

Benzothiazole Moiety with Sulphonamide as Anti-Inflammatory and Analgesic Activity: A Review

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Abstract: Triazines are a diverse class of compounds that possess three consecutively bonded nitrogen atoms. Triazines have been utilized in a variety of research areas. In organic synthesis, they have been used as protecting groups for aromatic amines, as linkers in solid-phase peptide synthesis and as synthons for novel heterocyclic compounds. In the present research work, we synthesized a series of novel Benzothiazole derivatives and Triazine derivatives by using some sulfa drugs. The Benzothiazole derivatives such as substituted 2-amino benzothiazole synthesized by a different procedure in which some sulfa drugs were reacted with ammonium thiocyanate and prepared substituted phenylthiourea. The cyclization of substituted phenylthiourea prepared in the presence of bromine solution with chloroform and then prepared Benzothiazole nucleus. Triazine derivatives such as substituted 4-[1(E)-3,3 dimethyl-1-triazene-1-yl] synthesized by a different procedure in which some sulfa drugs were reacted with dimethylamine in presence of 6M HCl and NaNO₂ and then prepared substituted 3,3 dimethyl-1-triazene-1-yl. These compounds were screened for anti-inflammatory activity by carrageenan induced paw oedema method in rats at a dose of 10 mg/kg body weight.

Keywords: Triazines, Benzothiazole, anti-inflammatory activity, analgesic activity, sulpha drugs.

1. INTRODUCTION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. The process establishing a new drug is exceeding a complex process and involves talent of people from variety of disciplines [1]. An important aspect of medicinal chemistry is to establish a relationship between chemical structure and pharmacological activity [2]. It has been established that half of therapeutic agents consists of heterocyclic compounds. The heterocyclic ring comprises of very core of the active moiety or the pharmacophore [3]. Generation of different heterocyclic derivative has created a boom in the field of medicinal chemistry. Thousands of new compounds are prepared annually throughout the world, many of them enter in the pharmacological screening to determine whether they have useful biological activity or not. This process of random screening results in the identification of new lead compounds. Once a new pharmaceutical lead compound has been discovered, then only extensively and costly efforts are usually made to prepare a series of analogue in a hope that even more active compounds can be obtained. Different heterocyclic compounds have shown various biological activities such as antibacterial, antifungal, antiviral, anticancer, antitubercular, anti-inflammatory and thus can be used as a lead in the discovery of new drug molecule [4]. Inflammation is a complex pathological condition associated with exaggerated human immune system involving various activated immune cells and bio-molecules. Treatment of inflammatory diseases particularly chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease etc. has been a big challenge for scientists as there are no safe drugs available for cure. Current therapeutic approaches to the treatment of inflammatory diseases are centered on cyclooxygenase (both COX-1 and 2) proinflammatory enzymes but present available drugs of this category are associated with undesirable gastrointestinal and cardiovascular side effects. Recent scientific advants draw out the secrets of inflammation cache and understanding the involvement of several factors acting as stimulators or inhibitors thus opening new avenues for drug discoveries. Several bio-molecules such as proinflammatory cytokines, components of signal transduction and matrix degrading enzymes resolve inflammatory responses, might be new targets for treatment of chronic inflammatory diseases. The recent advances in drug research focusing interleukin-1, TNF- α , p38 kinase, c-Jun N-terminal kinase MAP kinase, NF κ B, and matrix metalloproteinases. The biological roles of these inflammatory mediators

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are clearly understood thus offering new targets for design of novel inhibitors for incurable inflammatory diseases. This also provides an overview of the current nonsteroidal antiinflammatory agents [4]. Nonsteroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, but also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs), are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, anti-inflammatory effects [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs worldwide and are especially valued for their analgesic, antipyretic and anti-inflammatory properties. However, despite the great benefits associated with NSAID use, up to 25% of patients taking NSAIDs chronically experience upper gastrointestinal (UGI) adverse effects [6]. The term "nonsteroidal" is used to distinguish these drugs from steroids, which among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present [7]. The concept of inflammation has evolved since the discovery of cells in the 19th century. By this time, inflammation was seen to be preceded by cell and tissue injuries and that vascular changes including leukocyte emigration were secondary events [7]. Inflammation is a local response of living mammalian tissues to the injury. It is a body defense reaction in order to eliminate or limit the spread of injurious agents. There are various components to an inflammatory reaction that can contribute to the associated symptoms and tissue injury. Oedema formation, leukocyte infiltration and granuloma formation represent such components of inflammation [7]. The use of non-steroidal anti-inflammatory drug is well recognized for regional inflammatory disorders such as muscle pain, osteoarthritis and rheumatoid arthritis [8, 9]. 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 [10]. 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 [11]. 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 [12]. 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 [12]. Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial [13-17], anticancer [18-21], anthelmintic [22] and anti-diabetic [23] 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 imaging agents [24] and anticancer agents [25]. 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 [25, 26] and reported cytotoxic on cancer cells [26]. 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 [27]. 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 [28]. 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 thiazole which have different pharmacological activity and useful in the treatment of various diseases [29]. 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 [29].

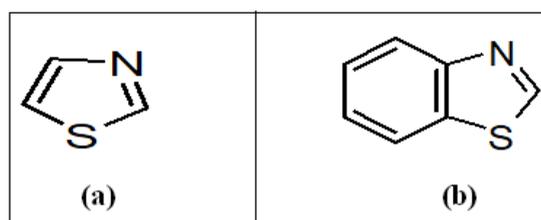


Figure-1.1: Structure of Thiazole and Benzothiazole

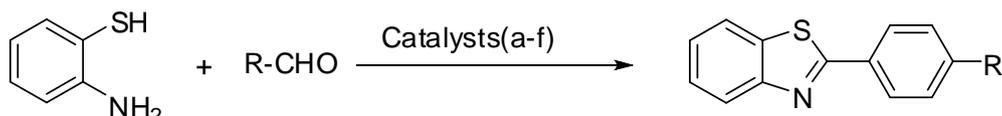
The benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities [21]. Benzothiazole is a colorless, slightly viscous liquid with a melting point of 2°C, and a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml (25°C). Benzothiazole has no household use. It is used in industry and research work purpose which are very beneficial for development [30]. A brief account of 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 [31].

1.1.1 Reaction of cyclization for Benzothiazole moiety:**1.1.1.1 Condensation of *o*-aminothiophenol with aldehydes [31]:**

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

Catalysts (a-f):

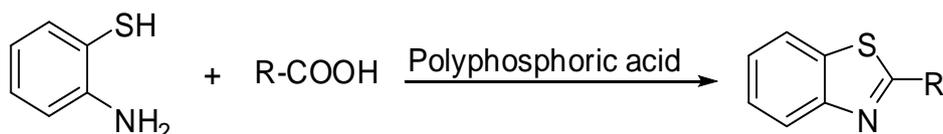
- Montmorillonite, SiO₂/Graphite; Microwave, p-TsOH
- Diethyl bromophosphonate/*tert*-Butyl hypochlorite; acetonitril
- Cerium (IV) ammonium nitrate
- H₂O₂/HCl system in ethanol
- AcOH /Air; Microwave/ Thermal Heating
- Baker's yeast, Dichloro methane



Scheme 1.1: Condensation of *o*-aminothiophenol with aldehydes in presence of different catalysts

1.1.1.2 Condensation of *o*-aminothiophenol with acids [31]:

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.



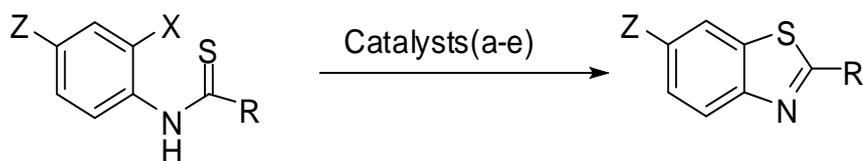
Scheme 1.2: Condensation of *o*-aminothiophenol with acids in presence of Polyphosphoric acid

1.1.1.3 Cyclization of thioformanilides using different reagents [31]:

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):

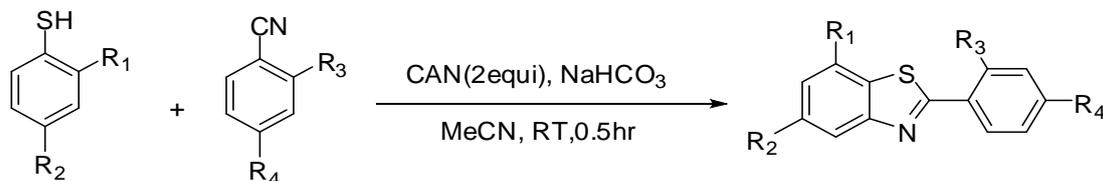
- CuI; 1, 10-Phenanthroline, CS₂CO₃, reflux
- Manganese triacetate
- CS₂CO₃, Dioxane
- Photochemical cyclization induced by chloranil
- Pd (PPh₃)₄/MnO₂ system under an oxygen atmosphere



Scheme 1.3: Cyclization of thioformanilides using different reagents

1.1.1.4 Coupling between thiophenols and aromatic nitriles [31]:

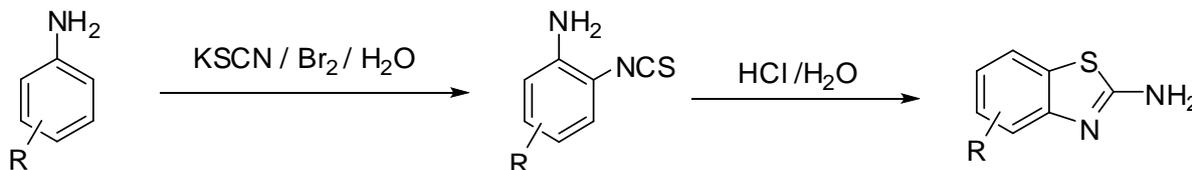
Thiophenols when treated with aromatic nitriles to affords a smooth reaction mediated by Ceric ammonium nitrate to give corresponding 2-arylbenzothiazoles in excellent yield.



Scheme 1.4: Coupling between thiophenols and aromatic nitriles

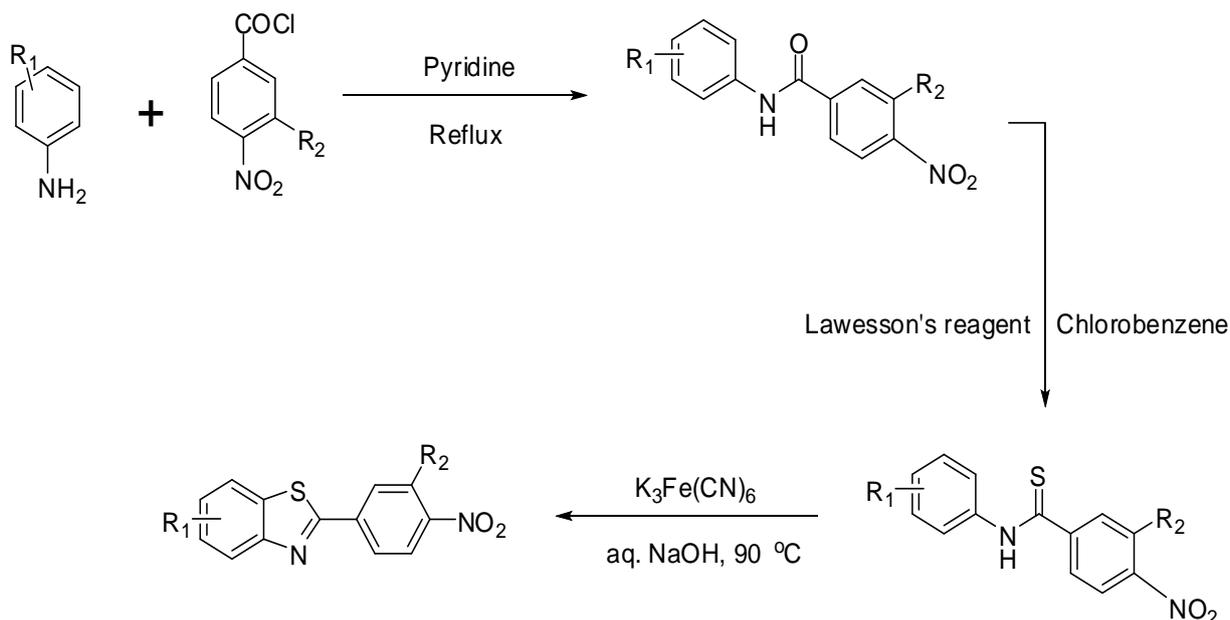
1.1.1.5 Synthesis using anilines [31]:

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



Scheme 1.5: 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 [32].

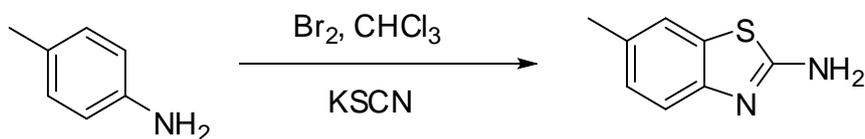


Scheme 1.6: Synthesis of benzothiazoles from substituted anilines with Lawesson's reagent

1.1.1.6 Bromine as catalyst [33]

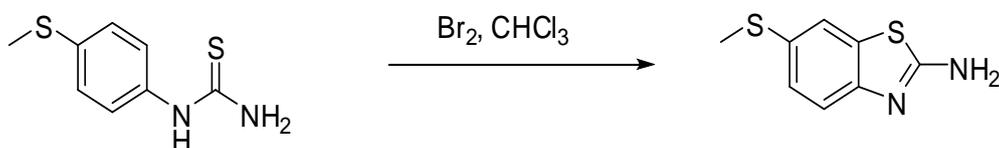
Recently several methods reported which utilize bromine as catalyst. Basically cyclization with bromine achieved by oxidation of aniline, substituted aniline and arylthiourea in acid or chloroform with alkali thiocyanate.

Hugerschhoff in early 1900s synthesized 2-aminobenzothiazole and found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiazoles [33].



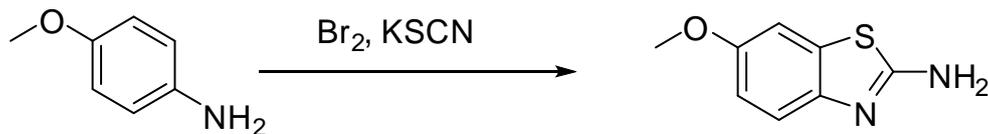
Scheme 1.7: Synthesis of 2-aminobenzothiazole with liquid bromine in chloroform

Johanson and Hamilton prepared 2-amino-6-ethylmercaptobenzothiazole by oxidation of 4-Methylmercaptophenylthiourea with bromine as a catalyst [33].



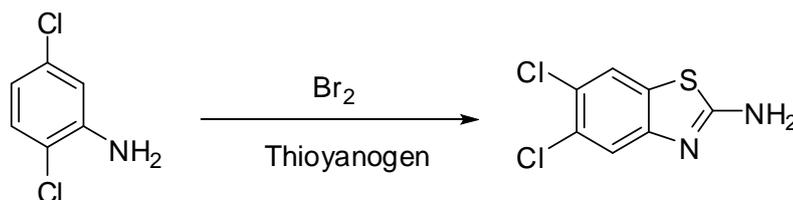
Scheme 1.8: Synthesis of 2-amino-6-ethylmercaptobenzothiazole

Stuckwisch used potassium thiocyanate to cyclize p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of bromine as a catalyst [33].



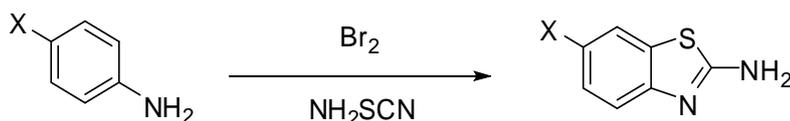
Scheme 1.9: Synthesis of 2-amino-6-substituted benzothiazole

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 [33].



Scheme 1.10: Synthesis of 2-amino-5, 6-dichloro and 2-amino-6, 7-dichlorobenzothiazole

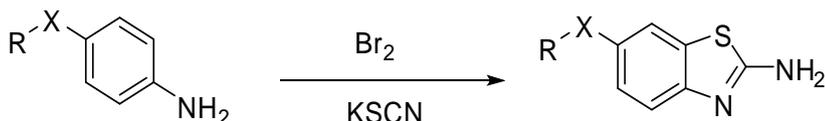
Li *et al.* prepared 6-substituted-2-aminobenzothiazole by cyclizations of p-substituted anilines with the help of ammonium thiocyanate and bromine [33].



X = Cl, Br, F, CH₃

Scheme 1.11: Cyclizations of p-substituted anilines with ammonium thiocyanate and bromine

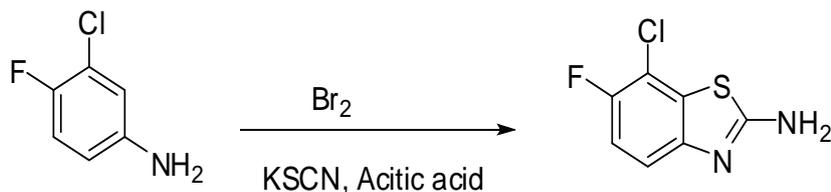
Naim *et al.*, synthesized 2-aminobenzoylthiazole-6-carboxylic acid and 2-amino-6-substituted-carbonyl benzothiazole by reaction of the corresponding 4-substituted anilines with potassium thiocyanate followed by oxidative cyclizations of the resultant thioureas with bromine [33].



X = CO
R = OH, O, alkyls

Scheme 1.12: Oxidative cyclizations of the resultant thioureas with bromine

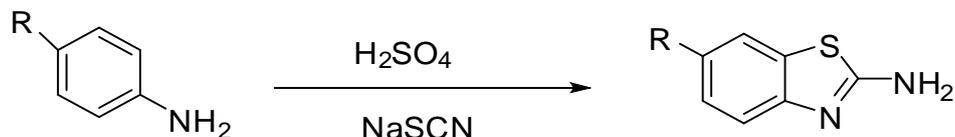
Dogruer, D. S and coworkers prepared 2-amino-6-fluoro-7-chlorobenzothiazole by cyclization of 3-chloro-4-fluoroaniline and potassium thiocyanate in presence of catalytic bromine. It is also synthesized by using similar method and materials by Nargund *et al.*, [33].



Scheme 1.13: Cyclization of 3-chloro-4-fluoroaniline and potassium thiocyanate in presence of catalytic bromine

1.1.1.7 Sulfuric acid as a catalyst [33]

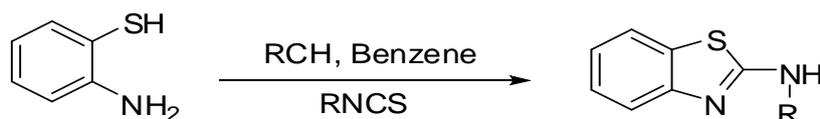
Allen used sodium thiocyanate and cyclize p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of sulfuric acid which act as a catalyst.



Scheme 1.14: Cyclizations of p-substituted aniline in the presence of sulfuric acid

1.1.1.8 Benzene as a catalyst [33]

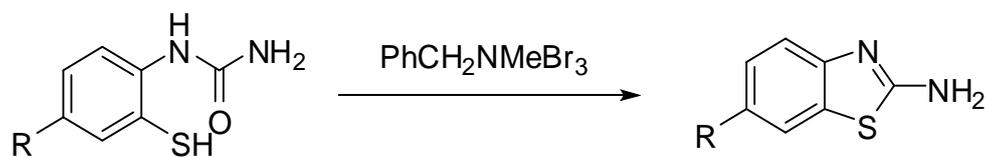
Tweit *et al.*, reported cyclizations of isothiocyanates to 2-aminobenzothiazole in presence of benzene.



Scheme 1.15: Cyclizations of isothiocyanates in presence of benzene

1.1.1.9 Benzyltrimethylammonium tribromide as catalyst [33]

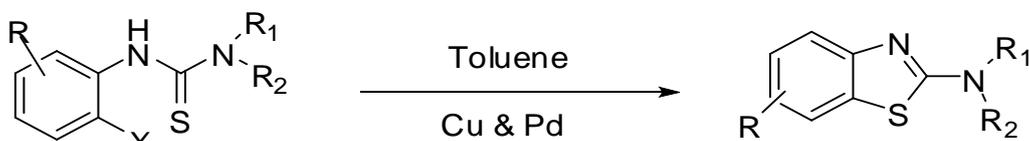
Jordan *et al.*, used Benzyltrimethylammonium tribromide ($\text{PhCH}_2\text{NMe}_3\text{Br}_3$), is an electrophilic bromine source for the conversion of substituted arylthioureas to 2-aminobenzothiazoles under mild conditions in a variety of solvents with good yields. One of the key benefits for this 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 1.16: Conversion of substituted arylthioureas to 2-aminobenzothiazoles by Benzyltrimethyl ammonium tribromide

1.1.1.10 Copper- and palladium-catalyzed cyclization [33]

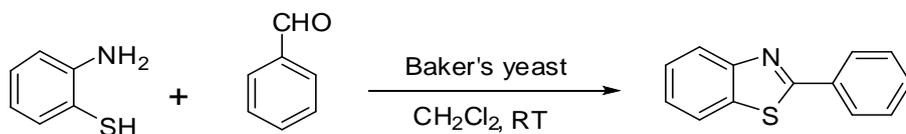
Batey *et al.*, reported the synthesis of 2-aminobenzothiazoles through analogous C-S bond forming methodologies. They formed the intramolecular C-S bond with the help of copper- and palladium-catalyzed. Copper- and palladium-catalyzed intramolecular C-S bond formation by cross-coupling between aryl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



Scheme 1.17: Copper- and palladium-catalyzed intramolecular C-S bond formation by cross-coupling

1.1.1.11 Baker's yeast to catalyze cyclization [34]

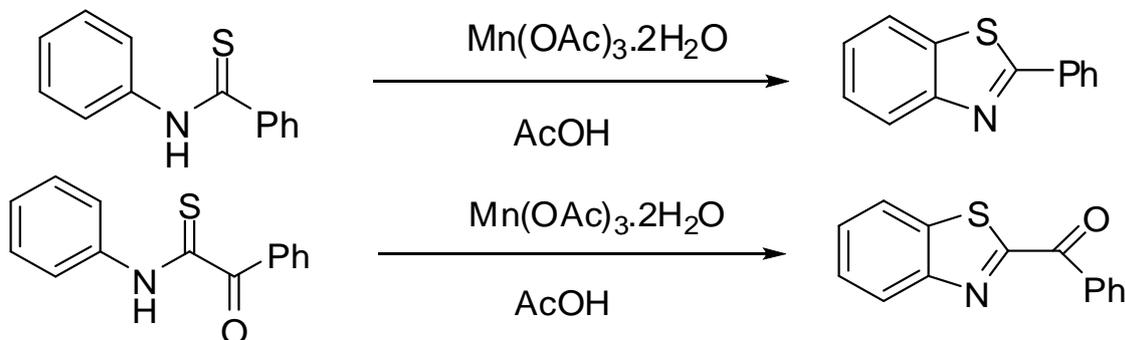
Umesh R. Pratap successfully employed baker's yeast to catalyze the condensation of 2-aminothiophenol and aldehydes in DCM to yield 2-substituted benzothiazoles in moderate to good yields under mild reaction condition.



Scheme 1.18: Baker's yeast to catalyze the condensation of 2-aminothiophenol and aldehydes

1.1.1.12 Manganese triacetate as a catalyst [35]

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.

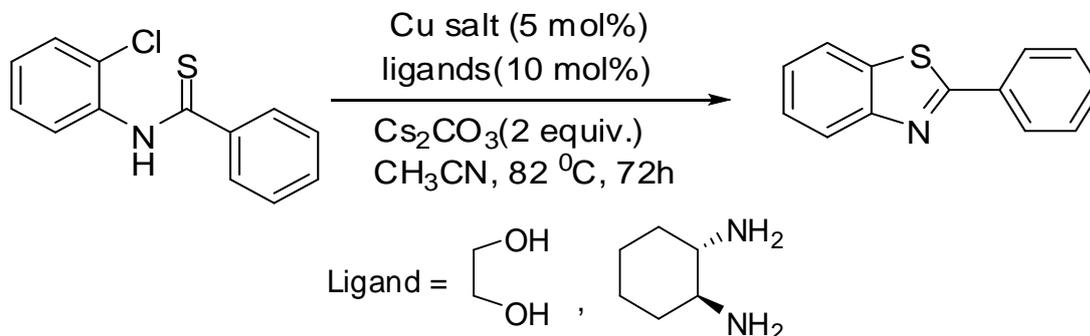


Scheme 1.19: Cyclization reactions with Manganese (III) triacetate

1.1.1.13 BINAM-Copper (II) as catalyst [36]

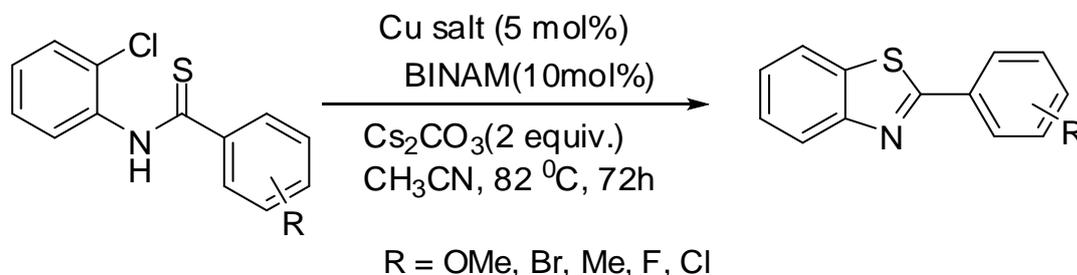
BINAM-Cu(II) complex as an efficient catalyst for the synthesis of benzothiazole through intramolecular coupling cyclization from N-(2-chlorophenyl) benzothioamide under mild reaction conditions. A wide range of 2-aryl or 2-alkyl-substituted benzothiazoles are synthesized through intramolecular C(aryl)-S 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 °C).

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



Scheme 1.20: Synthesis of 2-phenyl benzothiazoles via different ligands and copper salts

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

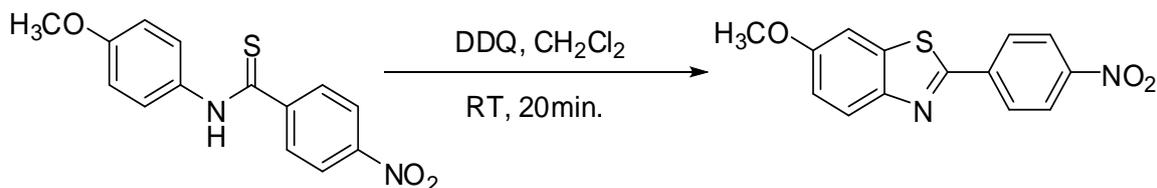


Scheme 1.21 Synthesis of benzothiazoles via copper (II)-catalyst

1.1.1.14 DDQ as catalyst³⁷

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

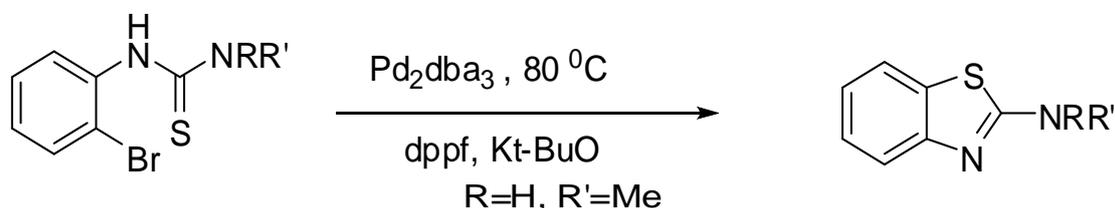
high degree of flexibility with regard to the functional groups that can be placed on the benzothiazole nucleus or 2-aryl moiety which in turn generates scaffolds for parallel synthesis.



Scheme 1.22: DDQ- mediated intramolecular cyclization of thioformanilide

1.1.1.15 Palladium as catalyst ³²

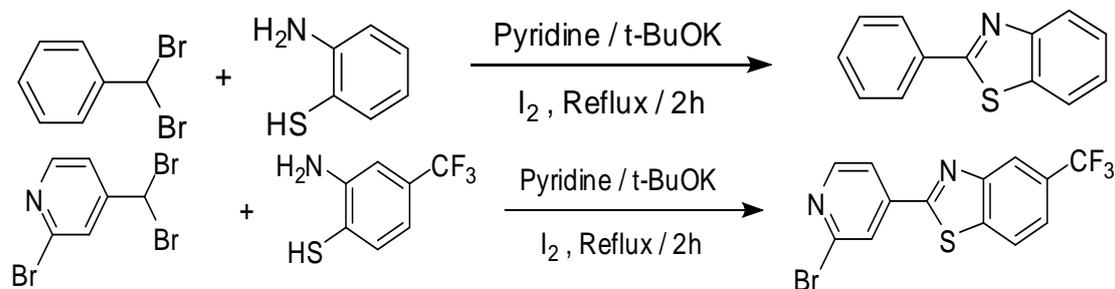
2-Amino-, and 2-alkyl-benzothiazoles have been efficiently prepared by palladium catalyzed cyclization of *o*-bromophenylthioureas and *o*-bromophenylthiamides. Results were best with the Pd₂(dba)₃/ monophosphine catalytic system. Palladium-catalyzed aryl-nitrogen bond forming reactions are highly useful 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, oxindoles, 2-aryl-2*H*-indazoles, 1-aryl-1*H*-indazoles, imidazoles, oxazepines and thiazepines, indulines, and other heterocycles.



Scheme 1.23: Cyclization reaction of 2-bromophenylthioureas catalyzed by Pd₂dba₃/ ligand

1.1.1.16 Pyridine as catalyst [38]

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 1.24: Synthesis of benzothiazoles from gem-dibromomethylarenes using 2-amino benzenethiols

1.1.1.17 PIFA as catalyst [39]

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 1.25: PIFA- mediated oxidation of thiobenzamides to benzamides

1.2 GENERAL DESCRIPTION OF TRIAZENE

Triazines are a diverse class of compounds that possess three consecutively bonded nitrogen atoms. The first nitrogen atom in a triazine is bonded to the second nitrogen atom by a double bond, which is bonded to the third nitrogen atom by a single bond. Such as [40].



Triazines have been utilized in a variety of research areas. In organic synthesis, they have been used as protecting groups for aromatic amines, as linkers in solid-phase peptide synthesis and as synthons for novel heterocyclic compounds [40].

Triazines have also been investigated as antitumor agents and incorporated into novel conductive aromatic polymers [40].

Certain triazines have technical importance as intermediates in the so-called "Rapidogen" dyeing process. Other triazines have been evaluated as carcinostatic agents on transplanted animal tumours. Aryldialkyltriazines in patents have been claimed as rodent repellents and herbicides [41].

In acid medium aryldialkyltriazines are easily hydrolysed to form aryldiazonium salts and secondary amine. For this reason triazines have been tested primarily by us for carcinogenic activity of diazotating and/or arylating agents [41].

1-Phenyl-3,3-dimethyltriazene (Fig 2) is a potent carcinogen in BD-rats, producing after oral as well as subcutaneous application mainly malignant tumours of the brain and nervous tissue (neurotropic action). Certain other 1-aryl-3,3-dialkyltriazines of the general formula [41].

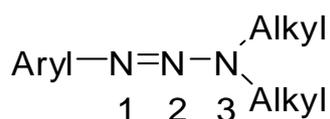


Figure 2: Structure of 1-Phenyl-3,3-dimethyltriazene

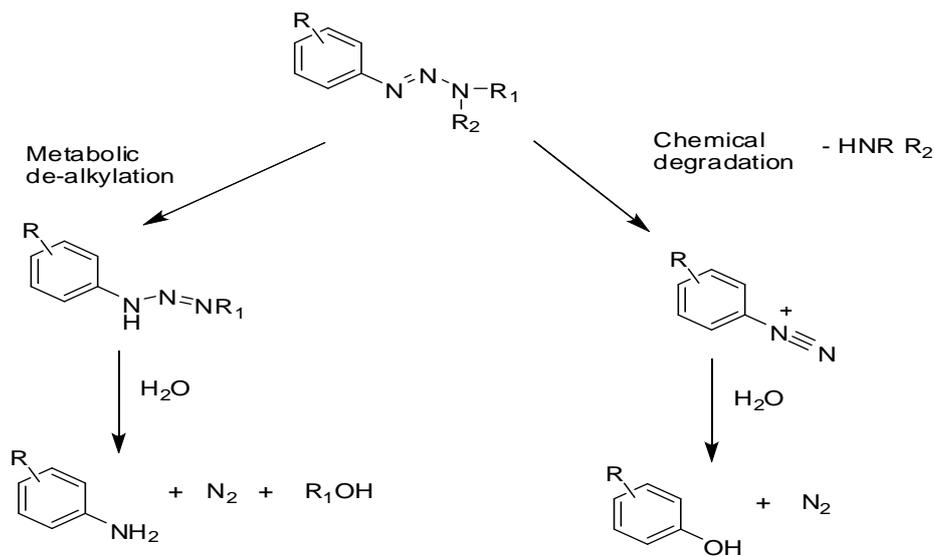
Are also carcinogenic in rats, as has been demonstrated in extensive work on structure-activity relationships in this group of compounds. Many triazines are carcinogenic even after application of a single dose of carcinogen [41].

The dimethyltriazines are a class of compounds endowed of different biological properties. In particular, a large series of derivatives have been widely studied for their mutagenic [42-44], carcinogenic [45, 46] and antitumor activities [47-49] and in some instances, quantitative structure-activity relationships have been made using several experimental models [50, 51]. Of these biological properties, a particular interest is given by their selective antimetastatic effects [52-54], since these compounds inhibit tumor dissemination in the absence of any significant toxicity for either tumor cells and host tissues [53, 54]. Besides the reported biological properties, two patent works, focused by Dr. J.L. Niesel in 1976 for Eli-Lilly and Company, (Indianapolis, MN) on the search of new non-steroidal drugs endowed of antirheumatic activity, describe the antiinflammatory action of some 3-aryl-triazene-1-oxides in experimental models. With the exception of these studies, no data appear from the literature on the possible antiinflammatory activity of dimethyltriazines.

1.2.1 Chemical Reaction of substituted 1-aryl- 3, 3- dimethyl triazene:

1.2.1.1 Chemical and metabolic breakdown of dimethyltriazines [55]:

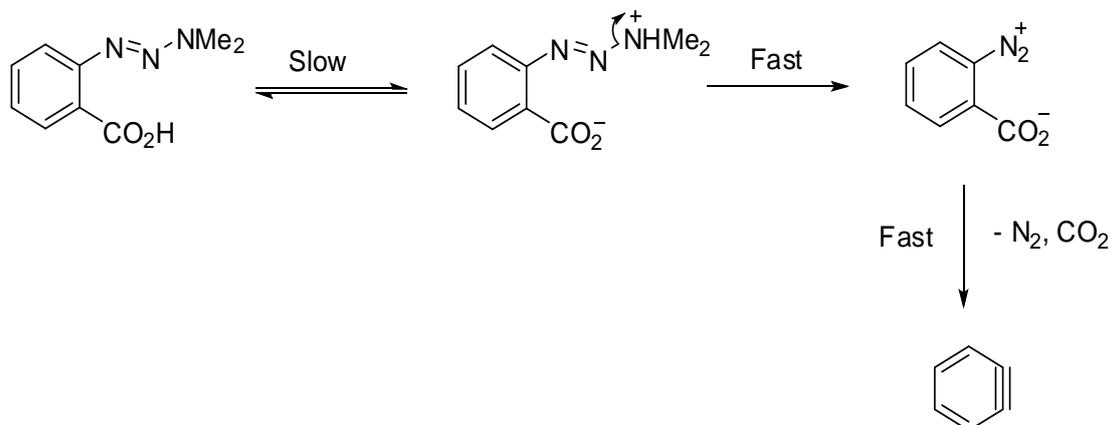
Gescher *et al.*, studied that the chemical and metabolic breakdown of dimethyltriazines is complex and may involve the generation of a number of potentially cytotoxic species. In order to identify those species which are selectively cytotoxic and compared the cytotoxicity of some of these breakdown products to two tumour cell lines in vitro; one tumour is sensitive to the dimethyltriazines in vivo (TLX5S lymphoma); the counterpart has an induced resistance to the effects of dimethyltriazines in vivo (TLX5R lymphoma). And other comparisons described for an estimation of whether an agent is non-selectively cytotoxic and so will kill both TLX5S and TLX5R cells or is selective and will kill only TLX5S cells [55].



Scheme 1.26: Chemical and metabolic breakdown of dimethyltriazenes

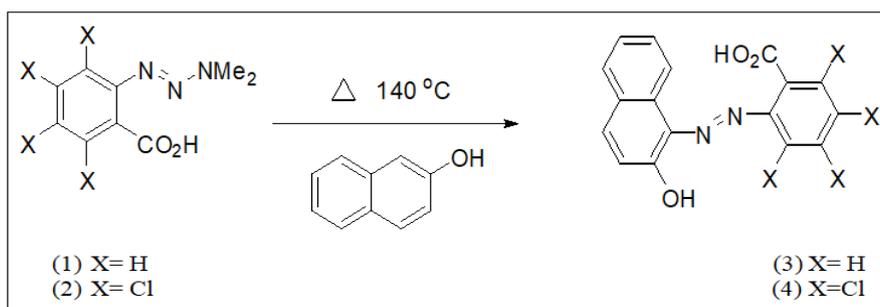
1.2.1.2 Aryne Formation from 1-(2-Carboxyaryl)-3,3-dimethyl triazenes [56]:

Buxton *et al.*, the study of the decomposition of 1-(2-carboxyphenyl)-3,3-dimethyltriazene and the tetrabromo and tetrachloro- analogues showed that the arenediazonium-2-carboxylates were intermediates in the formation of the corresponding arynes: the 1-(2-carboxytetrahalophenyl)-3,3 dimethyl triazenes are stable precursors that enable cycloaddition reactions of the tetrahalobenzenes to be carried out in acceptable yields using substrates such as N-methylpyrrole, p-xylene and m-dimethoxybenzene.



Scheme 1.27: Formation of aryne from dimethyltriazene

They heated both 1-(2-carboxyphenyl)-3,3-dimethyltriazene (1) and its tetrachloro-analogue (2) at 140 °C in 1,1,2,2-tetrachloroethane containing 2-naphthol and were pleased to be able to isolate the azo-dyes (3) and (4) in modest yields, thereby establishing the intervention of benzenediazonium-2-carboxylate and tetrachlorobenzenediazonium-2-carboxylate in the formation of the arynes from the triazenes [57].



Scheme 1.28: Formation of the arynes from the 1-(2-carboxyphenyl)-3,3-dimethyltriazene (1) and its tetrachloro-analogue (2)

CONCLUSION

The performing of pharmacological screening of synthesized compounds were found to be that the Benzothiazole derivatives were show more significant anti-inflammatory activity than standard drug *Nimesulide*. The some compounds were show significant activity but some compound was show more significant activity. So that the compounds were more potent anti-inflammatory agents of benzothiazole derivatives. The Triazene derivatives were show more significant anti-inflammatory activity than standard drug *Nimesulide*. The some compound of Triazene was show less significant activity but the some compound was show more significant activity than standard drug. After the performing the research work we concluded that among the tested compounds of benzothiazole derivatives, exhibited better antiinflammatory activity but some compound was more potent when compared to standard drug *Nimesulide* and also among the tested compounds of triazene derivatives, exhibited better antiinflammatory activity when compared to standard drug *Nimesulide*. Which show that heterocyclic ring with sulphonamides were inhibit the inflammation with better action and 3,3-dimethyl triazene with sulphonamides were also inhibit the inflammation with better action.

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