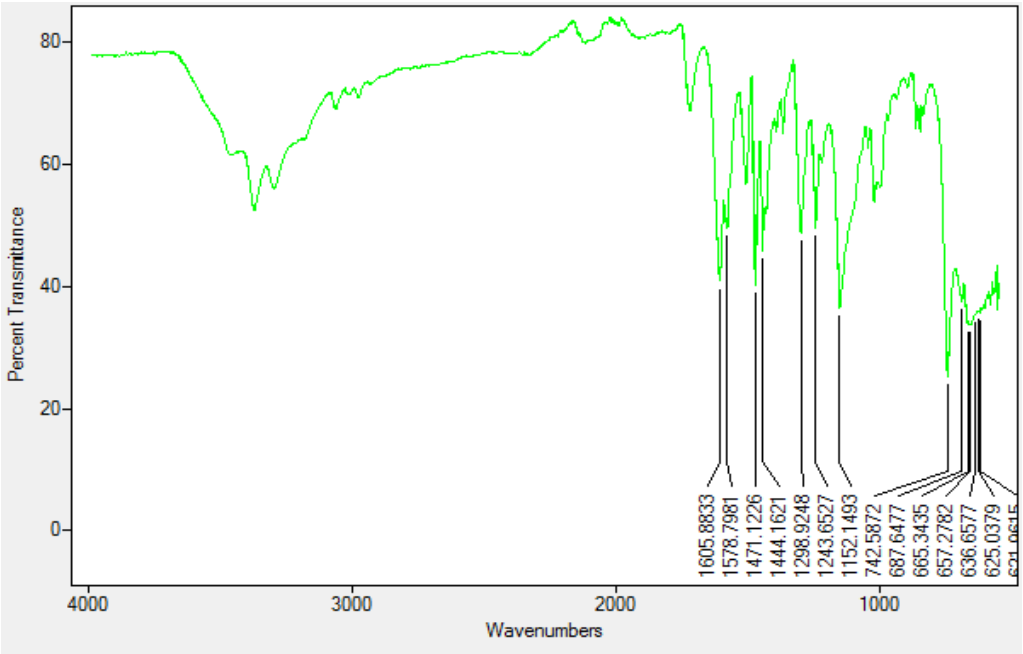
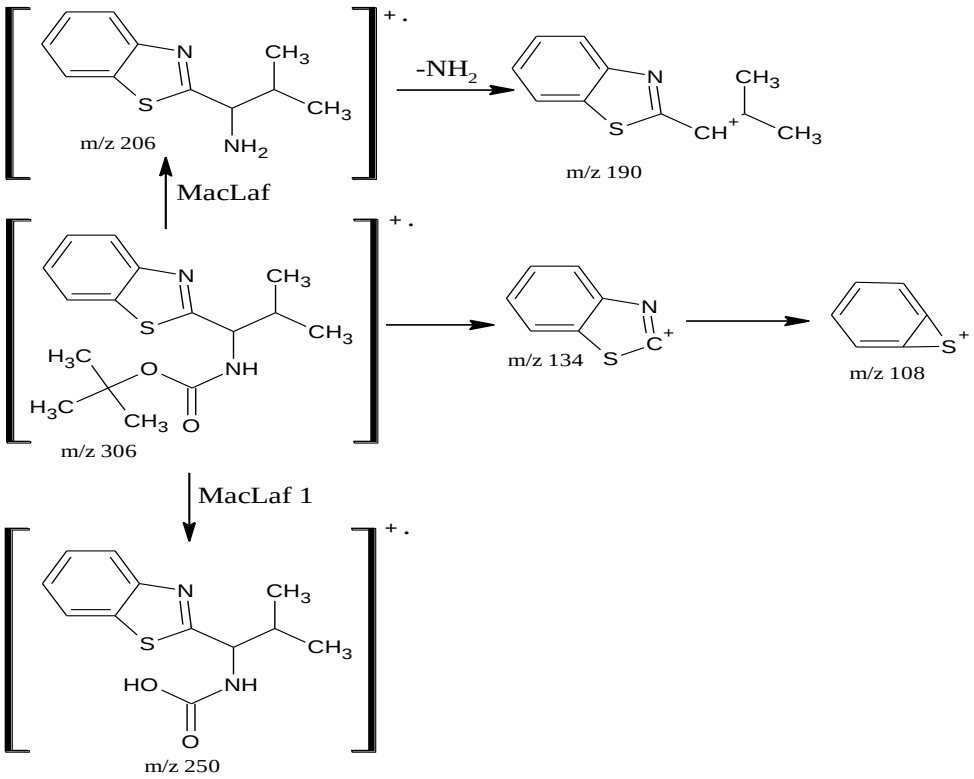


Figure 4.1: FTIR Spectrum of N-Boc Valine Benzothiazole.

GCMS confirmed benzothiazole synthesis. The peak at m/z 306 was due to M^+ ion that confirmed the formation of product. Peaks at m/z 206 and 250 were due to MacLafferty rearrangement. The loss of NH_2 group from 206 ion, a peak observed at m/z 190. Similarly peak at m/z 134 was due to benzothiazole ion that loses CN molecule giving peak at m/z 108. Detailed fragmentation pattern is given below:



Scheme 3.14: Mass Fragmentation Pattern of Compound 23.

3.7.7 N-Boc Phenyl Alanine Benzothiazole

L-Phenyl alanine is Boc protected and then is used to synthesize benzothiazole as per optimized reaction conditions. Presence of C=N at 1607 cm^{-1}, tert. butyl group band at 1366 cm^{-1} and absence of OH stretch at 3200-3400 cm^{-1} in FTIR spectroscopy indicated the synthesis of benzothiazole in Figure 4.2:

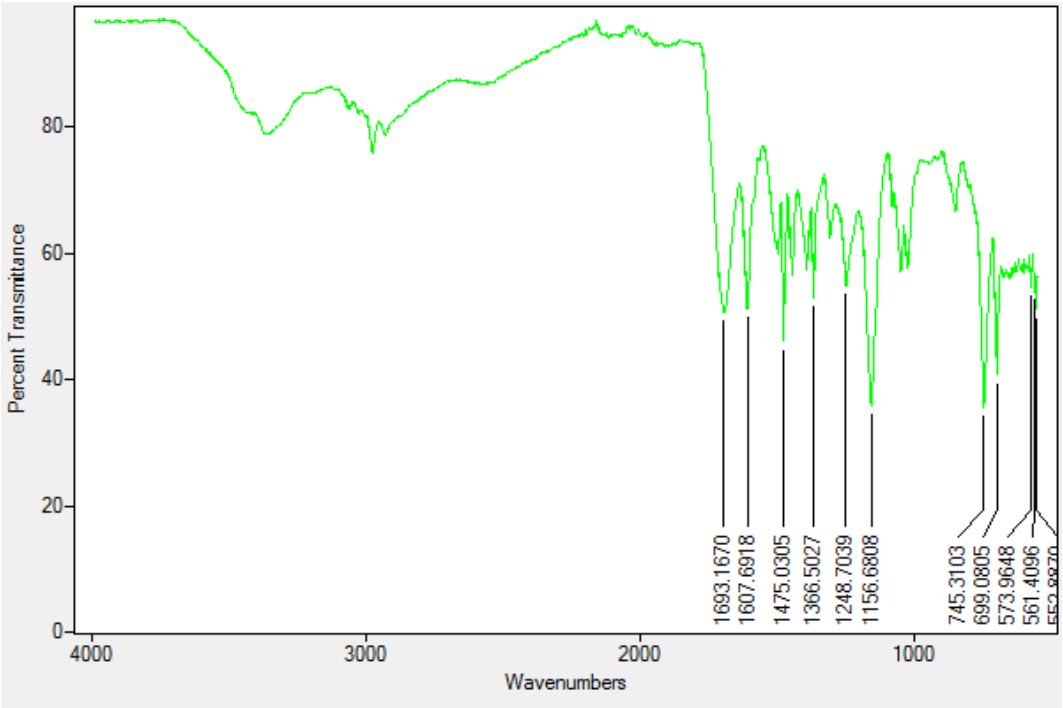
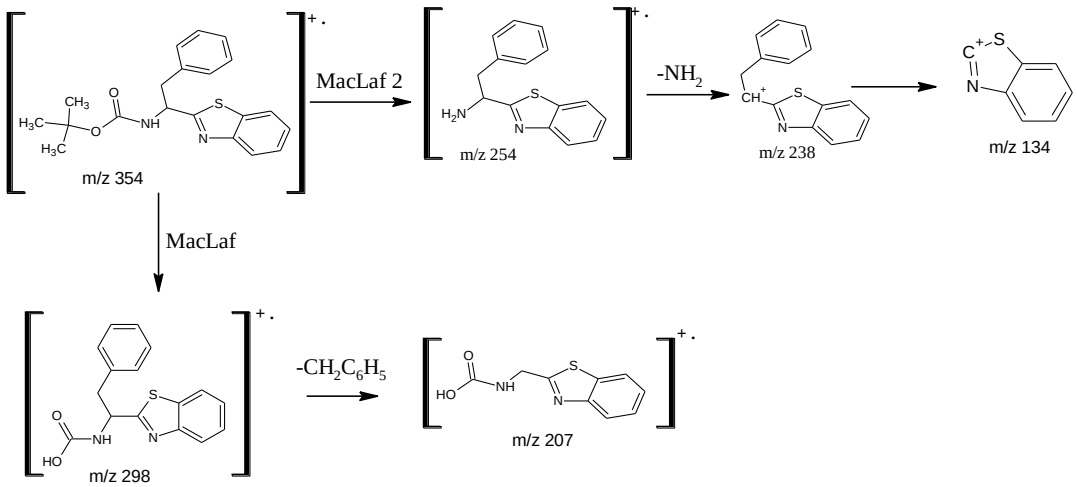


Figure 4.2: FTIR Spectrum of N-Boc Phenyl Alanine Benzothiazole.

GCMS data confirmed benzothiazole synthesis. The peak at m/z 355 was due to M^+ ion that confirmed formation of product. Peaks due to MacLafferty rearrangement were observed at m/z 298 and m/z 254 respectively. Fragment observed due to MacLafferty 2 loses NH_2 ion and peak at m/z 238 is observed. Second route is in which loss of phenyl ring and CH_2take place from MacLafferty 1 giving peak at m/z 207. The peak at 134 is due to benzothiazole nucleus. The detail fragmentation pattern is given below:



Scheme 3.15: Mass Fragmentation Pattern of Compound 24.

3.8 Comparing the Yield with Other Reactions that Used Iodine as a Catalyst

Reaction yield was compared with other reactions reported in literature that also used iodine catalyst. In comparison, it is found that our reaction (table 3.3 Entry 6)ended in better yield in short reaction time, without the use of solvent and at room temperature. The researchers used I_2 in combination with TMSOTf for enhancing the nucleophilicity of imine and additions of DMSO both the TMSOTf and DMSO are costly and even harmful. Further the reaction goes to completion in ten hours, this makes our scheme much simpler, more economic. Similarly, use of MW irradiation, use of harmful, chlorinated organic solvents like dichloromethane, acetonitrile, costly reagents like PTSA, dis Martin per Iodinate and equipment to generate molecular oxygen are all expensive this shows that our reaction is more economical and gives better yield in short reaction time. Then any of the reactions mentioned below in table 8.

Table 8: Comparison of Yield with Other Reactions.

Sr. no.	Catalyst	Solvent	Temp. ^oC	Reaction time (hr)	Yield %	Reference
1	I_2/ TMSOTf	DMSO	80	10	71	93
2	I_2	-	M.W.	3	95	49
3	DMP	CH_2Cl_2	95	0.25	95	88
4	I_2/ O_2	CH_3CN	R.T.	4	81	94
5	I_2/ PTSA	DMSO	75	24	84	95
6	I_2	DMF	110	0.5-1	78	48
7	**I_2**	**-**	**R.T.**	**0.5**	**97**	

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