Review Article

Cyclization Reactions for Synthesis of Benzthiazole- A Review

Parul Singh[1], Ashish Srivastava[2], Abhinav Prasoon Mishra[3], Reena Mehtab[4]

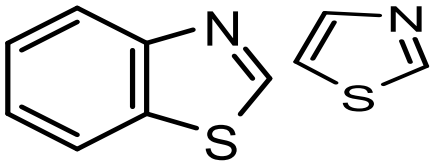
Abstract

Benzoheterocycles such as benzothiazoles can serve as unique and versatile scaffolds for experimental drug design. Among the all benzoheterocycles, benzothiazole has considerable place in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure. Development of combination of 2- aminobenzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering. In this review, we discussed various methods to synthesize as well as cyclization of benzothiazole derivatives and various structural alterations conducted on benzothiazole ring and preferential specificities imparted in their biological responses.

Keywords: Benzothiazole, Cyclization, Catalysts

Introduction

Thiazole (a) was first described by Hantzsch and Waber in 1887. Popp confirmed its structure in 1889. The numbering in thiazole starts from the sulphur atom. The basic structure of benzothiazole (b) consist of benzene ring fused with 4, 5 position of thiazole (Shivaraj, H. et al 2010).



(a) (b)

Thiazole is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter. Thiazole is a heterocyclic compound. Thiazole ring is a five-member ring consists of one nitrogen and one sulfur atom in the ring. Thiazole and their analogues such as benzothiazole play an essential role as a template in the development of tremendous derivatives of thaizole which have different pharmacological activity and useful in the treatment of various disease (Shivaraj, H. et al 2010).

Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds (Chaudhary, P. et al 2010).

The benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities (Hutchinson, I. et al 2001). Benzothiazole is a colorless, slightly viscous liquid with a melting point of 2ºC, and

[1]Advance Institute of Biotech and Paramedical Sciences, Naramau, Kanpur.

[2,3,4]Pranveer Singh Institute of Technology, Bhauti, Kanpur.

Correspondence: Praul Singh, Advance Institute of Biotech and Paramedical Sciences, Naramau, Kanpur.

E-mail Id: sparsh_paras@yahoo.co.in

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a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml (25ºC). Benzothiazole has no household use. It is used in industry and research work purpose which are very beneficial for development (Paramashivappa, R.et al 2003).

Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery (Gupta, A. et al 2010).

Benzothiazole is a privileged bicyclic ring system. Due to its potent and significant biological activities it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest. The small and simple benzothiazole nucleus if present in compounds involved in research aimed at evaluating new products that possess interesting biological activities (Gupta, A. et al 2010).

Benzothiazole moites are part of compounds showing numerous biological activities such as antimicrobial (Gupta, S. et al 2009, Kumbhare, R.M. et al 2009, Maharan, M. et al 2007, Murthi, Y. et al 2008, and Rajeeva, B. et al 2009), anticancer (Hutchinson, I. et al 2001, Kini, S. et al 2007, Stanton, H.L.K. 2008 and Wang, M. et al 2006), anthelmintic(Sreenivasa, M. et al 2009), and anti-diabetic(Pattan, S. et 2005) activities. They have also found application in industry as anti oxidants, vulkanisation accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents (Reddy, P. et al 2007) and anticancer agents (Heo, Y. et al 2006).

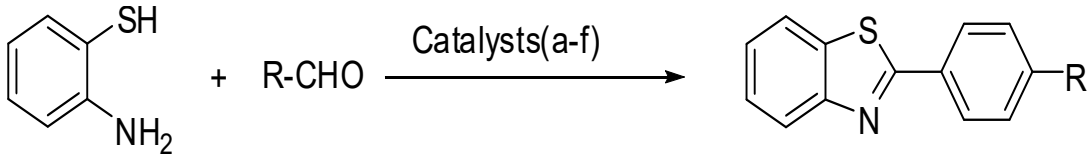
In this review, we discussed in brief about some commonly used methods to synthesize as well as cyclization of benzothiazole derivatives and various structural alterations conducted on benzothiazole ring and preferential specificities imparted in their biological responses.

Condensation of o-aminothiophenol with aldehydes: (Shukla, J. et al 2011)

Treatment of o-aminothiophenols with substituted aldehydes affords the synthesis of 2-substituted benzothiazoles using different catalysts and reaction conditions.

Catalysts (a-f)

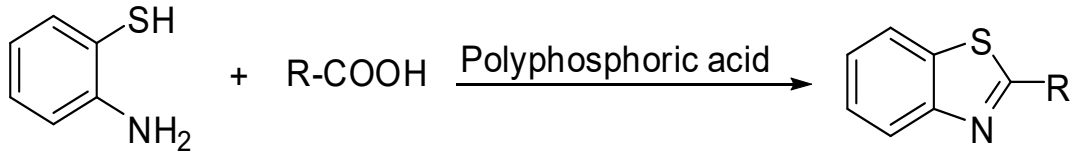
- Montmorillonite, SiO_2/Graphite; Microwave, p-TsOH
- Diethyl bromophosphonate/*t3332ert*-Butyl hypochlorite; acetonitril
- Cerium (IV) ammonium nitrate
- H_2O_2/HCl system in ethanol
- AcOH /Air; Microwave/ Thermal Heating
- Baker's yeast, Dichloro methane



Scheme 1.Condensation of *o*-aminothiophenol with aldehydes in presence of different catalysts

Condensation of o-aminothiophenol with acids: (Shukla, J. et al 2011)

Treatment of 2-aminothiophenol and substituted aromatic acids in presence of Polyphosphoric acid provides a good method to synthesize 2- substituted benzothiazoles and gives a good yield.



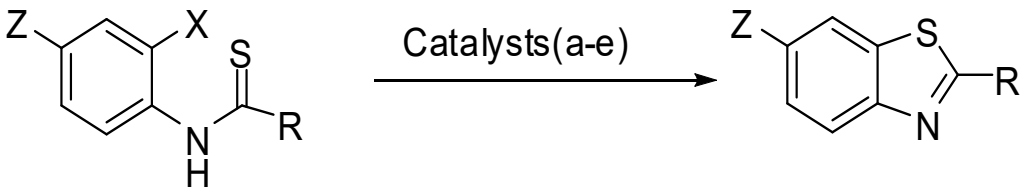
Scheme 2.Condensation of *o*-aminothiophenol with acids in presence of Polyphosphoric acid

Cyclization of thioformanilides using different reagents: (Shukla, J. et al 2011)

Substituted thioformanilides can be converted to 2-aminobenzothiazoles *via* intramolecular C-S bond formation/C-H functionalization utilizing various reagents and catalysts.

Catalysts (a-e)

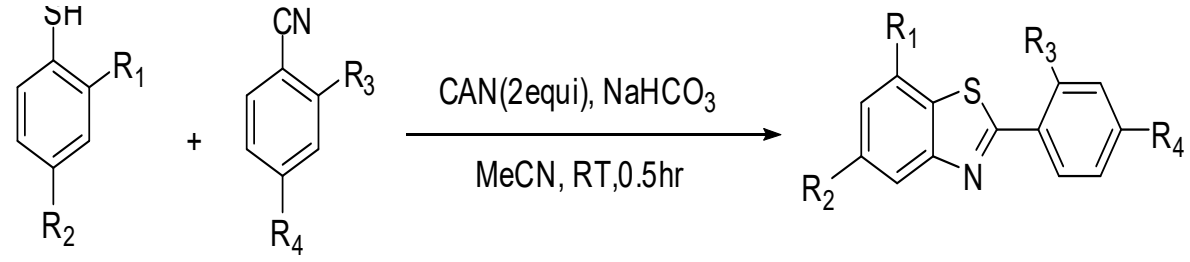
- CuI; 1, 10-Phenanthroline, CS_2CO_3, reflux
- Manganese triacetate
- CS_2CO_3, Dioxane
- Photochemical cyclization induced by chloranil
- Pd $(PPh_3)_4/MnO_2$ system under an oxygen atmosphere



Scheme 3.Cyclization of thioformanilides using different reagents

Coupling between thiophenols and aromatic nitriles: (Shukla, J. et al 2011)

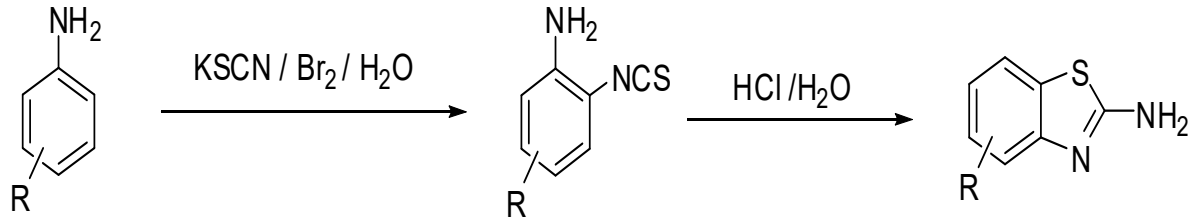
Thiophenols when treated with aromatic nitriles to affords a smooth reaction mediated by Ceric ammonium nitrate to give corresponding 2- arylbenzothiazoles in excellent yield.



Scheme 4.Coupling between thiophenols and aromatic nitriles

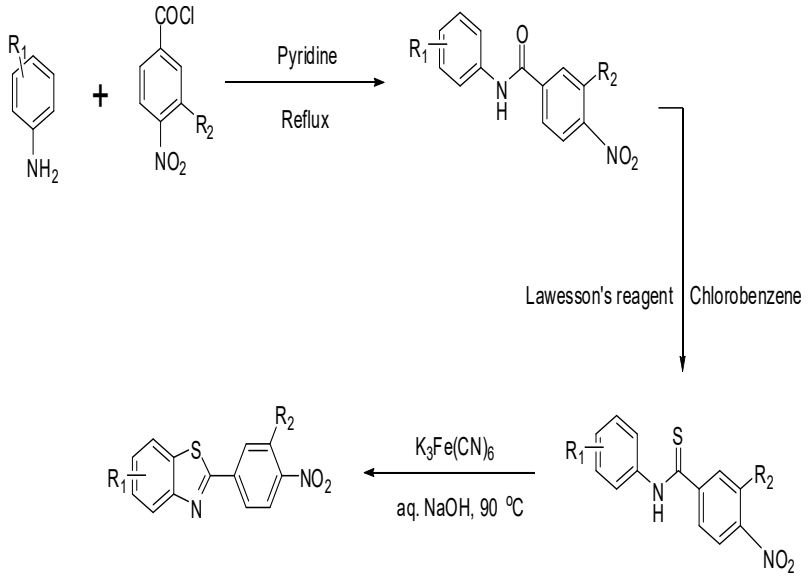
Synthesis using anilines and its derivatives by use of different reaction conditions

Different substituted anilines when treated with KSCN in presence of glacial acetic acid to synthesize 2-substituted benzothiazoles.



Scheme 5.Synthesis of benzothiazoles from substituted anilines

2-aryl substituted benzothiazoles can be synthesized using reaction of substituted anilines with nitrobenzoyl chloride in pyridine under reflux and further treatment with Lawesson's reagent and then cyclization of intermediate using Potassium ferricyanide (Khokra, S. L. et al 2011).

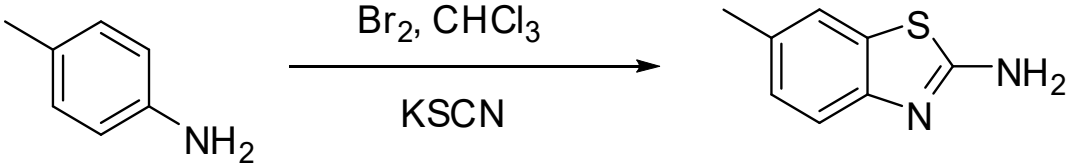


Scheme 6.Synthesis of benzothiazoles from substituted anilines with Lawesson's reagent

Bromine as catalyst

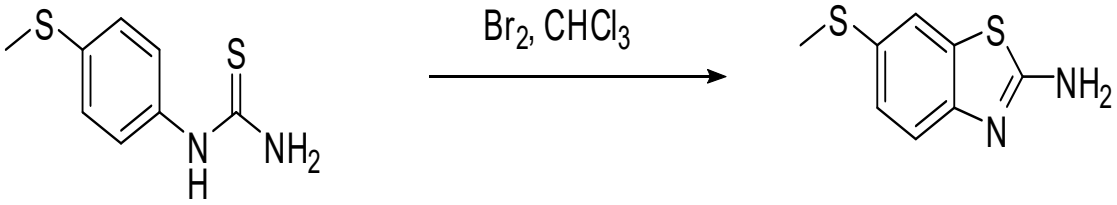
Recently several methods reported which utilize bromine as catalyst. Basically cyclization with bromine achieved by oxidation of aniline, substituted aniline and arylthiourea in acid or chloroform with alkali thiocyanate.

Hugerschoff in early 1900s synthesized 2-aminobenzothiazole and found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2- aminobenzothiaozles (Carolina, B. et al 2003).



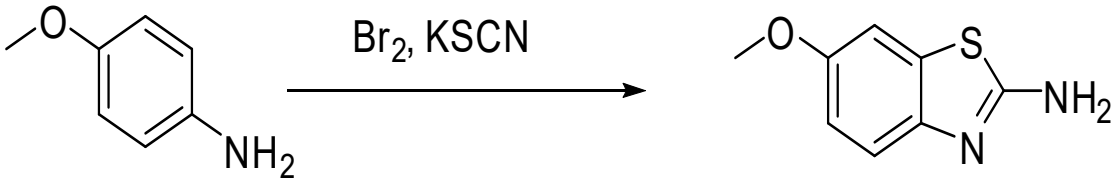
Scheme 7.Synthesis of 2- aminobenzothiazole with liquid bromine in chloroform

Johanson and Hamillton prepared 2-amino-6- ethylmercaptobenzothiazole by oxidation of 4- Methylmecaptophenylthiourea with bromine as a catalyst (Carolina, B. et al 2003).



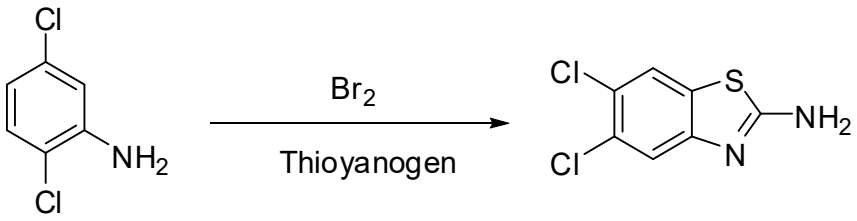
Scheme 8.Synthesis of 2-amino-6- ethylmercaptobenzothiazole

Stuckwisch used potassium thiocyanate to cyclize p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of bromine as a catalyst (Carolina, B. et al 2003).



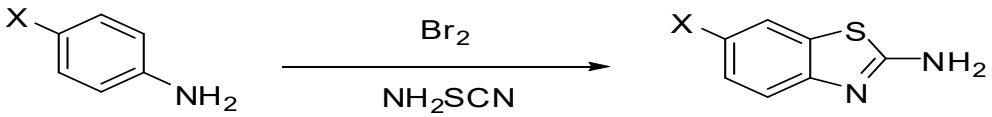
Scheme 9.Synthesis of 2-amino-6-substituted benzothiazole

Alaimo and coworkers prepared 2-amino-5, 6-dichloro and 2- amino-6, 7-dichlorobenzothiazole by cyclization of suitable substituted aniline with help of thiocyanogen (Carolina, B. et al 2003).



Scheme 10.Synthesis of 2-amino-5, 6-dichloro and 2- amino-6, 7-dichlorobenzothiazole

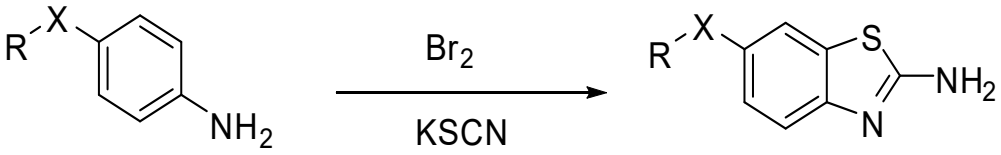
Li *et al*. prepared 6-substituted-2-aminobenzothiazole by cyclizations of p-substituted anilines with the help of ammonium thiocyanate and bromine (Carolina, B. et al 2003).



X = Cl, Br, F, CH_3

Scheme 11.Cyclizations of p-substituted anilines with ammonium thiocyanate and bromine

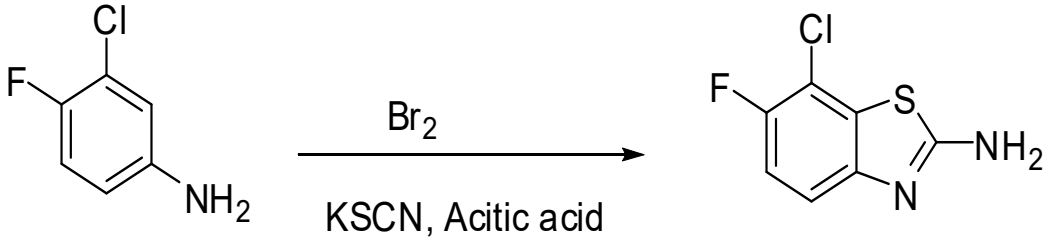
Naim *et al*. synthesized 2-aminobenzoyhiazole-6-carboxalic acid and 2-amino-6-substituted-carbonyl benzothiazole by reaction of the corresponding 4-substituted anilines with potassium thiocyanate followed by oxidative cyclizations of the resultant thioureas with bromine (Carolina, B. et al 2003).



X = CO
R = OH, O, alkyls

Scheme 12.Oxidative cyclizations of the resultant thioureas with bromine

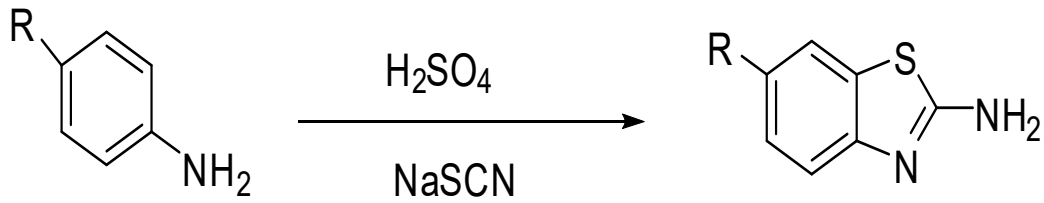
Dogruer, D. S and coworkers prepared 2-amino-6-fluoro-7- chlorobenzothiazole by cyclization of 3-chloro-4-fluoroaniline and potassium thiocyanate in presence of catalytic bromine. It is also synthesized by using similar method and materials by Nargund *et al* (Carolina, B. et al 2003).



Scheme 13.Cyclization of 3-chloro-4- fluoroaniline and potassium thiocyanate in presence of catalytic bromine

Sulfuric acid as a catalyst

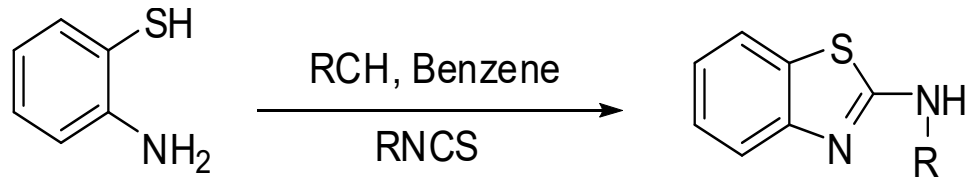
Allen used sodium thiocyanate and cyclize p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of sulfuric acid which act as a catalyst.



Scheme 14.Cyclizations of p-substituted aniline in the presence of sulfuric acid

Benzene as a catalyst

Tweit *et al*. reported cyclizations of isothiocyanates to 2- aminobenzothiazole in presence of benzene.

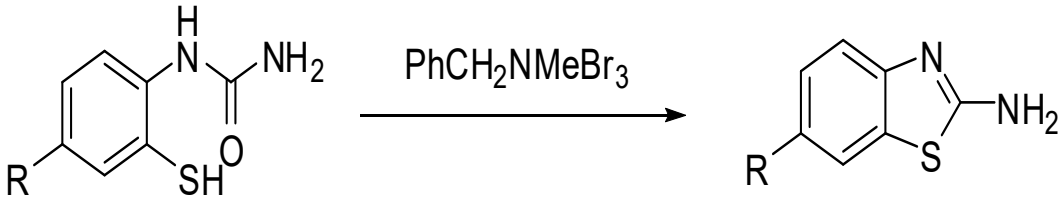


Scheme 15.Cyclizations of isothiocyanates in presence of benzene

Benzyltrimethylammonium tribromide as catalyst

Jordan *et al*. used Benzyltrimethylammonium tribromide ($PhCH_2NMe_3Br_3$), is an electrophilic bromine source for the conversion of substituted arylthioureas to 2-aminobenzothiazoles under mild conditions in a variety of solvents with good yields. One of the key benefits for

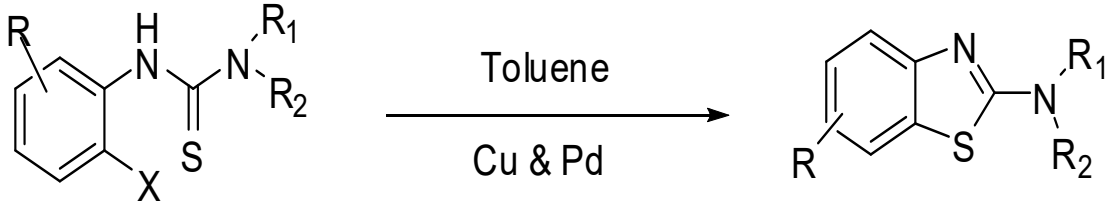
this reagent when compared with molecular bromine in ease of addition and handling, which minimizes the risk of forming brominated side products. They have extended the use of this reagent to a direct, one-pot synthesis of 2-aminobenzothiazoles from either aryl isothiocyanate and anilines or tetrabutylammonium thiocyanate and anilines.



Scheme 16.Conversion of substituted arylthioureas to 2- aminobenzothiazoles by Benzyltrimethyl ammonium tribromide

Copper- and palladium-catalyzed cyclization

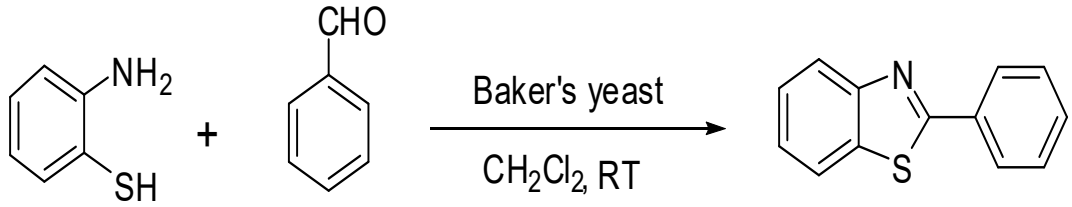
Batey *et al*. reported the synthesis of 2-aminobenzoyhiazoles through analogous C-S bond forming methodologies. They formed the intramolecular C-S bond with the help of copper-and palladium-catalyzed. Copper- and palladium-catalyzed intramolecular C-S bond formation by cross-coupling between aryl halide and thioureas functionality is demonstrated for the synthesis of 2-aminobenzothiazole.



Scheme 17.Copper- and palladium-catalyzed intramolecular C-S bond formation by cross-coupling

Bakers' yeast to catalyze cyclization

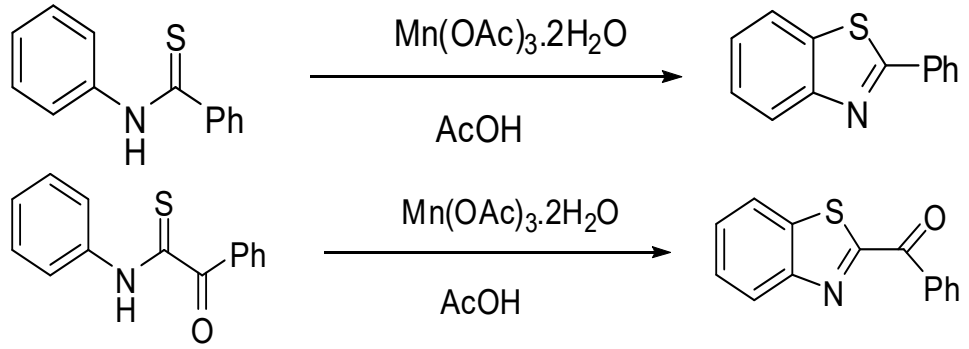
Umesh R. Pratap successfully employed bakers' yeast to catalyze the condensation of 2-aminothiophenol and aldehydes in DCM to yield 2-substituted benzothiazoles in moderate to good yields under mild reaction condition.



Scheme 18.Bakers' yeast to catalyze the condensation of 2-aminothiophenol and aldehydes

Manganese triacetate as a catalyst

Manganese (III) triacetate is an excellent one-electron oxidant, which has been widely employed to generate free radicals for cyclization reactions. Manganese triacetate is introduced as a new reagent to replace potassium ferricyanide or bromine for radical cyclization of substituted thioformanilides. 2-Substituted benzothiazoles are generated in 6 min under microwave irradiation.

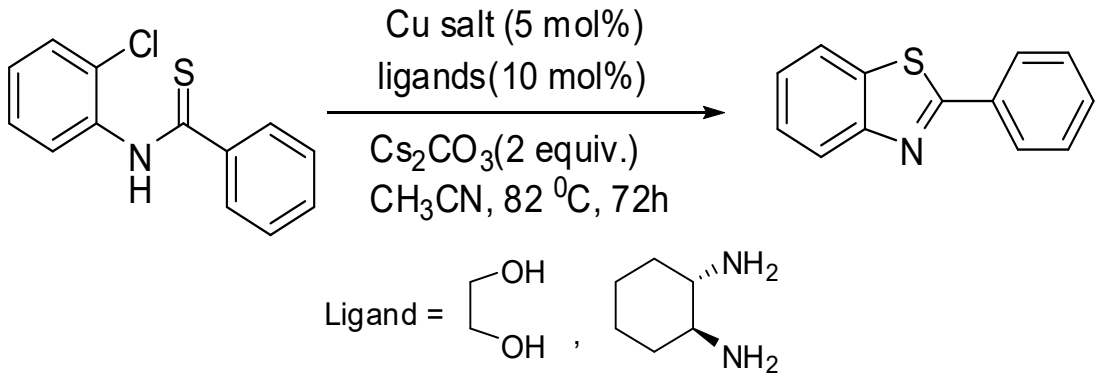


Scheme 19.Cyclization reactions with Manganese (III) triacetate

BINAM-Copper (II) as catalyst

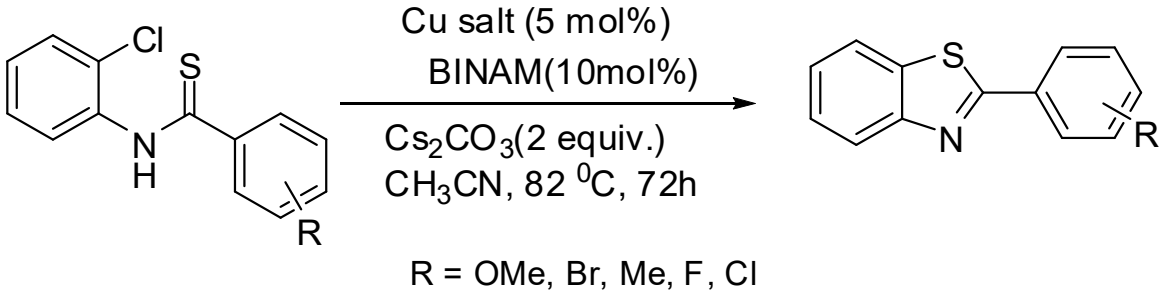
BINAM–Cu(II) complex as an efficient catalyst for the synthesis of benzothiazole through intramolecular coupling cyclization from N-(2-chlorophenyl) benzothioamide under mild reaction conditions. A wide range of 2-aryl or 2-alkyl-substituted benzothiazoles are synthesized through intramolecular C(aryl)-S bond forming-cyclization using copper(II)–BINAM-catalyzed coupling with using Cs_2CO_3 as a base in acetonitrile solvent of less reactive N-(2-chlorophenyl) benzo or alkylthioamide under mild reaction conditions (82 ^{0}C).

- Effect of different ligands and copper salts for the synthesis of 2-phenyl benzothiazoles



Scheme 20.Synthesis of 2-phenyl benzothiazoles via different ligands and copper salts

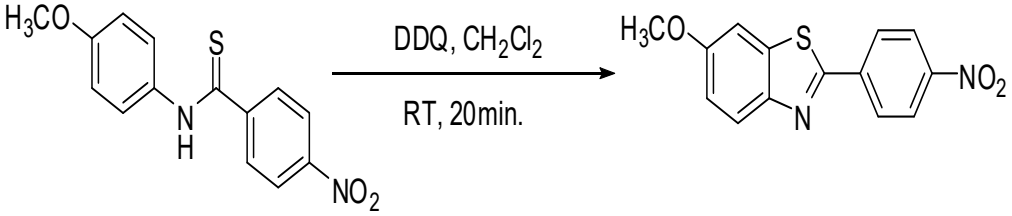
- Synthesis of benzothiazoles via copper(II)-catalyzed coupling of various N-(2- chlorophenyl) benzothioamides.



Scheme 21.Synthesis of benzothiazoles via copper(II)-catalyst

DDQ as catalyst

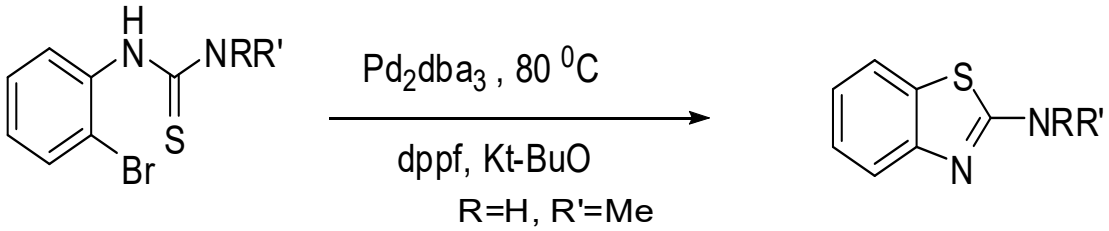
A new and practical method has been developed for the synthesis of substituted benzothiazoles via the intramolecular cyclization of thioformanilides using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in CH_2Cl_2 at ambient temperature. The reaction proceeds in high yields via the thiyl radical to give novel oxybis-benzothiazole, and offers a high degree of flexibility with regard to the functional groups that can be placed on the benzothiazole nucleus or 2-aryl moiety which in turn generates scaffolds for parallel synthesis.



Scheme 22.DDQ- mediated intramolecular cyclization of thioformanilide

Palladium as catalyst

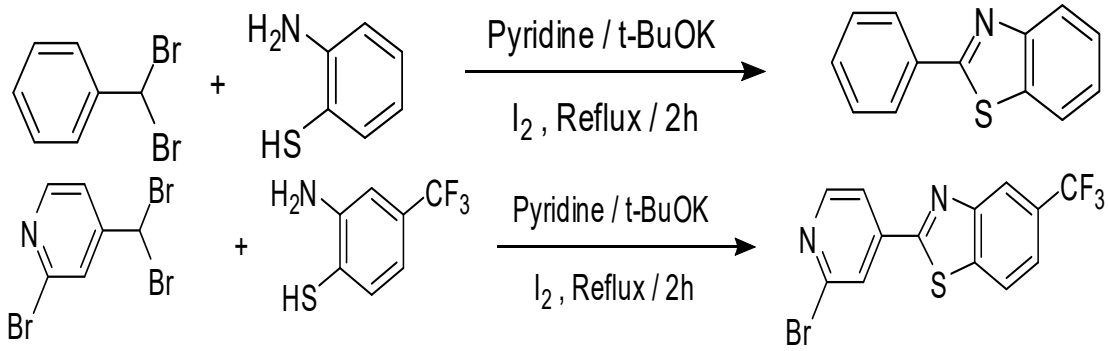
2-Amino-, and 2-alkyl-benzothiazoles have been efficiently prepared by palladium catalyzed cyclization of *o*-bromophenylthioureas and *o*-bromophenylthiamides. Results were best with the $Pd_2(dba)_3$/ monophosphine catalytic system. Palladium-catalyzed aryl_nitrogen bond forming reactions are highly useful for synthesizing arylamines and have found numerous applications in organic synthesis. Intramolecular palladium-catalyzed *N*- arylation reactions of aryl halides have been used to prepare indoles,oxoindoles, 2-aryl-2*H*-indazoles, 1-aryl-1*H*-indazoles, imidazoles, oxazepines and thiazepines, indulines, and other heterocycles.



Scheme 23.Cyclization reaction of 2-bromophenylthioureas catalyzed by Pd_2dba_3/ ligand

Pyridine as catalyst

The synthesis of 2-aryl benzothiazoles from gem-dibromomethylarenes using 2-aminoarylthiols with pyridine is obtained. Benzothiazoles were obtained in high chemical yields under mild conditions. This transformation would facilitate synthesis by short reaction times, large-scale synthesis, easy and quick isolation of the products, which are the main advantages of this procedure.



Scheme 24.Synthesis of benzothiazoles from gem-dibromomethlarenes using 2-amino benzenethiols

PIFA as catalyst

A new and general method has been developed for the intramolecular cyclization of thiobenzamides to benzothiazoles via aryl radical cations as reactive intermediates. The method utilizes phenyliodine(III) bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile at room temperature to effect cyclization within 30 min in moderate yields.

Scheme 25.PIFA- mediated oxidation of thiobenzamides to benzamides

Conflict of Interest: None

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