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The Different Kinds of Reaction involved in synthesis of 2-substituted Benzothiazole and its derivatives: A Review

Shiwani Jaiswal[1], Abhinav Prasoon Mishra[1]*, Ashish Srivastava[2]

[1] Advance Institute of Biotech $ Paramedical Sciences, Kanpur, India.
[2] Pranveer Singh Institute of Technology, Kanpur, India.

ABSTRACT

Benzoheterocycles such as benzothiazoles can serve as unique and versatile scaffolds for experimental drug design. Among the all benzohaterocycles, benzothiazole has considerable place in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. The small and simple benzothiazole nucleus possesses numerous pharmacological activities like- antitumor, antimicrobial, anti-inflammatory, anticonvulsant, and antidiabetic activities. Since, a wide range of different reactions are available for synthesizing 2-substituted benzothiazole nucleus and its derivatives by using different type of catalysts but a real need exists for new procedures that support many kinds of structural diversity and various substitution. The present review focuses on the different kind of reactions involved in synthesis as well as cyclisation of benzothiazole nucleus and its derivatives.

Keywords: - Benzothiazoles, Cyclization, Benzothiazole derivatives, Catalysts.

***Corresponding author**
Email: abhinavmph@gmail.com

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INTRODUCTION

A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. [1]

The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design. [2]

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.

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.

Benzothiazole moites are part of compounds showing numerous biological activities such as antimicrobial [3-7] anticancer [8-11], anthelmintic [12], anti-diabetic [13] activities. They have also found application in industry as anti-oxidants, vulkanisation accelerators. Various benzothiazoles such as 2-substituted benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents [14], and anticancer agents. [15]

In the 1950s, a number of 2-aminobenzothiazoles were intensively studied, as the 2-amino benzothiazole scaffold is one of privileged structure in medicinal chemistry [14, 16] and reported cytotoxic on cancer cells. [16] It must be emphasized that 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.

Benzothiazoles are fused member rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Thiazole is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter. 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. (Fig.1)

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(a) (b)

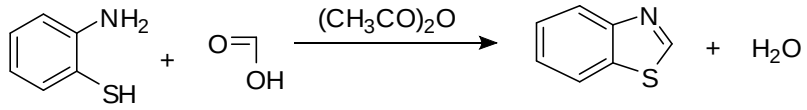
Fig.1

A brief account of some commonly used methods to synthesize as well as cyclization of benzothiazole derivatives by using different type catalysts and various structural alterations conducted on benzothiazole ring and preferential specificities imparted in their biological responses.

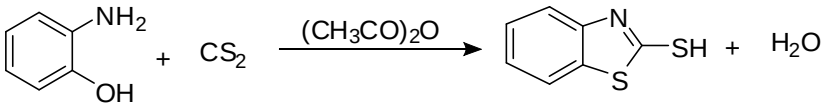
REACTION OF BENZOTHIAZOLE AND ITS DERIVATIVES:-

By using acetic anhydride to synthesized 2-substituted Benzothiazole:-

1. Benzothiazole may be prepared by action of acid anhydrides (or) chlorides on o-aminophenols and formic acid in presence of acetic anhydride. [17,18]

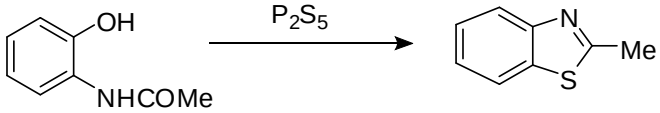


2. 2-mercaptobenzothiazole is vulkanisation accelerator it may be prepared as follows. [17,18]



By using Phosphorus pentasulfide to synthesized 2-substituted Benzothiazole:-

Benzothiazoles are also formed by action of phosphorus pentasulfide on o-acylaminophenoles.[17, 18]



By condensation of o-aminothiophenol to synthesized 2-substituted Benzothiazole:-

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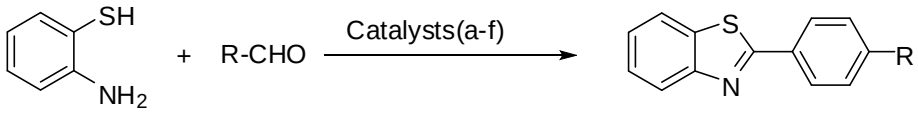
O-aminothiophoenol is a versatile starting material for synthesis of different kind of heterocyclic rings. 2- Substituted Benzothiazole can easily synthesize by applying condensation with aldehydes and substituted aromatic acids in presence of different catalyst.

(1.) Condensation of o-aminothiophenol with aldehydes [19]:

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

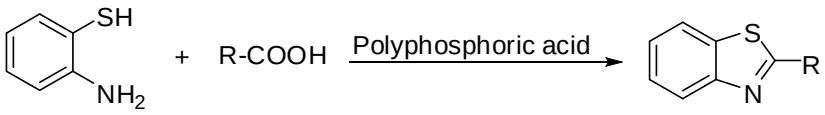
Catalysts (a-f):

a. Montmorillonite, SiO_2/Graphite; Microwave, p-TsOH
b. Diethyl bromophosphonate/tert-Butyl hypochlorite, acetonitrile
c. Cerium (IV) ammonium nitrate
d. H_2O_2 /HCl system in ethanol
e. AcOH /Air, Microwave/ Thermal Heating
f. Baker's yeast, Dichloro methane



(2.) Condensation of o-aminothiophenol with acids [19]:

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. [19



By cyclization to synthesized 2-substituted Benzothiazole [19]:-

Thioformanilides using different catalysts:- 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):

a. CuI; 1, 10-Phenanthroline, CS_2CO_3, reflux
b. Manganese triacetate
c. CS_2CO_3, Dioxane
d. Photochemical cyclization induced by chloranil
e. Pd (PPh3)4/MnO2 system under an oxygen atmosphere

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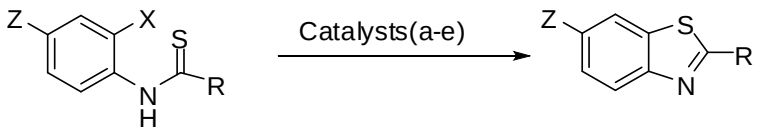
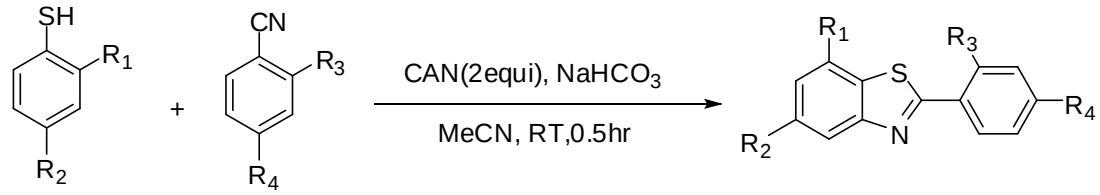


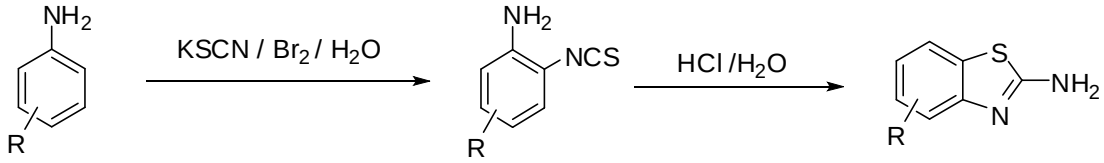
By coupling synthesized to 2-substituted Benzothiazole [19]:-

Coupling between thiophenols and aromatic nitriles: Thiophenols when treated with aromatic nitriles to affords a smooth reaction mediated by cericammonium nitrate to give corresponding 2- arylbenzothiazoles in excellent yield.

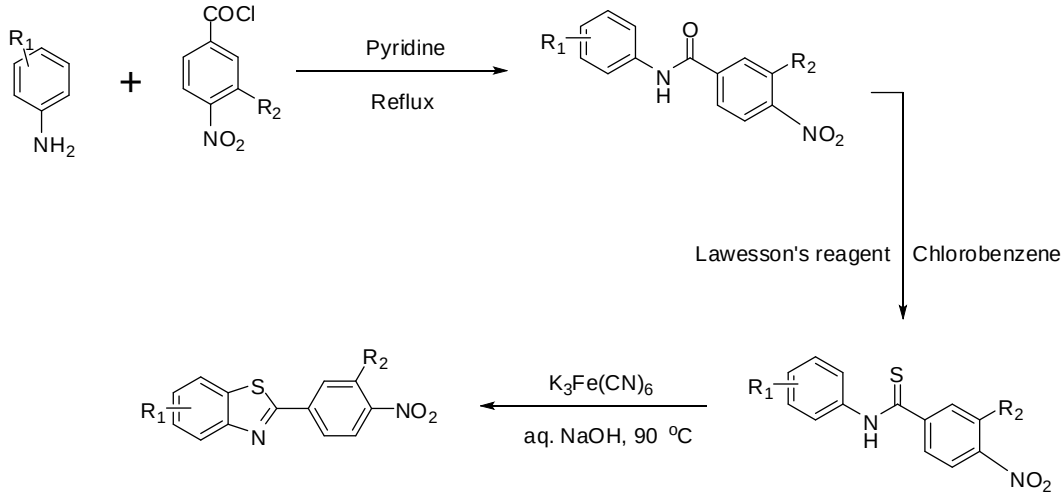


By synthesis using substituted anilines to synthesized 2-substituted Benzothiazole [19]:-

(1.) Different substituted anilines when treated with KSCN in presence of glacial acetic acid to synthesize 2-substituted Benzothiazole.



(2.) 2-aryl substituted Benzothiazole 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.



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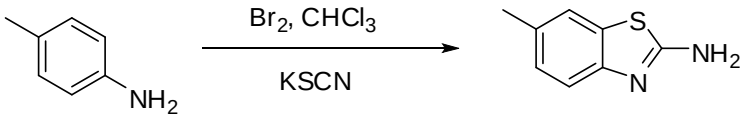
By using of different type of catalysts to synthesized 2-substituted Benzothiazole [19,20]**:-**

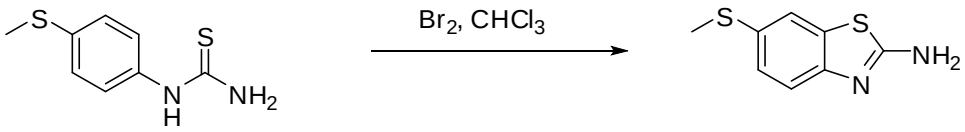
(A) Bromine as catalyst

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.

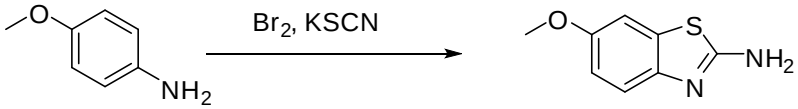
(1.) Hugerschoff et.al., in early 1900s synthesed 2-aminobenzothiazole and found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiaozles.



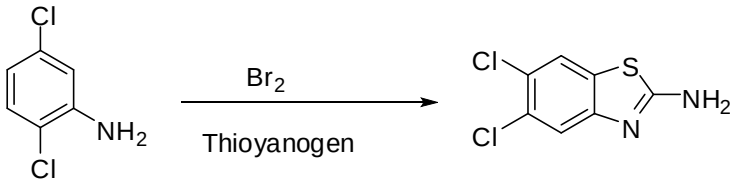
(2.) Johanson and Hamillton et.al., prepared 2-amino-6- ethylmercaptobenzothiazole by oxidation of 4- Methylmecaptophenylthiourea with bromine as a catalyst.



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



(4.) 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.



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

X = Cl, Br, F, CH_3

(6.) Naim et.al., synthesized 2-aminobenzoyhiazole-6-carboxalic acid and 2-amino-6-substituted-carbonyl benzothiazole by reaction of the corresponding 4-substituted anilines

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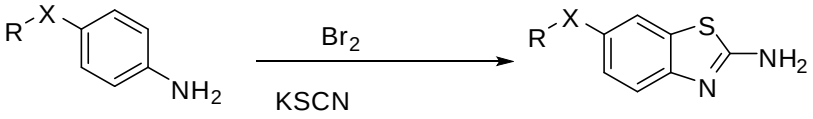
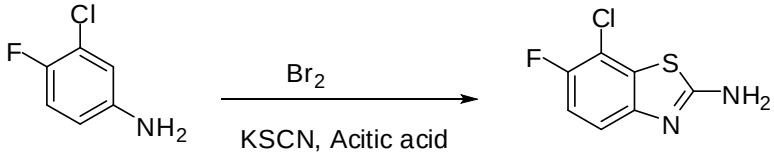
with potassium thiocyanate followed by oxidative cyclizations of the resultant thioureas with bromine.



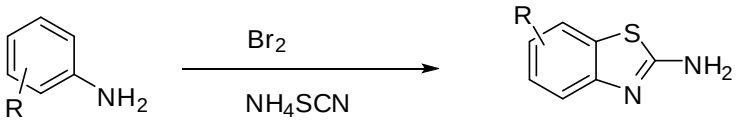
X = CO
R = OH, O, alkyls

(7.) 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.

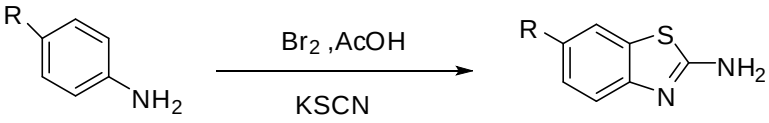


X = CO
R = OH, O, alkyls

(8.) Patel and Agrawal were synthesized various 4(5 or 6) - substituted-2-aminobenzothiazoles through reaction of 4(5 or 6)-substituted anilines with ammonium thiocyanate and bromine.

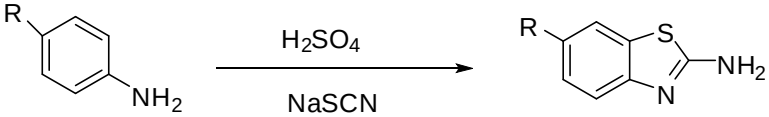


(9.) Matsui et. al. prepared 6-substituted-2-aminobenzothiazoles by the reaction of 4-substituted anilines with potassium thiocyanate in presence of bromine.



(B) 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.



(C) Benzene as a catalyst

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

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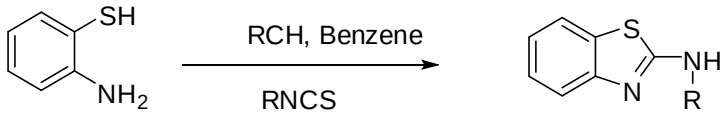
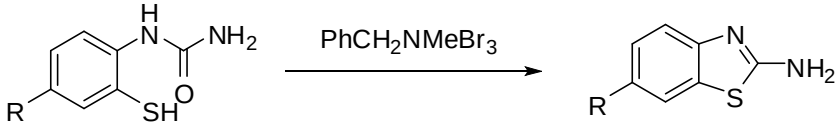


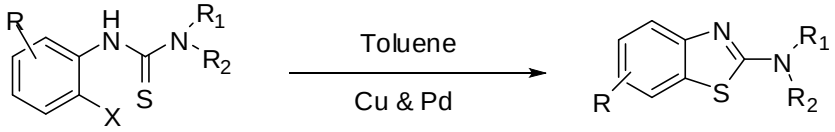
(D) Benzyltrimethylammonium tribromide as catalyst

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.



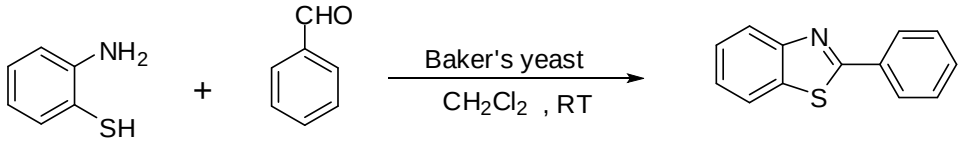
(E) Copper- and palladium-catalyzed cyclization

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-aminobenzothiazoles.



(F) Bakers' yeast to catalyze cyclization [21]:-

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.



(G) Manganese triacetate as a catalyst [22]:-

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.

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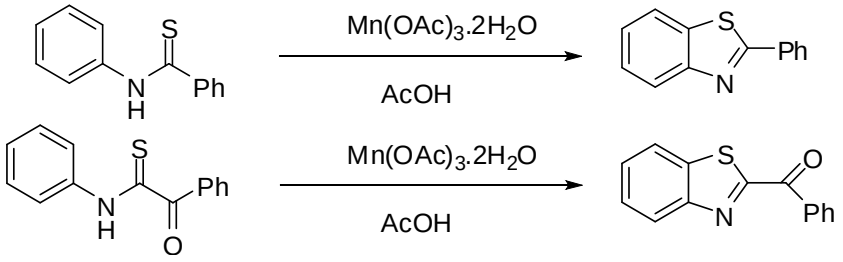
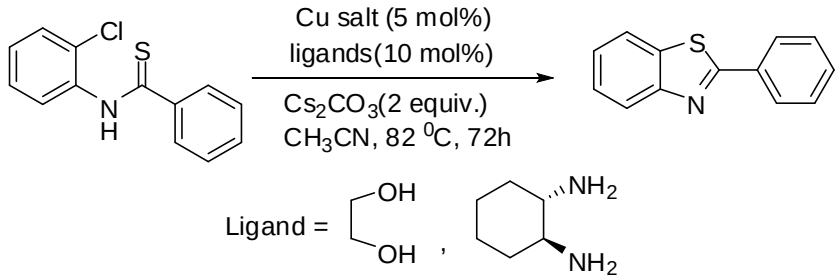


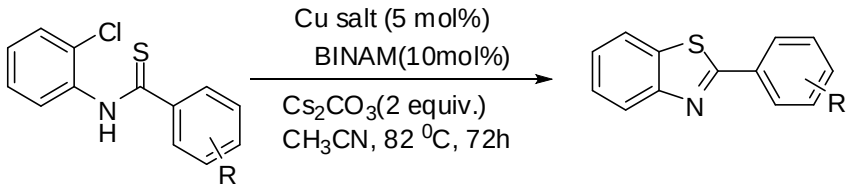
(H) BINAM-Copper (II) as catalyst [23]:-

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).

(a.) Effect of different ligands and copper salts for the synthesis of 2-phenyl benzothiazoles



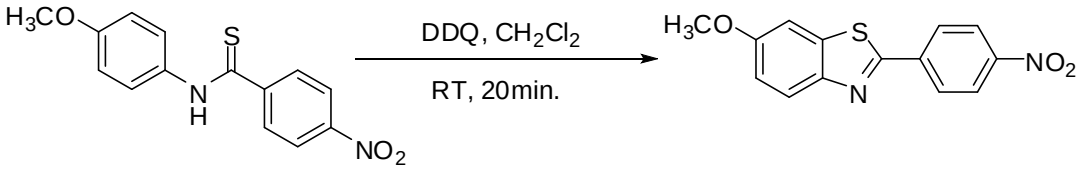
(b.) Synthesis of benzothiazoles via copper(II)-catalyzed coupling of various N-(2- chlorophenyl) benzothioamides



R = OMe, Br, Me, F, Cl

(I) DDQ as catalyst [24]:-

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.



DDQ- mediated intramolecular cyclization of thioformanilide

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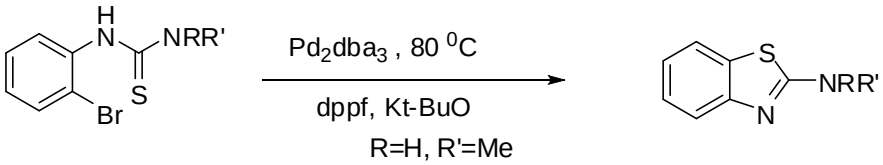
(J) Palladium as catalyst [25]:-

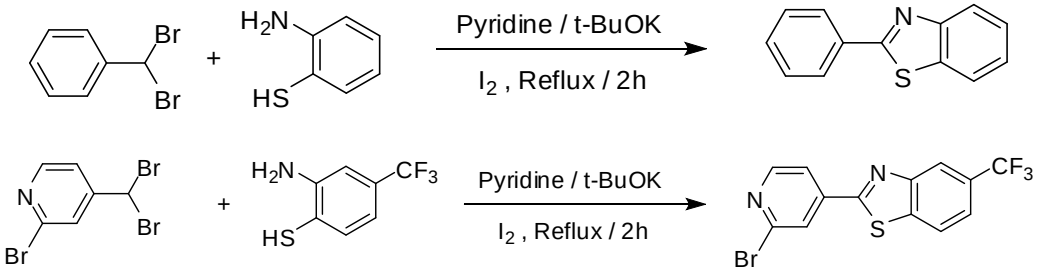
2-Amino-, and 2-alkyl-benzothiazoles have been efficiently prepared by palladium catalyzed cyclization of o-bromophenylthioureas and o-bromophenylthiamides. Results were best with the $Pd_2(dba)_3$/ monophosphine catalytic system. Palladium-catalyzed aryl_nitrogen bond forming reactions are highly useful 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-2H-indazoles, 1-aryl-1H-indazoles, imidazoles, oxazepines and thiazepines, indulines, and other heterocycles.



Cyclization reaction of 2-bromophenylthioureas catalyzed by Pd_2dba_3/ ligand

(K) Pyridine as catalyst [26]:-

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.



Synthesis of benzothiazoles from gem-dibromomethlarenes using 2-amino benzenethiol

(L) PIFA as catalyst [27]:-

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.

PIFA-mediated oxidation of thiobenzamides to benzamides.

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