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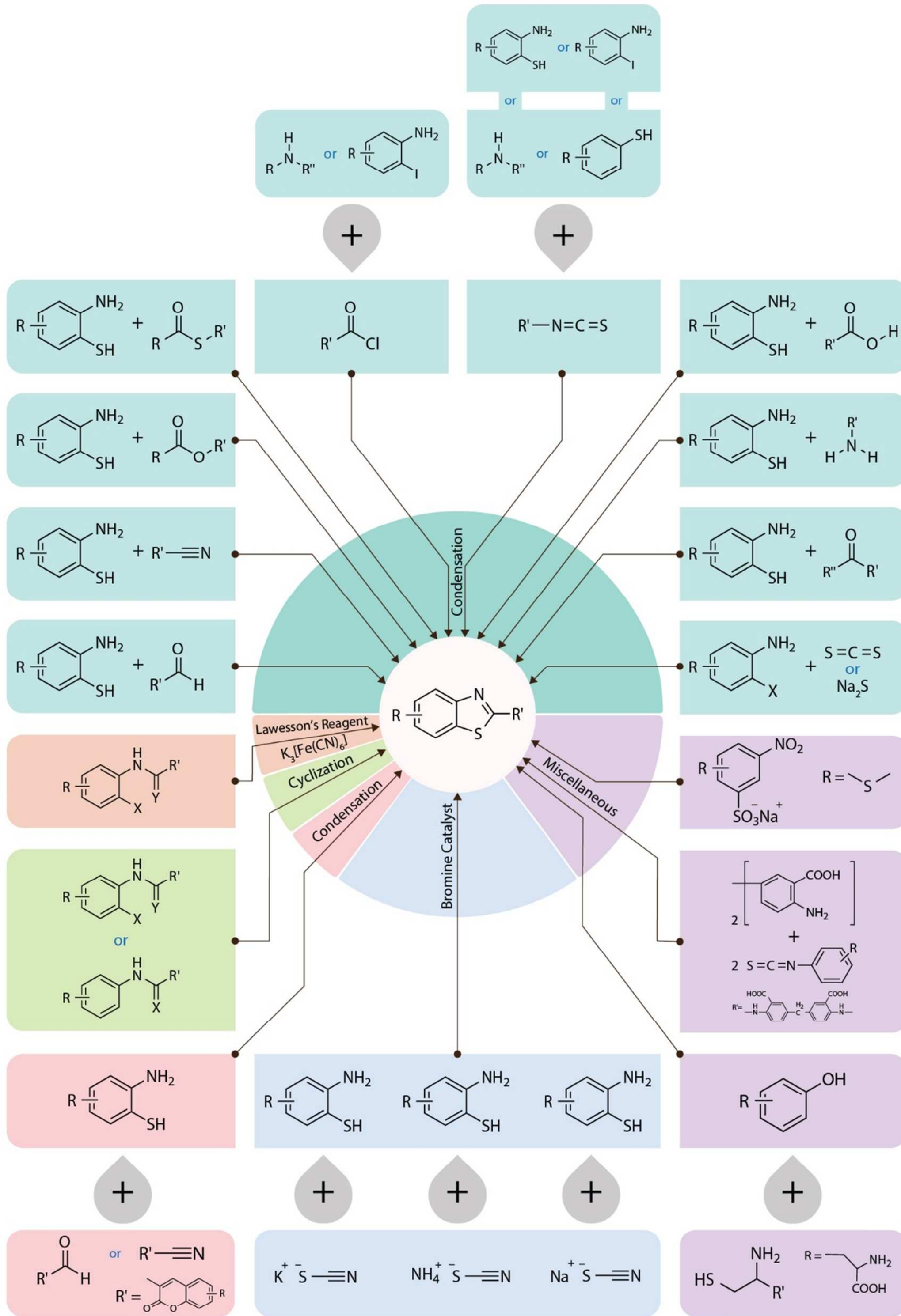
Recent advances in the synthesis of 2-substituted Benzothiazoles: A Review

Neelam P. Prajapati, Rajesh H. Vekariya, Mayuri A. Borad and Hitesh D. Patel*

Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad, India.

E-mail: drhiteshpatel1@gmail.com, Ph. (O) +91-079-26300969, (Fax) +91-079-2630854

Graphical Abstract:



“Recent advances in various synthetic protocols of 2-substituted benzothiazole derivatives”

Recent advance in the synthesis of 2-substituted benzothiazoles: A Review

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Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad, India.

E-mail: drhiteshpatel1@gmail.com, Ph. (O) +91-079-26300969, (Fax) +91-079-26308545

Abstract:

Benzothiazole can serve as unique and versatile scaffolds in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. This important class of derivatives possesses numerous pharmacological activities like- antitumor, antimicrobial, anti-inflammatory, anticonvulsant, antidiabetic activities and so on. Since, many scientists have developed wide range of methodologies for synthesis of 2-substituted benzothiazole nucleus and its derivatives by using different type of catalysts to improve the selectivity, purity and yield of the products. Thus, the present review article mainly focuses on the different kind of reactions involved in synthesis of 2-substituted benzothiazole nucleus and its derivatives.

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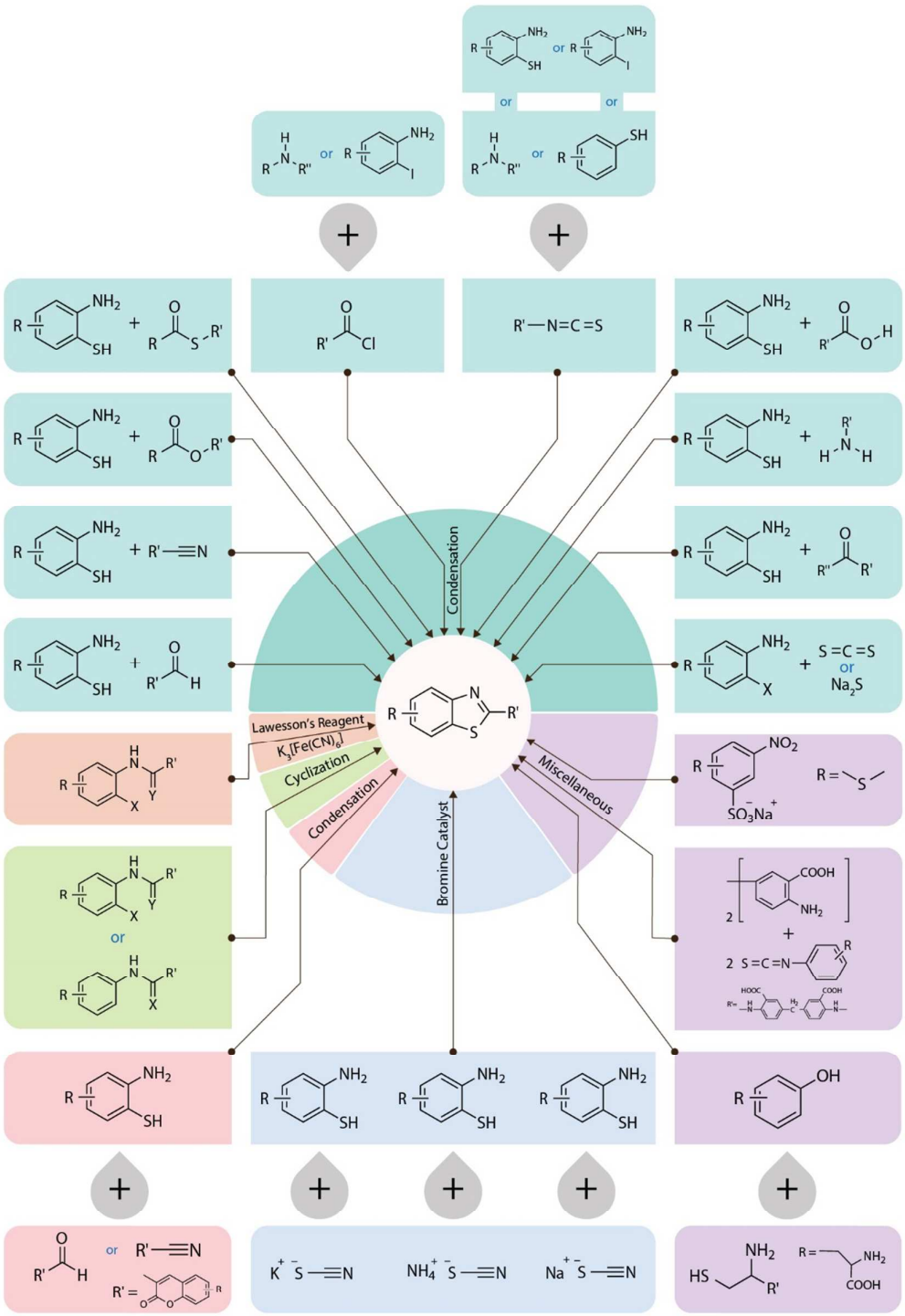


Content:

1. Introduction:

Benzothiazole is a privileged bicyclic ring system. It contains a benzene ring fused to a thiazole ring. Benzothiazole ring system is present in various marine and terrestrial natural compounds, which have wide range of pharmaceutical applications.[1-3] 2-Aminobenzothiazoles are highly reactive compounds and extensively utilized as reactants or reaction intermediates for the synthesis of variety of fused heterocyclic compounds.[4] Medicinal chemist's attention was drawn to this series, when the pharmacological profile of Riluzole (6-trifluoromethoxy-2-benzothiazolamine) (**Figure 1**) was observed as clinically available anticonvulsant drug.[5] Furthermore, Erythrazoles A and Erythrazoles B were isolated from mangrove sediments (**Figure 1**).[6]

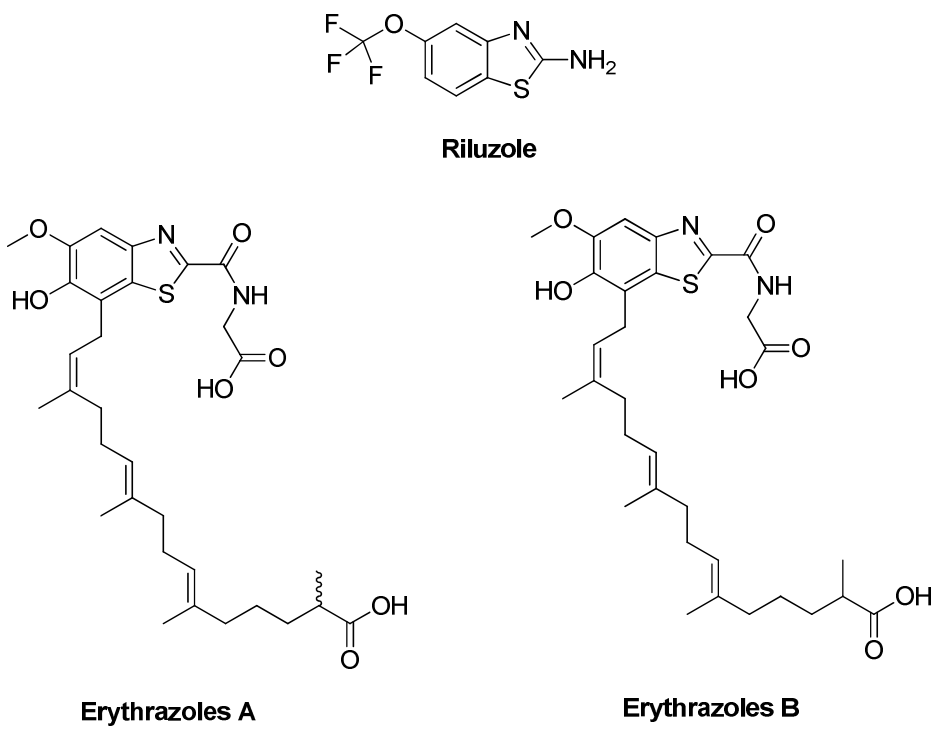


Figure 1: Naturally occurring benzothiazoles

Benzothiazole moiety plays an important role in chemistry and is also present in a variety of biologically active such as Anti-microbial,[7-10] Anti-cancer,[11-16] Anthelmintic,[17] Anti-diabetic,[18,

[19] Anti-tuberculotic,[13, 20, 21] Anti-tumor,[22-28] Anti-trypanosomal,[29] Anti-viral,[30-32] Antibacterial,[33-36] Anti-oxidant,[37] Anti-glutamate and Anti-parkinsonism,[38,39] Aanalgesic,[40] Anti-inflammatory,[41-43] Antifungal,[44-45] Antileishmanial,[46] Anticonvulsant,[47] Neuroprotective,[48] Muscle relaxant activities,[49] Vasodilator,[50] Orexin receptor,[51] Inhibitors of several enzymes,[52-53] Atherosclerosis,[54] Insomnia,[51] Epilepsy,[55] LTD_4 receptor antagonists,[56, 57] Antiparasitics and Photosensitizers,[58] Calcium channel antagonists,[59, 60] as imaging agents for Aβ plaques in cerebral amyloid angiopathy,[61] and as falcipain inhibitors.[62] In addition they shows other applications such as radioactive β-amyloid imagining agents,[63-67] and Schistosomicidal agents.[68] Due to its potent and significant biological activities it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest. The studies of structure-activity relationship (SAR) interestingly reveal that the change in the structure of substituent group at C-2 position commonly results the change of its bioactivity.

A simple and efficient transformation using readily available reagents under solvent-free and metal-free conditions is considered as a key solution for pollution problems generated by large-scale reactions. Thus, recently many protocols were developed for the synthesis of benzothiazole derivatives catalyzed by heterogeneous solid acid catalysts and ionic liquids, reaction under microwave irradiation as well as reactions performed under mild and solvent free conditions, which are included in this review. In addition, ultrasound promoted synthesis of benzothiazoles are also reported. The present article is intended to review briefly on recent research progress concerning the synthesis of various benzothiazole derivatives via different methodologies, which mainly includes condensation of *ortho*-amino thiophenols and acids/ acid chlorides/ aldehydes/ esters/ nitriles/ ketones/ thioesters. In addition, *ortho*-amino thiophenols condensed with carbondisulfide (CS_2)/ sodium sulphide (Na_2S) to afford various benzothiazole derivatives. Also, benzothiazole derivatives were synthesised through the condensation reaction of various *ortho*-amino thiophenols/ *ortho*-halo amines/ thiophenols with various isothiocynates.

Moreover, 2-amino benzothiazoles were synthesised using bromine (Br_2) through the condensation reaction of various aromatic amines with ammonium thiocyanate (NH_4SCN)/ sodium thiocyanate (NaSCN)/ potassium thiocyanate (KSCN). Benzothiazole derivatives were also synthesised by cyclization of different aromatic thiourea linkages. Moreover, the reaction of aromatic thiourea with Lawesson's reagent also afforded benzothiazole derivatives.

2. Synthesis of benzothiazole:

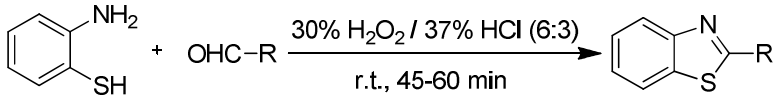
2.1. By Condensation Reaction:

2.1.1 Condensation of *ortho*-aminothiophenol with aldehyde:

2.1.1.1 Homogeneous catalysis:

Acid catalyzed condensation:

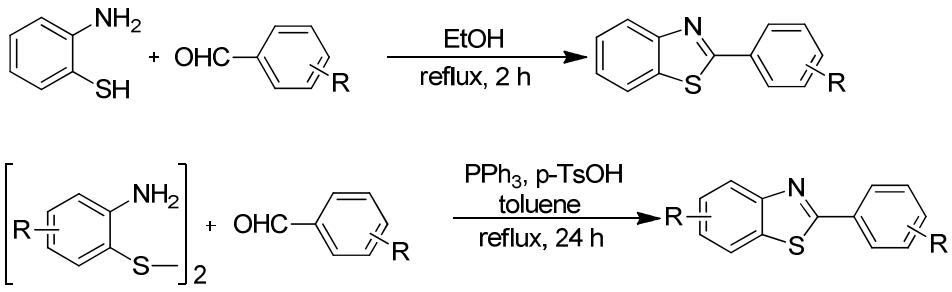
Acid catalysed homogeneous condensation of *ortho*-aminothiophenol and substituted aldehyde using H_2O_2/ HCl in ethanol at room temperature have demonstrated by Guo and co-authors **(Scheme 1)**.[69]



R= Ph; 2-OH/4-OHPh; 3-NO_2/4-NO_2Ph; 3,4-OMePh; 2,4-ClPh; 3,5-tBu-4-OHPh; 1-Naphthalene; 5-NO_2-1-Naphthalene; 9-Anthracene

Scheme 1

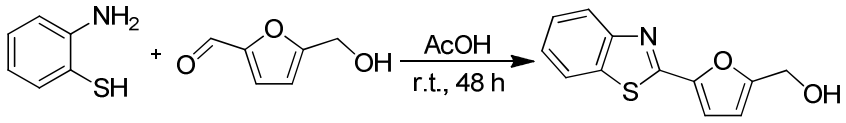
A series of novel 2-phenylbenzothiazoles was synthesized by Mortimer and colleagues by the reaction of *ortho*-aminothiophenol disulfides and substituted benzaldehydes under reducing conditions in ethanol (EtOH) **(Scheme 2)**.[70]



R= H; F; Cl; OMe; OH; Me; F; Cl; Br; I; OEt

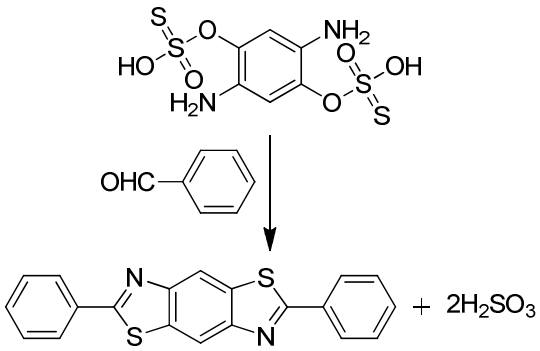
Scheme 2

(5-benzothiazol-2-yl)furan-2-yl)methanol was obtained in quantitative yield from the condensation of hydroxymethylfurfural (HMF) and *ortho*-aminobenzenethiol in the presence of acetic acid (AcOH) was pointed out by Sattler and co-authors **(Scheme 3)**.[71]



Scheme 3

The *para*-phenylenediamine-2,5-di-(thiosulfuric acid) was heated with benzaldehydes and formed a benzal derivative as an intermediate, which at higher temperature yielded the benzobisthiazole was reported by Perkin et al. **(Scheme 4)**.[72]

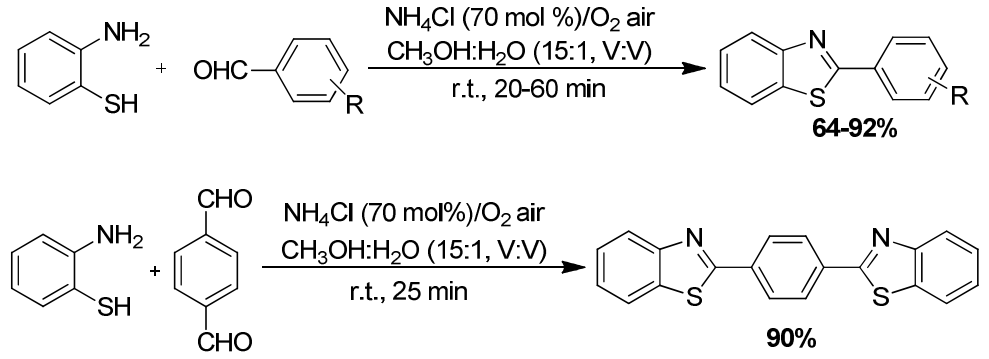


Scheme 4

Base catalyzed condensation:

Maleki et al. have developed mild and an efficient protocol for the synthesis of 2-arylbenzothiazole derivatives from condensation of *ortho*-aminothiophenol with aromatic aldehydes employing ammonium chloride as a catalyst in methanol/water (15:1 v:v) as a dual

solvent system at room temperature, which afforded high yield of the products **(Scheme 5a-b)**.[73] Here, the mechanism shows that ammonium chloride may first activate the carbonyl compounds by hydrogen bonding promote the reaction via the nucleophilic attack of amines afforded target molecules. The use of NH_4Cl is a very inexpensive, metal-free and readily available reagent is the superior feature of this protocol. For comparative study authors have employed various organic solvents such as ethanol (EtOH), water (H_2O), acetonitrile (ACN), dichloromethane (DCM) and chloroform ($CHCl_3$). However, methanol/water has been proven the best solvent system in terms of yield. Short reaction time, high yield of the product, recycling of the catalyst, mild reaction conditions, acid-free and metal-free system are the additional advantages of this method.

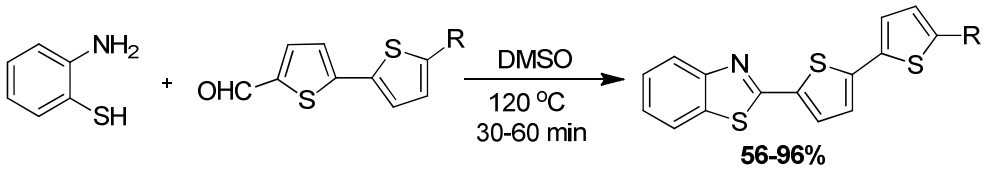


R= H; 3-NO_2; 4-Cl; 4-CN; 2-OH; 4-OH; 3-Br; 4-Br; 2-Me; 4-Me; 4-OMe; 2-OMe; 4-$N(Me)_2$

Scheme 5a-b

Solvent catalyzed condensation:

Bithienyl-1,3-benzothiazoles, another new derivatives of benzothiazole, were prepared using the condensation reaction of *ortho*-aminobenzenethiol and various 5-formayl-5'-alkoxy- or 5-formayl-5,-*N,N*-dialkylamino-2,2'-bithiophenes under the refluxing Dimethyl sulfoxide (DMSO) for 30-60 min by Batista et al. **(Scheme 6)**.[74] Assessment of the fluorescence properties of new benzothiazoles demonstrate that, they show strong fluorescence in the 450-600 nm.

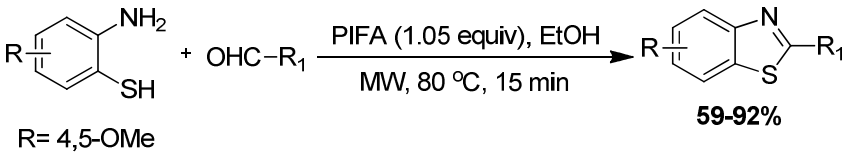


R= H; OMe; OEt; NMe_2; NEt_2; $N(i\text{-}Pr)_2$; piperidino; morpholino

Scheme 6

Microwave-induced condensation:

Praveen and co-workers disclosed microwave-assisted one-pot synthesis of benzothiazole and benzoxazole derivatives using phenyliodoniumbis(trifluoroacetate) (PIFA) as an effective oxidant for the cyclocondensation of *ortho*-aminothiophenols/ *ortho*-aminophenols with different aldehydes in ethanol at 80 ºC, which afforded high yield of the products **(Scheme 7)**.[75] Heterocyclic nucleus containing substituted aldehyde compounds such as pyridine, thiophene and furan allowed average yield due to the cleavage of these heterocycles in the microwave irradiation. According to the possible reaction mechanism, imine intermediate is formed. This protocol has advantages like PIFA (which works both as a Lewis acid and as an oxidant), wide substrate scope, short reaction time, microwave condition and satisfactory yields.



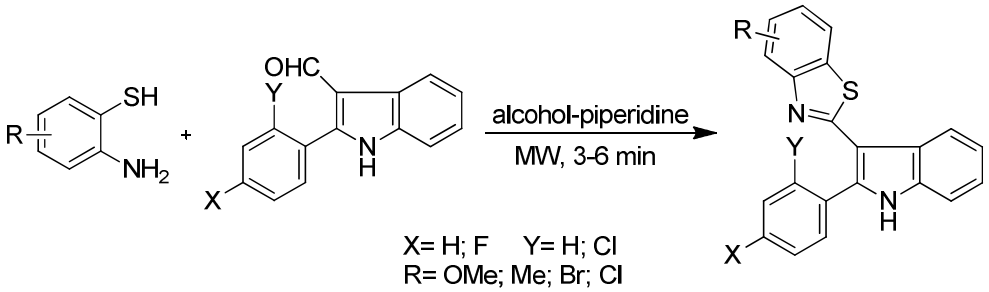
R= 4,5-OMe

R_1= Ph; 3-NO_2Ph; 2-OMe/4-OMePh; 3,4-OMePh; 4-CF_3Ph; 3-OMe-4-OBnPh; 3,5-OMe-4-OHPh; 3,5-OMe-4-OBnPh; 3-OMe-4-OH-5-BrPh; 4-$N(Me)_2$Ph; 2-Cl/4-ClPh; 2-Naphthalene; 4-CO_2MePh; 2-pyridine; 2-thiophene; 2-furan; 5-(benzo-1,3-dioxole); 2-(1-methylindole); 4-(3-(4-Br/OEt/Cl/OMe)-1-phenyl) pyrazole

Scheme 7

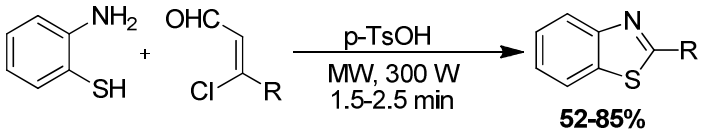
The condensation of appropriate 2-phenyl-1*H*-indole-3-carboxaldehyde and 5-substituted *ortho*-aminothiophenols in the presence of piperidine or *para*-toluenesulphonic acid (p-TSA) in ethanol (EtOH) or *N*,*N*-dimethylformamide (DMF) solvent under microwave irradiation (MWI) for 3-6 min at 240 W was reported by Dandia et al. **(Scheme 8)**.[76] Considerable

increase in reaction rate and improved yield was observed in case of microwave irradiation compared to classical methods.



Scheme 8

Paul et al. have developed a simple and efficient procedure for the synthesis of 2-arylbenzothiazoles by a one-pot condensation reaction of *ortho*-aminothiophenol with β-chlorocinnamaldehydes under microwave irradiation (MWI) using *para*-toluenesulfonicacid (*p*-TSA) **(Scheme 9)**.[77] Operational simplicity, fast reaction, environment friendly, general applicability and accommodating a variety of substitution patterns are the notable advantages of this procedure.



Scheme 9

2.1.2 Heterogeneous catalysis:

Acid catalyzed condensation:

Phosphorous pentoxide is an inexpensive reagent, acts as an acid catalyst. An efficient protocol for the synthesis of 2-arylbenzothiazole via condensation of various aldehydes and *ortho*-aminothiophenol, in the presence of Phosphorus pentoxide (P_2O_5) in methanol (MeOH) for 3–7 h at room temperature was reported by Nalage et al. **(Scheme 10, Method 1)**.[78]

The cobalt nitrate ($Co(NO_3)_2 \cdot 6H_2O$)/ hydrogen peroxide (H_2O_2) as a novel and efficient reagent for the synthesis of 2-arylsubstituted benzothiazoles, was investigated by

Chandrachood and colleagues **(Scheme 10, Method 2)**.[79] They have noted the effect of change of solvent, temperature and change in reagent quantity on the reaction and found the best results using cobalt nitrate and hydrogen peroxide in *N,N*-dimethylformamide (DMF). Aliphatic aldehydes do not give notable yield with this reagent.

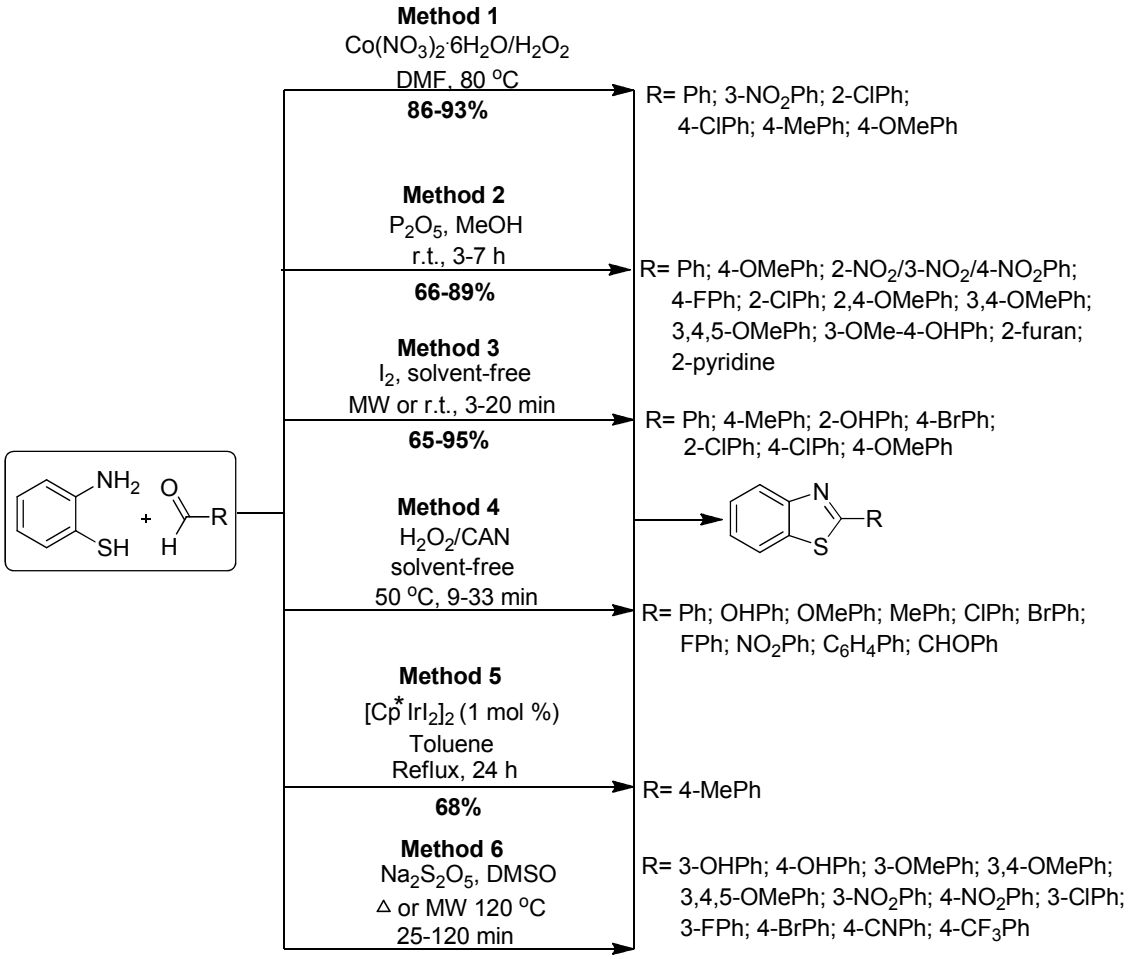
Rapid and effective condensation reactions of *ortho*-aminothiophenol with various aldehydes were carried out using I_2 in solvent-free conditions by Moghaddam et al. to afford the corresponding 2-substituted benzothiazole derivatives in a relatively short time in excellent yields **(Scheme 10, Method 3)**.[80]

Weekes et al. have reported a simple, one-pot and high-yielding protocol for the substituted 2-phenylbenzothiazoles under both thermal and microwave (MW) conditions from the condensation of various benzaldehydes and *ortho*-aminothiophenol using sodium metabisulfite ($Na_2S_2O_5$) as a mild oxidant in dimethylsulfoxide (DMSO) at 120 ºC **(Scheme 10, Method 4)**.[81] Here, less reaction time and simple isolation of product without column chromatography are the additional advantages of this method. Authors also achieved excellent yield of product using dimethylformamide (DMF) at 90 ºC as a solvent, though this reaction takes longer time (>2 h) because of the lower solubility of reaction components in DMF. However, DMSO is an efficient solvent for promoting this reaction, due to its optimal reagent dissolution and oxidizing agent properties.

Synthesis of 2-(*para*-tolyl)benzothiazole by transition metal-Ir-catalyzed hydrogen-transfer reactions of 4-methylbenzaldehyde with *ortho*-aminothiophenol have suggested by Blacker and colleagues **(Scheme 10, Method 5)**.[82]

The H_2O_2/CAN system as a novel and very efficient reagent for the convenient synthesis of benzothiazoles in good to excellent yields through the condensation of *ortho*-aminothiophenol and various substituted aryl aldehydes was described by Bahrami and co-

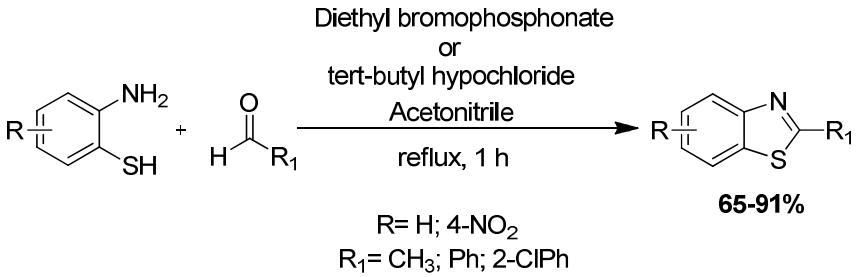
authors **(Scheme 10, Method 6)**.[83] Short reaction time, easy and quick isolation method, excellent chemoselectivity and good yields are the main advantages of this procedure.



Scheme 10

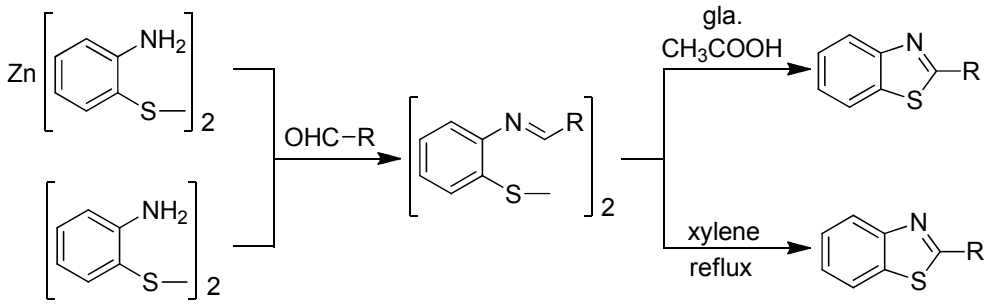
2-substituted benzothiazole and benzoxazole were synthesized by the condensation of aldehydes with *ortho*-aminothiophenol or *ortho*-aminophenol respectively through a one-pot reaction by applying diethyl bromo phoshonate and tert-butyl hypochlorite (*t*-BuOCl) in acetonitrile (MeCN) by Patil et al. **(Scheme 11)**.[84] Both the diethyl bromophosphonate and tert-butyl hypochlorite have been used for oxidative cyclization and intramolecular cyclization but the authors have extended this idea by oxidative cyclization of Schiff's base prepared from condensation of various aldehydes with *ortho*-aminophenol and *ortho*-aminothiophenol, which leads to the formation of benzoxazole and benzothiazole

respectively. The reaction was carried out at the different molar ratio of oxidant in various solvents showed that reactions proceeded well with 2 equiv. of both the oxidants in acetonitrile.



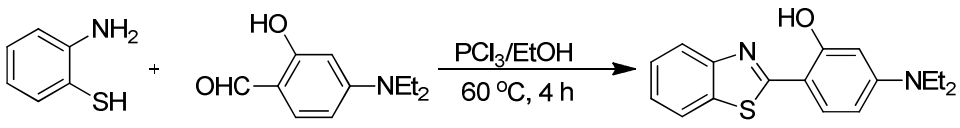
Scheme 11

Bogert and co-authors have investigated a method for the synthesis of 2-substituted benzothiazoles by the condensation of zinc bis(*ortho*-aminothiophenolate) or *ortho*-aminophenyldisulphide and substituted aldehydes **(Scheme 12)**.[85] In the formation of thiazoles from the aminothiophenols and aldehydes, the authors have demonstrated that the thiazolines are intermediate products.



Scheme 12

Condensation of *ortho*-aminothiophenol and 4-(diethylamino)-2-hydroxybenzaldehyde using PCl_3 as a catalyst in ethanol (EtOH) was reported by Padalkar et al. **(Scheme 13)**.[86]



Scheme 13 **70-83%**

Solid supported condensation:

Maleki et al. have suggested an efficient and improved catalyst, sulphuric acid immobilised on silica-gel (H_2SO_4·SiO_2) for the synthesis of 2-arylbenzothiazoles through condensation of vrious aldehydes and *ortho*-aminothiophenol **(Scheme 14, Method 1)**.[87] Here, H_2SO_4·SiO_2 is an inexpensive, heterogeneous and stable catalyst possessing very high reactivity compared to unsupported H_2SO_4. The authors have examined the effect on the yield by employing different amounts of catalyst in various solvent but considerable growth of the reaction rate and improvement of the yield were observed when 5 mg of H_2SO_4·SiO_2 in ethanol (EtOH) was used.

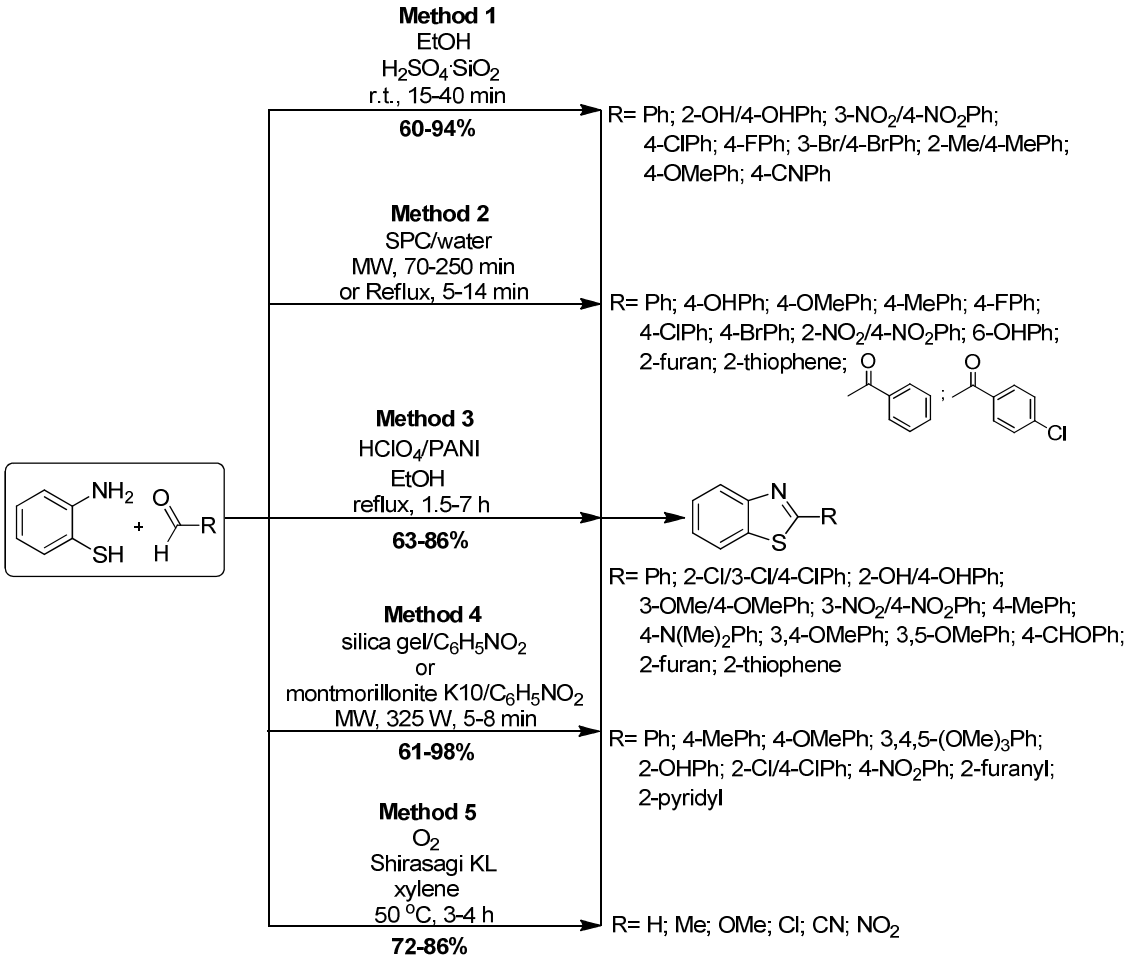
Shokrolahi et al. have reported the condensation of *ortho*-aminothiophenol with aldehyde using Sulfonated Porous Carbon (SPC) as a heterogeneous catalyst in water under reflux conditions and microwave irradiation to produce benzothiazole derivatives **(Scheme 14, Method 2)**.[88] Here, porous carbon materials can accomplish most of the required properties for a suitable catalyst support due to high surface areas and well-developed porosities which have attracted adequate attention. Authors have studied the optimization experiment using different amount of SPC for the condensation reaction in water by refluxing (90 min) or by microwave irradiation (6 min). Use of 0.1g of SPC shows the best results under these reaction conditions. The reusability and recyclability of the catalyst (SPC) was checked under similar reaction conditions and was concluded that, for the three catalytic cycles, the yields and reaction times remained the same. The present protocol has simple work up, environmentally benign, good yields, no requirement of extra oxidants and use of the cheap catalyst compared to previously reported methods.

The synthesis of 2-substituted benzothiazoles with efficiently in good yields by the reaction of *ortho*-aminothiophenol and various aldehydes in the presence of a catalytic amount of perchloric acid–doped Polyaniline ($HClO_4$/PANI) under refluxing ethanol (EtOH) was reported by Alibeik et al. **(Scheme 14, Method 3)**.[89] The superior characteristics of this

catalyst are the low cost, simple recovery and efficient reusability. The authors have studied the reusability of the catalyst and the results show that there is no considerable changes in the catalyst reactivity. There is only a steady downfall in the time and yield of the reaction till the third time of reuse, but this moderate deactivation is stopped in the fourth run.

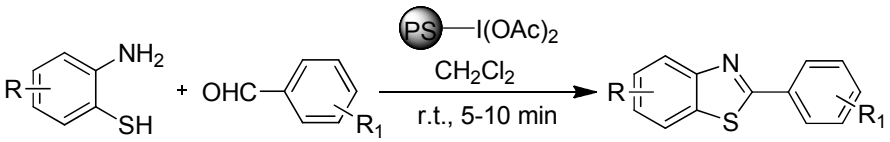
Alloum et al. have presented the condensation of various aldehydes with *ortho*-aminothiophenol on silica gel/ nitrobenzene or montmorillonite K-10/ nitrobenzene under microwave irradiation (MWI) afforded 2-arylbenzothiazoles in goodyields with highpurity **(Scheme 14, Method 4)**.[90]

Kawashita and co-workers have disclosed a simple and direct synthesis of 2-arylbenzothiazole by the aid of activated carbon (Shirasagi KL) **(Scheme 14, Method 5)**.[91] 2-Pyridylbenzothiazole, prepared by this method, was proven to work as a ligand in palladium-catalyzed Mizoroki-Heck reaction.



Scheme 14

Kumar and co-authors have attempted a synthesis of a library of 2-substituted benzothiazoles via condensation of various substituted amines with different aldehydes in the presence of poly[4-diacetoxyiodo] styrene (PDAIS) as a solid supported hypervalent iodine reagent in dichloromethane (DCM), which afforded excellent yield of the products **(Scheme 15)**.[92] A general mechanism for PDAIS mediated synthesis of benzothiazoles was shown that an imine intermediate is generated during the reaction of an amine with aldehyde, which undergoes intramolecular cyclization to afford the final product. In addition, PDAIS is converted to polymer supported iodobenzene which is recovered by filtration is the major benefit of this protocol.

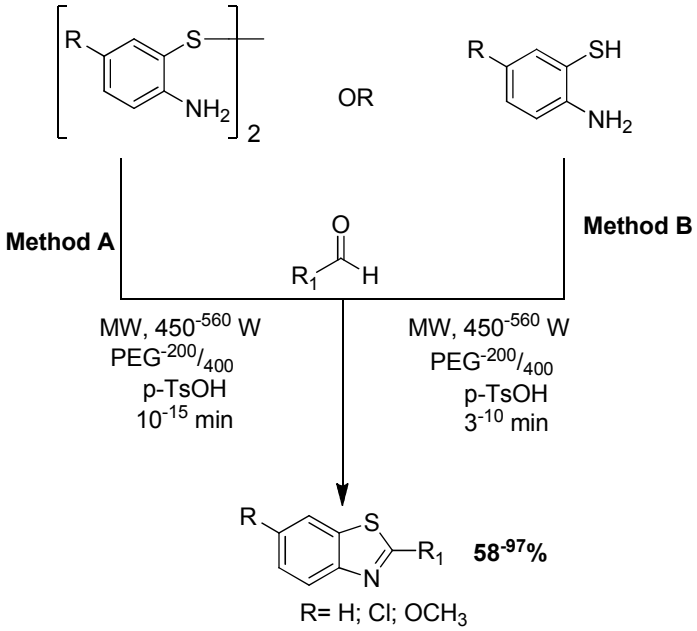


R= Cl; OMe
R_1= 2-Cl; 3-NO_2

Scheme 15

Polymer supported condensation:

Deligeorgiev and co-authors have surveyed a reliable, simple, highly reproducible and an improved green protocol for the preparation of 2-aryl- and 2-hetaryl-benzothiazoles by condensation of equivalent amounts of 2,2-diaminodiphenyldisulfides (method A) or *ortho*-aminothiophenols (method B) and diverse aromatic aldehydes applying PEG 200/400 under microwave irradiation (MWI) **(Scheme 16)**.[93] Here, short reaction time, easy work-up procedure, high purity of the products without the use of column chromatography, high yield and the use of green solvent PEG 200 or PEG 400 are the superior advantages of this protocol. Moreover, for the optimization of reaction conditions, the authors carried out this reaction in microwave irradiation. However, the best results were obtained by irradiation of the reaction mixture for 5 to 15 min at 560 W in the presence of *para*-toluenesulfonic acid (*p*-TSA) and green solvent PEG 200/400.



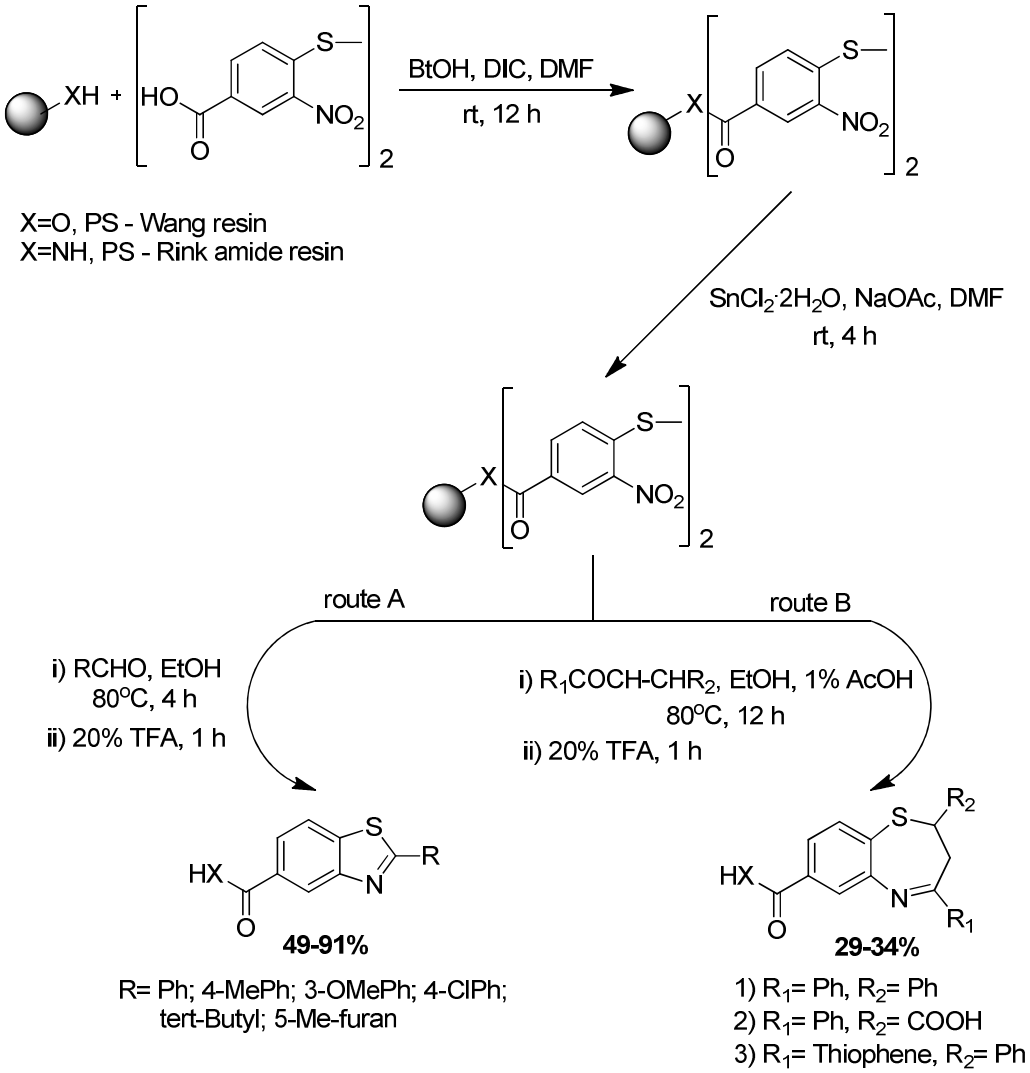
R= H; Cl; OCH_3

R_1= Ph; 2-OHPh; 4-OMePh; 4-$N(CH_3)_2$Ph; 4-$N(Et)_2$; 4-$CH(Me)_2$Ph; 4-CNPh; 3-NO_2Ph; 4-NO_2Ph; 2-OH-5-BrPh; 2-OH-3,5-BrPh; 2-ClPh; 4-piperidinePh; 4-morpholinePh; 4-acitamidePh; 4-CHOPh; 1-(4-OH)-naphthalene; 9-anthracene; 3-(9-ethyl)-carbazole; 2/3/4-pyridine; 2-furan

Scheme 16

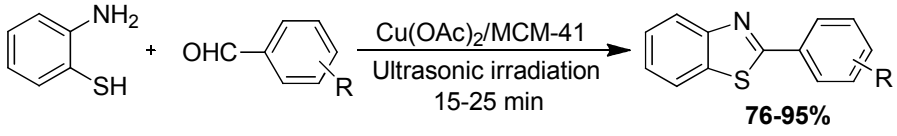
Resin supported condensation:

Lee and co-workers investigated the solid phase synthesis of benzothiazole derivatives using Wang resin and Rink amide resin, which was filled by bis-(2-nitro-4-carboxyphenyl) disulfide. The nitro group reduced to its amine by rupture of the disulfide bond using $SnCl_2 \cdot 2H_2O$ to afford 1-(2-nitro-4-carboxyphenyl)thiol with Wang resin and Rink amide resin, which was condensed with α-β substituted aldehyde in the presence of ethanol under reflux condition, followed by trifluoroaceticacid (TFA) cleavage and spontaneous oxidation to afford benzothiazole derivatives (route A). The bisnucleophilic attack of thiol with Wang resin and Rink amide resin on an unsaturated ketone in the presence of 1% CH_3COOH in ethanol under reflux condition gives 2,3-dihydro-[1,5]-benzothiazepine derivatives (route B) **(Scheme 17).**[94]



Scheme 17

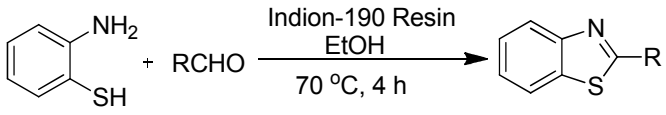
Sadjadi et al. have found a new applicative and solvent free approach for the synthesis of 2-arylbenzothiazole in the existence of MCM-41 supported $Cu(OAc)_2$, as a catalyst under ultrasonic irradiation to afforded excellent yield of the products **(Scheme 18)**.[95]



Scheme 18

A mild protocol has been developed for the preparation of benzothiazoles from reactions of aldehydes with *ortho*-substituted amino aromatics in the presence of catalytic amount of

Indion 190 resin by Padalkar and co-authors **(Scheme 19)**.[96] In order to find the optimum reaction conditions, the reaction has been carried out between *ortho*-phenylenediamine and benzaldehyde in the presence of different catalysts and solvents at various temperatures, and the results clearly shows the effective use of Indion 190 resin and ethanol (EtOH) as a solvent for the preparation of 2-phenylbenzimidazole. Authors have also investigated that lower temperatures required more time for the completion of the reaction and contrary higher amount of catalyst increases the acidity of the reaction medium, so the yield of the corresponding product decreases.



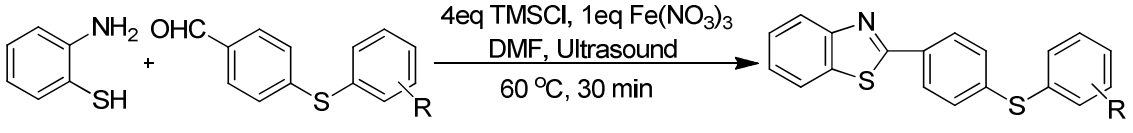
86-92%

R= Ph; 4-NO_2Ph; 2-OH-4-$N(Et)_2$Ph

Scheme 19

Organo-silicon supported condensation:

A mild and efficient reagent chlorotrimethylsilane (TMSCl) in dimethylformamide (DMF) as a promoter and water scavenger and $Fe(NO_3)_3$ as catalyst for the one-pot preparation of benzothiazoles from aromatic *ortho*-aminothiophenols and aldehydes under ultrasonic irradiation with good yield was explored by Yuan and colleagues **(Scheme 20)**.[97] The authors performed a set of experiments on 4-phenylsulfanyl-benzaldehyde and *ortho*-aminothiophenol by applying various amounts of TMSCl and $Fe(NO_3)_3$ at different reaction temperatures and educed that the best result was achieved by carrying out the reaction with TMSCl and $Fe(NO_3)_3$ (4:1) at 60 ºC for under ultrasonic irradiation in DMF or without solvent.

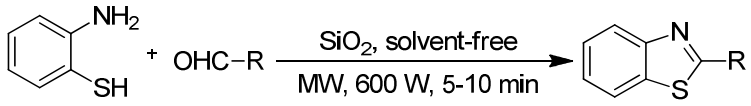


R= H; Cl; F; Me; OMe

78-96%

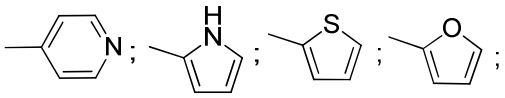
Scheme 20

Kodomari and colleagues have established a simple, convenient and rapid method for the synthesis of 2-substituted benzothiazoles by the condensation of aldehydes and *ortho*-aminothiophenol under microwave irradiation (MWI) in the presence of silica gel under solvent free condition **(Scheme 21)**.[98] The silica gel could be easily recovered and reused for consequential reactions without loss of their activity. Here, solvent-free condition, use of the non-toxic catalysts, high yield of the products and shorten reaction times are the advantages of this protocol.



61-97%

R= Ph; 2-Me/4-MePh; 2-OMe/4-OMePh; 2-NO_2/4-NO_2Ph; 2-OH/4-OHPh; 2-Cl/4-ClPh;

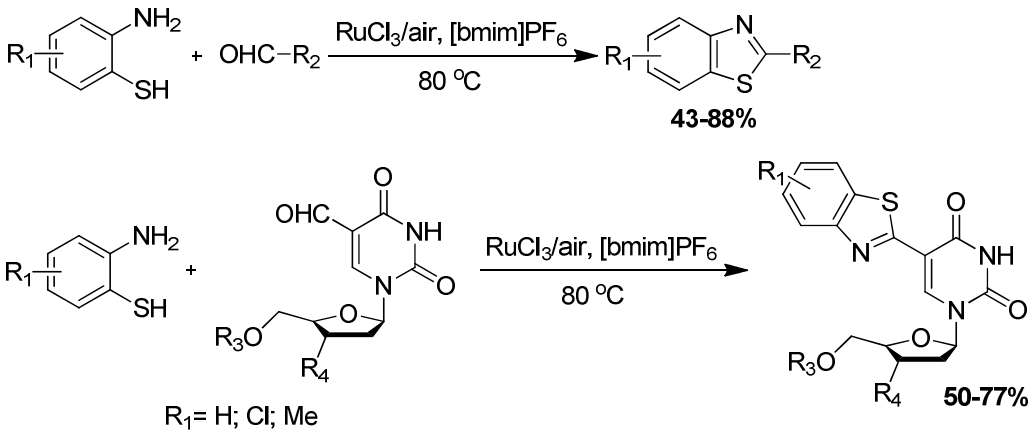


Et; $(CH_2)_2CH_3$; $(CH_2)_3CH_3$; $CH(CH_3)_2$; $CH_2CH(CH_3)_2$; $CH(CH_2CH_3)_2$; $(CH_2)_5CH_3$

Scheme 21

Ionic-liquid catalyzed condensation:

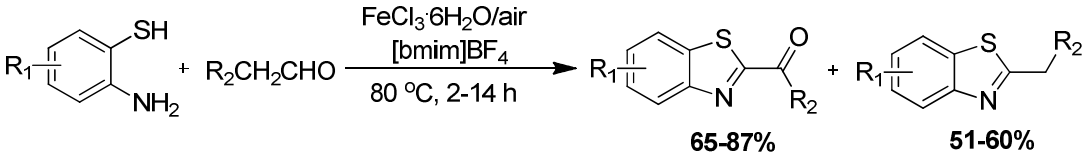
Fan et al. have developed an efficient, environmentally beneficial and practical procedure for the synthesis of 2-substituted benzothiazoles via oxidative condensation of *ortho*-aminobenzenethiol with various aldehydes in the presence of $RuCl_3$ as a catalyst in [bmim]PF_6 ionic liquid as the reaction medium and air as the oxidant **(Scheme 22a-b)**.[99] The authors have also studied the reaction under different conditions with regard to various catalysts, solvent, temperature and reaction time. However the best results were obtained in the case of 80 ºC in [bmim]PF_6 as a reaction media.



R_1= H; Cl; Me
R_2= Ph; BrPh; OMePh; CNPh; NO_2Ph; ClPh; MePh; n-propane
R_3= H; Ac
R_4= OH; OAc; N_3

Scheme 22a-b

Fan et al. have developed an applicative method for synthesis of 2-benzoylbenzothiazoles and 2-benzylbenzothiazoles via condensation of *ortho*-aminothiophenols and phenylacetaldehydes using $FeCl_3 \cdot 6H_2O$ as an oxidant and [bmim]BF_4 ionic liquid as both reaction medium and co-catalyst, which afforded excellent yield of the products **(Scheme 23)**.[100]



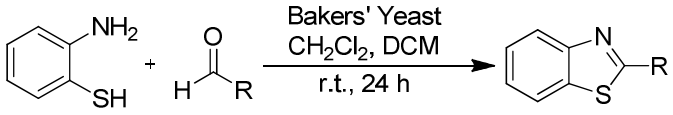
R_1= H; Cl; Me
R_2= Ph; 3-Me/4-MePh; 4-FPh; 4-BrPh; 4-ClPh; 4-NO_2Ph; 4-OMePh

Scheme 23

Using bio-reagent:

The cyclocondensation of *ortho*-aminothiophenol and aldehydes to produce 2-arylbenzothiazole and 2-heteroaryl benzothiazoles was discovered by Pratap and co-workers, in dichloromethane (DCM) using bakers' yeast as a catalyst in good yields. This protocol could be eco-friendly and an attractive way for the synthesis of highly functionalized bioactive benzothiazoles. To evaluate the effect of the solvent, the authors have carried out the model reaction in different solvents such as water (H_2O), ethanol/water, ethanol (EtOH),

methanol (MeOH), 1,4-dioxane, acetonitrile (ACN), N,N-dimethylformamide (DMF) and dichloromethane (DCM). However, the yield of benzothiazoles was found relatively better in dichloromethane **(Scheme 24).**[101]

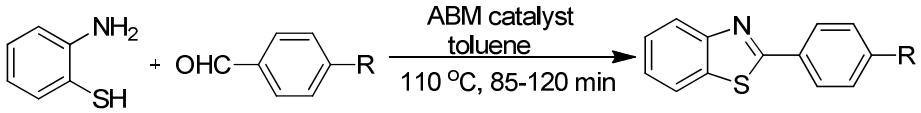


51-84%

R= Ph; 4-OMePh; 4-N(Me)$_2$Ph; 4-MePh; 2-OHPh; 2-ClPh; 4-ClPh; 4-BrPh; 4-FPh; 3-NO$_2$Ph; 4-NO$_2$Ph; 2-pyridyl; 2-furyl

Scheme 24

Riadi et al. have efficiently synthesized a series of benzothiazoles by the condensation of *ortho*-aminothiophenol with aromatic aldehydes in the presence of catalytic amounts of Animal Bone Meal (ABM) and Lewis acids doped ABMs under reflux conditions in air **(Scheme 25)**.[102] The remarkable features of this new protocol are high conversion, short reaction times, cleaner reaction profiles, straight forward procedure and reduction in catalyst toxicity.



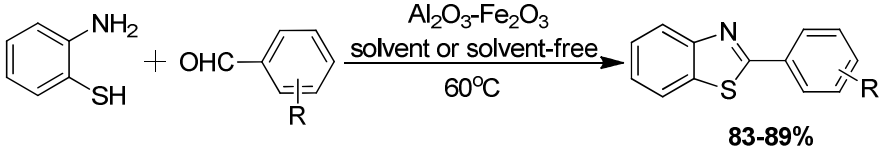
22-72%

R= H; Cl; F; Me; OMe; NO$_2$

Scheme 25

Metal nanoparticle catalysed condensation:

An efficient procedure for the synthesis of 2-substituted benzothiazoles was employed using *ortho*-aminothiophenol and substituted aldehydes in the presence of Al_2O_3-Fe_2O_3 nanocrystals (5 % w/w of *ortho*-aminothiophenol), as a heterogeneous catalyst at 60 ºC by Bandyopadhyay and colleagues **(Scheme 26)**.[103]



83-89%

R= H; Et; OH; OMe; OEt; Br; NO$_2$; CH(Me)$_2$

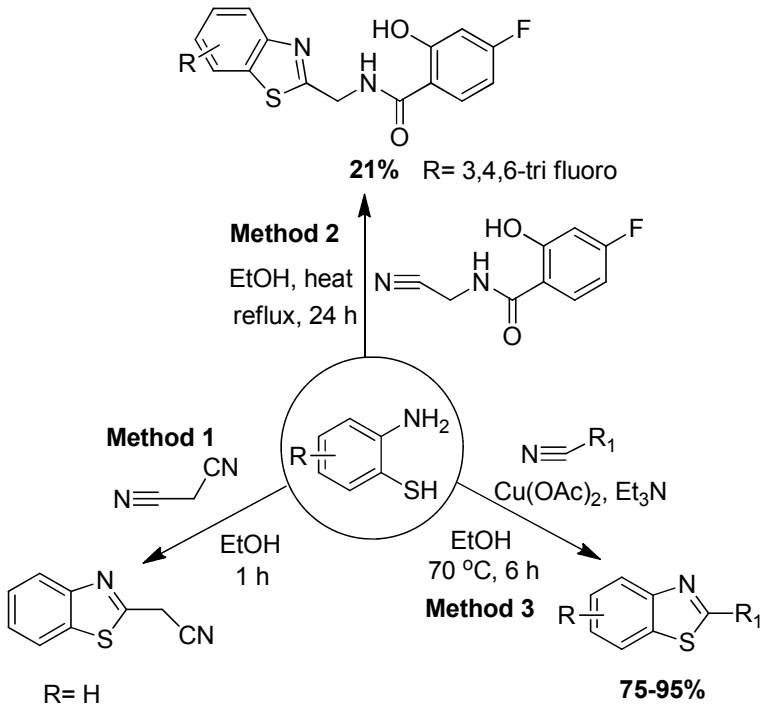
Scheme 26

2.1.2 Condensation of *ortho*-aminothiophenole with nitrile:

Mokhir et al. have mention the synthesis of 2-cyanomethyl benzothiazole from the condensation of *ortho*-aminothiophenol and malonodinitrile in the presence of glacial acetic acid (gla. CH_3COOH) **(Scheme 27, Method 1)**.[104] The suspention of 2-cyanomethyl benzothiazole in iso-propanol and water containing potassium nitrite (KNO_2) was further treated with conc. HCl to yield 2-benzothiazolylcyanoxime, which is good multidentate ligand for co-ordination chemistry.

Zandt and colleagues have reported the synthesis of 4-fluoro-2-hydroxy-*N*(4,5,7,-trifluoro-benzothiazol-2-ylmethyl)-benzamide using *N*-cyanomethyl-4-fluoro-2-hydroxy-benzamide and 2-amino-4,5,7-trifluorothiophenol hydrochloride in refluxing ethanol (EtOH) for 24 h **(Scheme 27, Method 2)**.[105]

Copper acetate catalysed formation of 2-substituted benzothiazoles in excellent yields via condensation of *ortho*-aminobenzenethiols with wide range of nitriles containing different functional groups was developed by Sun et al. **(Scheme 27, Method 3)**.[106] Optimization of the reaction conditions explored that the optimal catalytic conditions consist of $Cu(OAc)_2$ (10 mol %) and Et_3N (1.0 equiv.) in ethanol (EtOH) at 70 ºC for 6 h gives best results in terms of yield. According to the investigation of the reaction mechanism, sulfilimine formation and intramolecular cyclization occurs to furnish benzothiazoles.



R= H; Cl

R_1= Ph; 4-Me/4-OMe/4-CH(Me)$_2$/4-N(Me)$_2$/4-CF_3/4-CN/4-F/4-Cl/4-Br/4-IPh; 3-Br-4-MePh; 2-naphtalene; 2-furan; Me; 1-cyclopropane; 1-ethylPh; 1-ethyl(3-OMe)Ph; 2-ethylpyridine; 3-ethylthiophene; 1-(3-OMe)propane; 1-(4-Ph)butane; 1-dodecane

Scheme 27

2.1.3. Condensation *ortho*-aminothiophenole with ester:

2.1.3.1. Condensation *ortho*-aminothiophenole with simple ester:

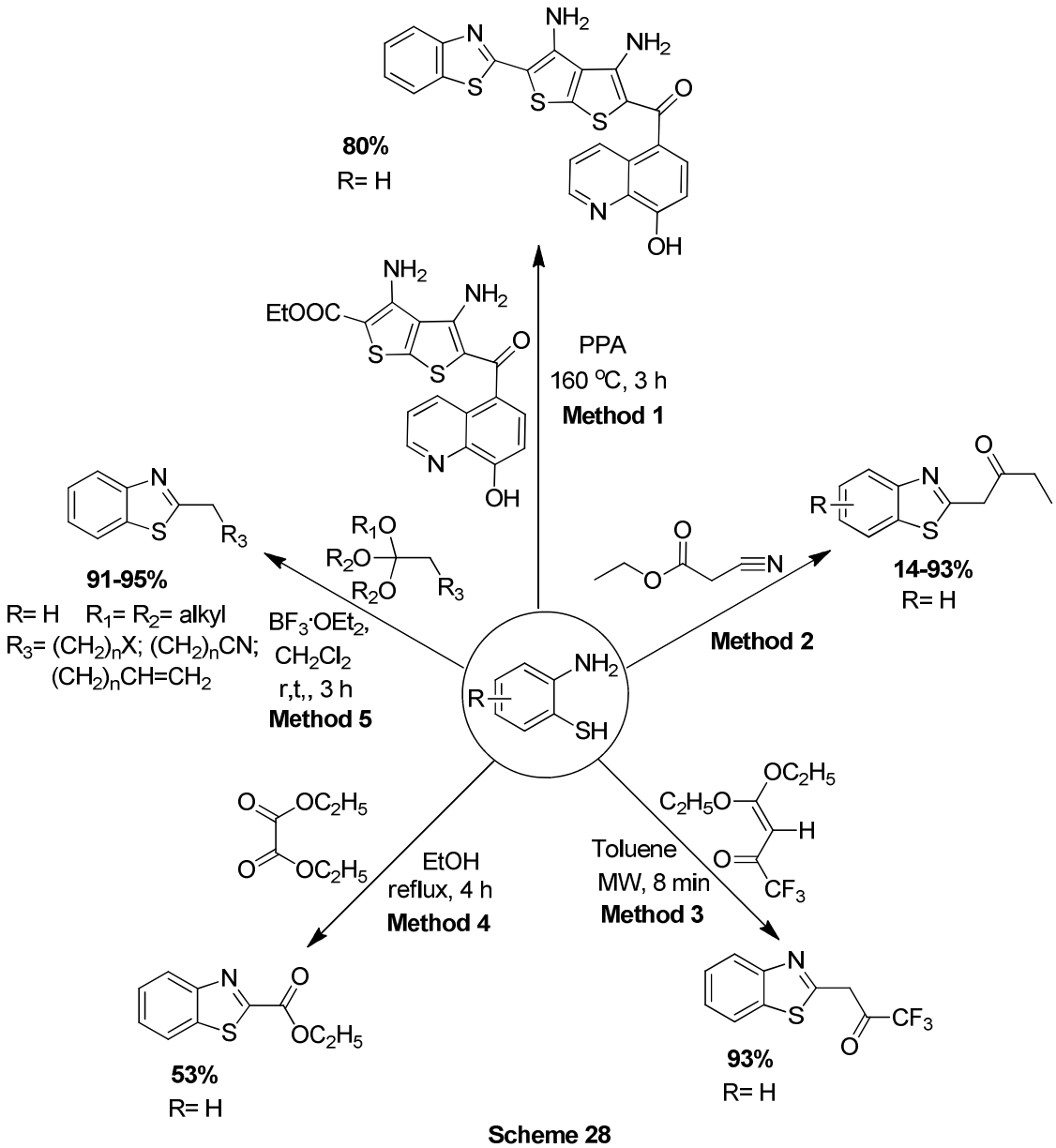
Khalil et al. have surveyed that an amino ester and the selected *ortho*-substitued aromatic amines such as *ortho*-aminothiophenol was condensed in the presence of poly phosphoric acid (PPA) at 160 ºC for 3 h followed by neutralization with aq. ammonia to yield corresponding 2-substituted benzothiazole **(Scheme 28, Method 1)**.[107]

Manfroni et al. have synthesized the 5-substituted ethyl-2-(benzothiazol-2-yl)acetate by the condensation of various substituted *ortho*-aminothiophenol and ethyl cyanoacetate at 120 ºC, which afforded high yield of the products **(Scheme 28, Method 2)**.[108]

Reddy et al. have investigated the distinctive formation of trifluoroacetonyl benzothiazole by condensation of *ortho*-aminophenol with trifluoroacetyl ketene diethyl acetal under microwave irradiation (MWI) in toluene for 8 min **(Scheme 28, Method 3)**.[109]

Shantakumar et al. have presented some new banzothiazole derivatives by the reaction of benzothiazolyl carboxyhydrazide with variant aryl acids using phosphoryl chloride ($POCl_3$) **(Scheme 28, Method 4)**.[49]

The convenient, flexible, connective and efficient preparation of various benzothiazole derivatives by the condensation of substituted anilines with functionalized orthoesters in good to excellent yields under mild conditions was established by Bastug and colleagues **(Scheme 28, Method 5)**.[110] The development of new libraries of multifunctional sites containing heterocycles is the versatility of this protocol. A broad range of variety of substituted orthoesters were prepared using the modified Pinner sequences which widen the scope of this condensation.



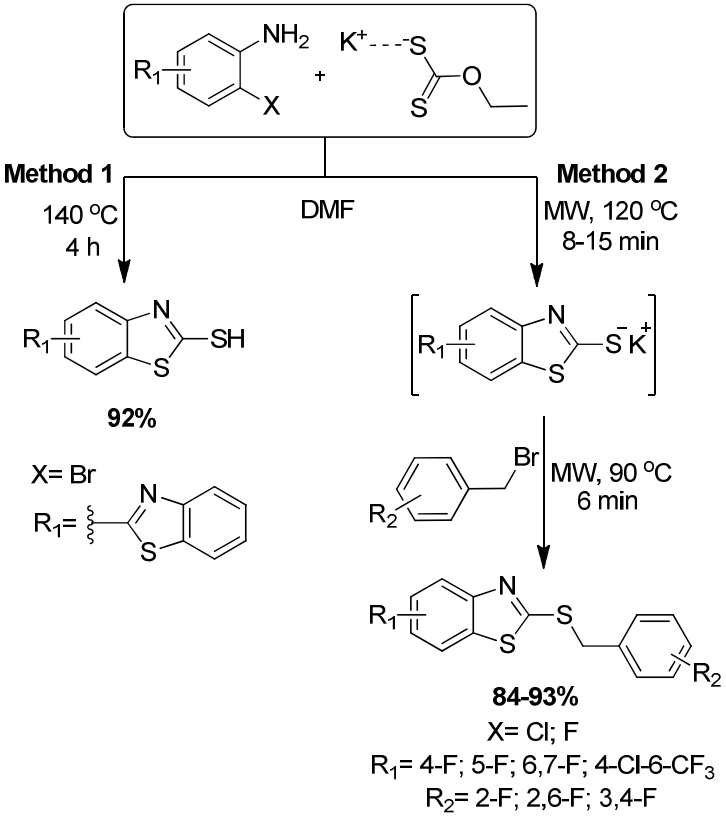
Scheme 28

2.1.3.2. Condensation *ortho*-aminothiophenole with thionoester:

Karlsson and co-workers have described the protocol for the synthesis of (2,6'-bibenzothiazole)-2'-thiol via the condensation of 4-(benzothiazole-2-yl)-2-bromoaniline with potassium *ortho*-ethyl dithiocarbonate using dimethyl formamide (DMF) at 140 ºC for 4 h **(Scheme 29, Method 1)**.[111]

Yang et al. have suggested a synthetic approach for a highly efficient assembly of polyfluorinated 2-benzylthiobenzothiazoles by readily available starting materials such as

various substituted anilines and potassium *ortho*-ethyl dithiocarbonate, which consume shorter reaction time and allow good to excellent yield **(Scheme 29, Method 2)**.[112]



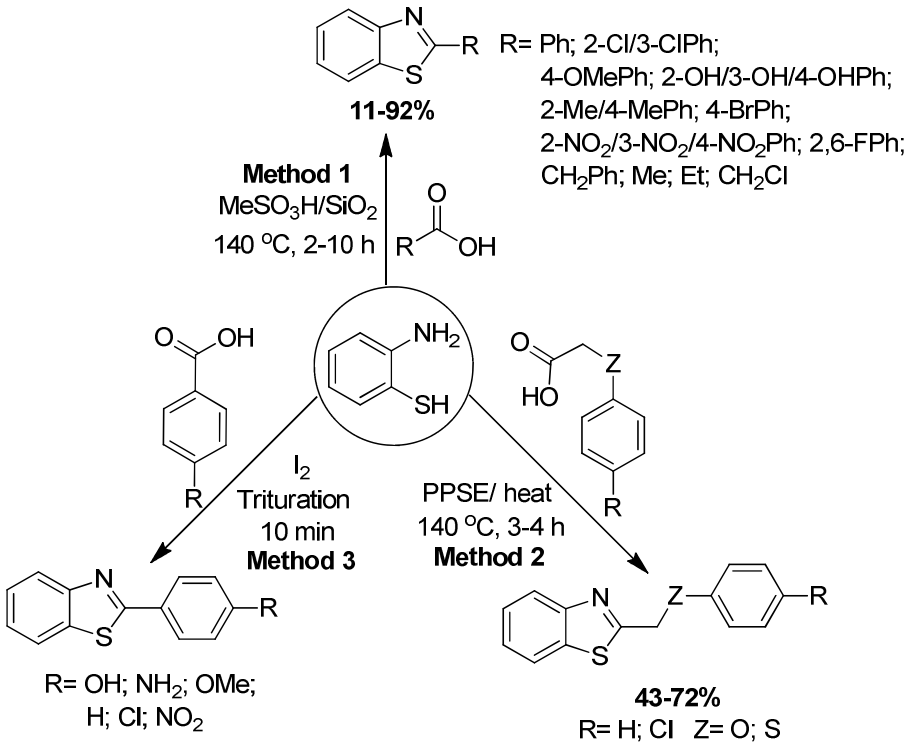
Scheme 29

2.1.4 Condensation of *ortho*-aminothiophenol with acid:

Sharghi et al. have indicated an efficient, one-pot and high yielding procedure for the synthesis of 2-substituted benzothiazoles from the *ortho*-aminothiophenol and different aliphatic or aromatic carboxylicacids in novel methane sulfonic acid/ silica gel ($MeSO_3H$/ SiO_2) at 140 ºC for 2-12 h **(Scheme 30, Method 1)**.[113] Silica gel was recovered and reused many times without loss of its efficiency.

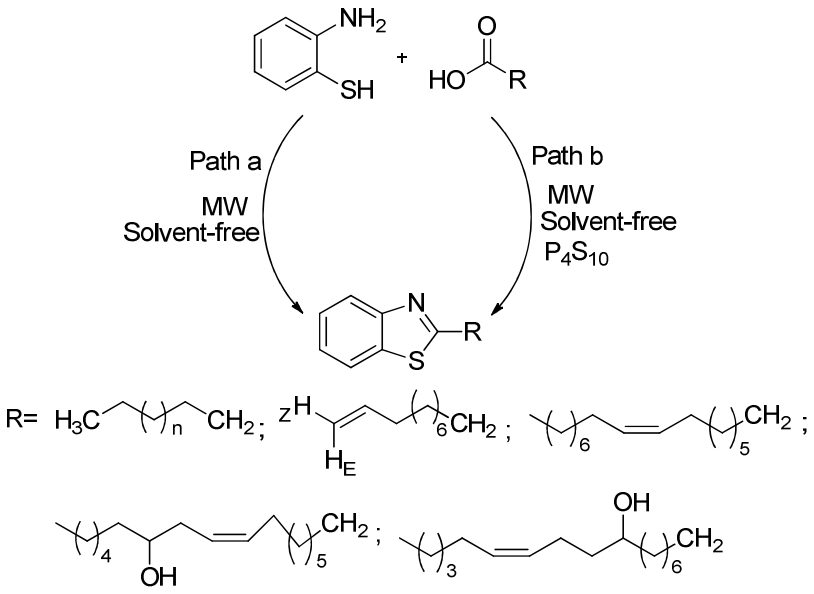
Yildiz et al. have reported the viable methodology for the synthesis of various 2-substituted benzothiazoles from *ortho*-aminothiophenols and corresponding carboxylic acids refluxing in trimethylsilylpolyphosphate ester (PPSE) at various temperatures and time to afford various derivatives in excellent yield **(Scheme 30, Method 2)**.[114]

Molecular iodine was employed by Gupta and co-workers in a one-pot, solid-phase, solvent-free and microwave assisted reaction of *ortho*-aminothiophenol and various benzoic acids to obtain high yield of various benzothiazole derivatives, compared to polyphosphoric acid (PPA) and [pmim]Br catalyzed microwave assisted reactions **(Scheme 30, Method 3)**.[115] The reaction was completed within 10 min and requires a very small amount of iodine. The authors have studied that this new protocol has lower cost with compare to PPA and [pmim]Br, because no additional chemicals and solvents are essential during this transformation. This protocol is an inexpensive, solvent-free and less time consuming.



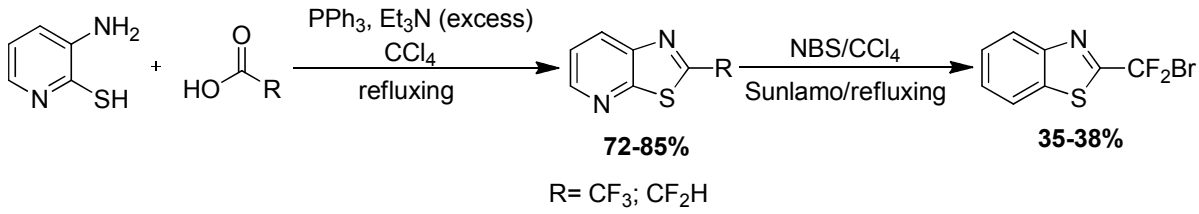
Scheme 30

Rauf et al. have proposed rapid, efficient and solvent-free one-pot synthesis of 2-substituted benzothiazole by the condensation of various fatty acids with *ortho*-aminothiophenol using P_4S_{10} as a catalyst under microwave irradiation (MWI), which afforded high yield of the products **(Scheme 31)**.[116] Here, reaction was completed within 3-4 min with good yield in the presence of catalyst (path-a), while it takes 30 min without catalyst with poor yield (path-b).



Scheme 31

An efficient and one-pot synthesis of 2-trifluoro- and 2-difluoromethyl substituted benzothiazole derivatives in excellent yields by the condensation reaction of trifluoroacetic acid and difluoroacetic acid with commercially available *ortho*-aminobenzenethiols, respectively, was examined by Ge and co-workers **(Scheme 32)**.[117]



R= CF_3; CF_2H

Scheme 32

2.1.5 Condensation with acyl chloride:

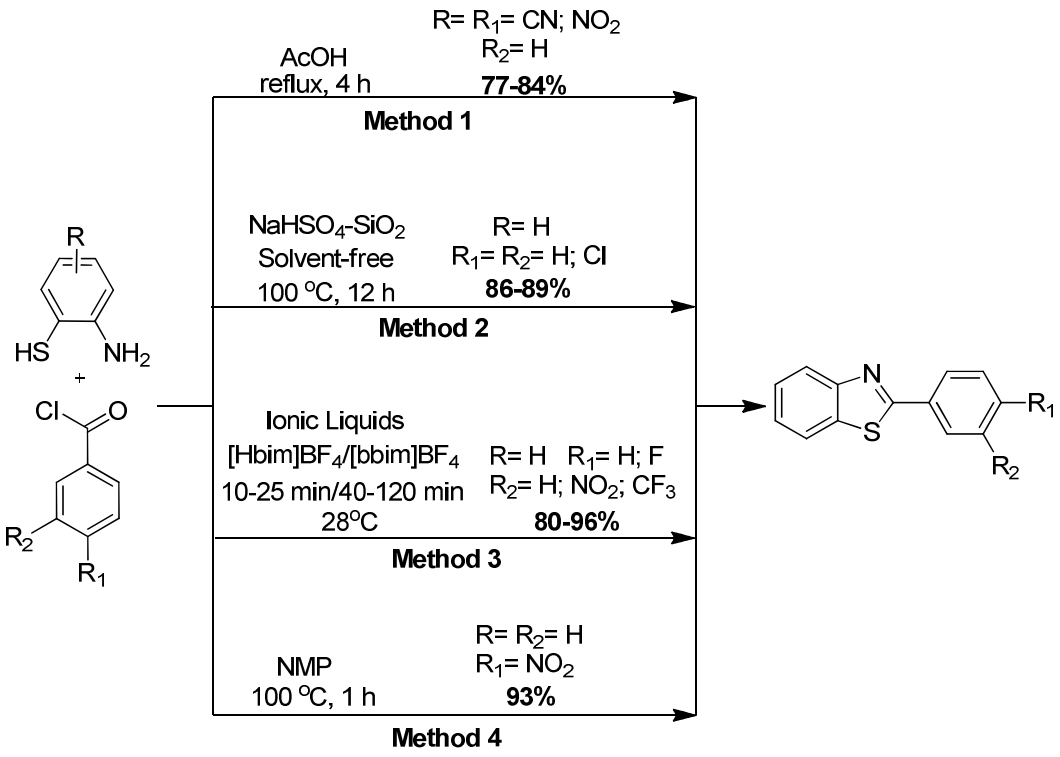
2.1.5.1 Condensation of *ortho*-aminothiophenol with acyl chloride:

Racane et al. have reported that the bis-nitrile and nitro-nitrile derivatives of 2-phenylbenzothiazole were prepared by the condensation reaction of cyano or nitro-substituted *ortho*-aminobenzothiole with commercially available 4-cyano or 4-nitrobenzoylchloride, respectively, under reflux condition in acetic acid (AcOH) for 4 h **(Scheme 33, Method 1)**.[118] An efficient and environment friendly catalyst $NaHSO_4$-SiO_2 promoted solvent-free synthesis of library of benzothiazole derivatives by the condensation reaction of various acyl chlorides

with *ortho*-aminothiophenol was developed by Kumar and co-workers **(Scheme 33, Method 2)**.[119] This reaction is heterogeneous in nature, so the catalyst can be easily recovered by simple filtration. The use of nontoxic, inexpensive, easily available, reusable and green catalyst makes the reaction protocol inexpensive and eco-friendly. $NaHSO_4$-SiO_2 catalyst can be used four times with consistent yield, which shows importance for the large scale operations and industrial point of view. Authors have also investigated the effect of time, temperature and solvent on the reaction. From this study they have concluded that best results were obtained, when $NaHSO_4$-SiO_2 refluxing at 100 ºC for 12 h without use of any solvent.

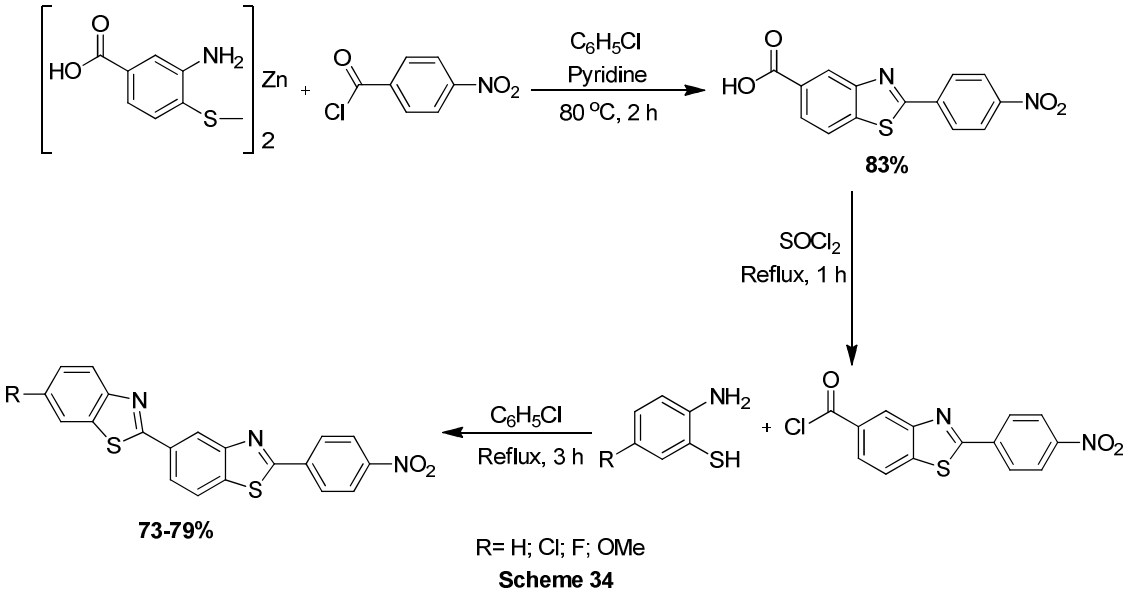
A novel one-pot regioselective synthesis of 2-aryl benzothiazoles has been developed by Nadaf and co-worker using 1-butylimidazolium tetraflouroborate ([Hbim]BF_4) and 1,3-di-*n*-butylimidazoliumtetrafluoroborate ([bbim]BF_4) ionic liquids (ILs) as reaction media at room temperature in excellent yields **(Scheme 33, Method 3)**.[120] Ambient reaction conditions, absence of a catalyst and recyclability of the non-volatile ILs makes this protocol green and environment-friendly.

Karlsson et al. have given a minor change in the condensation reaction of *ortho*-aminothiophenol with 4-nitrobenzoyl chloride by applying *N*-methyl-2-pyrrolidone (NMP) as an oxidant at 100 ºC for 1 h to give 2-(4-nitrophenyl)benzothiazole **(Scheme 33, Method 4)**.[121]



Scheme 33

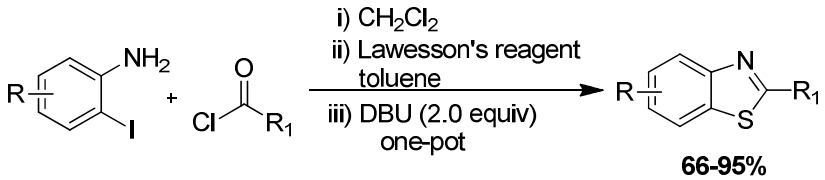
Novel dibenzothiazole derivatives were synthesized by Wu and colleagues, in which zinc salt of 4-amino-3-mercaptobenzoic acid was suspended in pyridine with *para*-nitro benzoyl chloride at 80 ºC for an hour to produce 2-(4'-nitrophenyl)-6-(benzothiazolyl)benzothiazole, which was converted in to 2-(4'-nitrophenyl)-benzothiazole-6-carbonyl chloride by treatment with thionyl chloride ($SOCl_2$) **(Scheme 34)**.[122] To a suspension of 2-(4'-nitrophenyl)-benzothiazole-6-carbonyl chloride in chlorobenzene, 5-substituted aminothiophenols were added, heated to reflux for 3 h to afford di-benzthiazole contining compounds. Both benzothiazole ring were prepared using condensation of acid chloride with *ortho*-aminothiophenol.



Scheme 34

2.1.5.2 Condensation of *ortho*-iodoaniline with acyl chloride:

Ding et al. have found a metal-free, simple and an efficient one-pot synthesis of 2-substituted benzothiazoles by the condensation reaction of *ortho*-iodoanilines and various acid chlorides in the presence of Lawesson's reagent, which afforded good to excellent yields of the products **(Scheme 35)**.[123] The predicted reaction mechanism for this protocol was decoded as the *ortho*-iodoanilines reacted with acid chlorides to afford benzamides, which transferred to benzothioamides in the presence of Lawesson's reagent and intramolecular cyclization of benzothioamides generates the expected benzothiazoles. Easy accessibility of starting materials, high efficiency, good substrate generality and suitability to combinatorial format are the attracting features of this protocol.



R= H; 4-CH_3; 4-F; 4-CF_3

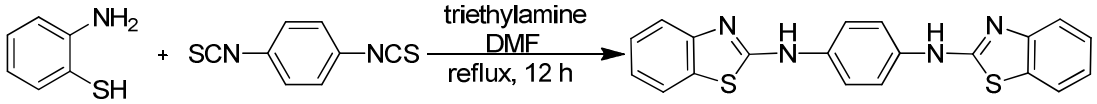
R_1= Ph; 2-OMe/4-OMePh; 3-MePh; 3,5-$(CF_3)_2$Ph; 2-furyl; Me

Scheme 35

2.1.6 Condensation with isothiocyanate:

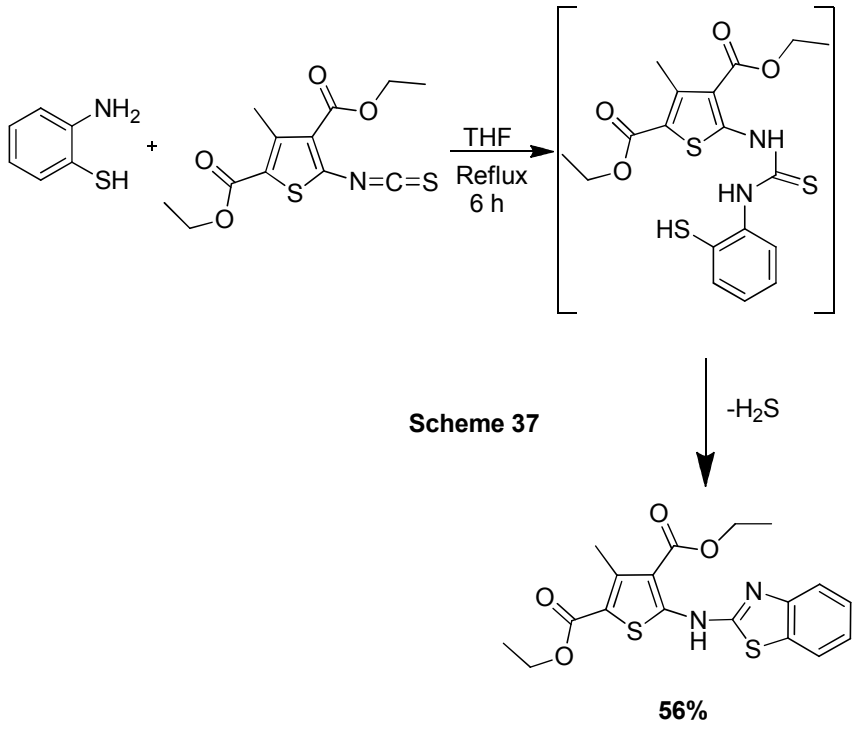
2.1.6.1 Condensation of *ortho*-aminothiophenol with isothiocyanate:

El-Sharief and colleagues have introduced an exclusive condensation reaction of 1,4-phenylenediisothiocyanate with *ortho*-aminothiophenolto produce *N,N'*-Bis-(benzothiazole-2-yl)-benzene-1,4-diamine using triethanolamine/ *N,N*-dimethylformamide (TEA/ DMF) as a reaction media **(Scheme 36)**.[124]



Scheme 36 **84%**

Ghorabet al. have reported the condensation reaction of *ortho*-aminothiophenol with isothiocyanete derivative of thiophene for the synthesis of 5-(Benzothiazole-2-yl-amino)-3-methylthiophene-2,4-dicarboxylicacid diethyl ester in tetrahydrofuran (THF) under reflux condition for 6 h, which afforded good yield of the product **(Scheme 37)**.[125]



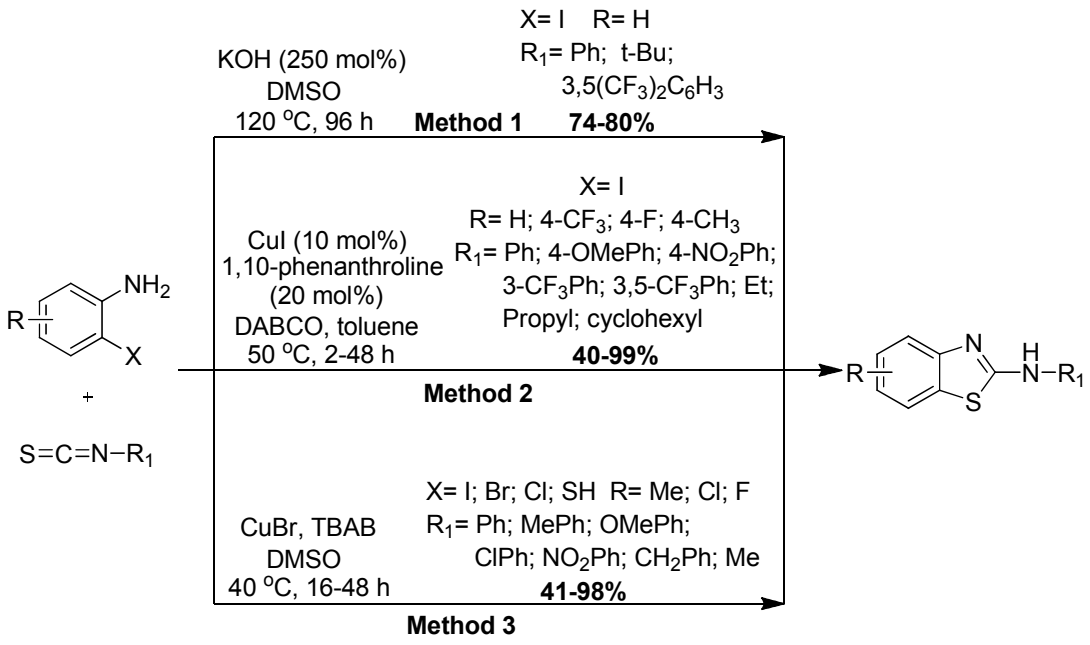
Scheme 37 **56%**

2.1.6.2. Condensation of *ortho*-iodoaniline with isothiocyanate:

Cano et al. have described the similar reaction of equimolecular amounts of *ortho*-iodoaniline and various isothiocyanato derivatives in presence of combination of dimethyl sulfoxide (DMSO) and an excess of potassium hydroxide (KOH) at 120 ºC for 96 h, which afforded *N*-substituted benzothiazol-2-amine derivatives with good yields **(Scheme 38, Method 1)**.[126] The predicted pathway of reaction mechanism involve the *in situ* generation of the corresponding intermediate-benzyne and isothiocyanato derivatives were acts as a strong electrophile. The reaction could be performed with a broad range of substrates, which makes this protocol having high synthetic utility.

Copper(I)-catalysed tandem reaction of *ortho*-iodobenzenamine with isothiocyanates under mild conditions for the synthesis of 2-substituted benzothiazoles in good yield was disclosed by Ding et al. **(Scheme 38, Method 2)**.[127] High efficiency, mild reaction conditions and experimental ease are the key features of this method. Authors have applied various ligands and base in different solvent for optimization of the reaction condition by means of good yield and time. From that study, they have concluded that the best results were obtained, when the reaction of *ortho*-iodoaniline and phenyl isothiocyanates catalysed by CuI(I) (10 mol %) in the presence of ligand (1,10-phenanthroline) and base (1,4-diazabicyclo[2.2.2]octane) (DABCO) in toluene at 50 ºC.

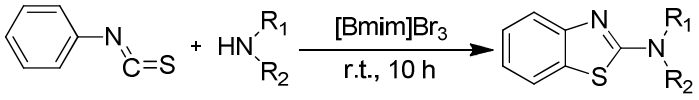
Guo et al. have reported a ligand- and base-free, copper-catalyzed reaction of *ortho*-halobenzenamine derivatives with various isothiocyanates using copper(I)bromide (CuBr) and tetra-n-butyl ammoniumbromide (TBAB-additive) as the promoter at 40 ºC, afforded various 2-aminobenzothiazoles in moderate to excellent yields **(Scheme 38, Method 3)**.[128]



Scheme 38

2.1.6.3. Condensation of substituted amine with isothiocyanate:

Le and colleagues have investigated the one-pot methodology for the synthesis of various substituted 2-aminobenzothiazoles in high yield from phenyl isothiocyanate and various amines in the presence of 1-butyl-3-methylimidazoliumtribromide ([Bmim]Br_3) and 1-butylmethylimidazoliumtetraflouoroborate ([Bmim]BF_4) ionic liquids **(Scheme 39)**.[129] This method is highly useful because of its superior advantage like recovery of ionic-liquid many times without loss of its activity.



60-81%

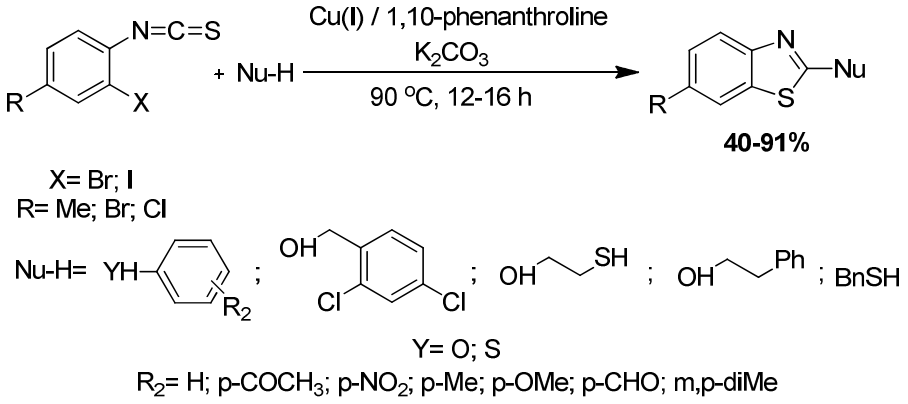
NHR_1R_2= $MeNH_2$; $PrNH_2$; i-$PrNH_2$; $HOCH_2CH_2NH_2$; $MeOCO(CH_2)_3NH_2$; pyrrolidine; piperidine

Scheme 39

2.1.6.4 Condensation of substituted benzenethiol with isothiocyanate:

Murru and co-authors have developed an efficient cascade method for the synthesis of a series of 2-substituted-1,3-benzothiazoles directly by intramolecular C–S bond formation

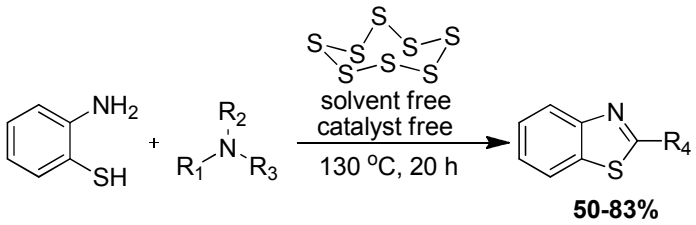
from *ortho*-haloarylisothiocyanates and various O or S containing aromatic nucleophiles catalyzed by Cu(I)–L (1,10-phenanthroline) **(Scheme 40)**.[130] The thiocarbamate or dithiocarbamate generated *in situ* by the reaction of *ortho*-haloaryl isothiocyanates with O or S containing aromatic nucleophiles. This methodology is viable for the efficient synthesis of both O- and S-substituted 1,3-benzothiazoles with equal ease. On the other hand, alcohols and thiols were less reactive in this protocol.



Scheme 40

2.1.7 Condensation of *ortho*-aminothiophenol with aryl amines:

A novel, efficient, solvent-free, catalyst-free and metallic contaminants free chemoselective oxidative coupling of various alkylamines and substituted *ortho*-mercaptoaniline for the synthesis of substituted benzothiazoles using elemental sulphur (as a convenient alternative to oxygen) was developed by Nguyen and co-authors **(Scheme 41)**.[131] The present method possess valuable advantages such as availability of all reaction components including sulphur and the remarkably simple and catalyst-free reaction conditions at moderate temperature.



R_1= CH_2Ph; CH(Me)Ph; Et; Propyl; CH(3/4-pyridin)
R_2=R_3= H; Et; Propyl
R_4= Ph; CH_2Ph; Me; Et; 3-pyridin; 4-pyridin

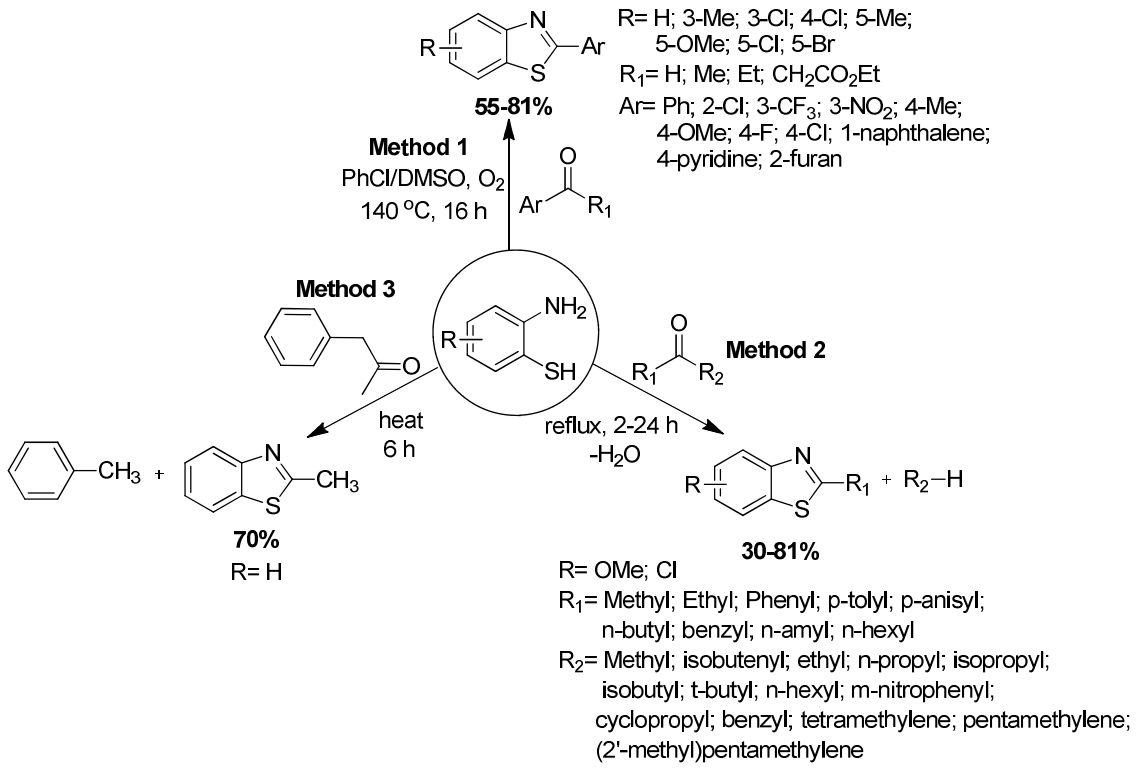
Scheme 41

2.1.8 Condensation of *ortho*-aminothiophenol with ketones:

Liao et al. have developed an inexpensive and an efficient formation of various 2-aryl benzothiazole from substituted *ortho*-aminobenzenethiols and various aryl ketones using molecular oxygen as oxidant under metal-free and I_2-free conditions in a mixture of dimethyl sulfoxide (DMSO)/ chlorobenzene (ClC_6H_5) to afford high yields of the products **(Scheme 42, Method 1)**.[132] Solvent played an important role in this transformation. Functional groups such as methyl (CH_3), methoxy (OCH_3), fluoro (F), chloro (Cl), bromo (Br) and nitro (NO_2) groups were all well endured during the study of the optimized reaction conditions. Here, imine intermediate is formed, which is cyclised and the methyl group is converted to aldehyde by O_2 and the elimination of proton generate final product.

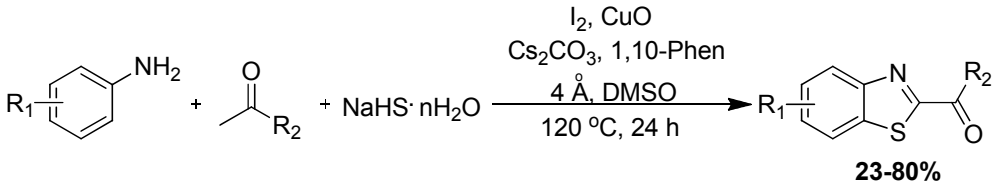
The reaction of various derivatives of *ortho*-aminobenzenethiol with verious ketones to yield 2,2-disubstituted benzothiazolines, which converted into 2-substituted benzothiazoles by the pyrolysis with the elimination of concomitant hydrocarbon under reflux condition, have examined by Elderfield and colleagues **(Scheme 42, Method 2)**.[133]

Kreysa and co-workers have investigated a new protocol for the synthesis of 2-methylbenzothiazole using benzyl methyl ketone and *ortho*-aminobenzenethiol. During this reaction, toluene results as a by-product **(Scheme 42, Method 3)**.[134]



Scheme 42

The condensation reaction of simple and readily available aromatic ketones with substituted anilines by employing $NaSH{\cdot}nH_2O$ and CuO/CuI in the presence of base (Cs_2CO_3) and ligand (1,10-phenanthrolin) in dimethyl sulfoxide (DMSO) at 120 ºC for the preparation of 2-acylbenzothiazoles, which assembles six reactions in one-pot was reported by Xue and co-authors **(Scheme 43)**.[135]



R1= Ph; 4-MePh; 4-FPh; 4-ClPh; 4-OMePh; 4-OEtPh; 4-NO_2Ph; 4-OHPh; 4-C_6H_5Ph; 2-thiophene; 2-furan; 2-benzofuran; 1,4-benzodioxan; 2-naphthalene
R2= H; 4-OMe; 4-Me; 4-Cl; 4-CF_3; 4-F

Scheme 43

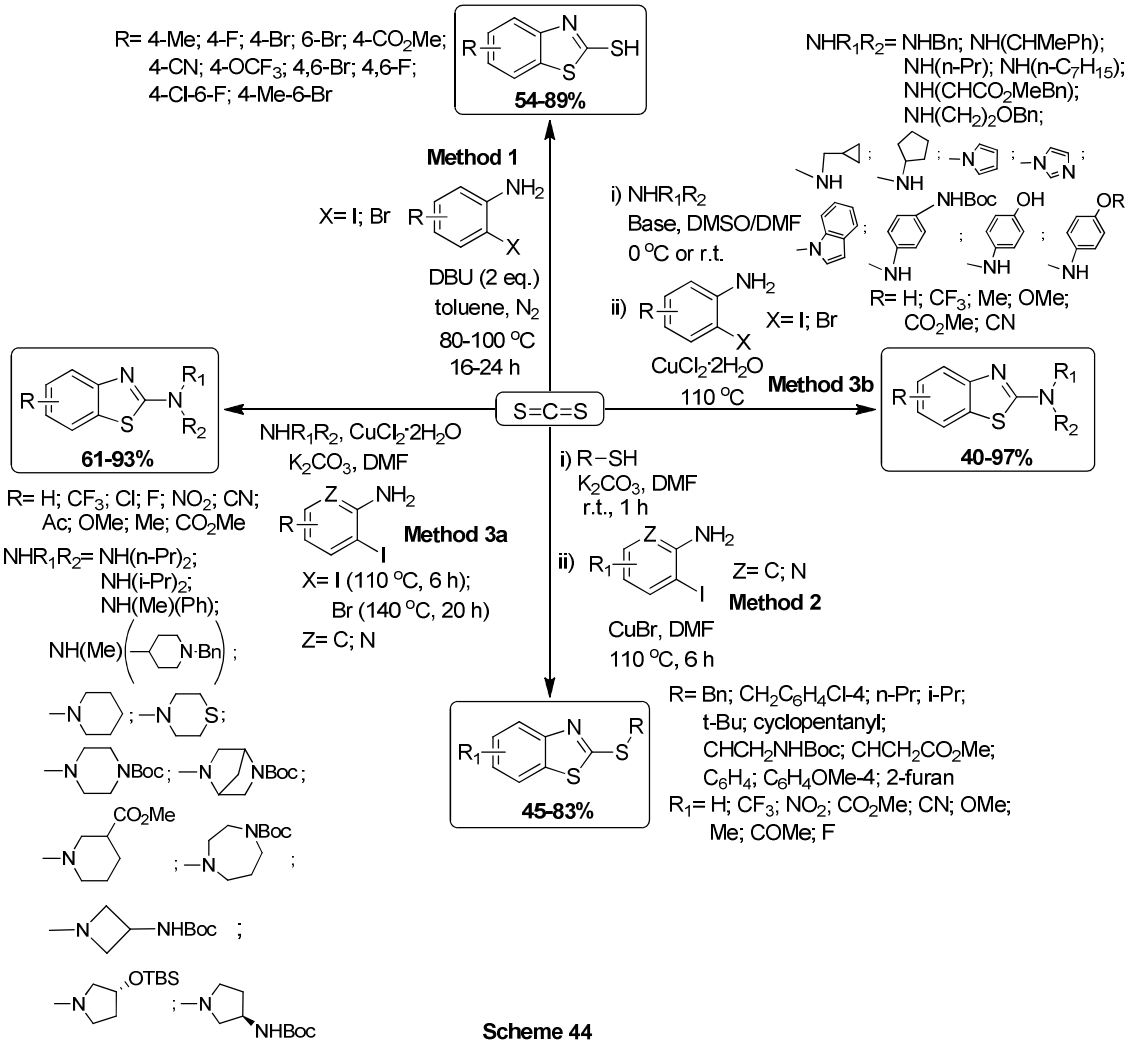
2.1.9 Condensation of *ortho*-haloaniline with disulfide/ sulfide:

A simple, practical and highly efficient protocol for the synthesis of a variety of 2-mercaptobenzothiazole derivatives in good to excellent yield from the various *ortho*-

haloaniline and carbon disulphide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) have discovered by Wang et al. Furthermore, this reaction avoids utilization of any metals **(Scheme 44, Method 1)**.[136]

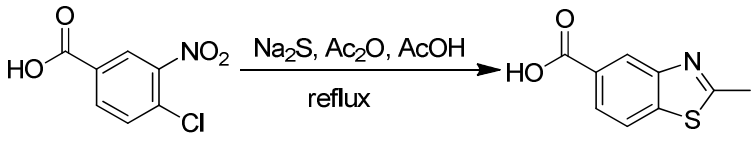
Shi and colleagues have surveyed a facile and diverse protocol for assembling both aliphatic and aromatic 2-thio-substituted benzothiazoles from *ortho*-iodoanilines and substituted aromatic or aliphatic thiol (RSH) by using conveniently available reagents such as carbon disulfide (CS_2), base (K_2CO_3) and catalyst (CuBr) wich afforded good yield of the products **(Scheme 44, Method 2)**.[137] Condensation of carbondisulfide with thiols in the presence of K_2CO_3 generates carbonotrithioate salts *in situ*, which undergo coupling with *ortho*-iodoanilines and subsequent intramolecular condensation and elimination under assistance of CuBr to afford 2-thiosubstituted benzothiazoles.

Ma and colleagues have identified that the reaction of dithiocarbamate salts, which are excellent coupling partners for copper-catalyzed arylation, with substituted *ortho*-haloanilines can undergo intramolecular condensation in the presence of base (K_2CO_3) and dimethylformamide (DMF) to afford 2-*N*-substituted benzothiazoles in good yield **(Scheme 44, Method 3a-b)**.[138] This protocol enables the library of 2-*N*-substituted benzothiazoles with great diversity.



Scheme 44

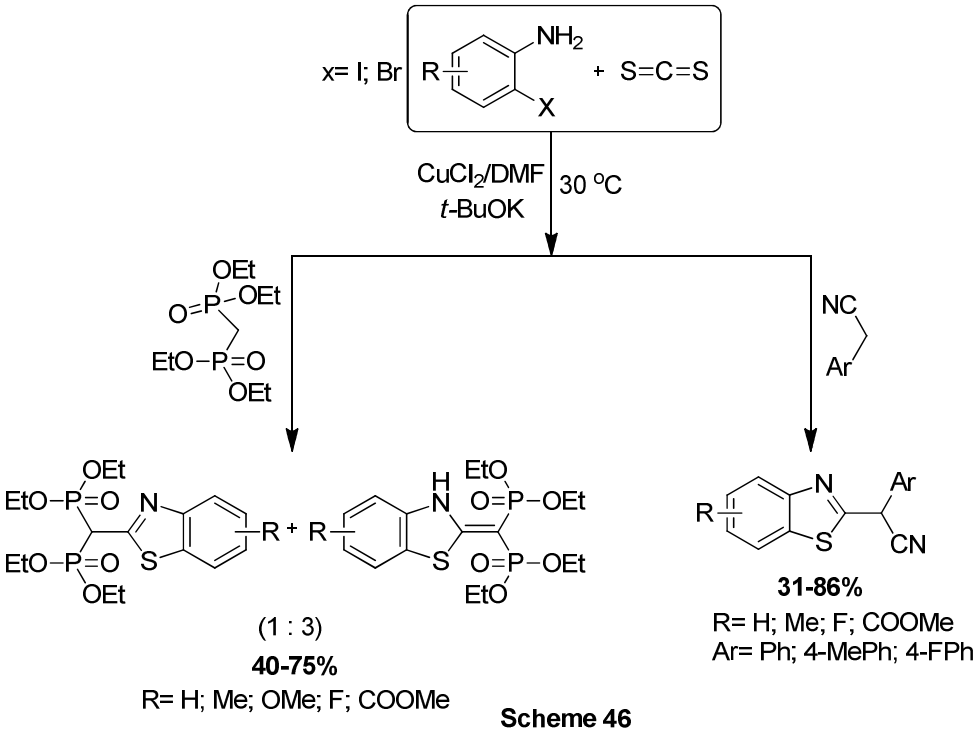
2-methylbenzothiazole-5-carboxylicacid was obtained from 4-chloro-3-nitrobenzoicacid in a one-pot reaction using sodium sulfide (Na_2S) in the presence of acetic anhydride (Ac_2O) and acetic acid (HOAc) was reported by Klar and co-authors **(Scheme 45)**.[139]



Scheme 45

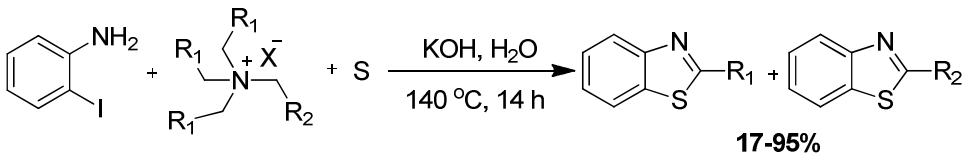
Inspired by the above developments, xiang et al. has been investigated that a similar transformation would occur to synthesize 2-substituted benzothiazoles if *in situ* generated carbanions as nucleophiles instead of N and/or S nucleophiles in this cascade three-

component reaction in the presence of bases. Nitrogen-containing bisphosphonates (N-BPs), 2-methylbisphosphonate-substituted benzothiazoles, and a-aryl-substituted nitriles, a-benzothiazol-substituted nitriles could readily be obtained by employing bis(diethoxyphosphoryl)methanides and cyano(phenyl)methanides generated *in situ* respectively as nucleophiles with the optimized reaction conditions (1.2 equiv. CS_2, 3 equiv. BuOK, 1 equiv. $CuCl_2$ in DMF at 30 °C for 12 h) in hand **(Scheme 46)**.[140] Two series of extremely useful 2-C-substituted benzothiazoles containing gem-bisphosphonates and aryl-substituted nitriles were synthesized. The yields of products were severely affected by the substituent's properties. It was also observed that weak electron-donating and electron-withdrawing substituents such as -Me and -F gave similar or slightly lower yields than 2-iodoaniline without any substituent. However, When stronger electron-donating and electron-withdrawing substituents such as -OMe and -COOMe were introduced into the benzene ring, the expected products were obtained in moderate yields. N-BPs are very useful in numerous pharmaceuticals and agrochemicals due to their broad range of biological activities and are also very valuable building blocks to gain amides, carboxylic acids, primary amines, ketones, heterocycles and biologically active compounds with or without the nitrile group.



Scheme 46

Pan and colleagues have developed a simple, one-pot and an eco-friendly methodology for the synthesis of various substituted benzothiazoles by three-component reactions of *ortho*-iodoaniline, quaternary ammonium salt and sulfur powder in water with moderate to excellent yields up to 95% **(Scheme 47)**.[141] Quaternary ammonium salt works both as a phase transfer reagent and an alkylation reagent. Authors have also proposed a plausible reaction pathway which shows quaternary ammonium salt was firstly reacted with sulfur powder to generate dialkyl disulphide, which would react with *ortho*-iodoaniline to give 2-(alkylthio)benzenamine. Then, the intramolecular cyclization reaction of 2-(alkylthio)benzenamine occurs to yield the targeted product.



17-95%

X= F; Cl; Br; I; OH; HSO_4; $OCOCH_3$

R_1= Me; Et; $CH_3(CH_2)_2$; $CH_3(CH_2)_5$; $CH_3(CH_2)_6$

R_2= Et; $CH_3(CH_2)_2$; $CH_3(CH_2)_5$; $CH_3(CH_2)_6$; Ph

R_3= H; Me; Et; Cl; F; Br

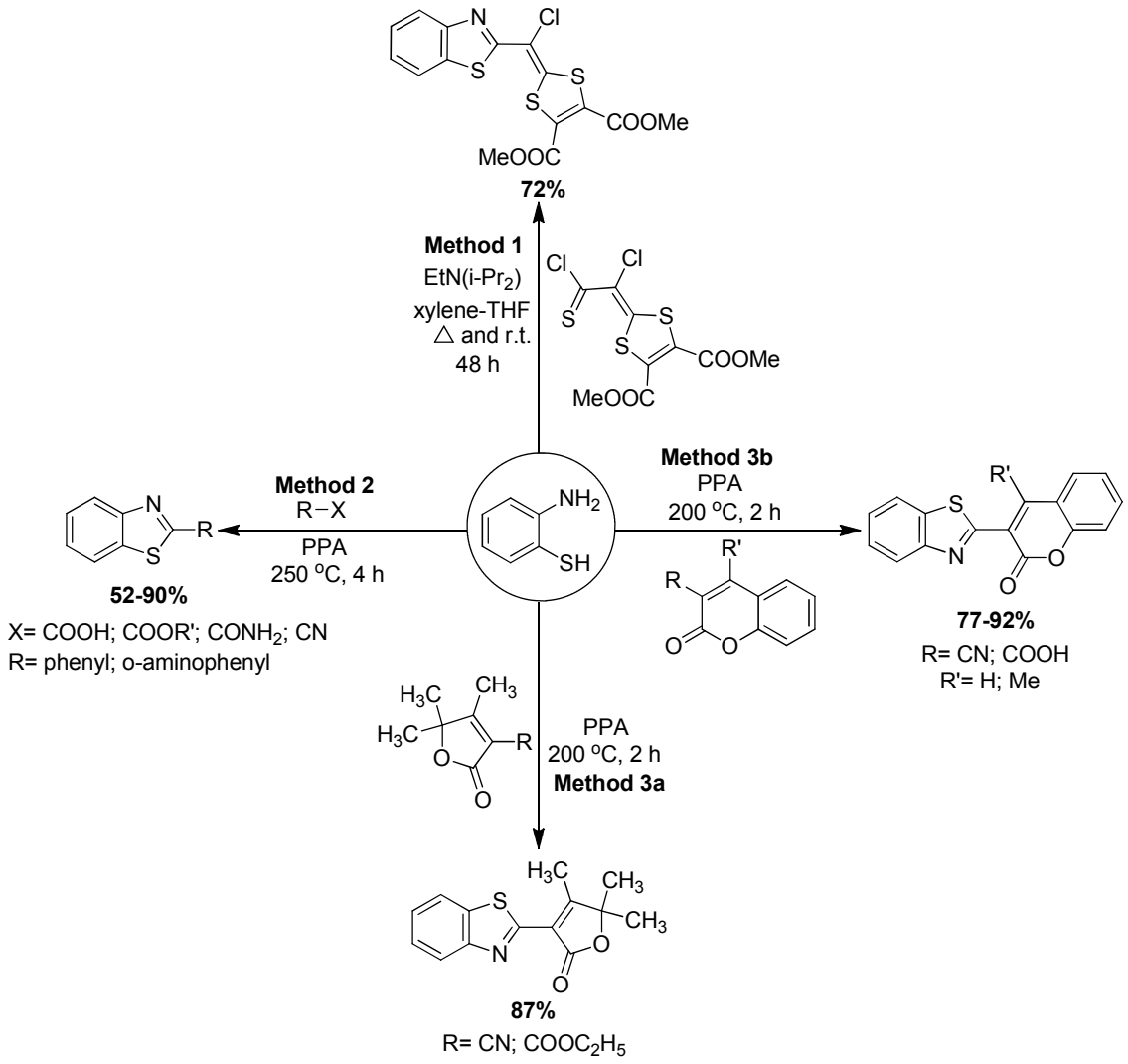
Scheme 47

2.1.10 Miscellaneous:

Ogurtsov et al. have noted that a 1,3-dipolar cycloaddition of 4,5-Dichloro-1,2-dithiole-3-thione in dimethyl acetylenedicarboxilate (DMAD) gave stable aliphatic thioacyl chloride, which is highly reactive towards nucleophiles such as *ortho*-substituted amines to afford benzothiazole derivatives of 1,3-dithioles in good yield **(Scheme 48, Method 1)**.[142] This new protocol for the synthesis of 2-substituted benzothiazole can be performed in one-pot at room temperature using 4,5-dichloro-1,2-dithiole-3-thione in a 3:1 mixture of xylene and tetrahydrofuran (THF) by adding DMAD and then heating with the corresponding *ortho*-substituted aniline without the isolation of thioacylchloride.

The formation of 2-aryl- and 2-alkyl-substituted benzothiazoles, benzimidazoles and benzoxazoles in excellent yield by polyphosphoricacid (PPA) catalyzed condensation of carboxylic acid, ester, amide or nitrile with an *ortho*-mercapto-, *ortho*-hydroxy- or *ortho*-amino-arylamine respectively has been examined by Hein and co-authors. **(Scheme 48, Method 2)**.[143]

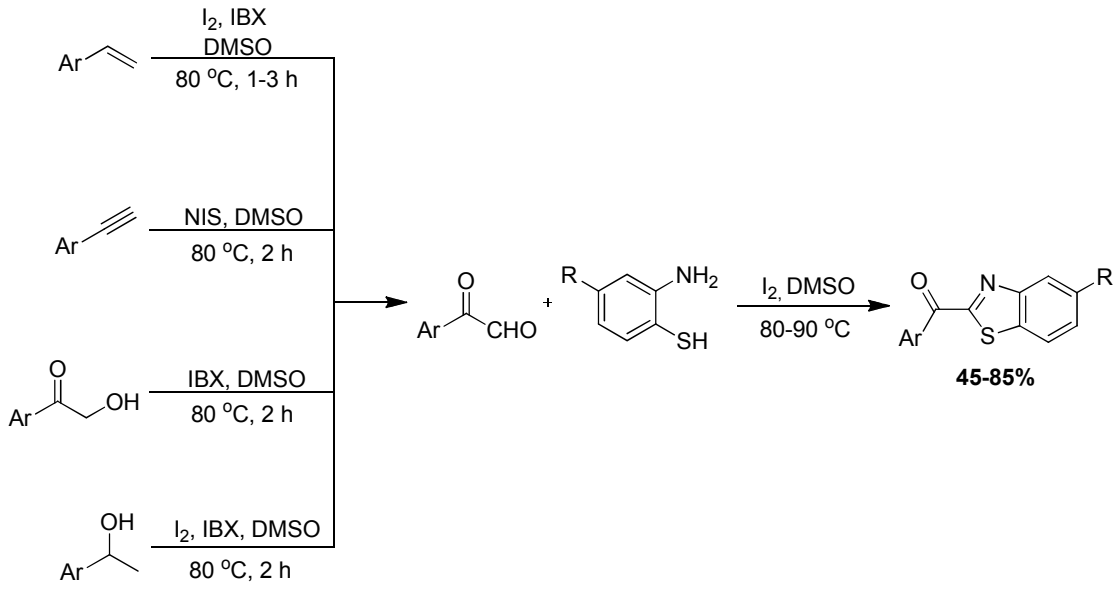
Substituted benzothiazole derivatives were synthesized using condensation reactions of γ-lactone and 3-carboxy- or 3-cyano-4-methylcoumarin derivatives with *ortho*-aminothiophenol at 200 ºC for 2 h using polyphosphoric acid (PPA) as a reagent was reported by Melikyan and co-workers **(Scheme 48, Method 3a-b)**.[144]



Scheme 48

A variety of 2-acylbenzothiazoles were synthesized using a multipathway coupled domino approach by Zhu et al. from multiform substrates arylethenes, arylacetylenes, 2-hydroxy-aromatic ketones and 1-arylethanol via four distinct pathways. They converted in to aryl substituted glyoxal *in situ*, which condensed with various *ortho*-aminothiophenol in one-pot metal-free reaction **(Scheme 49)**.[145] This synthetic approach embodied four specific reaction pathways. For optimisation of reaction conditions, the author have carried out this reaction in the presence of various oxidants and additives in dimethyl sulfoxide (DMSO). However, the excellent reaction conditions for this reaction turned out to be styrene (1.1 mmol) and *ortho*-aminobenzenethiol (1.2 mmol) using iodine/ *ortho*-iodobenzoic acid (I_2/ IBX, 2.0 mmol/ 1.5

mmol) in DMSO at 80 ºC. Arylethenes, 2-hydroxy-aromatic ketones and 1-arylethanol follow the same optimal procedure, but arylacetylenes occur in good yield using *N*-iodosuccinimide (NIS) as catalyst. In pursuance of the possible reaction mechanism, all four substrates are converted into phenacyl iodine through consecutive iodination and oxidation in I_2/ IBX or NIS, which is further converted to phenylglyoxal in DMSO. Finally, Phenylglyoxal reacted with *ortho*-aminothiophenol via condensation to afford the desired product.



R= H; Cl

Ar= Ph; 3-Me/4-MePh; 2,4-MePh; 2,6-MePh; 4-ClPh; 3-Br/4-BrPh; 4-FPh; 4-CNPh; 2-OMe/4-OMePh; 4-C_6H_5Ph; 4-tBu; 2-naphthalene

Scheme 49

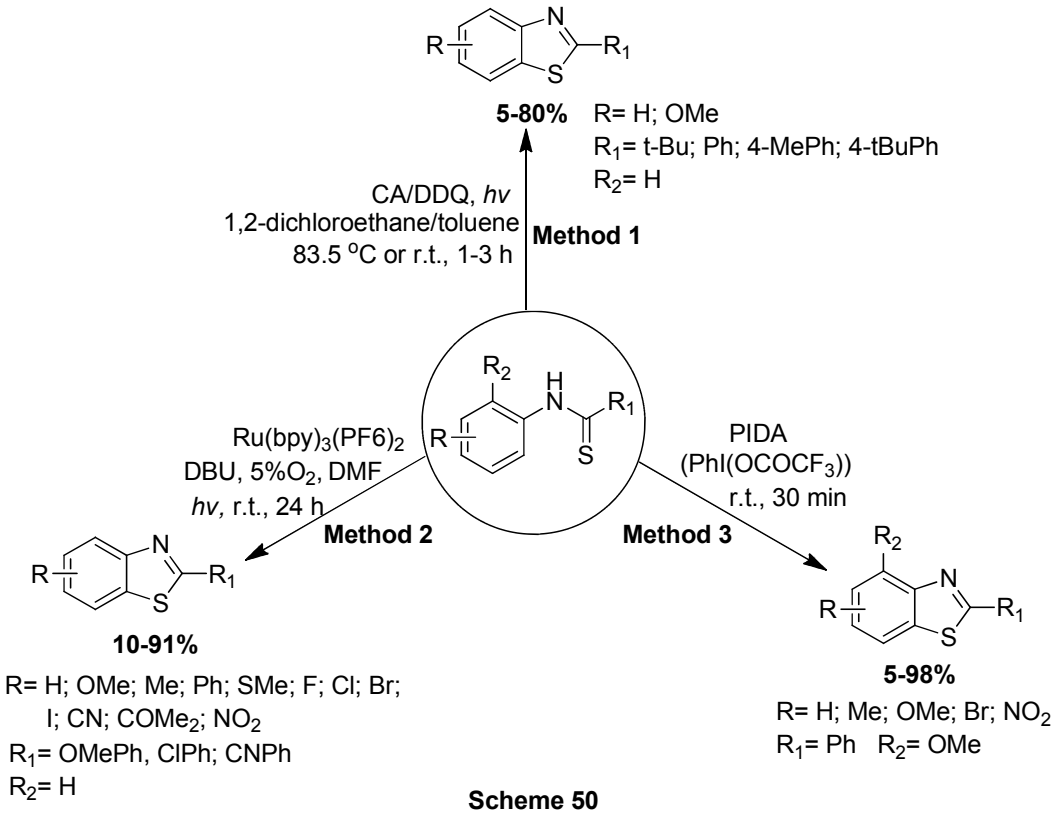
2.2 By cyclization reaction:

Wide range of derivatives of benzothiazole were synthesized by the cyclization of various substituted thioformanilides using different reagents and novel methods.

Rey and co-authors have investigated a simple and affordable methodology for the synthesis of 2-substituted benzothiazoles by the photochemical cyclization of thioformanilides propelled by chloranil under irradiation in 1,2-dichloroethane (DCE) and toluene at 80 ºC **(Scheme 50, Method 1)**.[146] The key step of the reaction mechanism was hydrogen atom abstraction from thiobenzamide by triplet chloranil.

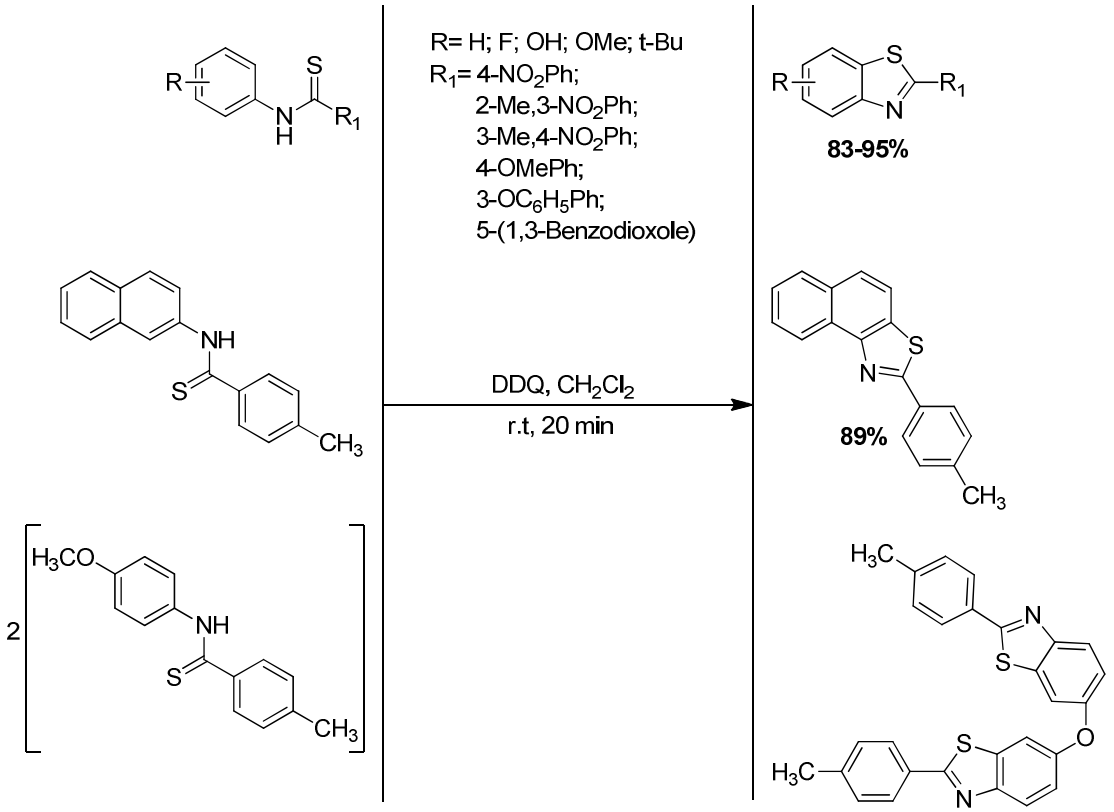
Another aerobic visible-light promoted photo redox catalytic formation of 2-substituted benzothiazoles have accomplished by Cheng et al. via radical cyclization of thioanilides without metal involvement except the sensitizer **(Scheme 50, Method 2)**.[147] Various catalyst and solvents were applied for optimization of the reaction conditions and the results shows that tris(bipyridine)ruthenium(II)hexafluorophosphate ($Ru(bpy)_3(PF_6)_2$) works as an optimal catalyst and *N,N*-dimethyl formamide (DMF) works as an optimal solvent for this new protocol. Visible-light as the reaction driving force, molecular oxygen as the terminal oxidant and water as the only by-product are the salient features of this protocol. Authors also have studied the intramolecular kinetics and proposed mechanism of this protocol.

Downer et al. have introduced a new and applicable protocol for the intramolecular cyclization of thiobenzamides to benzothiazoles through the aryl radical cations as reactive intermediates **(Scheme 50, Method 3)**.[148] The protocol uses phenyliodine(III)bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile to enhance the cyclization within 30 min at room temperature, which afforded moderate yield of the products.



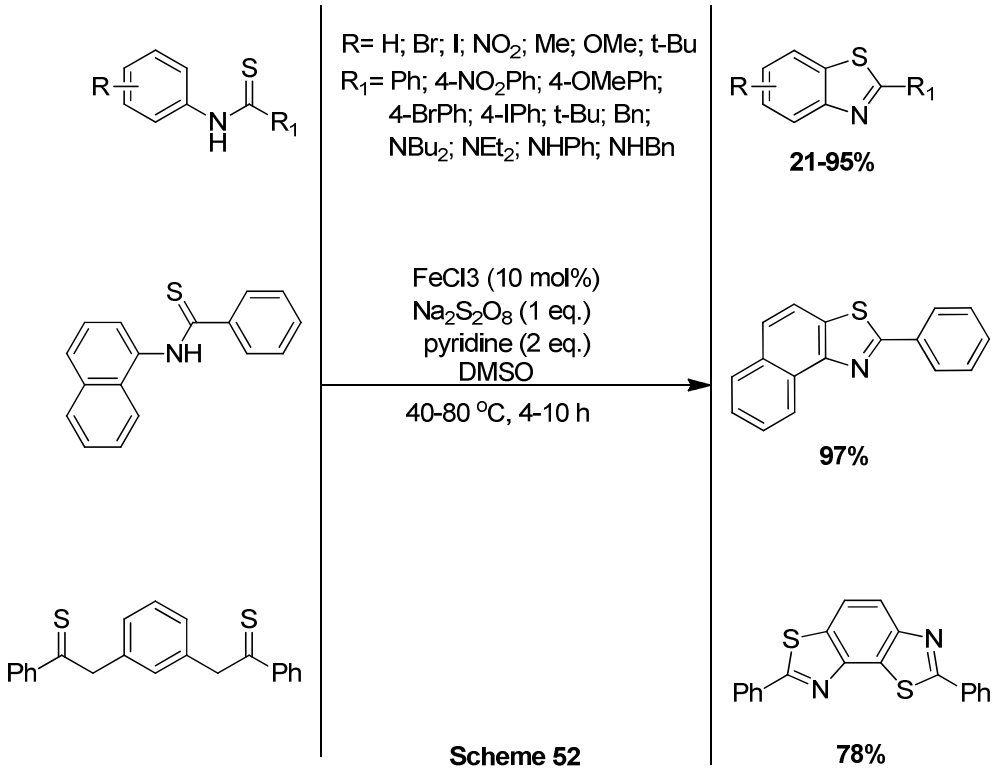
Scheme 50

Bose et al. have introduced a new, practical and highly efficient route for the one step conversion of thioformanilides to 2-substituted benzothiazoles in high yield with selectivity by applying 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as catalyst and dichloromethane (DCM) as a solvent at room temperature **(Scheme 51)**.[149] This protocol also follows the 1,5-homolytic radical cyclisation of thiyl radical to give 2-arylbenzothiazoles. 2-(*p*-tolyl)naphthothiazole has been also synthesized in moderate yield from 4-methyl-*N*-(naphthalen-2-yl)benzothioamide using this protocol.



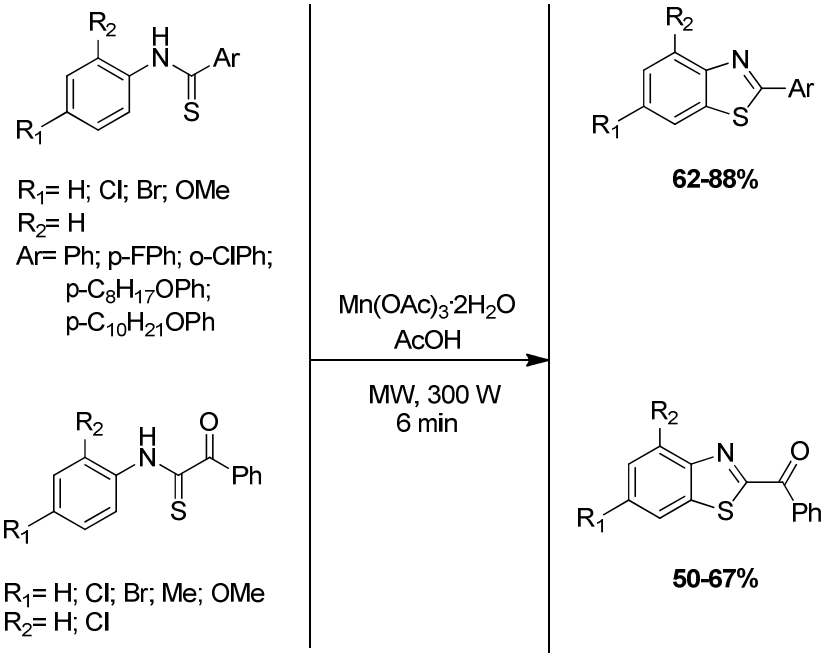
Scheme 51

An efficient and transition metal catalysed intramolecular cyclization for synthesis of benzothiazole derivatives using $Na_2S_2O_8$ as the oxidant in dimethylsulfoxide (DMSO) with 10% $FeCl_3$ as the catalyst and pyridine as the additive at 80 ºC was developed by Wang and co-authors **(Scheme 52)**.[150] Preliminary mechanistic studies shows that the pyridine played a significant role for the high yields and selectivity of the products. According to possible reaction mechanism, the thioyl radical intermediate was formed when the *N*-phenyl benzothioamide was oxidized by Fe(III), meanwhile Fe(III) was reduced to Fe(II). The thioyl radical intermediate was cyclised and oxidised in the presence of $Na_2S_2O_8$ to give the product 2-phenyl benzothiazole.



Scheme 52

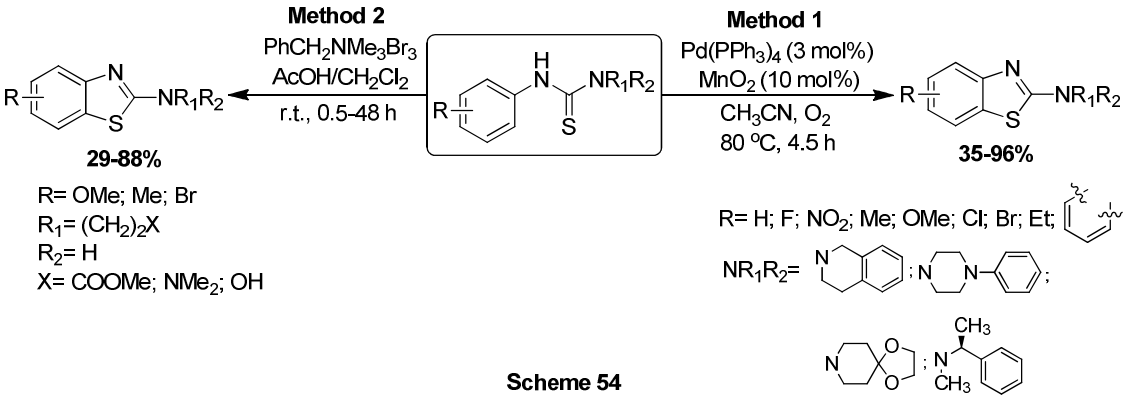
Mu and co-authors have developed highly efficient method for the preparation of 2-benzoyl-benzothiazoles and 2-arylbenzothiazoles using manganese(III)triacetate ($Mn(OAc)_3$) promoted radical cyclization of benzoylthioformanilides and arylthioformanilides under microwave irradiation (MWI) **(Scheme 53)**.[151] Here, $Mn(OAc)_3$ is introduced as a new reagent to replace potassium ferricyanide ($K_3[Fe(CN)_6]$) or bromine (Br_2), which are generally used for the radical cyclization of substituted thioformanilides.



Scheme 53

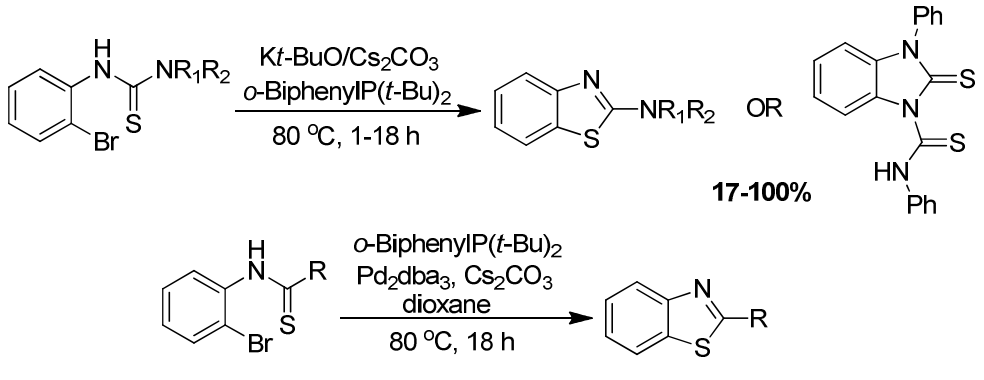
Joyse et al. have investigated the synthesis of 2-aminobenzothiazoles from *N*-Arylthioureas, via intramolecular C-S bond formation/ C-H functionalization by employing an unusual co-catalytic $Pd(PPh_3)_4$/ MnO_2 system under an oxygen atmosphere at 80 ºC, which afforded excellent yield of the products **(Scheme 54, Method 1)**.[152] The chemoselective cyclization of substrates suggest that the reaction is very sensitive to steric effects at the *ortho*-position next to the C-H bond functionalization.

Jordan have developed one-pot synthesis of 2-aminobenzothiazoles from either aryl isothiocyanates and amines or tetrabutylammonium thiocyanate and anilines in the presence of a stoichiometric amount of $PhCH_2N(Me)_3(Br_3)$, which afforded excellent yield of the products **(Scheme 54, Method 2)**.[153] Here, $PhCH_2N(Me)_3(Br_3)$ is a stable, electrophilic bromine source for the conversion of substituted arylthioureas to 2-aminobenzothiazoles under mild conditions in a variety of solvents with good yields.



Scheme 54

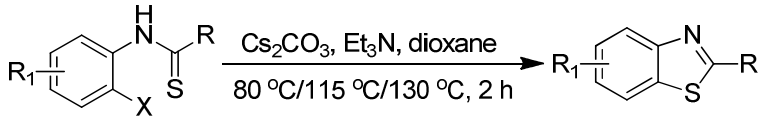
Benedi and co-authors investigated a direct and efficient procedure for the synthesis of 2-amino- and 2-alkyl-benzothiazoles by cyclization of *ortho*-bromophenylthioureas and *ortho*-bromophenylthiamides in the presence of Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$)/ monophosphine catalyst **(Scheme 55)**.[154] Authors have also studied the effect of various ligands on the reaction, such as monophosphine (1,1'-bis(diphenylphosphino)ferrocene(dppf)), monophosphine (o-biphenylP(t-Bu)$_2$) and n-BuPAd$_2$, however highly hindered alkyl monophosphines has proved to be the most efficient ligand for this transformation.



Scheme 55

Feng et al. have developed an efficient, economical, convenient and a novel protocol for the synthesis of 2-substituted benzothiazoles from the *N'*-substituted-*N*-(2-halophenyl)thioureas, *O'*-substituted-*N*-(2-halophenyl)carbamothioates, or *N*-(2-halophenyl)thioamides through a

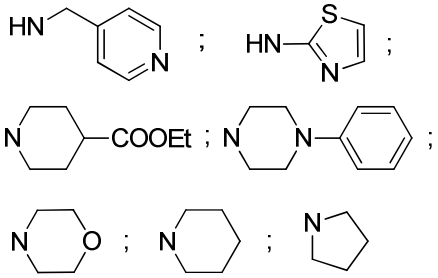
base-promoted intramolecular C-S bond coupling cyclization in dioxane without the use of any transition metal afforded high yield of the product **(Scheme 56)**.[155] To optimize the reaction conditions, author have studied the effect of various solvent and base on this reaction, however the best results were obtained by using Cs_2CO_3 as a base, dioxane as a solvent at 100-140 ºC temperature for this reaction.



X= I; Br
R= Ph; CH_2Ph; C_6H_{12}; NR_1R_2; OR_3
R_1= H; F; Cl; OMe; CF_3

OR_3= OMe; OCH_2Me; OCH_2Ph; $O(CH_2)_2C{\equiv}CH$

NR_1R_2= $NHCH_2Ph$; $NHCH_2$(2-OMe/3-OMe/4-OMe)Ph; $NHCH_2$(3-CF_3)Ph; $NHCH_2$(4-F)Ph; NHPh; $NH(CH_2)_3Me$; $N(CH_2Me)_2$;



Scheme 56

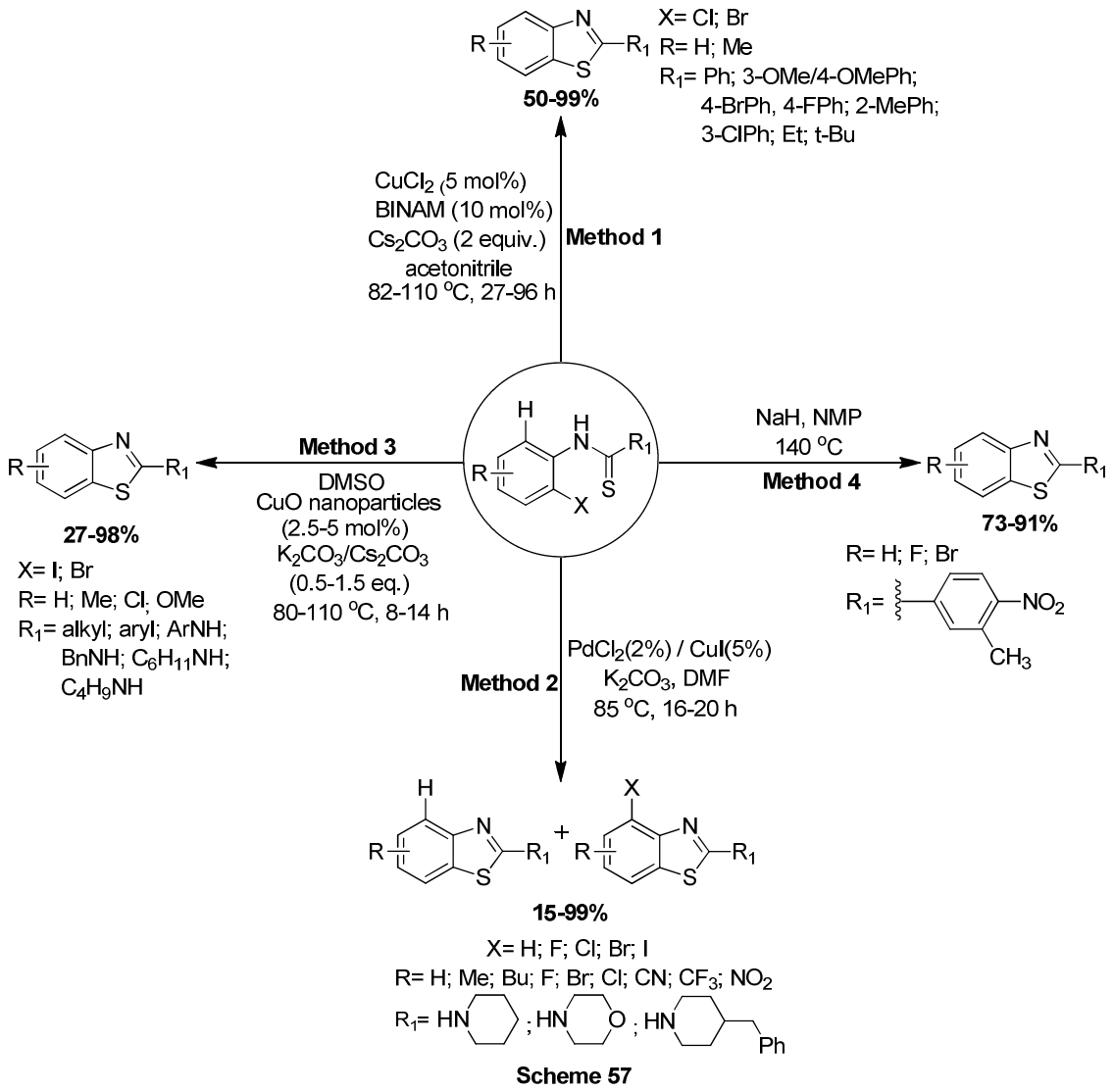
Jaseer et al. pointed out 1,1'-binaphthyl-2,2'-diamine (BINAM)-Cu(II) complex as a competent catalyst for the preparation of a broad range of 2-aryl/alkyl-substituted benzothiazoles by intramolecular C-S bond forming cyclization of poorly reactive *N*-(2-chlorophenyl)benzo or alkyl-thioamide under mild reaction conditions in the presence of acetonitrile at 82-110 ºC for 27-96 h **(Scheme 57, Method 1)**.[156]

A regioselective intramolecular C-S bond formation was indicated by Sahoo and colleagues during the formation of 2-aminobenzothiazoles from *ortho*-halothioureas using both Cu(I) and Pd(II) transition metal as a catalyst **(Scheme 57, Method 2)**.[157] Authors have noted that Cu preferred a dehalogenative way and Pd preferred predominantly C-H activation way for the creation of 2-aminobenzothiazoles. Here, Pd favoured C-H activation and Cu was unreactive in the absence of 2-chloro and 2-fluoro groups. However, for 2-bromo and 2-iodo

aryl thioureas, identical selectivity was observed for both Cu- and Pd-catalyzed methods. Wide range of substituted derivatives were developed by this protocol which shows its wide synthetic utility.

Saha and colleagues have found a simple, general and efficient synthesis of substituted 2-aminobenzothiazoles via intramolecular cyclization of *ortho*-bromoaryl derivatives using copper(II)oxide nanoparticles as a catalyst in dimethyl sulfoxide (DMSO) solvent without the additional external chelating ligands to afford high yield of the products **(Scheme 57, Method 3)**.[158] It is a heterogeneous process so the catalyst can be recovered and recycled without the loss of activity and selectivity of this methodology.

Hutchinson and colleagues have presented the regiospecific synthesis of a library of substituted 2-arylbenzothiazoles in the presence of sodium hydride (NaH) and *N*-Methyl-2-pyrrolidone (NMP) at 140 ºC from *ortho*-bromothiobenzanildes in excellent yield **(Scheme 57, Method 4)**.[159] In this method a bromine atom, existed *ortho* to the anilido nitrogen, which was used to direct a regiospecific cyclisation but in the absence of bromine atom the mixture of regioisomers is appear. This protocol is applicable to the synthesis of 2-arylbenzothiazoles having both electron-withdrawing and electron-donating substituents on the aryl ring.



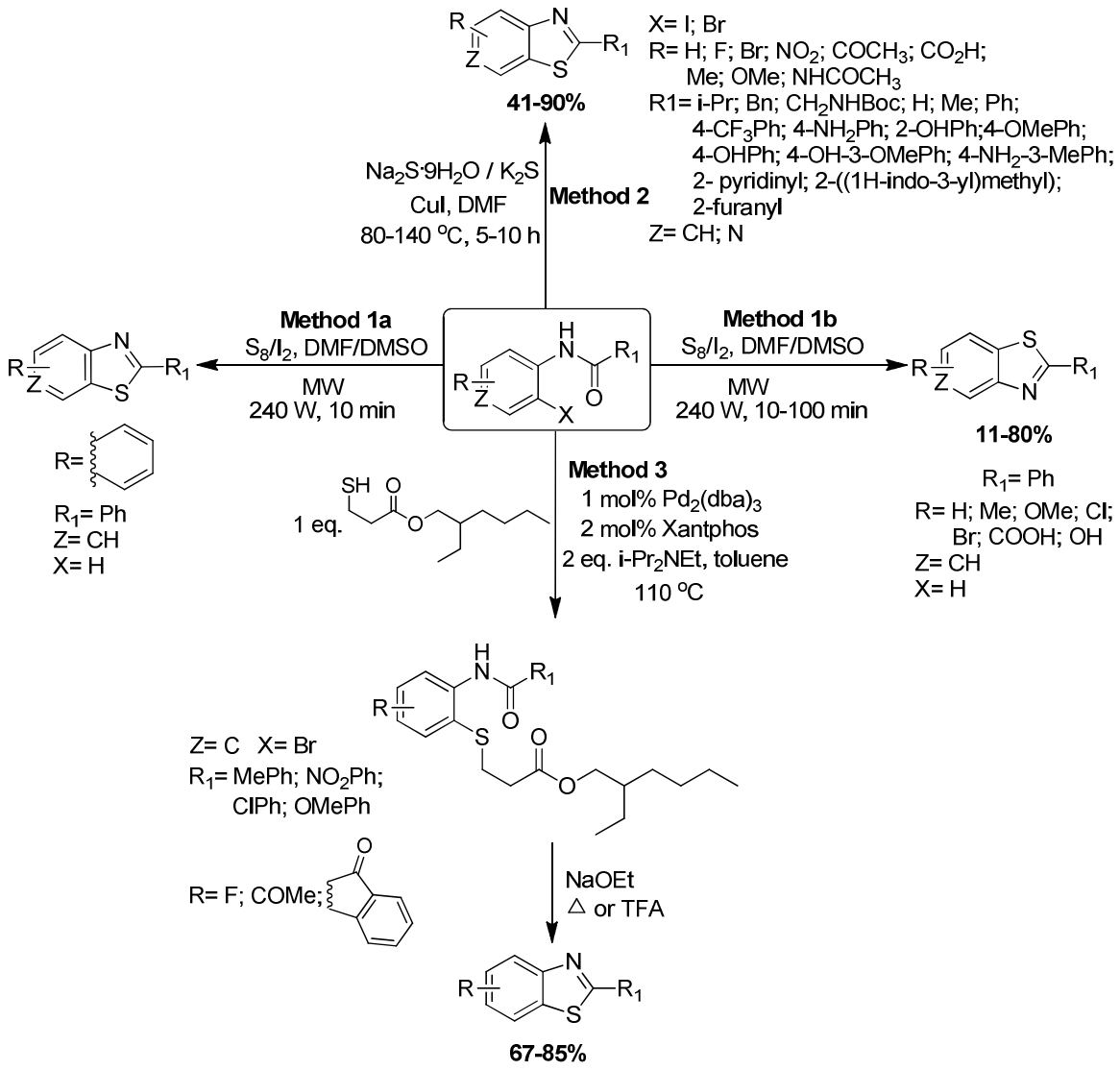
Scheme 57

Pal et al. have found a new and easy protocol for the preparation of 2-phenylbenzothiazole from benzanilide by direct thiation under microwave irradiation (MWI) in the presence of catalytic amount of iodine (I_2) afforded moderate to good yields **(Scheme 58, Method 1a-b)**.[160] This reaction was carried out in various solvents and also under solvent-free conditions but the best result was obtained using dimethylformamide (DMF) as a solvent, in terms of yield of the product and time of the reaction. This method has considered as a wide synthetic utility because of a variety of the benzoates of aromatic amines were employed with unsubstituted *ortho*-positions in this protocol. Experimental addition of a small amount of formic acid (HCOOH) gave increasing results, even if the reaction in formic acid as solvent

was unsuccessful. For this reaction, authors have discussed two probable mechanism path way. First is it may involve [4 + 2] cycloaddition of the iminol intermediate tautomer of benzoate and second is it may proceed via the electrophilic attack of sulfur at C-2 of benzoate as the mechanism of the Willgerodt–Kindler reaction.

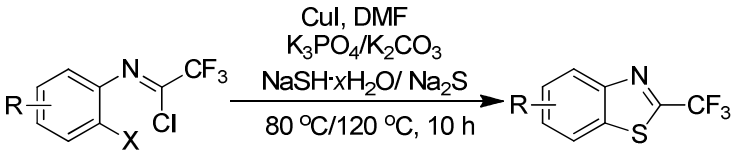
An efficient and economical access to substituted benzothiazoles have introduced by Ma et al. using copper-catalyzed (CuI/ L-proline) coupling of *ortho*-haloanilides with metal sulphides ($Na_2S{\cdot}9H_2O_2$) in *N,N*-dimethylformamide (DMF) as a solvent with excellent yields of products **(Scheme 58, Method 2)**.[161]

Various *ortho*-bromobenzanilides were successfully converted into the corresponding benzothiazoles using a novel protocol, in which C–S bond formation occurred with the mercaptopropionate surrogate with pd/ xantphos catalytic system followed by sequential deprotection and condensation, have demonstrated by Mase and co-authors **(Scheme 58, Method 3)**.[162] Preliminary study for the preparation of sulfide, authors approved the reaction of *ortho*-bromoacetanilide with the mercaptopropionate surrogate catalysed by $Pd_2(dba)_3$/ xantphos system to afford the corresponding sulfide in good yield, which was further treated with sodium ethoxide (NaOEt) in ethanol (EtOH) at room temperature to procedure the sodium thiolate trailed by heating at reflux to give 2-methylbenzothiazole in 82% yield.



Scheme 58

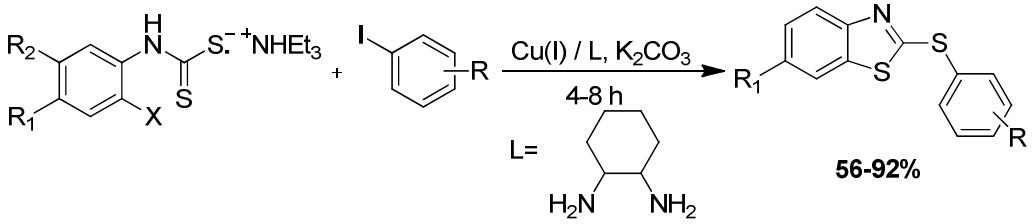
Copper-catalyzed double thiolation reaction of 1,4-dihalides with sulfides have suggested by Li et al. for selective synthesis of 2-trifluoromethyl benzothiazoles **(Scheme 59)**.[163] The thiolation annulation of a variety of *N*-(2-haloaryl)trifluoroacetimidoyl chlorides smoothly undergo in the presence of CuI with sodium hydrosulfide hydrate (NaHS) and potassium phosphate (K_3PO_4), to afford 2-trifluoromethylbenzothiazoles in moderate to good yields.



X= I; Br; Cl
R= H; Me; F; CF_3; NO_2; Cl

Scheme 59

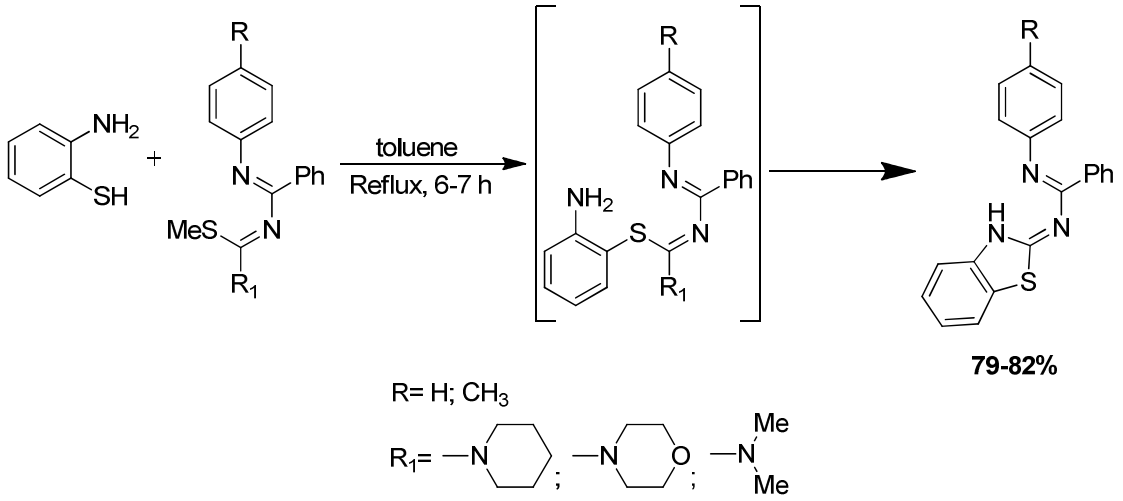
Murru and co-workers have developed the direct synthesis of arylthiobenzothiazoles via Cu(I) catalysed sequential intra- and intermolecular S-arylations in presence of dimethyl sulfoxide (DMSO) solvent **(Scheme 60)**.[164] This protocol is superior to all reported methods for the preparation of the arylthiobenzothiazole due to low catalyst loading, inexpensive metal catalyst and ligand, lower reaction temperature and shorter reaction time.



X= I; Br
R_1= H; Me; Cl; Br; OMe;
R_2= H; Me
R= H; Me; OMe; NO_2; NHAc; Cl; COOMe

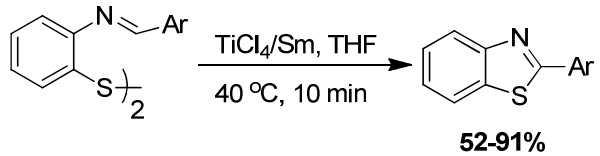
Scheme 60

Jayakumar et al. have examined the reaction of *ortho*-aminothiophenol with various substituted 1,3-diazabuta-1,3-dienes(4-tertiaryamino-4-methylthio-1,3diazabuta-1,3-dienes) under reflux condition in dry toluene to afford *N*-benzothiazol-2-yl-*N'*-aryl benzamidines in good yields **(Scheme 61)**.[165]



Scheme 61

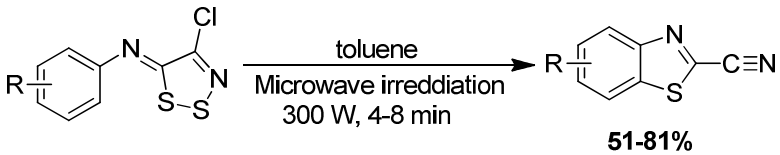
Shi et al. have found the novel reductive cyclization of bis-(2-benzalaminophenyl)disulfide promoted by the titanium tetrachloride ($TiCl_4$)/ samarium (Sm) system using tetrahydrofuran (THF) as a solvent for the synthesis of 2-arylbenzothiazole derivatives in good yields **(Scheme 62)**.[166] Low-valent titanium was prepared from titanium tetrachloride and samarium powder. Various low-valent titanium reagent system were surveyed by the authors. According to the results, $TiCl_4$/ Sm shows the best activity as a reductive reagent among those surveyed. Moreover, investigation of the reaction conditions disclosed that a 1:2 ratio of $TiCl_4$ and Sm at 40 ºC gave better results than those having the other reaction conditions. The advantages of this new method are the easily accessible starting materials, short reaction time and moderate to good yields. Here, Bis-(2-benzalaminophenyl)disulfide was reduced by Ti(0), then the nucleophilic attack of S^- negative ion on C=N group to give cyclized intermediate and after that aromatization gives the expected product 2-arylbenzothiazole.



Ar= Ph; 4-MePh; 4-OMePh; 3,4-OMePh; 3,4,5-OMePh; 4-ClPh; 4-BrPh; 3,4-ClPh; 4-N(Me)$_2$Ph; 2-thiophene; 5-(1,3-benzodioxole)

Scheme 62

Beneteau et al. have noted that the 2-cyanobenzothiazoles can be prepared rapidly by applying microwave irradiation (MWI) (300W) on neat *N*-arylimino-1,2,3-dithiazoles in screw capped glass vials using apple's salt for 4 to 8 min with good yield **(Scheme 63)**.[167] Here, no reaction was observed, when the irradiations were carried out in open vessel. Comparison of the preparation of 2-cyanobenzothiazoles by thermolysis procedure and MWI procedure was recorded by authors. However, they concluded that the best procedure for the preparation of 2-cyanobenzothiazoles is under microwave irradiation, which allows a striking reduction in reaction time.

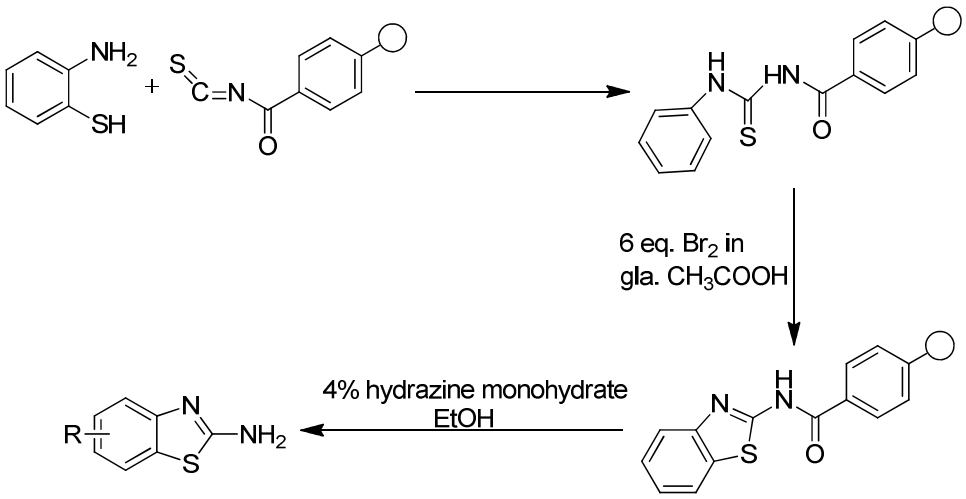


51-81%

R= H; OMe; F

Scheme 63

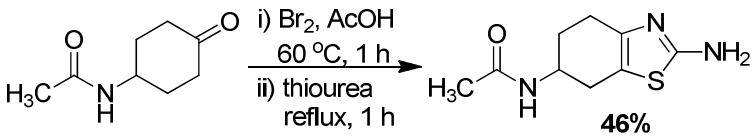
Piscitelli et al. have synthesized various substituted 2-aminobenzothiazole by solid supported novation, using resin bounded isothiocyanate and various aniline derivatives **(Scheme 64)**.[168] The resin bounded isothiocynate were converted to *N*-acyl or *N*-phenyl thioureas which cyclized to 2-acyl aminobenzothiazole by the treatment of 6 equiv. of bromine in acetic acid. Finally the desired compounds were obtained by treatment of 2-acyl aminobenzothiazole with 4% hydrazine monohydrate in ethanol (EtOH).



Scheme 64

2.3 Using bromine as a catalyst:

Schneider and colleagues have developed an efficient protocol for the preparation of 2,6-diamino tetrahydrobenzothiazole from 4-acetamidocyclohexane by brominating it in acetic acid (AcOH) and immediately treated with thiourea to give the acetamido thiazole derivative in good yield **(Scheme 65)**.[169]



Scheme 65

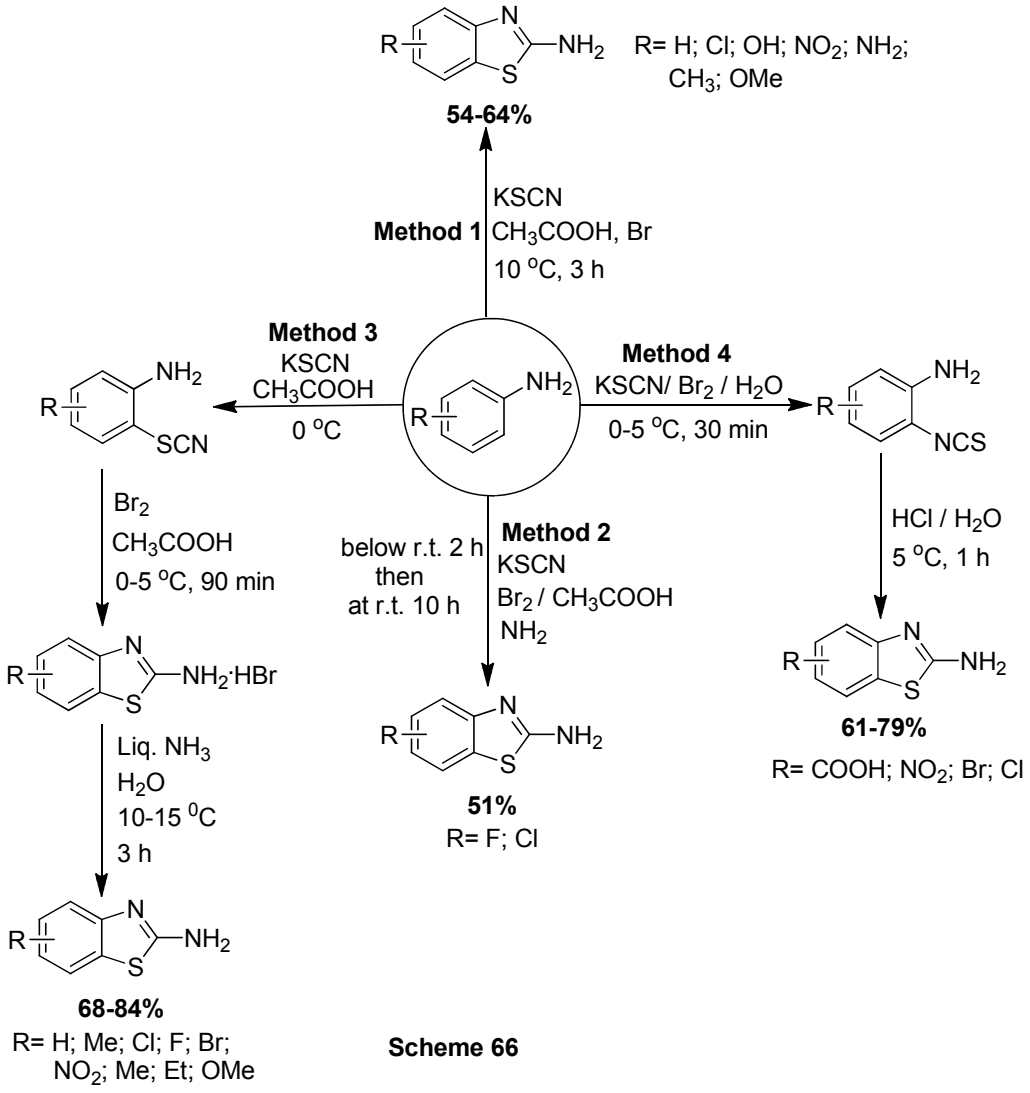
2.3.1 Using KSCN (potassium thiocyanate):

Desmukh et al. have recorded the synthesis of *N*-substituted-1,3-benzothiazol-2-amine by the reaction of substituted aniline and potassium thiocyanate (KSCN) in the presence of glacial acetic acid and bromine (gla.CH_3COOH/ Br_2) at the temperature below 10 ºC for 3-4, which afforded good to excellent yields of the products **(Scheme 66, Method 1)**.[170]

Singh and co-workers have synthesized the novel 2-amino-7-chloro-6-fluorobenzothiazole from 3-chloro-4-fluoroaniline and potassium thiocyanate (KSCN) in the presence of bromine (Br_2) inglacial acetic acid (gla.CH_3COOH/ Br_2) followed by the basification with ammonia using the standard procedure **(Scheme 66, Method 2)**.[171]

A series of 2-amino-substituted benzothiazoles were synthesized from the various substituted anilines by Himaja et al. utilizing potassium thiocyanate (KSCN) in the presence of bromine/ glacial acetic acid (gla.CH_3COOH/ Br_2) **(Scheme 66, Method 3)**.[171]

Synthesis of various novel derivatives of 2-substituted-benzothiazole using potassium thiocyanate (KSCN) in presence of gla. aceticacid and different substituted anilines have reported by Malik et al. **(Scheme 66, Method 4)**.[172]



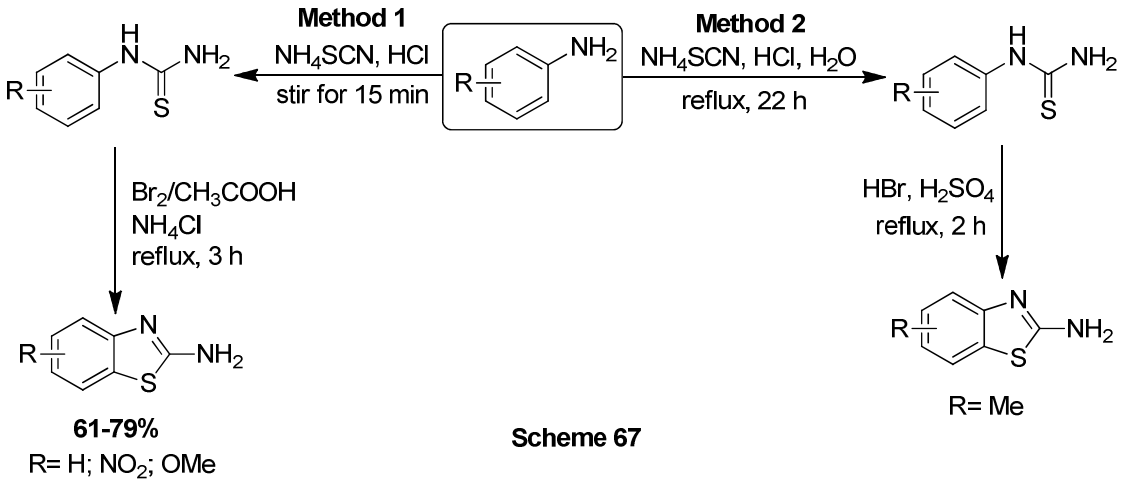
Scheme 66

2.3.2 Using NH_4SCN (ammonium thiocyanate):

Manju thej TR et al. have proposed the synthesis of 2-aminobenzothiazoles using equimolar quantities of substituted aniline and ammonium thiocyanate (NH_4SCN) in ethanol (EtOH)

containing few ml of conc. hydrochloric acid (conc. HCl) and then it was treated with bromine (Br_2) in glacial acetic (gla. CH_3COOH) acid for 3 h with good yields of the products **(Scheme 67, Method 1)**.[173]

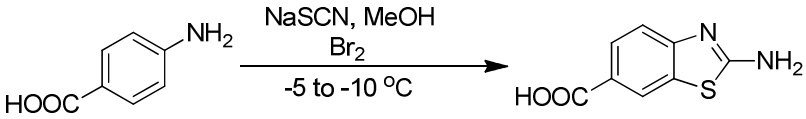
Alang and colleagues have indicated the synthesis of new derivative 2-amino-6-methylbenzothiazole in two steps by the reaction of *para*-toluidine with ammonium thiocyanate (NH_4SCN) refluxing in HCl/ H_2O for 22 h afforded *para*-tolylthiourea in excellent yield, which was further reacted with HBr and H_2SO_4 to produce 2-amino-6-methylbenzothiazole **(Scheme 67, Method 2)**.[174]



Scheme 67

2.3.3 Using NaSCN (sodium thiocyanate):

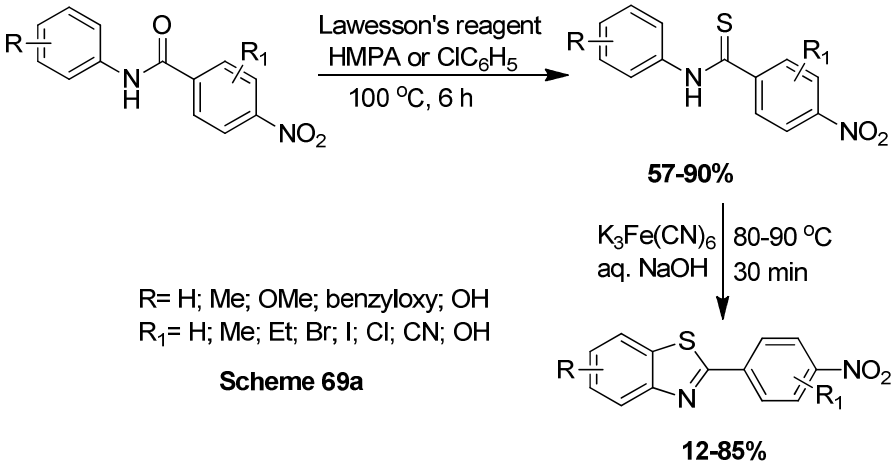
Chow et al. have synthesized 2-amino-6-carboxybenzothiazole by reacting *para*-aminobenzoicacid (PABA) with sodium thiocyanate (NaSCN) and Br_2 in methanol (MeOH) as a solvent **(Scheme 68)**.[175]



Scheme 68

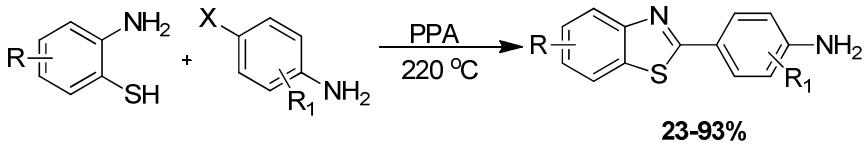
2.4 Using Lawesson's reagent and $K_3Fe(CN)_6$:

A new library of 2-(4-aminophenyl)benzothiazoles were synthesized by Shi et al. using Lawesson's reagent in hexamethylphosphoramide (HMPA) or chlorobenzene (ClC_6H_5) followed by the treatment of potassium ferricyanide ($K_3[Fe(CN)_6]$) in aq. sodium hydroxide at 80-90 ºC, which afforded excellent yield of the products **(Scheme 69a)**.[176]



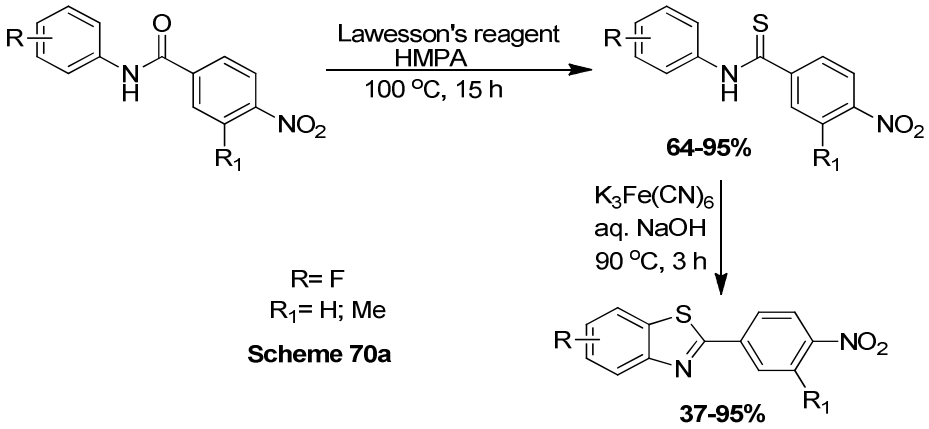
Scheme 69a

Authors have also synthesized the new library of benzothiazole using suitable methods for each benzothiazole moiety **(Scheme 69b)**.[176]



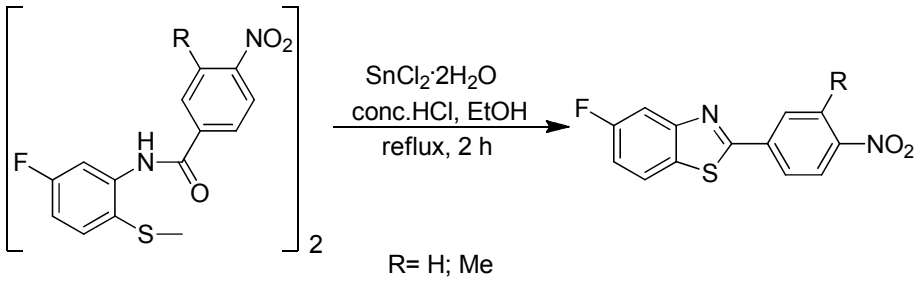
Scheme 69b

Different methods were used to synthesize different derivatives of mono- and difluorinated 2-(4-nitro-3-substituted phenyl)benzothiazoles by Hutchinson et al. **(Scheme 70a-d)**.[12]



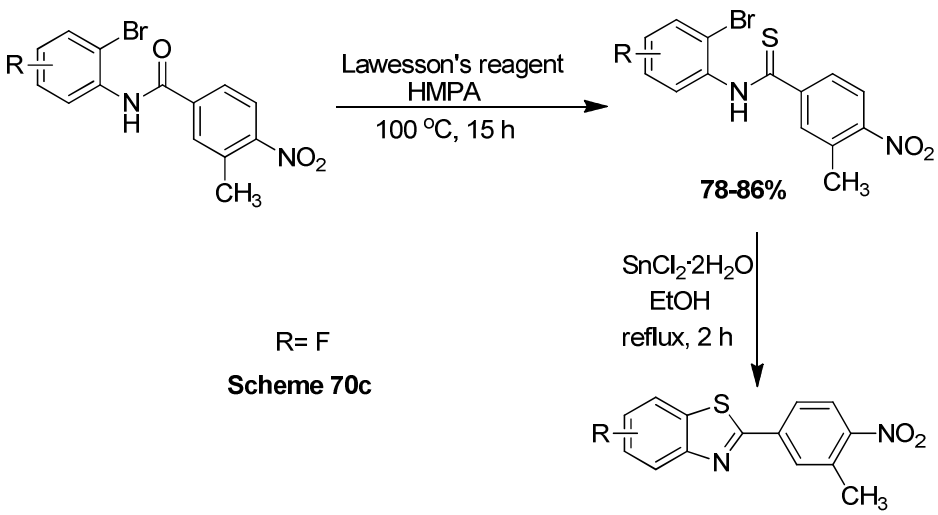
R= F
R_1= H; Me

Scheme 70a



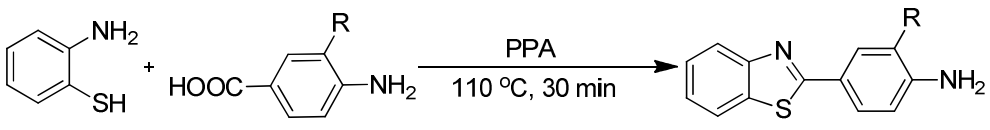
R= H; Me

Scheme 70b



R= F

Scheme 70c



R= F; CF_3

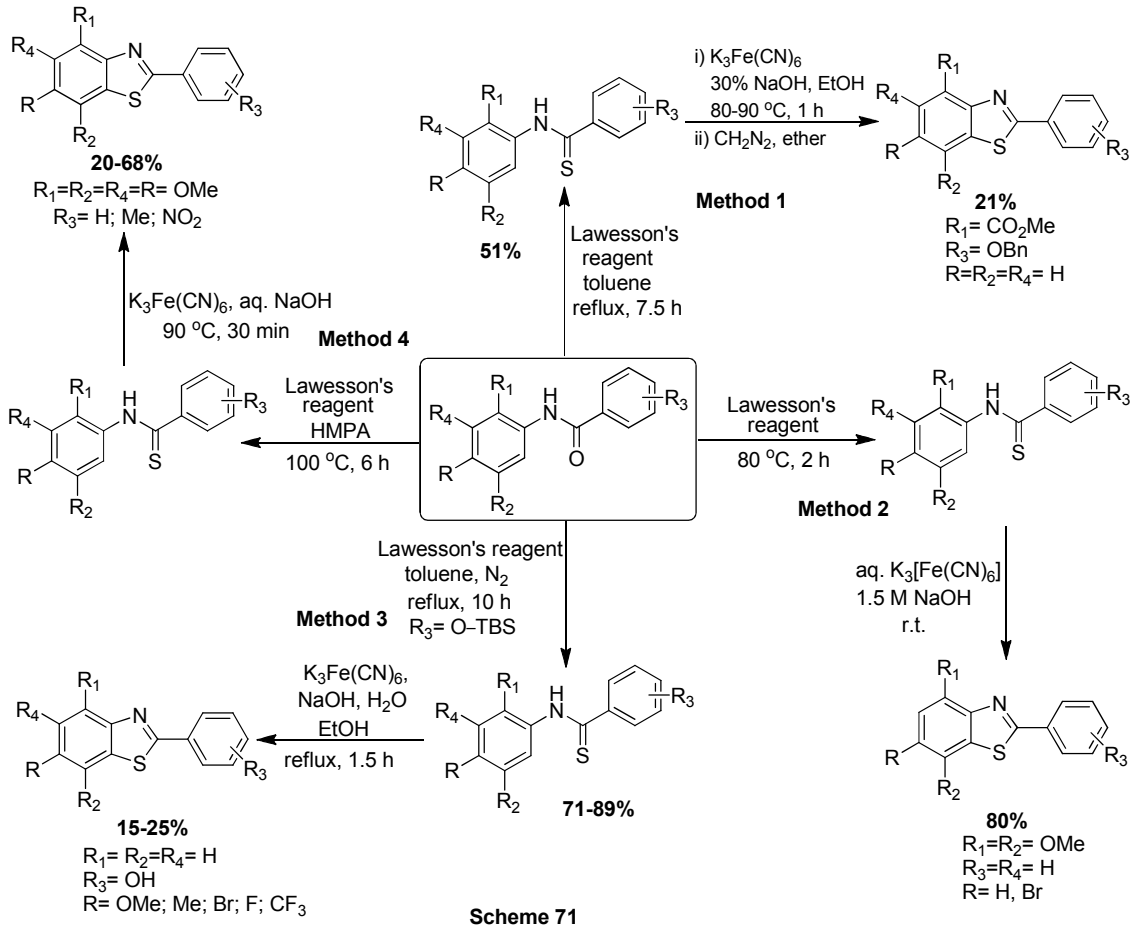
Scheme 70d

Huang et al. have report the new benzothiazole derivative using the same method as Shi et al. **(Scheme 71, Method 1)**.[177]

Lyon and co-workers have also synthesized the substituted 2-phenylbenzothiazole using the method discussed above **(Scheme 71, Method 2)**.[178]

Some other derivatives of 2-(6-substituted-benzothiazol-2-yl)phenol were synthesized by Wang and colleagues from various substituted anilines and *ortho*-hydroxybenzoicacid by the method described above **(Scheme 71, Method 3)**.[179]

Kashiyama and co-authors have synthesized the series of 2-phenyl-1,3-benzothiazole from *N*-phenylbenzamide using Lawesson's reagent and Potassium ferricyanide ($K_3[Fe(CN)_6]$) **(Scheme 71, Method 4)**.[28]

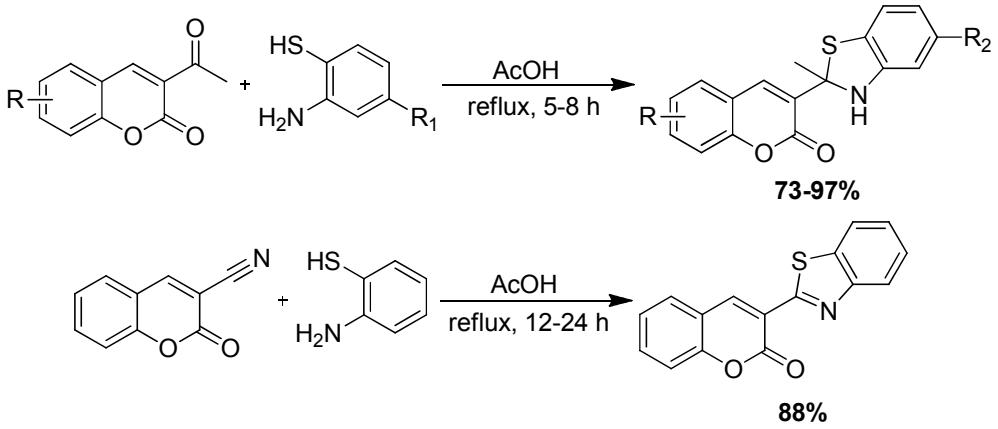


Scheme 71

2.5 From coumarin :

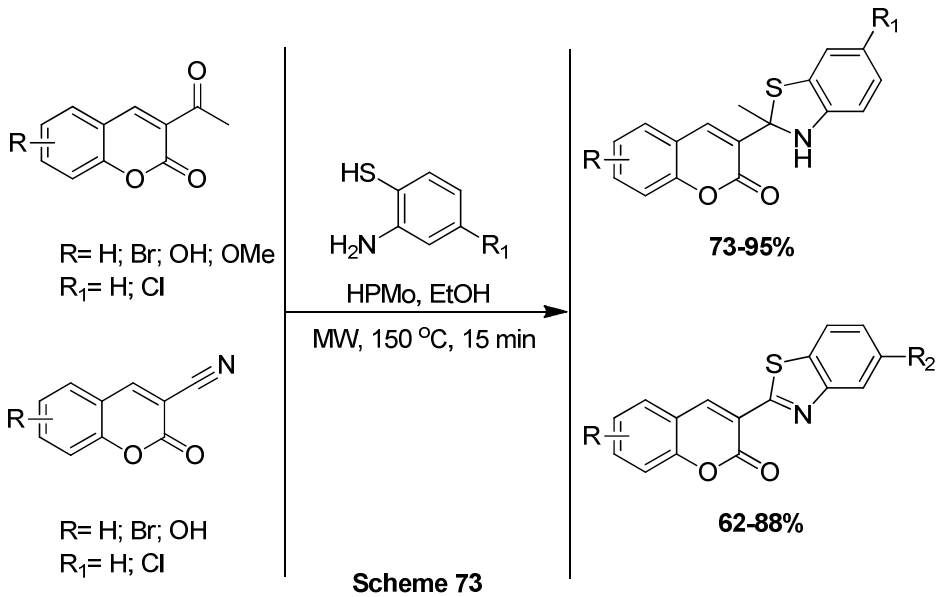
The synthesis of a series of coumarin derivatives containing 2-methylbenzothiazoline moiety and related compounds have prepared by Khoobi and co-workers via the reaction of 3-

acetylcoumarins with *ortho*-aminothiophenol derivatives in the presence of acetic acid (AcOH) under reflux conditions **(Scheme 72)**.[180] Some of these coumarin derivatives have synthesized by the reaction of 3-cyanocoumarin with *ortho*-aminothiophenol using the same reaction conditions.



Scheme 72

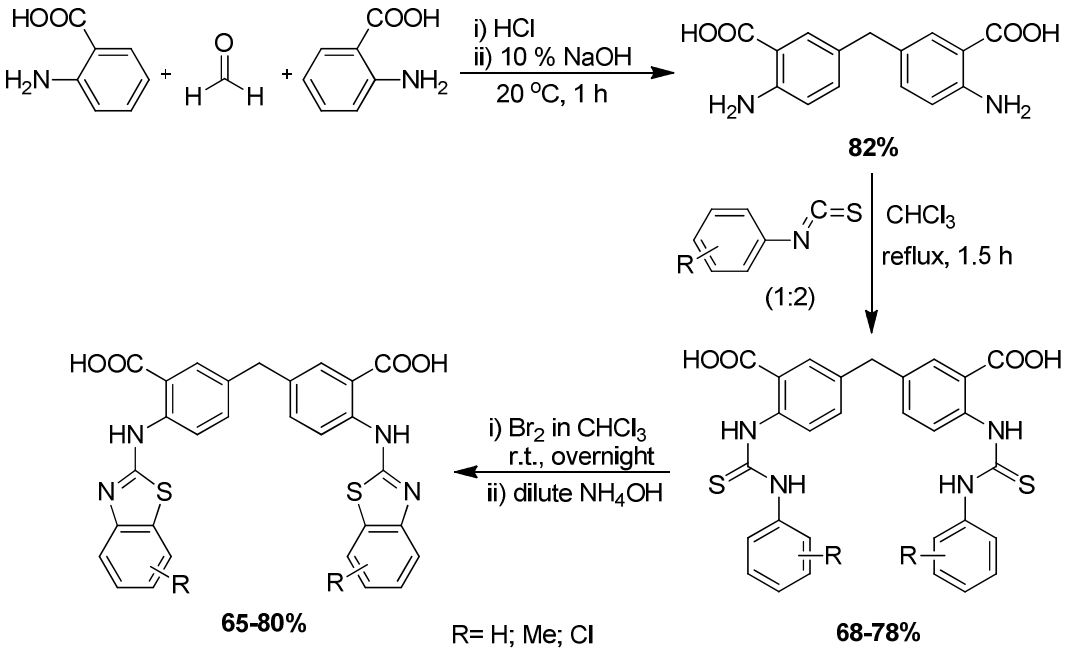
Khoobi et al. have introduced a rapid, simple and convenient microwave-assisted protocol for the synthesis of 3-substituted coumarin derivatives by the reaction of 3-acetyl and 3-cyanocoumarins with *ortho*-aminothiophenol derivatives in the presence of acetic acid (AcOH) or catalytic amount of the HPMo in good to excellent isolated yields **(Scheme 73)**.[181] Generality, simplicity, easy work up, clean reactions and improved yields are the beneficial points of this methodology.



Scheme 73

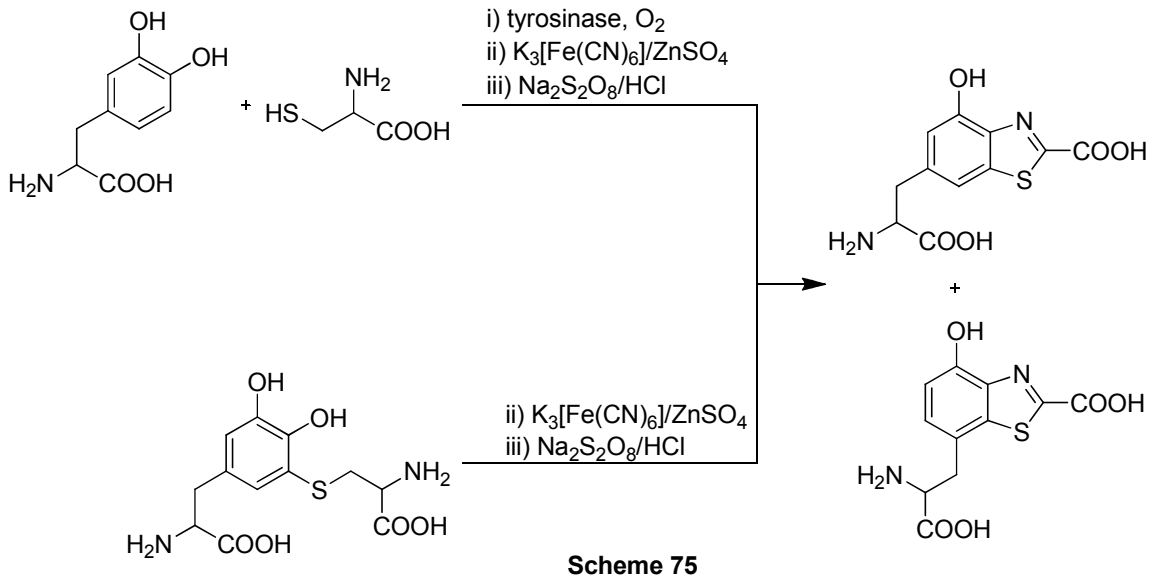
2.6 Miscellaneous:

Deohate have investigated a novel series of {4-[4-(6-substituted-benzothiazol-2-yl-amino)-3-carboxy-benzyl]-2-carboxyphenyl}-6-substituted-benzothiazol-2-ylamines, which were synthesized by oxidative cyclization of 1-{4-[4-(3-aryl thiocarbamido)-3-carboxy-benzyl]-2-carboxy-phenyl}-3-aryl thiocarbamides refluxing in the solution of bromine in chloroform (Br_2 in $CHCl_3$) followed by the basification with dilute ammonium hydroxide (NH_4OH) solution **(Scheme 74)**.[182] 1-{4-[4-(3-aryl thiocarbamido)-3-carboxy-benzyl]-2-carboxy-phenyl}-3-aryl thiocarbamides were prepared by the collaboration of diverse aryl isothiocyanates with 4,4'-methylenebis-(anthranilicacid).



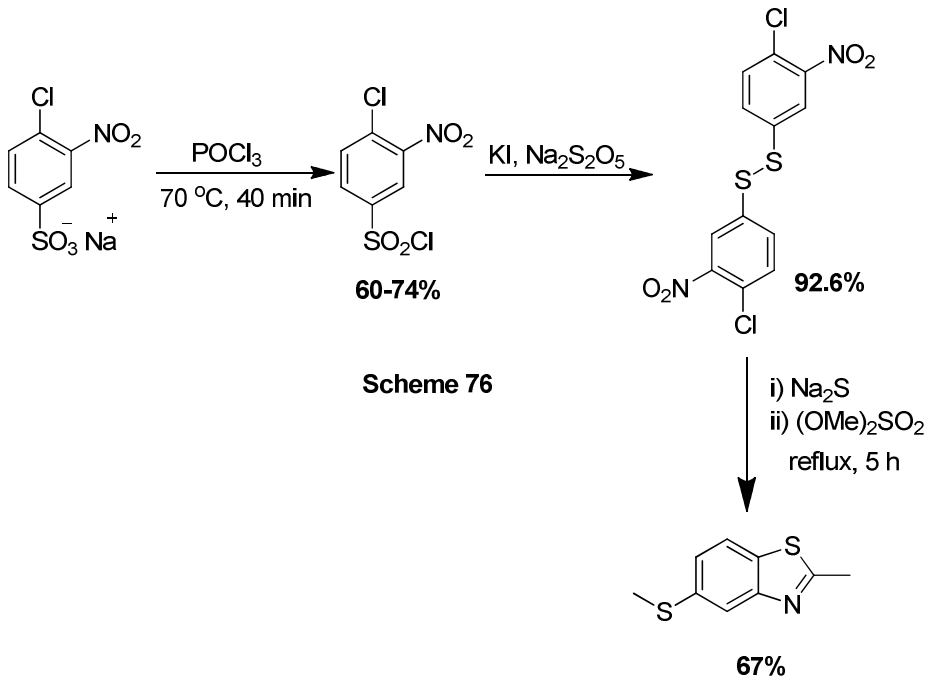
Scheme 74

The novel and first practical one-pot methodology for the synthesis of 4-hydroxy-6-(2-amino-2-carboxyethyl)benzothiazole and 4-hydroxy-7-(2-amino-2-carboxyethyl)benzothiazole and their corresponding 2-carboxy-derivatives were reported by Greco et al. involving sequential Zn^{2+}-assisted biomimetic oxidation of L-dopa and L-cysteine, 5-S-cysteinyldopa or 2-S-cysteinyldopa **(Scheme 75)**.[183] In this protocol, biogenetic origin of pheomelanins from L-tyrosine and L-cysteine occurs via tyrosinase catalyzed conversion to 5-S- and 2-S-cysteinyldopa conjugates and then 2-carboxy-6-(2-amino-2-carboxyethyl)benzothiazole and 2-carboxy-7-(2-amino-2-carboxyethyl)benzothiazole are generated by pigment degradation.



Scheme 75

A convenient and efficient 4-step synthesis of 2-methyl-5-(methylthio)benzothiazole, which uses inexpensive reagents and starting materials, have demonstrated by Lynch and colleagues **(Scheme 76)**.[184] It is efficient, scalable, clean and convenient methodology for the synthesis of substituted benzothiazole. Preparation of 4-chloro-2-nitrobenzenesulfonylchloride from 4-chloro-3-nitrobenznesulfonic acid, sodium salt was performed using phosphorous oxychloride ($POCl_3$) and sulfolane(2,3,4,5-tetrahydrothiophene-1,1-dioxide) according to a general procedure described by Fujita et al. Then, reduction of the sulfonyl chloride was performed with 55 % hydriodic acid and a catalytic amount of potassium iodide (KI) and sodium metabisulfite ($Na_2S_2O_5$) using an organic synthesis procedure gave bis-(4-chloro-3-nitrophenyl)disulfide. The disulfide was reduced to the thiol with sodium sulfide (Na_2S) and then treated with dimethyl sulphate ($SO_2(OMe)_2$) according to the procedure of Bourquin et al. to give the required benzothiazole. The one-pot conversion of l-chloro-4-(methylthio)-2-nitrobenzeneinto 2-methyl-5-(methylthio)benzothiazole is the key step in this process.



Scheme 76

Conclusion:

Benzothiazole and its derivatives possess wide spectrum of biological as a well as industrial applications. The numbers of procedures for the their synthesis have been developed from time to time, because of the development of green and environmentally friendly chemical processes due to the cost-effectiveness, better selectivity, operational simplicity and high yield of the products. It is interesting to note that, the condensation of *ortho*-amino thiophenols with various acids/ aldehydes/ ketones/ nitriles/ esters have been achieved more attention for the synthesis of benzothiazole derivatives. However, 2-amino benzothiazoles were efficiently synthesised from the reaction between various aromatic amines and ammonium thiocyanate/ sodium thiocyanate/ potassium thiocyanate using bromine. Here, we have made the efforts to compile most of these method, which are reported recently. This review will be very useful to the scientists, who are working in this area of research. Thus, this work represents a valuable complement to the all over development for the synthesis of benzothiazole derivatives by various synthetic routes.

Acknowledgements:

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