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Review Article

SYNTHESIS, REACTIONS, AND PHARMACOLOGICAL APPLICATIONS OF 2-AMINOBENZIMIDAZOLES: AN UPDATE

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ABSTRACT

Many drug molecules comprises of benzo fused heterocycles with two nitrogen atoms, that is, benzimidazole and its derivatives. Many biological active molecules contain that 2-aminobenzimidazole cores are among the foremost common structural components in medicinal chemistry. 2-aminobenzimidazole and its derivative have wide range of biological and pharmaceutical activities. In this review, the authors summarize synthesis, various chemical reactions, and biological activities of 2-aminobenzimidazole and its derivative.

Keywords: 2-Aminobenzimidazoles, Derivatives of 2-aminobenzimidazole, Pharmacological applications, Reactions.

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INTRODUCTION

2-Aminobenzimidazole may be a readily available chemical and may even be easily prepared within the laboratory. This review highlights different methods for the preparation of varied 2-aminobenzimidazoles. The utility of this organic synthon in preparing a good type of substituted benzimidazoles and benzimidazole heterocycles is systematically discussed with the applications of such compounds for the event of some new chemotherapeutic agents [1]. 2-aminobenzimidazole may be a member of the category of benzimidazoles, that's benzimidazole during which the hydrogen at position 2 is replaced by an amino group. 2-aminobenzimidazole (white shiny plates; m.p.220–222°C) is one in every of the longest known nitrogen heterocycles and has been recently recognized as a useful building block for the synthesis of a good kind of substituted benzimidazoles and benzimidazole heterocycles of educational, pharmaceutical, and industrial interest. The polyfunctionality resulting from the cyclic guanidine residue has made 2-aminobenzimidazole a flexible material in organic synthesis [2].

The 2-amino derivative is often found within the medicinal chemistry literature as a starting material [3]. A plethora of medicinal properties has been shown by derivatives of 2-substituted benzimidazole as a target molecule [4].

SYNTHESIS OF 2-AMINOBENZIMIDAZOLE

Using cyanamide

2-aminobenzimidazole is a crucial parent substance, for example, pesticides. Although it is often obtained by ring closure of o-phenylenediamine with cyanogen bromide [5], this process is unsuitable for industrial work. We have been able to prepare in almost quantitative yield and in excellent purity by treating o-phenylenediamine with cyanamide, which is quickly available on an industrial scale [6] (Scheme 1).

Using mercuric oxide

The present invention consists a process for preparing 2-aminobenzimidazole comprising ring-closing an N-(o-aminophenyl) thiourea with mercuric oxide to administer a 2-aminobenzimidazole [7] (Scheme 2).

Scheme 1: Synthesis of 2-aminobenzimidazole using cyanamide

SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES

Using thiourea and related derivatives

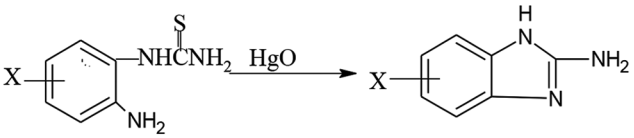
The reaction is occur through formation of carbodiimides as an intermediate further cyclization of 1-(2-amino-phenyl)thiourea results in the formation of 2-Alkyl-2-aryl and 2-acylaminobenzimidazoles [8] (Scheme 3).

The cyclisation carried out with help of lead oxide and mercuric oxide in dry chloroform. Dimethyl sulfate and methyl iodide in ethanol mercury(II)chloride were proposed as a reagent [9-13]. The cyclization of (o-aminophenyl) thiourea was resulted in benzimidazole thione as a product, instead of synthesizing unsubstituted 2-aminobenzimidazole [14,15]. The formation of 2-alkoxycarbonylaminobenzimidazole was prepared from reaction of N-[alkoxy(methylthio)methylene] and o-phenylenediamines with alkyl esters of carbalkoxythiocarbamic. The synthesize of carbamates was planned by Murray and Dains, in 1934, using o-phenylenediamine with 1,3-bis(alkoxycarbonyl)-S-methylisothiourea [16-22].

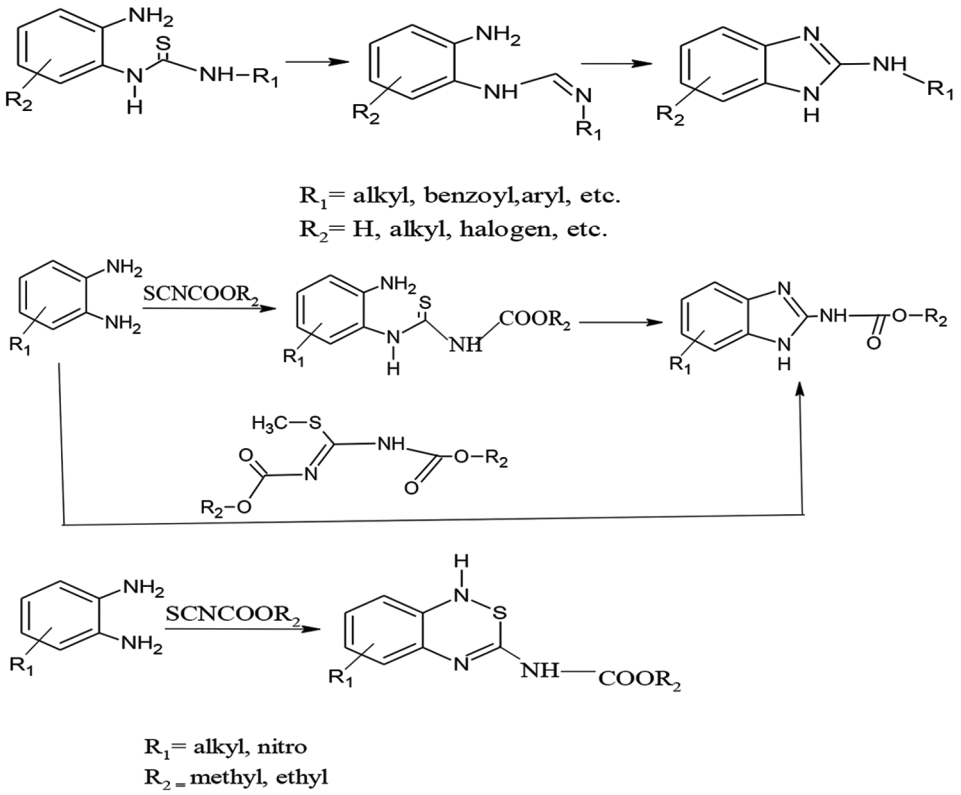
Using cyanogen halide, cyanamide and cyanoguanidines

The synthesis of several 2-aminobenzimidazole is synthesized using the Pierron process [23].

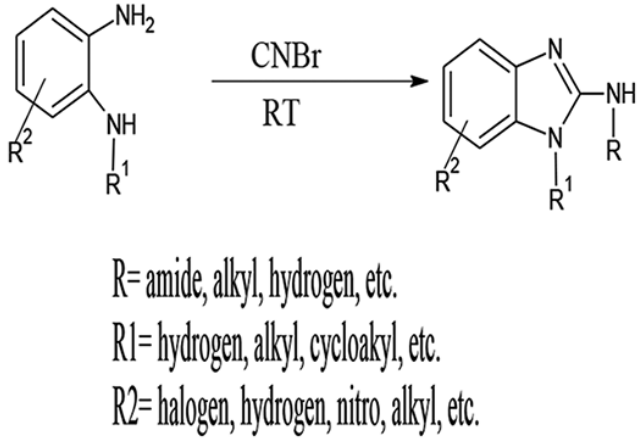
2-amino and 2-dimethylaminobenzimidazoles produce with reaction of dimethyl cyanamide and hydrochloride salts of o-phenylenediamine with cyanamide, in low yields [24-26]. The reaction of chlorocarbonic acid esters and acyl chlorides with cyanamide in the presence of pyridine or hydroxide triethylamine or with calcium cyanamide to obtain ethoxycarbonyl substituted cyanamide [27-31] (Scheme 4).



Scheme 2: Synthesis of 2-aminobenzimidazole using mercuric oxide



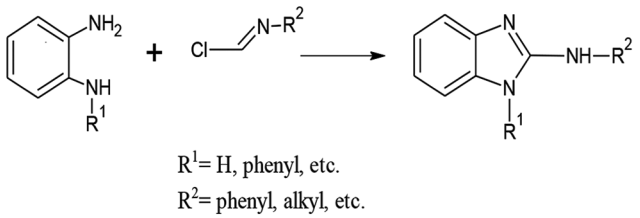
Scheme 3: Synthesis of 2-aminobenzimidazole using thiourea and similarly assembled compounds



Scheme 4: Preparation of 2-aminobenzimidazole using cyanogens halide

Using N-substituted carbon imidoyl dichlorides

2-sodio-l-methyl benzimidazole and O-methylhydroxylamine were used as unsuccessful attempts to made the corresponding amine derivatives. The formation of 2-diethylamino-l-methylbenzimidazole derivative in low yield with the action of BrN(C2H5)2 on the 2-sodio byproduct. The synthesis of 2-aminobenzimidazole has synthesized by the help of N-substituted carbon imidoyl dichloride. The reaction between o-phenylenediamine and N-phenyl-o-phenylenediamine with N-aryl carbon imidoyl dichloride was resulted in 2-arylaminobenzimidazoles and 1-phenyl-2- anilinobenzimidazole. Exploitation of N-alkoxy carbonyl carbon imidoyl dichloride resulted in 2-alkoxycarbonylaminobenzimidazoles in the presence of dioxane, choloroform and triethylamine [32,33] (Scheme 5).



Scheme 5: Synthesis of 2-aminobenzimidazoles using N-substituted carbon imidoyl dichloride

Benzimidazole derivatives initiated by rearrangement with some quinoxaline derivatives by photochemically, the yield depends on the pH of the medium and the solvent [34] (Scheme 6).

Using urea derivatives with aryl substituted guanidines

Cyclisation of (N-Phenacyl amino) phenyl urea and phosphorus oxychloride by heating leads to 1-phenacyl-2- aminobenzimidazole and 2-benzylaminobenzimidazole resulted using 1-(o-amino phenyl)-3- benzyl urea in toluene and p-toluene acid by reflux [35-37] (Scheme 7).

Cyclization of N-(o-Amino phenyl)-N-methyl-N',N"-disubstituted guanidines to aminobenzimidazole by treating with CS_2, $CSCl_2$, and $HC(OC_2H_5)_3$ [38]. De composition of 2-Acyloxyguanidines results in 2-dialkylaminobenzimidazoles at room temperature [39]. An imino nitrene intermediate was obtained as result of the rearrangement of N-aryl-N-hydroxyamidines to benzimidazoles [40,41] (Scheme 8).

REACTIONS OF 2-AMINOBENZIMIDAZOLE

Oxidation reaction

2-acetyl aminobenzimidazole results from 2-aminobenzimidazole and acetic anhydride. Benzimidazoles are stable to oxidation (Scheme 9).

A little amount of imidazoledicarboxylic acid was obtained in the presence of strong oxidizing agent. A spread of benzimidazole carboxylic acids is prepared by the substituent group [42].

Electrophilic reaction

Nuclear substitutions of 2-aminobenzimidazoles using various electrophiles have yielded several 5,6-substituted benzimidazoles. Thus, 2-amino-5-chlorobenzimidazole is obtained by reaction of 2-aminobenzimidazole with oxide or hydrochloric acid or sodium hypochlorite. Within the latter case, four other benzimidazoles were also isolated from the reaction mixture [43]. Similarly, bromination of 1-alkyl-2-aminobenzimidazoles gave both 5-bromo- and 5,6-dibromobenzimidazoles (1) and (2). Nitration of 1-alkyl-2-aminobenzimidazoles and 1,3-diethyl-2-iminobenzimidazole yielded 5,6-dinitro-2-aminobenzimidazoles and therefore the corresponding 2-imino derivative, respectively. However, nitration of 1,3-dimethyl-2-iminobenzimidazole gave both 5-nitro- and 5,6-dinitro-1,3-dimethyl-2-iminobenzimidazoles [44] (Scheme 10).

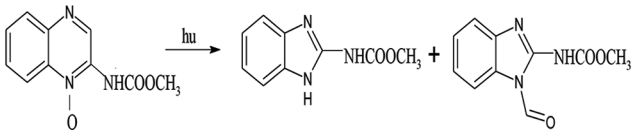
Reaction with nitriles

2-aminobenzimidazole reacts with cyanates to yield 1-substituted-2-aminobenzimidazoles (3), which can be cyclized with an aldehyde or ketone in presence of an acid or a base to yield the triazinobenzimidazoles(4) [45,46]. Similarly, treatment of 2-aminobenzimidazole with N-cyanoformimidates yields aminobenzimidazo[1,2-a]-1,3,5-triazines which can have the structures (5) or (6). The structure (5) was proved by its unambiguous synthesis from 2-guanylbenzimidazole and triethyl orthoformate [47] (Scheme 11).

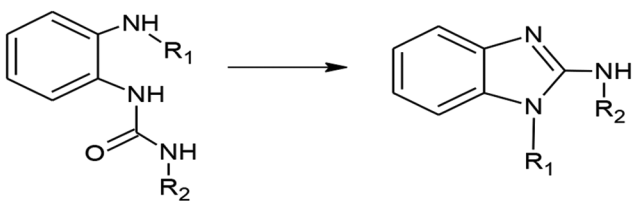
Substitution reactions

Alkylation and arylation reactions

Alkylations and arylations of 2-aminobenzimidazoles with alkyl or aryl halides create to moderate yields of 1-substituted-2-aminobenzimidazoles or 1,3-disubstituted-2-iminobenimidazoles, depending on the reactivity of organic compound, which ends up



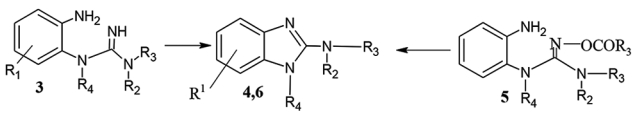
Scheme 6: Synthesis of 2-aminobenzimidazole using N-substituted carbon imidoyl chlorides



R_1= H, alkyl, benzyl, etc.

R_2= H, alkyl, benzyl, etc.

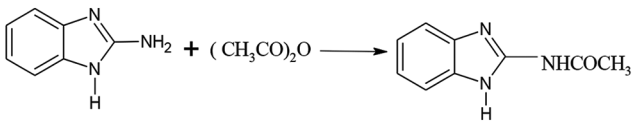
Scheme 7: Synthesis of 2-aminobenzimidazole using urea derivatives



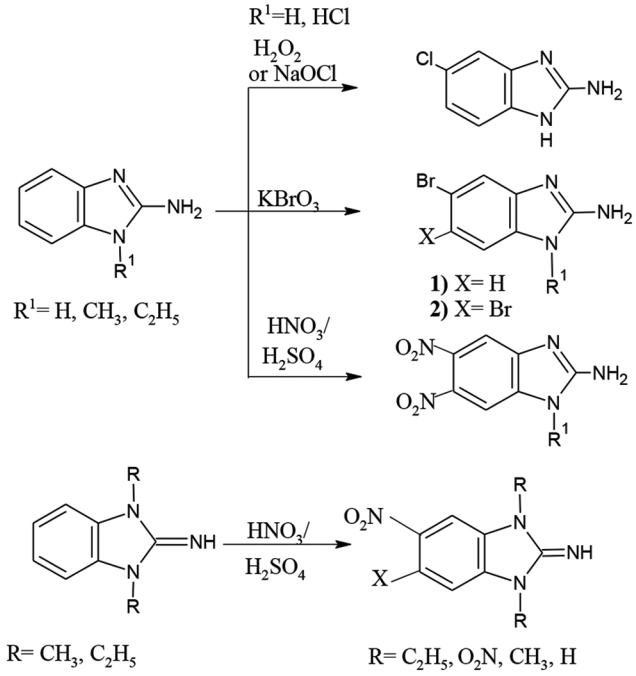
In 3,4 R_1,R_2,R_3,R_4= H, alkyl

In 5,6 R_1,R_2,R_3,R_4= H, alkyl, benzyl, phenyl, phenyl amine

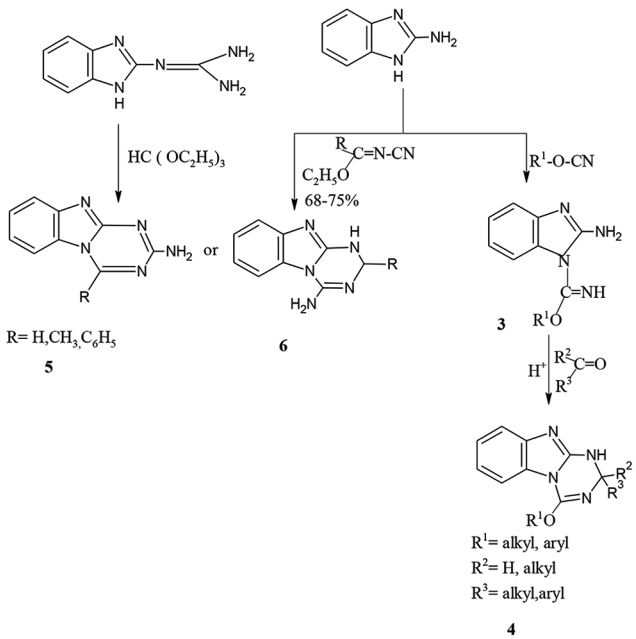
Scheme 8: Synthesis of 2-aminobenzimidazole using Aryl substituted guanidines



Scheme 9: Oxidation reaction of 2-aminobenzimidazole



Scheme 10: Electrophilic reaction of 2-aminobenzimidazole



Scheme 11: Reaction of 2-aminobenzimidazole with nitriles

from their respective quaternary salts on action with a base. In an alternate method, 1-alkyl-2-aminobenzimidazole could also be treated with an organic compound to afford the corresponding 1,3-dialkyl-2-iminobenzimidazoles, which also involves quaternary salts as an intermediate product. Reaction of 2-aminobenzimidazole with alkyl iodides with hydrated oxide is to afford 1-alkyl-2-aminobenzimidazoles [48] (Scheme 12).

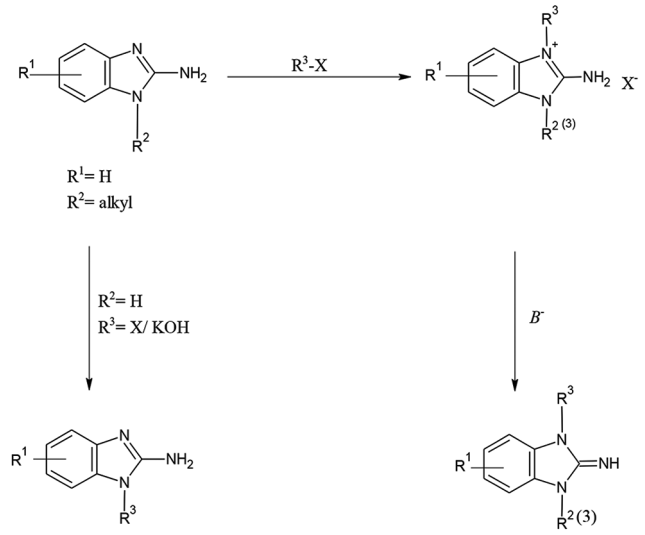
Another simple method to organize 1,3-dimethyl-2-methyliminobenzimidazole involves the methylation of 2-aminobenzimidazole with dimethyl sulfate. An identical reaction of 2-phenylaminobenzimidazole with dimethyl sulfate gives 1,3-dimethyl-2-phenyliminobenzimidazole [49] (Scheme 13).

Acylation and aroylation reaction

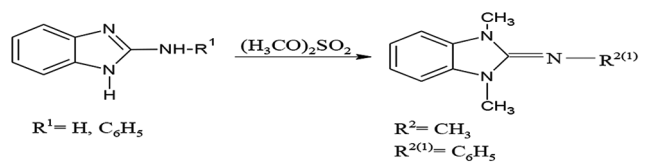
Acylation of 2-aminobenzimidazoles with an oversized form of alkyl carbonhalidates gives alkyl benzimidazole-2-carbamates in good yields. Better yields of alkyl benzimidazole-2-carbamates could also be obtained by treating 2-aminobenzimidazole, generated in place, with alkyl carbonochloridates [50]. The latter can also be prepared either by reacting 2-aminobenzimidazole with alkyl carbonates in presence of a base or with ethylene carbonate in presence of an alcohol and a base. The formation of alkyl benzimidazole-2-carbamate may proceed through the formation of the mono- or disubstituted benzimidazoles which when treated with a base, bring about to alkyl benzimidazole-2-carbamate [51] (Scheme 14).

Using an appropriate quantity of alkyl carbonohalidates or the dialkyl carbonates within the above reaction, the tricarboxylates 1-ethoxycarbonyl-2-(-diethylcarbonylamino)-benzimidazole and 2-ethoxycarbonylimino-1,3-diehoxycarbonyl-1,3-dihydrobenzimidazole were isolated from the reaction mixture; these compounds could also be also obtained by reaction of 1-ethoxycarbonyl-2-aminobenzimidazole with dialkyl carbonates. Better yields of 1-ethoxycarbonyl-2-(-diethylcarbonylamino)-benzimidazole were obtained by treating 2-ethoxycarbonylamino benzimidazole with ethyl carbonochloridate. The merchandise 1-ethoxycarbonyl-2-(-diethylcarbonylamino)-benzimidazole is hydrolyzed with alkaline ethanol to afford the corresponding 2-(N,N'-dialkoxycarbonylamino)-benzimidazole [52] (Scheme 15).

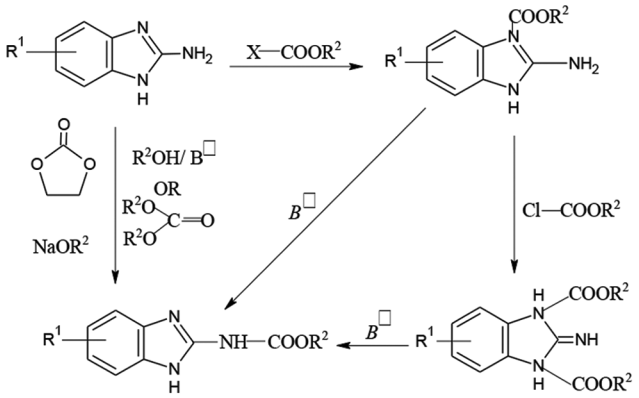
The opposite 2-N-acylaminobenzimidazoles could also be obtained by treating 2-aminobenzimidazole with acyl halides or acetic anhydride [53] (Scheme 16).



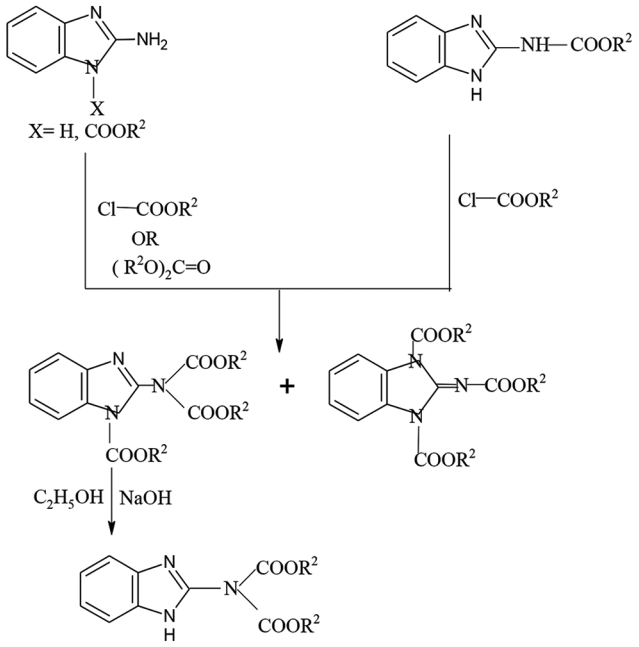
Scheme 12: Alkylation and arylation reaction of 2-aminobenzimidazole



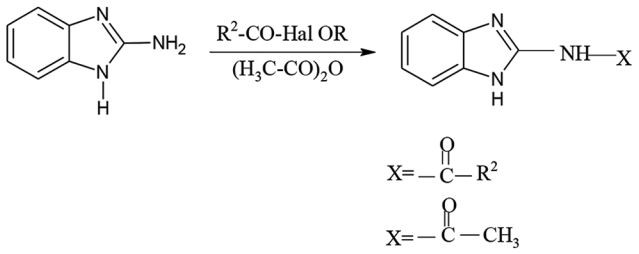
Scheme 13: Alkylation and arylation reaction of 2-aminobenzimidazole



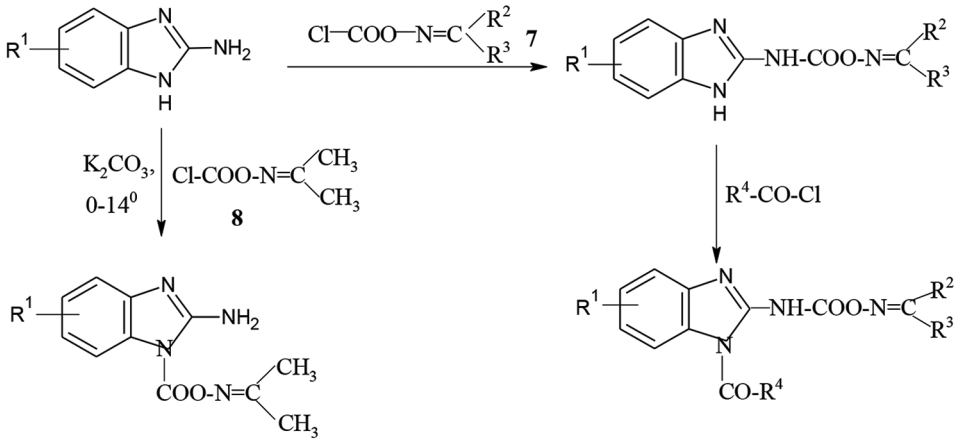
Scheme 14: Acylation reaction of 2-aminobenzimidazole



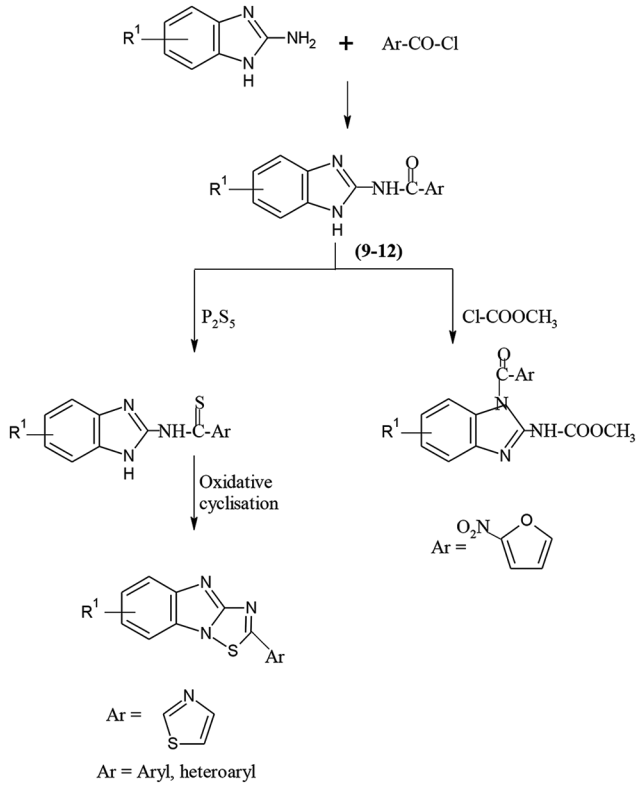
Scheme 15: Acylation reaction of 2-substituted aminobenzimidazoles



Scheme 16: Acylation reaction of 2-substituted 2-aminobenzimidazole



Scheme 17: Acylation reaction of 2-aminobenzimidazole



Scheme 18: Aroylation reaction of 2-aminobenzimidazole

A number of benzimidazolyl carbamates are prepared as potential antiparasitic agents. Thus, reaction of 2-aminobenzimidazole with (7) gave the corresponding benzimidazole-2-carbamate, some of which were further acylated to afford the desired 1,2-disubstituted benzimidazoles. When the reaction of 2-aminobenzimidazole with (8) was allotted in acetone or dichloromethane within the presence of potassium carbonate at 0–140°C, a 74% yield of the 1-substituted-2-aminobenzimidazole was obtained [54] (Scheme 17).

The aroylation of 2-aminobenzimidazole yields both mono- and disubstituted benzimidazoles with a broadspectrum of biological activity. Thus, reaction of 2-aminobenzimidazole with aromatic acid chlorides yields the corresponding 2-aroylaminobenzimidazoles (9-12), which can be further acylated to allow 1,2-disubstituted benzimidazoles or thiolated to the corresponding thiones. The latter was cyclized within the presence of bromine to present the 2-substituted-1,2,4-thiadiazolo[2,3-a]benimidazoles. Several other thiadiazolo[2,3-a] benzimidazoles have also been prepared similarly [55] (Scheme 18).

Another method to arrange various 2-[N-(2-benzimidazo)-carbonyl] aminobenzimidazoles involves the nucleophilic ring opening of 6,13-dioxo-6H,13H-pyrazino[1,2-a:4,5-a]bisbenzimidazoles with 2-aminobenzimidazole [56] (Scheme 19).

Benzoylation of 2-amino-1-methylbenzimidazole with benzoyl chloride in acetone at temperature gave the benzimidazolium chloride, which afforded 2-benzoylamino-1-methylbenzimidazole when heated with a base in chloroform. The merchandise 2-benzoylamino-1-methylbenzimidazole was obtained through an imine intermediate; the structure of an imine intermediate was established by converting it into 1-methylamino-2-methylbenzimidazole [57] (Scheme 20).

Further work on the mechanism of the aroylation of 2-aminobenzimidazoles involved reaction with various aroyl chlorides to make intermediate 1,3-diaroyl-2-iminobenzimidazoles which were readily transformed into 2-N-(aroylamino)-benzimidazoles within the presence of a base. The structure of 2-(N-aroylamino)-benzimidazoles was supported by the very fact that reaction of 2-(N-aroylamino)-benzimidazoles with benzyl chloride yielded 1-benzyl-2-(4-chloro-3-nitrobenzoyl)-aminobenzimidazole which was alternatively obtained by treating 1-benzyl-2-aminobenzimidazole with 4-chloro-3-nitrobenzoyl chloride [58] (Scheme 21).

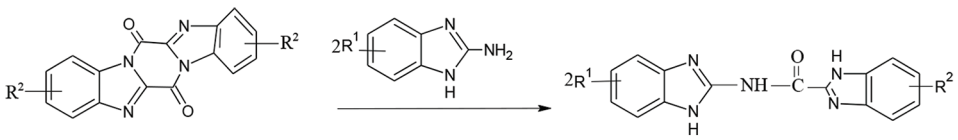
Sulphonylation reactions

Reaction of 2-aminobenzimidazoles with various sulphonyl chlorides yields, in general, 1-sulphonyl-2-aminobenzimidazoles, which, as an example when X=m-O_2 N---C_6H_4, afford, after the treatment with caustic soda, 2-aminobenzimidazole benzenesulfonate. Some 1-sulphonylamino-2-aminobenzimidazoles are acylated to yield the corresponding 1,2-disubstituted benzimidazoles possessing fungicidal activity. One such compound (13), obtained by treating 1-sulphonyl-2-aminobenziidazole with methylmagnesium bromide, showed 100% *in vitro* inhibition of the expansion of polio virus at a amount of 1.5 μg/ml [59] (Scheme 22).

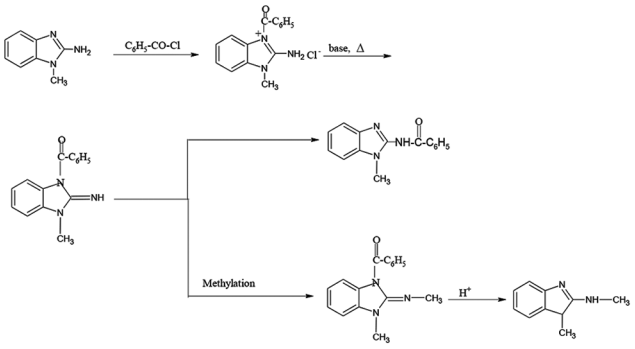
The preparation of 2-(4-acetylaminobenzenesulphonyl)-aminobenzimidazole is achieved by treating 2-aminobenzimidazole with 4-acetaminobenzenesulphonyl chloride, while its deacetylated product (14) can be obtained by the reaction of o-phenylenediamine with p-aminobenzenesulphonylguanidine. The latter is obtained by reaction of p-aminobenzenesulfonamide with dicyanodiamide (Scheme 23).

Reaction with carbonyl compounds

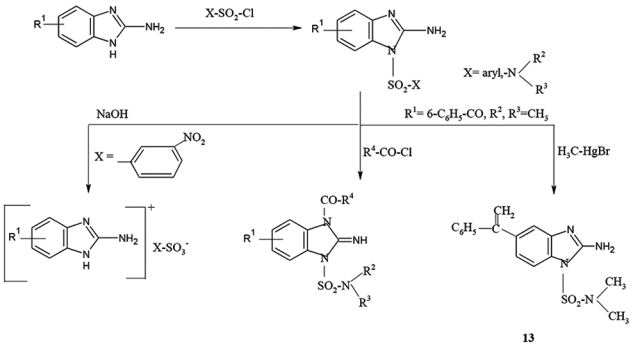
A number of aldehydes and ketones are known to react with 2-aminobenzimidazolestocreatethecorrespondingSchiffbaseswithabroad



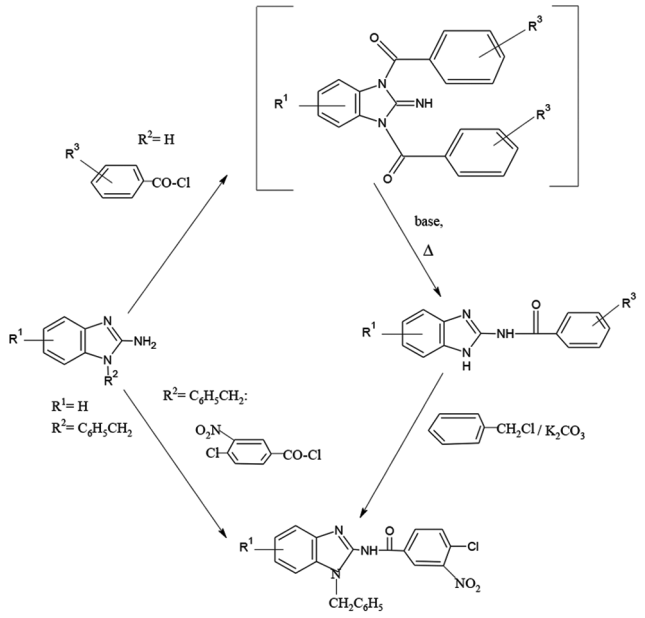
Scheme 19: Aroylation reaction of 2-aminobenzimidazole



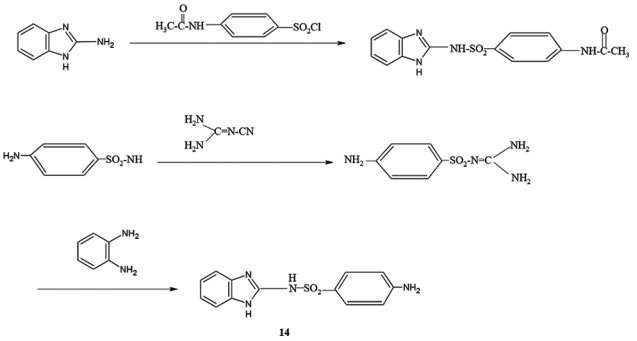
Scheme 20: Aroylation reaction of 2-aminobenzimidazole



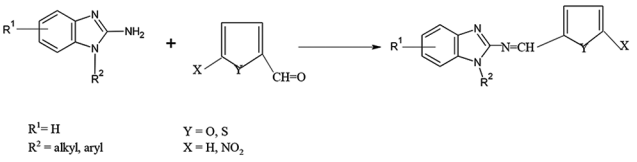
Scheme 22: Sulfonylation Reaction of 2-aminobenzimidazole



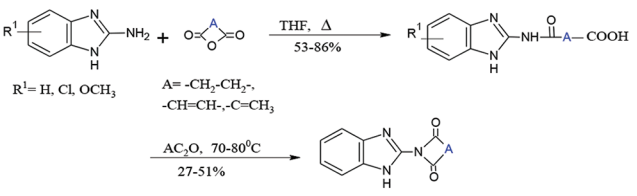
Scheme 21: Mechanism of aroylation reaction of 2-aminobenzimidazole



Scheme 23: Sulfonylation reaction of 2-aminobenzimidazole



Scheme 24: Reaction of 2-aminobenzimidazole with 2-substituted carboxyaldehyde



Scheme 25: Reaction of 2-aminobenzimidazole with aliphatic anhydrides

spectrum of biological activity. Thus, reaction of 2-aminobenzimidazole with 5-substituted furfural or 2-thiophenecarboxaldehyde yielded 2-[(5-substituted furfurylidene/thiophenylidene)-amino]benzimidazoles (azomethines) [60] (Scheme 24).

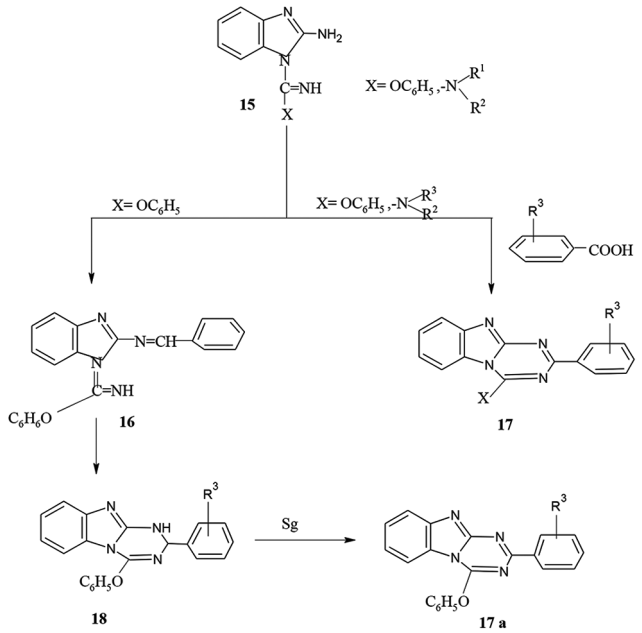
Treatment of various aliphatic anhydrides with 2-aminobenzimidazoles results in the formation of the monoamides which can be cyclized with anhydride to yield the corresponding imides (Scheme 25).

Condensation of 2-aminobenzimidazolyl-1-phenylimidate(15a) and 2-aminobenzimidazolyl-1-amidines (15b) with aromatic aldehydes or acids resulted within the formation of 2-aryl-4-substituted-s-triazino[1,2-a]benzimidazoles (17a) or (17b), respectively. The reaction of (15a) with an aromatic aldehyde first gives the azomethine (16) which cyclizes to create 2-aryl-4-phenoxy-1,2-dihydro-s-triazino[1,2-a] benzimidazole (18). Dehydrogenation of (18) with sulfur yields (17a) (Scheme 26).

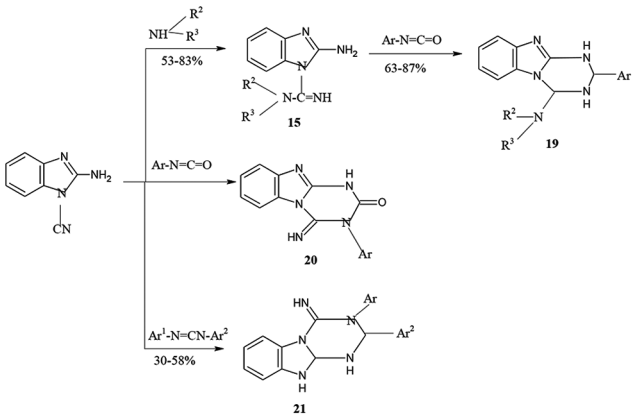
The preparation of (15a) is also accomplished by treating 2-aminobenzimidazole with phenyl cyanate while (15b) is obtained by reaction of 2-amino-1-cyanobenzimidazole with the required amines. Among these compounds, (15b) and 2-amino-1-cyanobenzimidazole react with aryl isocyanates to afford 2-aryl-4-amino-1,2-dihydro-s-triazino[1,2-a]benzimidazoles(19) and 2-oxo-3-aryl-4-imino-1,2,3,4-tetrahydro-s-triazino[1,2-a]benzimidazoles(20), respectively.

In addition, 2,3-diaryl-4-imino-1,2,3,4-tetrahydro-s-triazino[1,2-a] benzimidazole(21) could also be prepared by condensing 2-amino-1-cyanobenzimidazole with various azomethines [61] (Scheme 27).

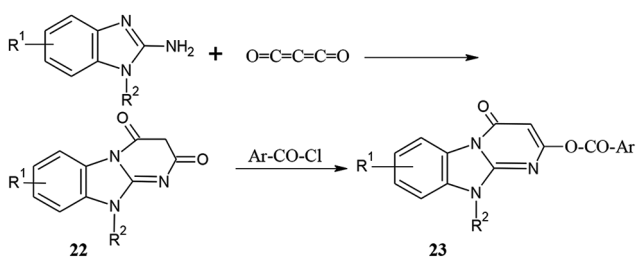
Carbon suboxide is thought to react with 2-aminobenzimidazole to afford 2,3-(dioxotetrahydropyrimidino)-benzimidazoles (22) in high yields, which can be aroylated to grant the corresponding O-aryl product (23) [62] (Scheme 28).



Scheme 26: Condensation reaction of 2-substituted aminobenzimidazole



Scheme 27: Reaction of 2-aminobenzimidazole with phenyl cyanate, aryl isocyanate, and azomethines



Scheme 28: Reaction of 2-aminobenzimidazole with carbon suboxide

Reaction of 2-aminobenzimidazole with 2-hydroxymethylene-3-androstanones (24 a-d) in absolute ethanol yielded androstano(or androst-4-eno or cholestano)[3,2-b]-(pyrimido[1,2-a]benzimidazoles) (25 a-d) in good yields [63] (Scheme 29).

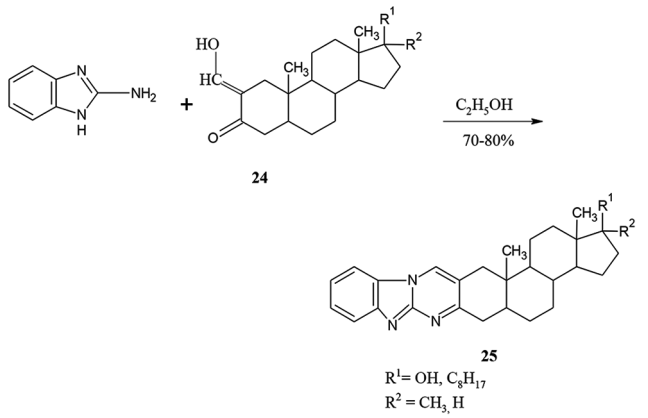
A series of 2,4-unsymmetrically dialkylated pyrimido[1,2-a] benzimidazoles (27) as possible antibacterial and antiarrhythmic agents has been prepared by treating 2-aminobenzimidazole with the β-diketones (26). Other heterocycles associated with (27) may additionally be prepared by treating 2-aminobenzimidazoles with β-dicarbonylcompounds [64] (Scheme 30).

Cyclocondensation of 2-aminobenzimidazole with diphenylcyclopropenone (28) gives diphenyl-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (29) [65] (Scheme 31).

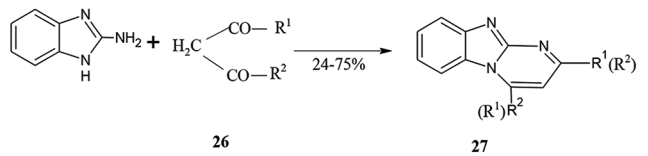
Substitutions involving heterocyclization

Reaction of 2-aminobenzimidazole with ethoxycarbonylacetonitrile at 100°C resulted within the 2-N-acylation to make 2-(1-cyanoacetyl)-aminobenzimidazole. However, when the above reaction was disbursed at 140°C, it absolutely was impractical to isolate 2-(1-cyanoacetyl)-aminobenzimidazole; instead 4-imino-2-oxo-1,2,3,4-tetrahydropyrimidol[1,2-a]benzimidazole was isolated from the reaction mixture. An analogous reaction occurred when 2-aminobenzimidazole was treated with ethyl acetoacetate, dimethyl acetylenedicarboxylate, or diethyl malonate resulting in the formation of the cyclocondensation products(30). The preparation of (30) can also be achieved by treating 2-aminobenzimidazole with a β –aminocrotonate (Scheme 32).

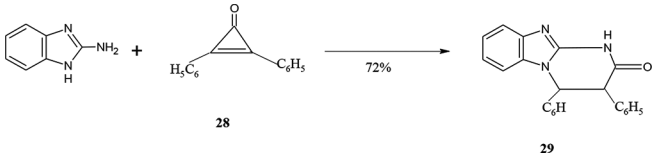
The above reaction has also been extended to synthesize a good form of heterocycles of a sort (31-33) by condensing ethyl



Scheme 29: Reaction of 2-aminobenzimidazole with 2-hydroxymethylene-3-androstanones



Scheme 30: Reaction of 2-aminobenziidazole with β-diketones



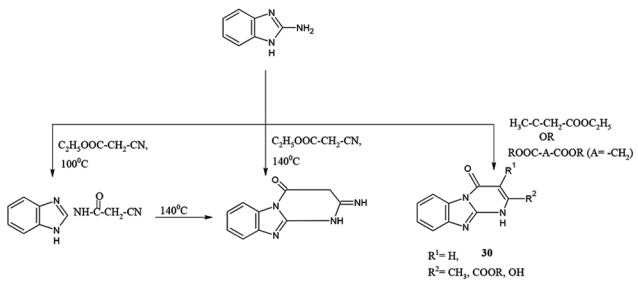
Scheme 31: Cyclocondensation of 2-aminobenzimidazole with diphenylcyclopropenone

2-oxocyclohexanecarboxylate,ethyl 2-oxocyclopentanecarboxylate, β-aminocrotonitrile, or β-aminocinnaminonitrile, respectively, with 2-aminobenzimidazole [66] (Scheme 33).

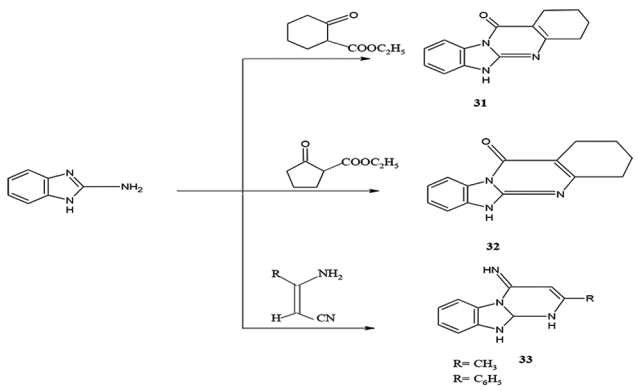
A similar kind of cyclocondensation occurs when 2-aminobenzimidazole is treated with the β-enaminoesters to convey the corresponding 2-amino-4-oxo-3,4-dihydropyrimidol[1,2-a]benzimidazoles in 76-82% yields [67] (Scheme 34).

Treatment of the two-amino-1-aminocarbonylbenzimidazole with diphenyl carbonate affords the 2,4-dioxo-1,2,3,4-tetrahydro-s-triazino[1,2-a]benzimidazoles, which can even be prepared by condensing 2-aminobenzimidazole with the N-chlorocarbonyl urea (Scheme 35).

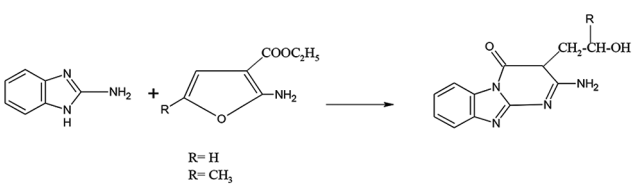
A number of activated acid chlorides react with 2-aminobenzimidazole to yield several benzimidazole-heterocycles of diverse biological interest. Thus, reaction of 2-aminobenzimidazole with diethylmalonic acid dichloride in anhydrous pyridine gave 3,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole, which was converted into 3-[2-benzimidazolylaminocarbonyl]-2-ethyl-3-oxobutanoic acid by reaction with aqueous caustic potash. Dehydration of 3-[2-benzimidazolylaminocarbonyl]-2-ethyl-3-oxobutanoic acid with anhydride gives back 3,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole. The actual fact that 2-aminobenzimidazole acts as a primary amine within the above reaction and not as a phenyleneguanidine was evident by its reaction with chemical compound to yield N,N'-bis[2-benzimidazolyl] thiourea [68] (Scheme 36).



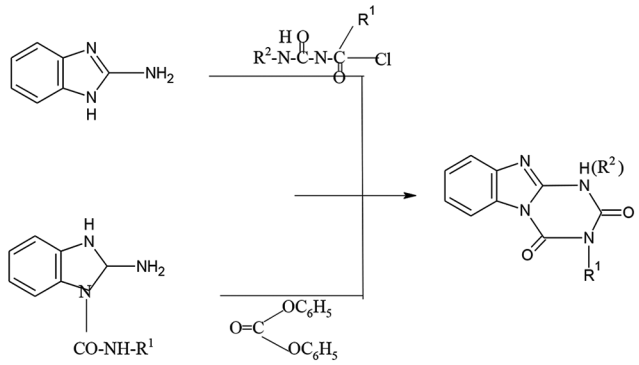
Scheme 32: Reaction of 2-aminobenzimidazole with ethoxycarbonylacetonitrile and β-aminocrotonate



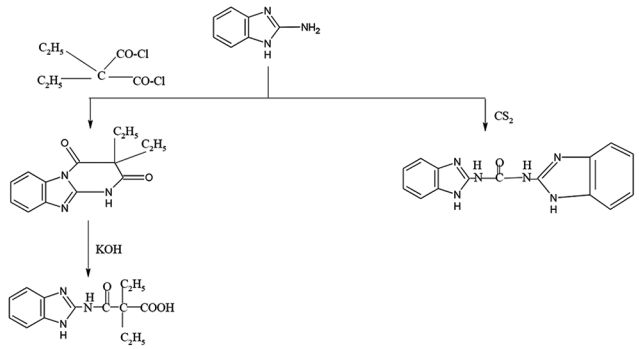
Scheme 33: Condensation reaction of 2-aminobenzimidazole



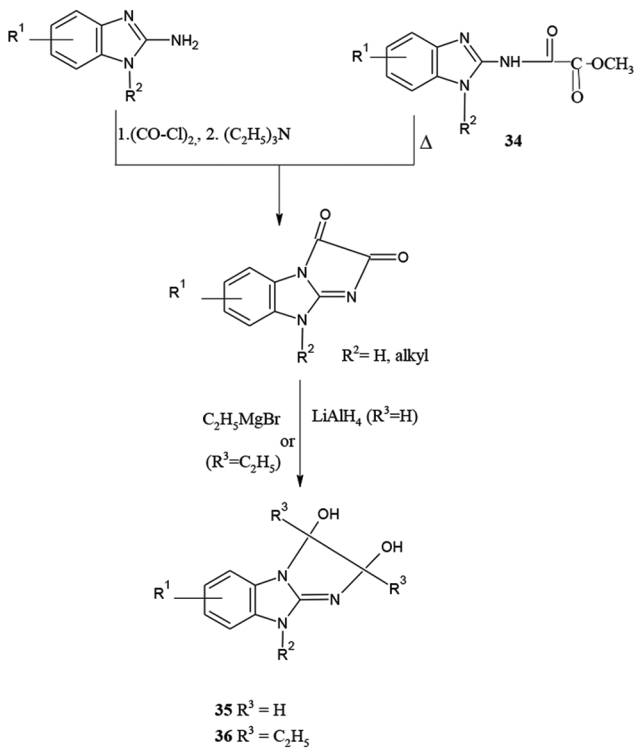
Scheme 34: Cyclocondensation reaction of 2-aminobnzimidazole with β-enaminoesters



Scheme 35: Reaction of 2-aminobenzimidazole with diphenyl carbonate and N-chlorocarbonyl urea



Scheme 36: Reaction of 2-aminobenzimidazole with diethylmalonic acid dichloride and carbon disulfide

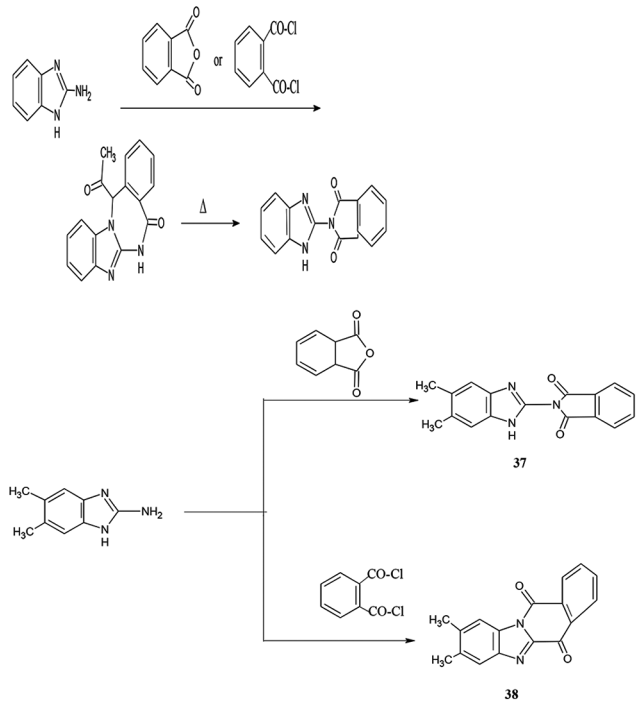


Scheme 37: Reaction of 2-aminobenzimidazole by the action of oxalyl chloride and triethylamine

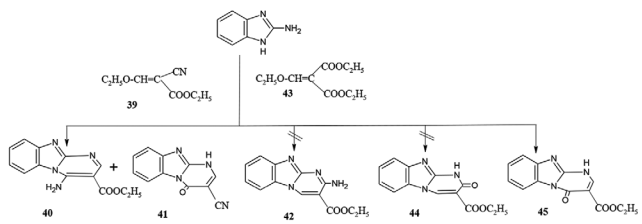
2,3-Dioxo-2,3-dihydro-9H-imidazo[1,2-a]benzimidazoles were prepared by the action of oxalyl chloride on the corresponding 2-aminobenzimidazole in absolute dioxam followed by thermal cyclization of the resulting intermediate in presence of triethylamine. Compound 2,3-dioxo-2,3-dihydro-9H-imidazo[1,2-a]benzimidazoles was also obtained in 20–70% yield by thermal cyclization of (34) [69] and further wont to prepare (35,36) by action of lithium aluminum hydride and ethylmagnesium bromide, respectively (Scheme 37).

Katritzky and Yates have studied the phthaloylation reaction of 2-aminobenzimidazole and 2-amino-5,6-dimethylbenzimidazole with phthaloyl chloride and anhydride. Reaction of 2-aminobenzimidazole with the phthaloylating agents gave 6H-benzimidazol[1,2-b][2,4] benzodiazepin-7,12-dione which underwent thermal isomerization to afford 2-phthalamidobenzimidazole. However, reaction of 2-amino-5,6-dimethylbenzimidazole with phthaloyl chloride gave (38) while (37) was obtained by treating 2-amino-5,6-dimethylbenzimidazole with anhydride (Scheme 38).

Reaction of 2-aminobenzimidazole with diethyl ethoxy-methylenemalonate(43) and ethyl ethoxymethylene-cyanoacetate (39) failed to yield ethyl 2-oxo-1,2-dihydropyrimido[1,2-a]benzimidazole-3-carboxylate (44) and ethyl 2-aminopyrimido[1,2-a]benzimidazole-3-carboxylate(42); instead their isomeric esters(40) and (45) were obtained, respectively. Within the latter case, the nitrile (41) was also obtained [70] (Scheme 39).



Scheme 38: Phthaloylation reaction of 2-aminobenzimidazole



Scheme 39: Reaction of 2-aminobenzimidazole with diethyl ethoxy-methylenemalonate and ethyl ethoxymethylene-cyanoacetate

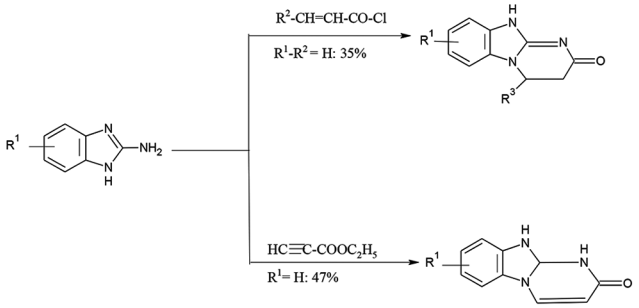
However, reaction of 2-aminobenzimidazole with α,β-unsaturated acid chlorides or esters gave 2-oxo-3,4-dihydro-2H,10H-pyrimido[1,2-a] benzimidazoles. Similarly, reaction of 2-aminobenzimidazole with ethyl propynoate yielded 2-oxo-1,2-dihydropyrimido[1,2-a]benzimidazoles. Using 2-amino-1-methylbenzimidazoles, Trachenkoet [71] have prepared (46) by cyclization of (47) and (48), obtained by reaction of the previous with α,β-unsaturated acid chlorides, by refluxing in ethanol (Scheme 40 and 41).

Reaction of 2-aminobenzimidazole with phenacyl bromide in acetone gives both mono- and diphenacyl derivatives (49) and (50) in 41 and 56% yields, respectively. They need been characterized by cyclizing them to corresponding imidazobenzimidazoles (51) and (52), respectively, in boiling hydrochloric acid. Compounds of the kind (51) have also been obtained by reaction of 1-alkyl-2-aminobenzimidazoles with anilides of chloroacetic acid followed by cyclization of the resulting product with phosphoryl chloride [72] (Scheme 42).

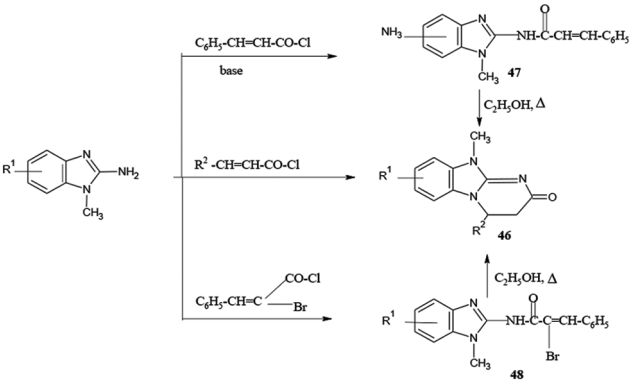
Alkylations and acylations [73] of 2-amiobenzimidazoles using the alkyl and acyl halides, possessing another reactive center, have yielded a series of benzimidazole heterocycles [53-56] (Scheme 43).

PHARMACOLOGICAL ACTIVITY

Benzimidazole a flexible heterocycle is possessing good spectrum of biological activity because of the incorporation of an imidazole nucleus which is a biologically accepted pharmacophore within the benzimidazole molecule. Benzimidazoles is having antiparasitic, anticancer, antiprotozoal, antihelmintic, anti-HIV, antiepileptic, anti-inflammatory, antiherpetic, anti-allergic, anti-histaminic, vasodilative, a narcotic analgesic, medication, antifungal, antiulcer, and pharmacological activities; one except the same activities from 2-aminobenzimidazole.



Scheme 40: Reaction of 2-aminobenzimidazole with α,β-unsaturated carboxylic acid chlorides and esters



Scheme 41: Reaction of the 2-aminobenzimidazole with α,β-unsaturated carboxylic acid chlorides

Anticonvulsant activity

2-aminobenzimidazole also protected the experimental animals against hyperbaric oxygenation convulsions at different dose levels [74].

Antihelmintic activity

Antihelmintic agents either kill or expel infesting helminthes. The synthesis of alkyl 5(6)-substituted benzimidazole-2-carbamates by treatment of 2-amino-5(6)-substituted benzimidazoles with alkyl carbonochloridate forms a brand new class of potent helminthes in man and domestic animals [75].

Antimicrobial activity

A series of 2-disubstituted-1H-benzimidazole-N alkylated-5-carboxamidine derivatives is terribly potent medication agents against S. aureus and methicillin-resistant *S. aureus*. The study disclosed the most effective activity, with MIC values of 0.78–0.39 μg/ml against these species. Numerous mono halogens and dihalogen substituted benzimidazole additionally possess antibacterial activities [76].

CNS depressant and anti-inflammatory activity

Several 1- and 1,3-disubstituted benzimidazoles and pyrimido[1,2-a] benzimidazoles are known to exhibit CNS depressant and anti-inflammatory activity. 2-aminobenzimidazole has also been found to possess cardiovascular activity [77].

Anti-ulcer agents

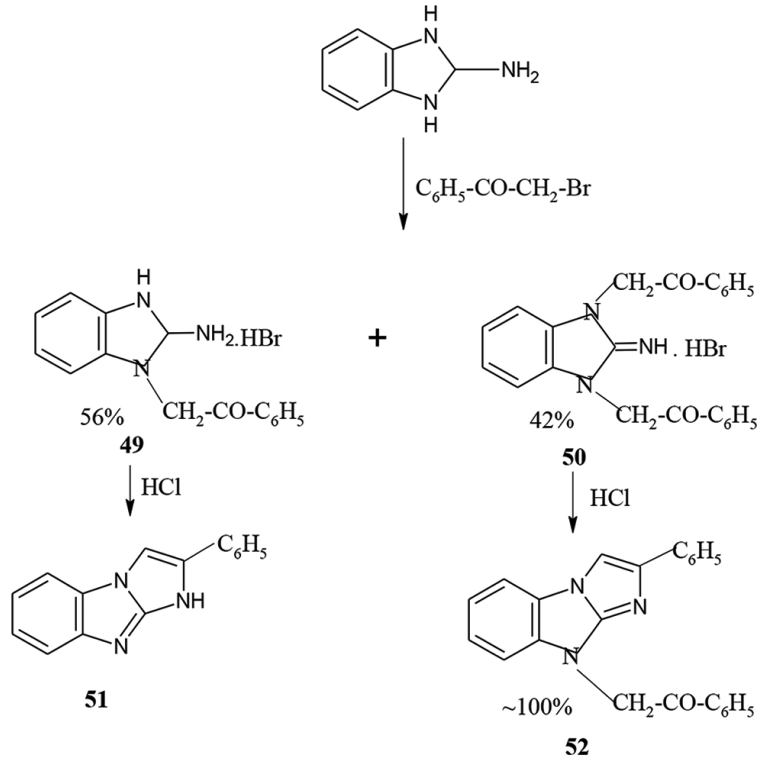
Both basal and stimulated gastric acid secretion are inhibited by these drugs. Lansoprazole, rabeprazole, antacid, pantoprazole, etc. are some drugs that possess benzimidazole nucleus [78].

Antithyroid activity

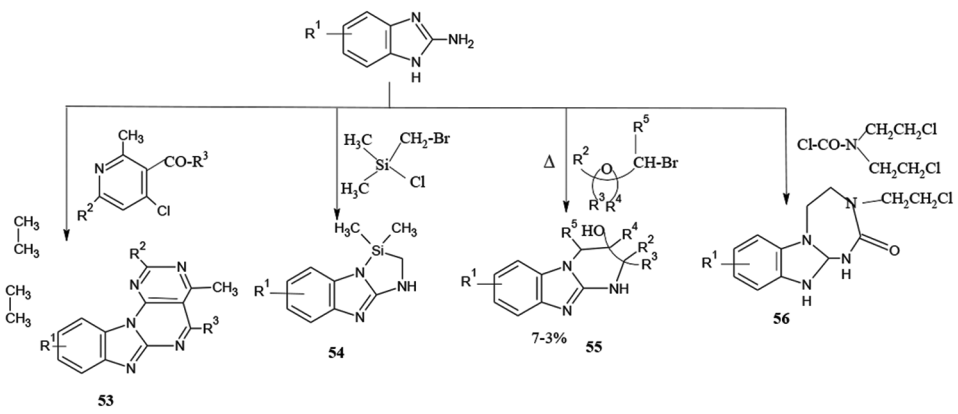
2-aminobenzimidazole, benzimidazole-2-thione, and N-phenyl-N'-(2-benzimidazolyl)-thiourea exhibit varying degrees of antithyroid activity [79].

UTILIZATION OF 2-AMINOBENZIMIDAZOLE

It has been used successfully to harden epoxy resins. It has been used to improve photographic emulsions. In addition, it should even be used to



Scheme 42: Reaction of 2-aminobenzimidazole with phenacyl bromide



Scheme 43: Alkylation and acylation of 2-aminobenzimidazole using alkyl and acyl halides

prepare yellow to orange dyes with bright and fast shades [80].

CONCLUSION AND OUTLOOK

The present survey has clearly demonstrated that 2-aminobenzimidazole also successfully want to synthesize a good kind of benzimidazole heterocycles of educational and pharmaceutical interest. Moreover, in general, the required compounds are also obtained during a single step with high yields. Thus, the look of a molecule supported that the 2-aminobenzimidazole nucleus is also expected to guide to compounds with pharmacodynamic properties.

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