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Recent Synthesis and Biological Applications of Novel Benzotriazoles: A Review

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ABSTRACT

The area of pharmaceuticals and synthetic organic chemistry continued to remain dependent on the heterocyclic compounds due to their wide array of properties both biological and synthetic. However, their extensive clinical use as medicinal drugs and their synthetic applications has been prompting the chemists to develop new structural triazole derivatives. Benzotriazole is benzene fused azole derivative exhibiting tremendous application in medicinal and synthetic chemistry. Benzotriazole bearing compounds possess various activities such as anticancer, antifungal, antibacterial, antitubercular, antiviral, antioxidative, antiparasitic, antioxidative. Also, the versatility and usefulness of benzotriazole methodology in synthesis protocol has grown from an obscure level to extreme popularity, since benzotriazole moiety can easily be introduced into a molecule by variety of reactions, thus allowing numerous transformations, and finally its stability and ease of removal at the of the reaction sequence. In this review, we briefly describe the development of new benzotriazole compounds having wide range of applications during the period of 2011 to 2016.

Keywords: Benzotriazole, antibacterial, antimicrobial, peptide, hydrazides.

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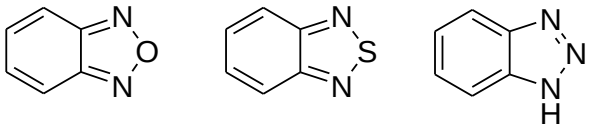
INTRODUCTION

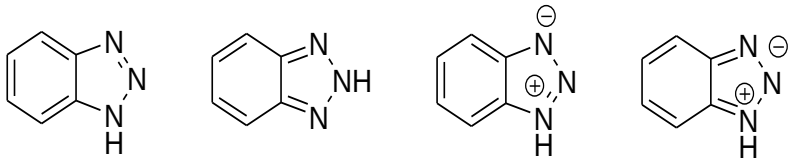
Novel, economical and efficient synthetic protocols for the development of heterocyclic compounds are perhaps the endmost goal of synthetic organic chemists. In particular, Nitrogen heterocycles exhibit diverse biological and pharmacological applications[1], especially triazole scaffold which plays an important role in medicinal chemistry[2]. Benzo-condensed azoles are prime structures being studied in all fields; in particular, benzo-fused azoles[3] containing three heteroatoms have received vast attention for their properties and applications such as benzo[1,2-*c*][1,2,5]oxadiazole **1**, benzo[1,2-*c*][1,2,5]thiadiazole **2**, and benzotriazole (1H or 2H isomer) **3** (Figure 1).



1 **2** **3**

Figure 1: **Benzo-fused azole heterocycles**

Among these, benzotriazole (BT) and its derivatives have been paid increasingly special attention and a large number of research have been focused on this due to their wide range of applications as medicinal drugs[4], man-made materials[5], corrosion inhibitors[6] and superamolecular ligands.[7] Alizaprid[8] (antiemetic drug) and Tinuvin P[9] (UV absorber) are also important benzotriazole derivatives. Benzotriazole derivatives are more ready to bind with a variety of enzymes and receptors in biological systems *via* diverse non-covalent interactions due to the presence of large conjugated system and its three nitrogen atoms.



A **B** **C** **D**

Figure 2: Tautomerism in benzotriazole

Additionally, benzotriazole compounds could bind with different metal ions to afford benzotriazole containing metal complexes, which may offer the bioactivities of both benzotriazole derivatives themselves and superamolecular agents, thus possibly exerting double action mechanisms to tame drug resistances[10]. These properties make benzotriazole moiety to be commonly employed for the construction of innovative drug molecules[11]. Benzotriazole can exist

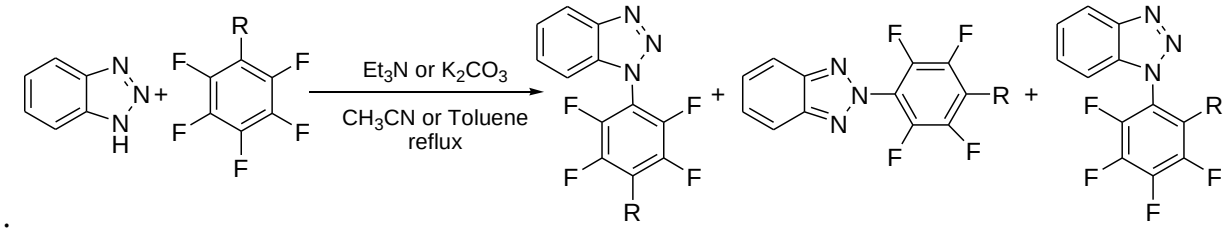
in tautomers A and B, and the derivatives of both tautomers, structures C and D can also be produced[12] (Figure 2).

From a solely chemical point of view, benzotriazole moiety continued to be used as a synthetic auxiliary[13,14] and also act as a good leaving group[15]. Benzotriazole also acts as an electron-donor or a precursor of radical or carbanions. However, the principal interest on benzotriazole is focused mainly in the pharmaceutical field, owing to their property to boast different biological properties, including plant growth regulator,[16] choleretic,[17] antibacterial,[18] antiprotozoal,[19] antiviral[20] and antiproliferative[21] activity. Thus, new synthetic methods for preparation of benzotriazole substituted compounds are highly desirable. Also recently, a lot of benzotriazole derivatives with effective pharmacological properties, few side effects, low toxicity, little multi-drug resistance, good water solubility, promising bioavailability, diversity of drug administration as well as broad bioactive spectrum have been discovered, with large development value and potentiality as medicinal drugs.[22]

The aim of this paper is to provide an overview on the recent synthesis and biological application of the novel benzotriazole based heterocycles synthesized during the period of 2011 to 2016.

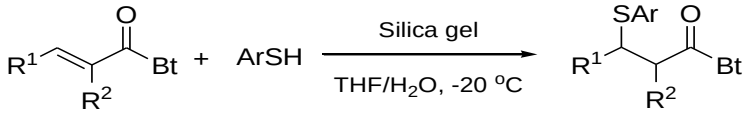
Benzotriazole Substituted Heterocycles

Zhao *et al.*[23] reported a convenient method for the synthesis of several benzotriazole, Bt(*N*1)-substituted pentafluorobenzenes derivatives (Scheme 1). Synthesis of these Bt(*N*1)-substituted derivatives was investigated with relevance to the solvent, base and the electron-withdrawing group at 4-position on the perfluorophenyl ring.



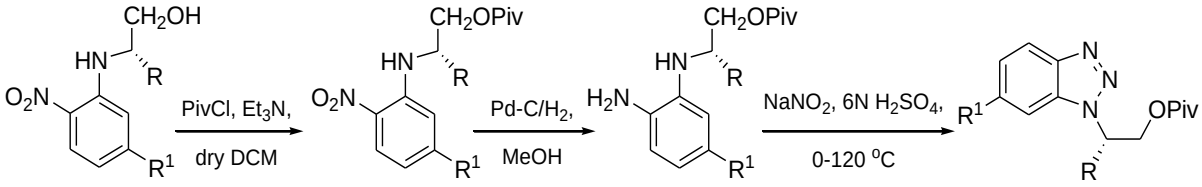
Scheme 1: Regioselective reaction of BtH with pentafluorobenzene derivatives

Research group of Xia[24] performed the regioselective addition of thiophenol to α, β-unsaturated *N*-acylbenzotriazoles under controlled conditions resulting into the formation of a variety of α, β-unsaturated thioesters, β-thiophenoxy substituted *N*-acylbenzotriazoles (Scheme 2) and β-thiophenoxy substituted thioesters in good to excellent yields.



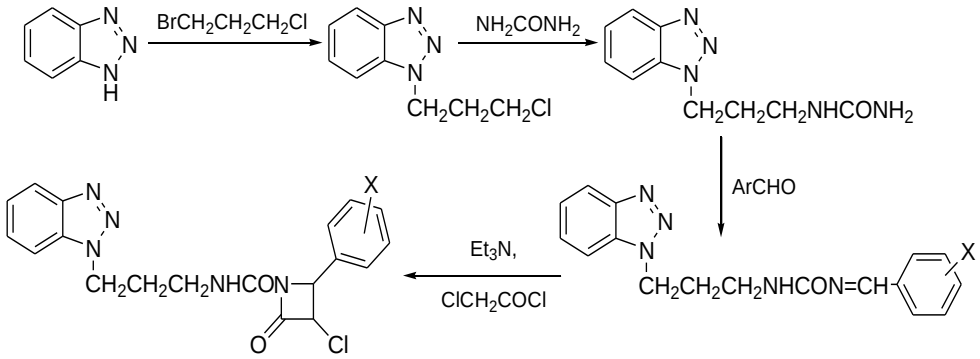
Scheme 2: Regioselective addition of thiophenol to α, β-unsaturated *N*-acylbenzotriazoles.

Bera *et al.*[25] reported an unprecedented diazo-oxygen (N=N-O) bond formation leading to an entirely new kind of amino acid-derived enantiomerically pure substituted benzo[d][1,2,3,6]oxatriazocines heterocycles via one-pot three step sequence, (i) diazotization (ii) TBDMS deprotection, and (iii) cyclization (Scheme 3). This is the first diazo-oxygen bond formation in acidic medium reported in literature.



Scheme 3: Synthesis of 1-alkyl benzotriazoles derivatives

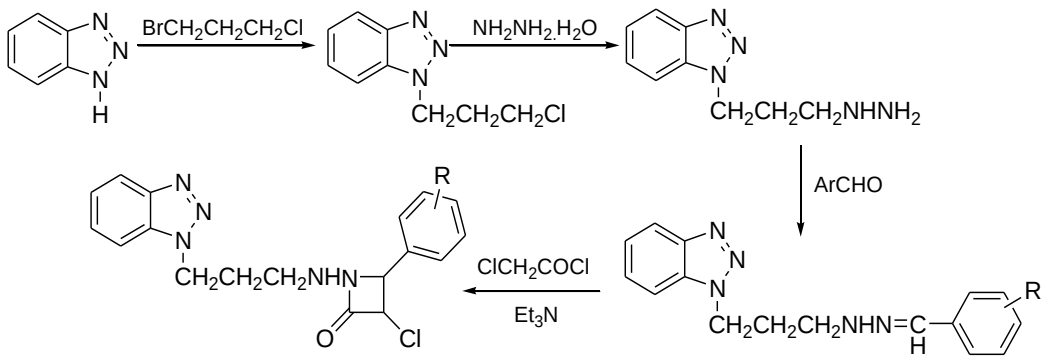
Synthesis of a new series of *N*-[3-(1*H*-1,2,3-benzotriazol-1-yl)propyl]-2-(4-substituted phenyl)-3-chloro-4-oxo-1-azetidinecarboxamides from 1,2,3-benzotriazole as starting substrate in four steps (Scheme 4) was performed by Sharma and group.[26]



Scheme 4: Synthesis of *N*-benzotriazolyl substituted β-lactams

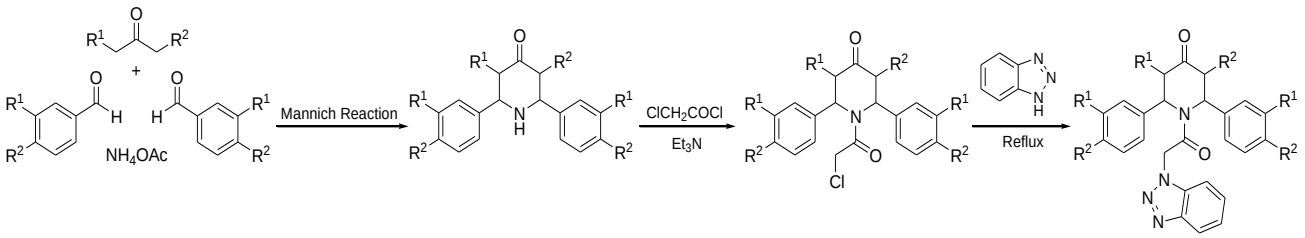
All the compound were shown to possess good to moderate antibacterial, antifungal and antitubercular activities.

Other azetidinone derivatives of benzotriazole were synthesized by Dubey *et al.*[27] in both conventional and microwave irradiation conditions (Scheme 5). Microwave assisted method was found to be superior over conventional method, as it result in reduction of reaction time along with yield enhancement. Synthesized compounds were also screened for their antitubercular (against *Mycobacterium tuberculosis* H37RV) and antimicrobial activity. Some of the derivatives showed better activities than the reference drugs.



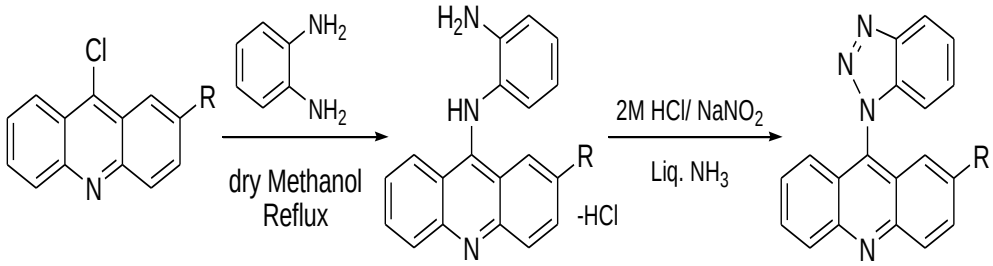
Scheme 5: Synthesis of *N*-benzotriazolyl substituted β-lactams

Ramachandran *et al.*[28] have reported the synthesis of variously substituted 1-[2-(1*H*-benzotriazol-1yl)acetyl]-2,6-diarylpiperidin-4-ones (Scheme 6). The synthesized derivatives were also examined for *in vitro* antibacterial and antifungal activities against pathogenic microbial strains. Some synthesized compounds showed superior inhibition activity against B. *subtilis* and *E. Coli* microbial strains.



Scheme 6: Synthesis of *N*-benzotriazolyl substituted β-lactams

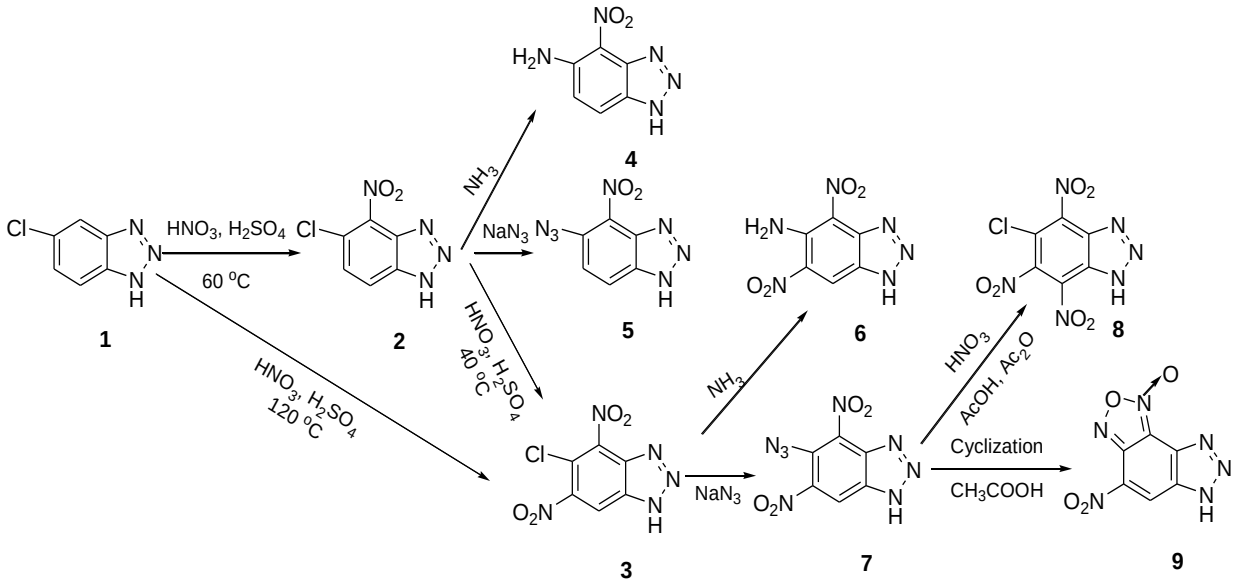
Another heterocycle containing benzotriazole was reported by Singh *et al.*[29] They carried out the synthesis of benzotriazole substituted acridine derivatives through the cyclization of 9-substituted acridine derivatives (Scheme 7) followed by their antibacterial activity screening. It was seen that compound having free amino group showed moderate activity while good activity was observed with compounds lacking free amino groups.



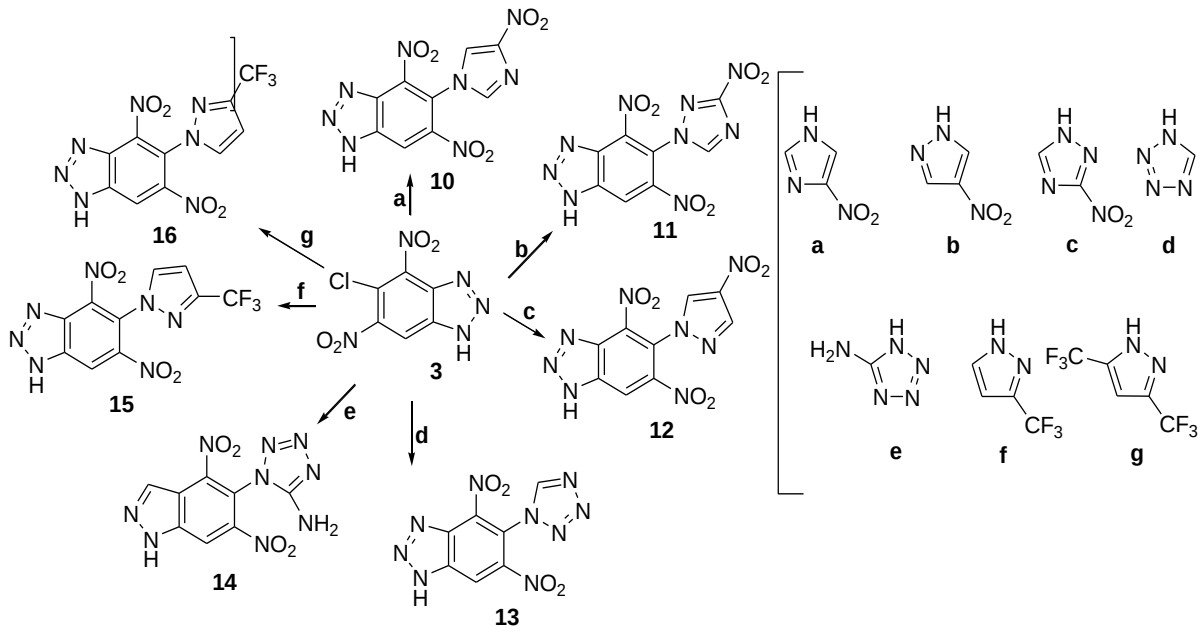
Scheme 7: Synthesis of *N*-benzotriazolyl substituted acridine

Srinivas *et al.*[30] have synthesized a number of amino, azido, nitro and nitrogen-rich azole-substituted derivatives of 5-chloro-1*H*-benzo[1,2,3]triazole by using simple, scalable methods

without the need for complicated purifications (Scheme 8 and 9). These compounds were synthesized for their use as energetic material applications.

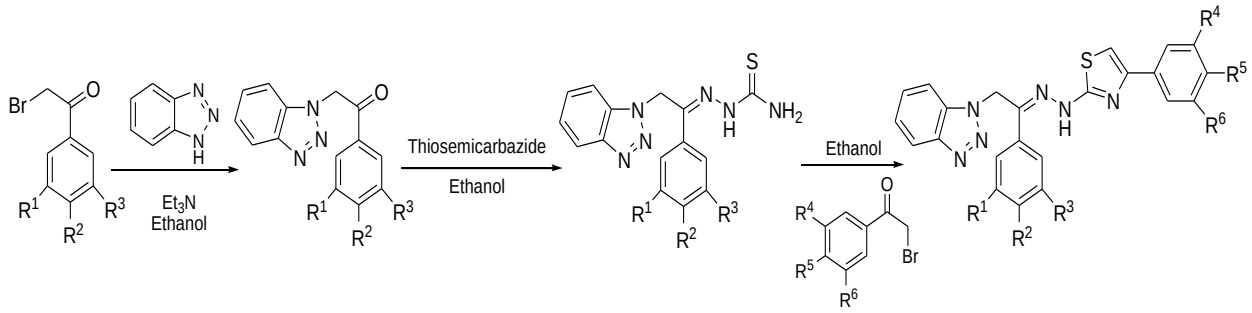


Scheme 8: Synthesis of amino-, azido- , nitro-, and nitrogen-rich azole derivatives of benzotriazole

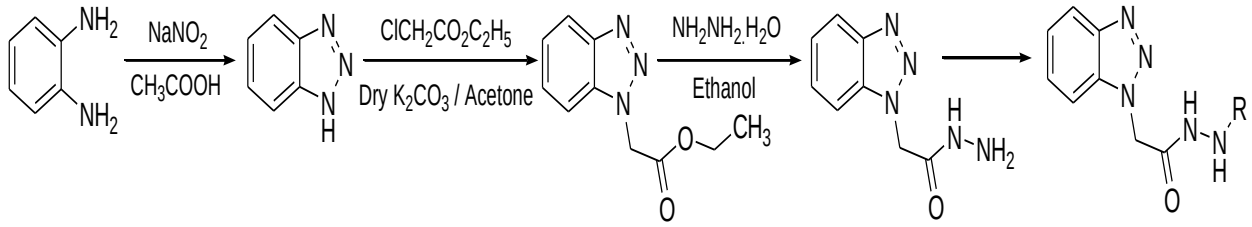


Scheme 9: Catalytic N arylation of substituted azoles with 3 by using CuI.

Novel hybrid molecules containing thiazole and benzotriazole templates (Scheme 10) were synthesized by Gaikwad and group.[31] The pharmacological studies were also done to evaluate the effect of substituents for their antimicrobial activities. Majority of the compounds exhibited moderate to good activity towards bacterial as well as fungi species.



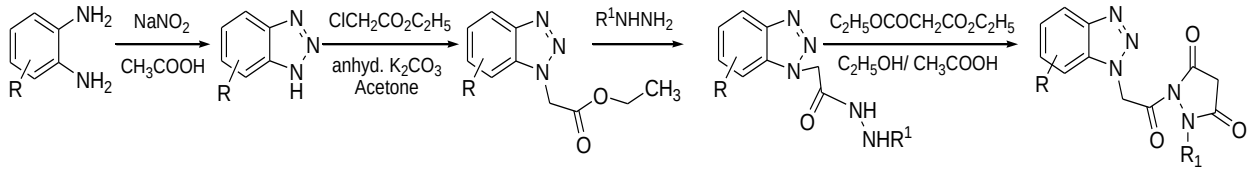
Scheme 10: Synthesis of thiazole derivatives of benzotriazole



Scheme 11: Synthesis of *N*-substituted derivatives of benzotriazole

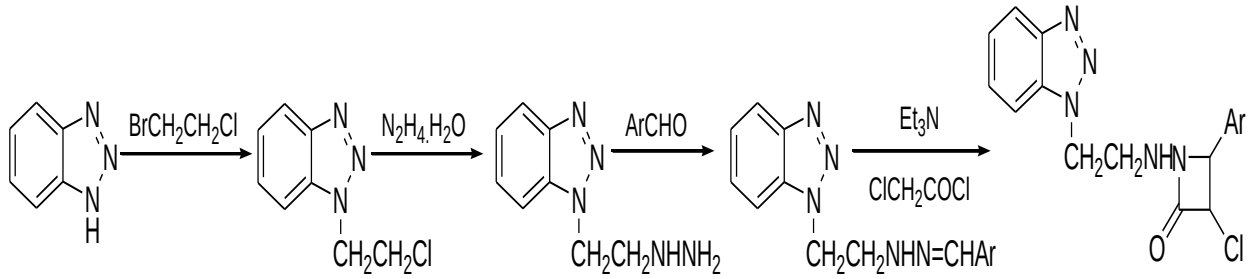
Patel and co-workers[32] have reported the synthesis of various N-substituted 2-(1H-benzotriazol-1-yl)acetohyrazide from 2-(1H-benzotriazol-1-yl)acetohyrazide and substituted sulfonyl chlorides (Scheme 11) and evaluated them for their antibacterial and antifungal activities. All the synthesized compounds showed good to moderate activity but less than that of standards taken.

Substituted benzotriazole derivatives containing pyrazilidin-3,5-dione moieties were synthesized from benzotraizole substituted hydrazide and diethyl propanedioate (Scheme 12) by Suma and group[33]. These compounds exhibited considerable antimicrobial, antifungal and antibacterial activity due to the presence of two biologically active heterocycles.



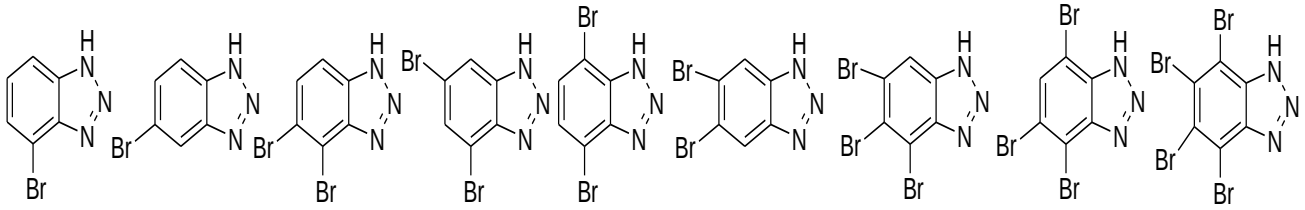
Scheme 12: Synthesis of pyrazilidin-3,5-dione derivatives of benzotriazole

Sharma *et al.*[34] have synthesized a new series of *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(substituted-phenyl)-3-chloro-2-oxo-1-iminoazetidines (Scheme 13) followed by their screening for antibacterial, antifungal and antitubercular activities. All compounds showed acceptable activities against various microbial strains in reference to the standards drugs.



Scheme 13: Synthesis of azetidin-2-one derivatives of benzotriazole

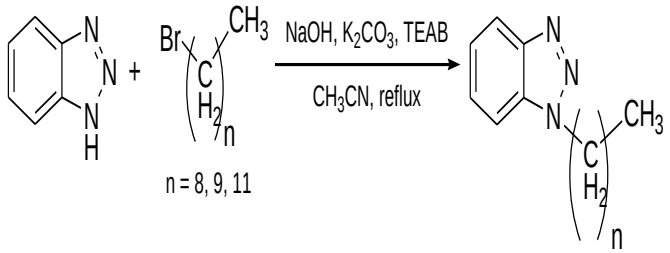
Wąsik *et al.*[35,36] have prepared all the possible two mono-, four, di-, and two tri-bromobenzotriazoles and determined their physiochemical properties in aqueous medium (Scheme 14).



Scheme 14: Synthesis of bromo derivatives of benzotriazole

Further, they have examined the inhibition (IC_{50}) of human CK2a by these bromobenzotriazoles derivatives relative to that of 4,5,6,7-tetrabromotriazole (TBBT). Some of the bromobenzotriazole derivatives showed enhanced inhibitory activity in comparison to TBBT while other possessed moderate activity.

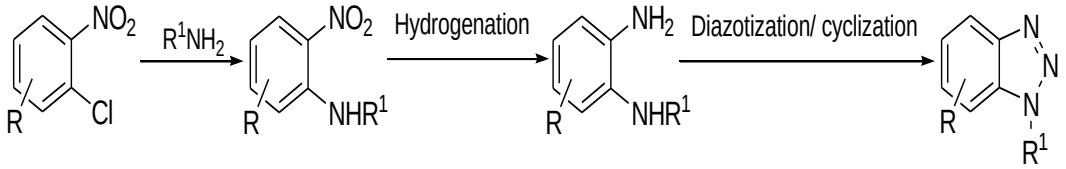
Khabnadideh and co-workers[37] synthesized alkyl derivatives of benzotriazole by reacting benzotriazole with bromoalkanes using tetrabutyl ammonium bromide as a catalyst (Scheme 15) followed by antifungal activity evaluation by broth micro dilution method. Moderate activity of the compounds was observed against various strains chosen.



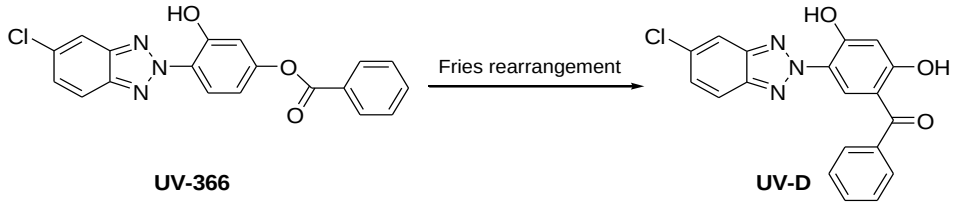
Scheme 15: Synthesis of alkyl derivatives of benzotriazole

Chen and Buchwald[38] developed an efficient and regiospecific synthesis of 1-substituted benzotriazoles bearing various N-substituted groups, including alkyl, aryl and heteroaryl, from chloronitrobenzenes and amines by a C-N bond formation/hydrogenation/diazotization/ cyclization sequence under continuous-flow conditions (Scheme 16). Two approaches were used starting with

a SnAr reaction or Pd catalysis to prepare unsymmetrically substituted benzotriazoles with a range of substituents.



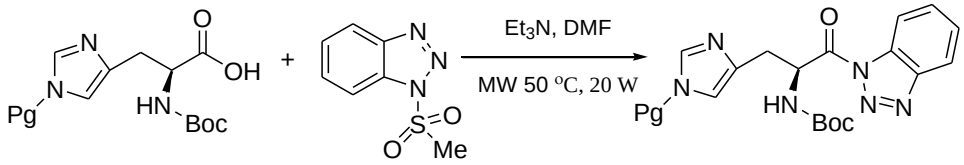
Scheme 16: Multistep strategy for the synthesis of 1-substituted benzotriazoles under continuous-flow conditions



Scheme 17: Synthesis principle of UV-D

Pei *et al.*[39] have synthesized a novel UVA/UVB absorber UV-D based on the first principle theory-guided design, by combining two anti-UV functional groups i.e. Cl-substituted benzotriazole (ClBTZ) and hydroxybenzophenone (HBP), which absorbs UVA and UVB radiations with high efficiency (Scheme 17). This work shows that organic synthesis and quantum-chemistry-calculation-guided design can do great in the development of high efficiency UV absorbers.

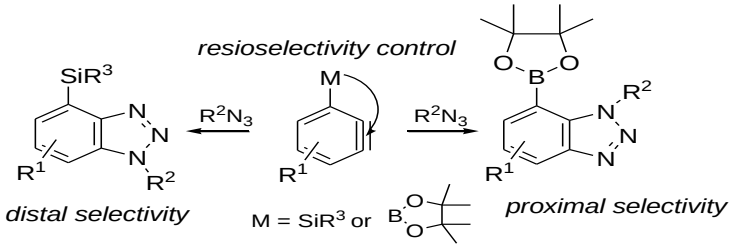
Bajaj and group[40] reported a novel crystalline coupling reagent containing benzotriazole moiety i.e. N^{α}-Boc-N^{im}-4-toluenesulfonyl-$_L$-histidyl-benzotriazole (Scheme 18). This reagent is (i) sufficiently stable to form amide and ester bond at ambient temperature, (ii) provides good to excellent yields without detectable racemization and (iii) is inexpensive to prepare. Hence, it offers an efficient synthetic route for preparing *N*-protected histidine-containing peptides and conjugates with *N*-, *O*-, *S*- and *C*-nucleophiles in good yields without racemization.



Scheme 18: Synthesis of N^{α}-Boc-N^{im}-protected-$_L$-histidylbenzotriazole

Ikawa and co-workers[41] described the synthesis of both regioisomers of multisubstituted benzo-fused azole derivatives such as benzotriazole, 1H-imdazoles, and benzo[d]isoxazoles through the

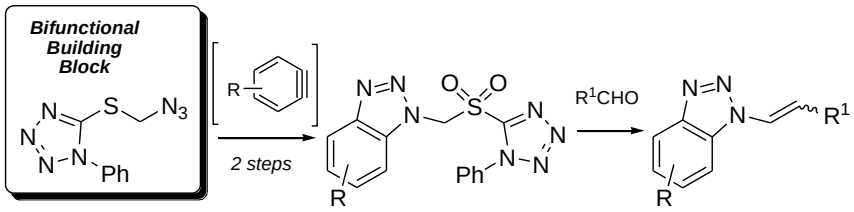
regiocomplementary (3+2) cycloaddition reactions of 3-boryl- and 3-silylbenzynes with 1,3-dipoles by the unique substituent effect of the boryl and silyl groups (Scheme 19).



Scheme 19: Synthesis of both regioisomers of multisubstituted benzotriazole

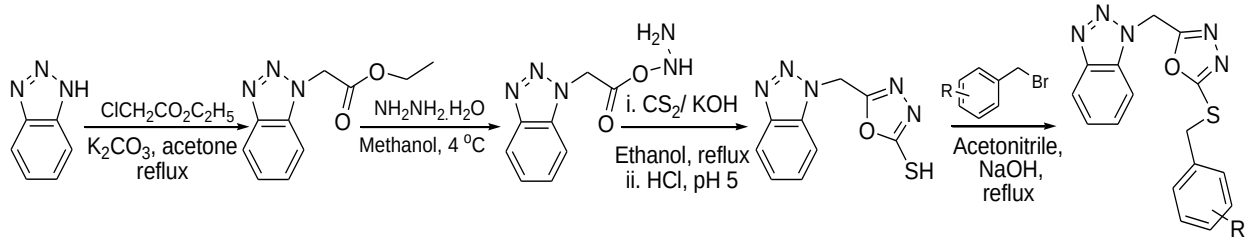
Problem of the regioselectivity of substituted benzynes can be solved by the use of boryl and silyl group as these groups can easily be converted into carbon, nitrogen, and oxygen substitutes.

A facile and modular approach to *N*1-vinyl benzo-, substituted benzo-, and naphthotriaoles (Scheme 20) has been reported by Singh *et al.*[11] This method offered a highly flexible route for the introduction of substituents at both the vinyl and the benzotriazolyl moieties and eliminates the *N*1/*N*2 regioisomer problem encountered in alkylation reactions.



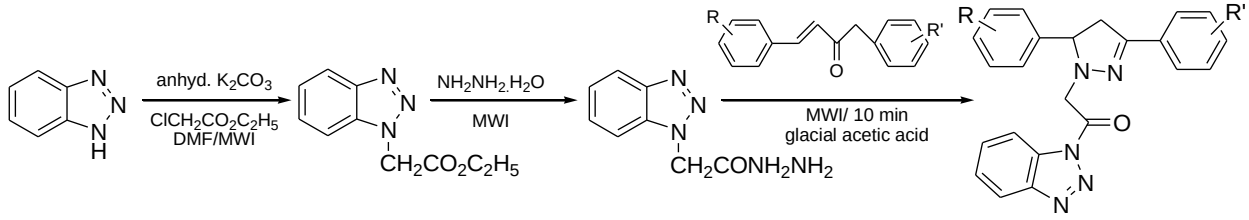
Scheme 20: Synthesis of *N*1-vinyl benzo-, substituted benzo-, and naphthotriazoles

A series of new 1,3,4-oxadiazole derivatives containing benzotriaozle moiety (Scheme 21) has been synthesized and evaluated for their anticancer activity against MCF-7 (human breast cancer) and HT29 (human colorectal cancer) cell lines by Zhang and group.[42] Among the series compound containing *ortho*-fluoro group was found to be potent anticancer agent.



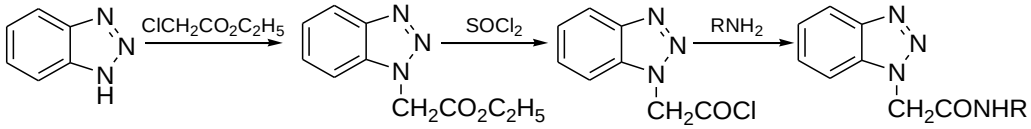
Scheme 21: Synthesis of 1,3,4-oxadiazole derivatives of benzotriazole

Tiwari and co-workers[43] have carried out the microwave assisted synthesis of pyrazoles containing benzotraizole moiety through cyclocondensation of substituted chalcones with benzotraizoles hydrazides (Scheme 22) followed by their evaluation for antibacterial and antimicrobial activities against various microbes and were found to show significant activity.



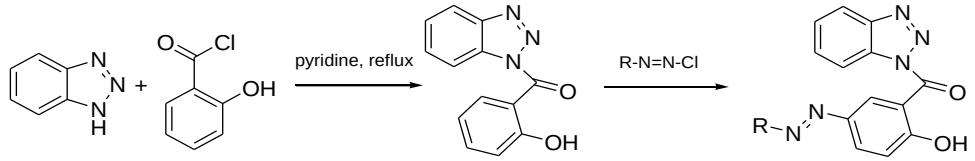
Scheme 22: Synthesis of pyrazoles containing benzotriazole

Synthesis of ten benzotriazole substituted with *N*-phenylacetamide and acetylcarbamic acid (Scheme 23) was done by Jamkhandi and Disouza.[44] The derivatives were screened for their antioxidant activity. Moderate to excellent antioxidant was shown by the synthesized benzotriazole derivatives.

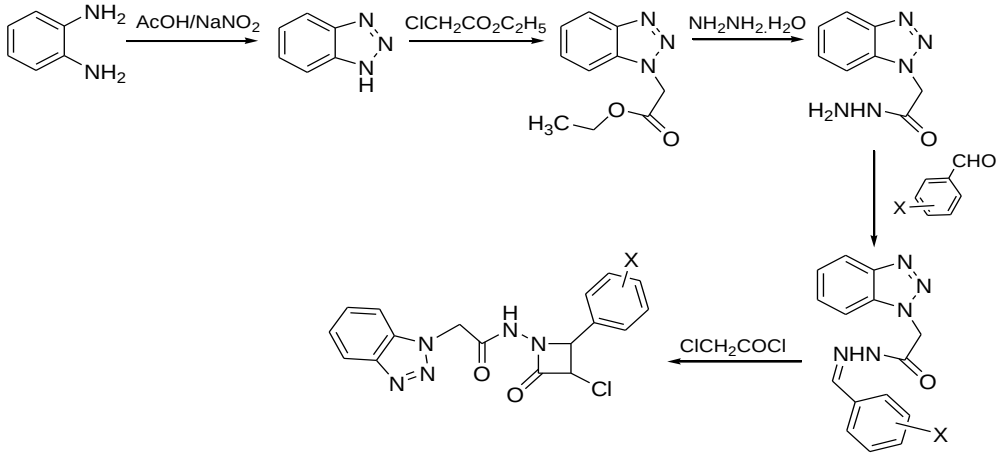


Scheme 23: Synthetic pathway for Benzotriazole derivatives

Newer antimicrobial 2,3-dihydro-1*H*-benzotriazol-1-yl(2-hydroxy-5-[(*E*)-phenyldiazenyl] phenyl)methanone derivatives (Scheme 24) were synthesized by Jamkhandi and Disouza[45] by coupling 1*H*-benzotriazol-1-yl(2-hydroxyphenyl) methanone with various aromatic diazonium salts. Remarkable zone of inhibition, good antibacterial and antifungal activities were shown by most of the compounds.



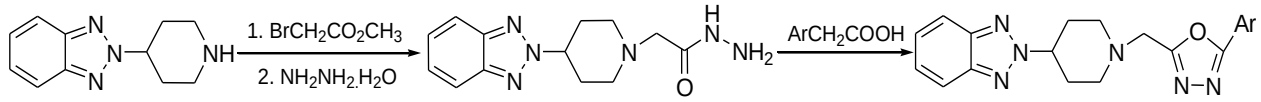
Scheme 24: Synthesis of 2,3-dihydro-1*H*-benzotriazol-1-yl(2-hydroxy-5-[(*E*)-phenyldiazenyl]phenyl) methanone derivatives



Scheme 25: Synthesis of β-lactam derivatives of benzotriazole

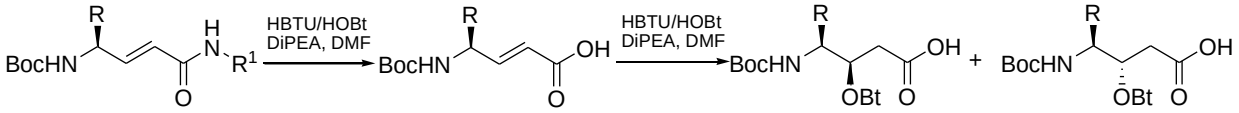
Elrayess and group[46] have synthesized a series of benzotriazole derivatives bearing β-lactam moiety through cyclization of benzotriazole hydrazides with 2-chloroacetyl chloride (Scheme 25). Most of the synthesized compounds possess good antibacterial activity but no anticandida activity.

Vankadri *et al.*[47] have described the synthesis of benzotriazole analogs bearing the 2-[1-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperdin-4-yl]-2*H*-benzotriazole skeleton (Scheme 26). The representative compounds were screened invitro for their antibacterial and antifungal activities. Significant antibacterial and moderate antifungal activity was observed.

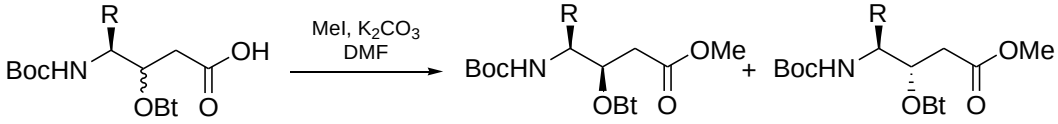


Scheme 26: Synthesis of oxadiazole derivatives of benzotriazole

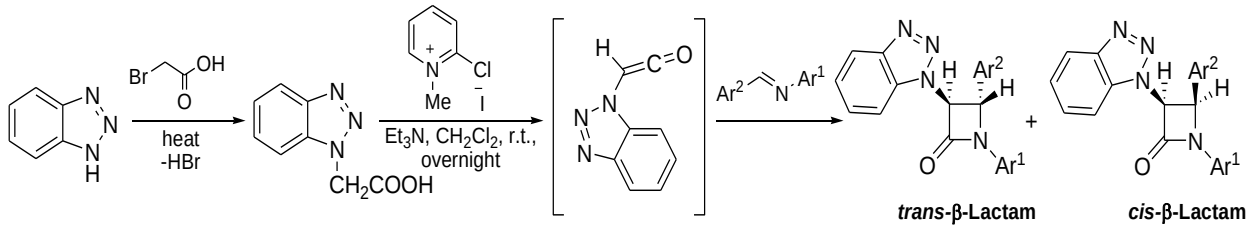
A mild and facile conjugate addition of HOBt to *E*-vinylogous γ-amino acids mediated by the HBTU was reported (Scheme 27, 28) by Mali and co-workers.[48] The reaction yielded novel β-benzotriazole N-oxide (β-BtO) substituted γ-amino acids which were further utilized in tripeptide Boc-Phe-γLeu(β-BtO)-Ala-OMe synthesis.



Scheme 27:Amide coupling and conjugate addition of HOBt with *E*-vinylogous γ-amino acids

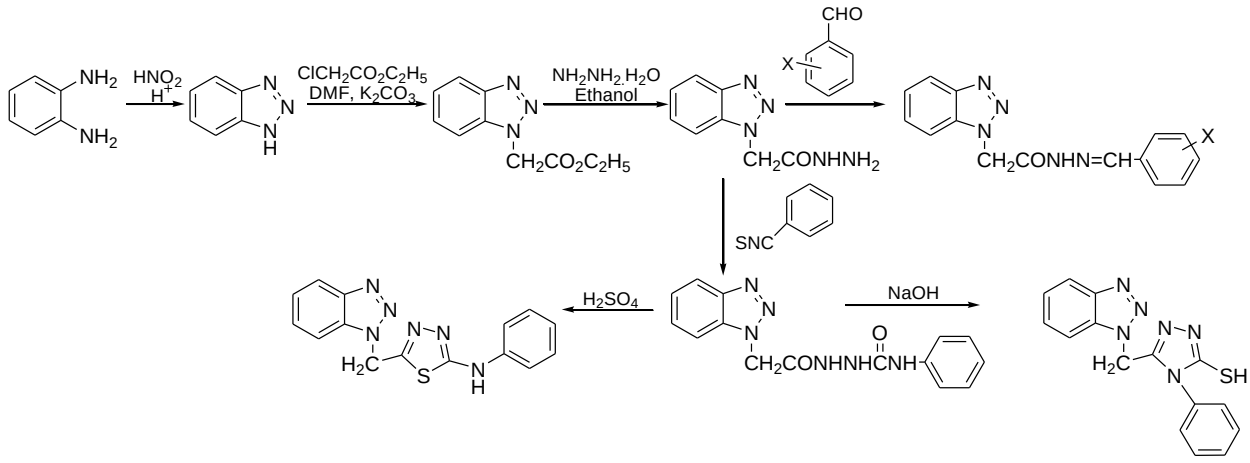


Scheme 28: Esterification of the HOBt conjugate addition product of γ-amino acids



Scheme 29: β-Lactams from benzotriazolylketene

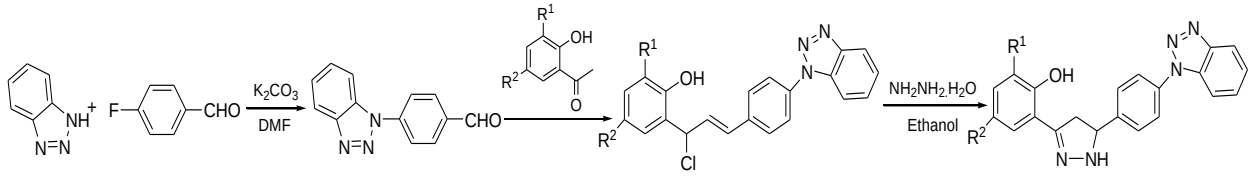
Another important class of novel benzotriazole substituted azetidinones was synthesized stereoselectively by reacting benzotriazolylacetic acid with aromatic amines (Scheme 29) by Zigheimat *et al.*[49] using Mukaiyama's reagent.



Scheme 30: Synthesis of benzotriazole derivatives

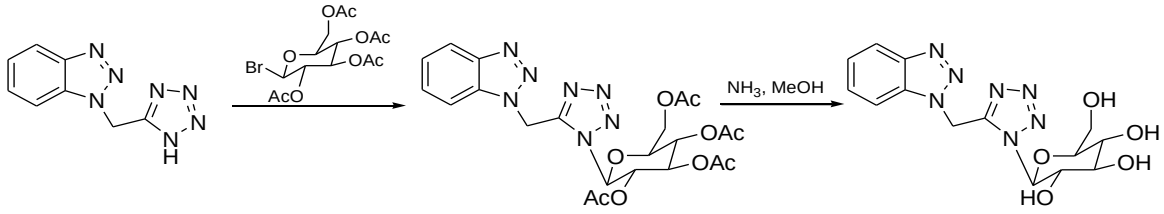
New derivatives of benzotriazole (Scheme 30) were synthesized and evaluated for their antifungal and antibacterial activities by Kumar and group.[50] Some of the compounds showed moderate to good antimicrobial activity.

Shaikh *et al.*[51] have synthesized a series of 2-(5-(4-(1H-benzo[d][1,2,3]triazol-1-yl)phenyl)-4,5-dihdro-1H-pyrazol-3-yl)phenols derivative from (*E*)-3-(4-(1H-benzo[d][1,2,3]triazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-ones in ethanol and hydrazine hydrate under reflux condition (Scheme 31) followed by their antimicrobial activity evaluation against various microbial strains. Good to moderate activity was shown by most of the synthesized copounds.

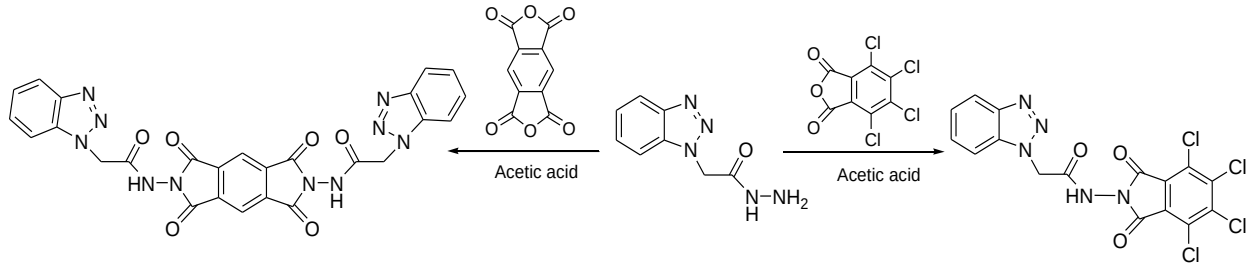


Scheme 31: Synthesis of pyrazole derivatives of benzotriazole

Ali and group[52] synthesized and evaluated a series of deprotected nitroglycoside derivatives and tetrazolomethylbenzo[d][1,2,3]triazole derivatives (Scheme 32, 33) as antimicrobial agents from benzotriazole. Some compounds showed potent antifungal and antibacterial activity in comparison to standard drug taken.

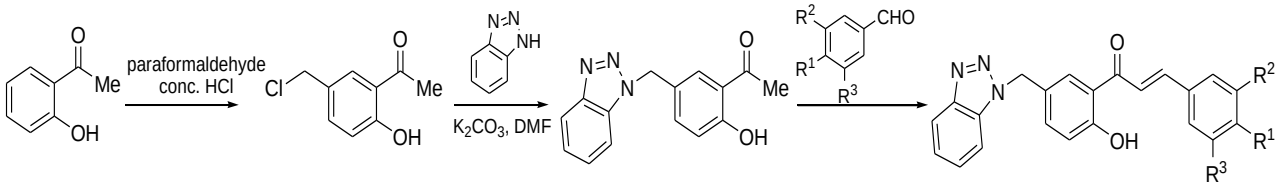


Scheme 32: Synthesis of deprotected nitroglycoside derivative



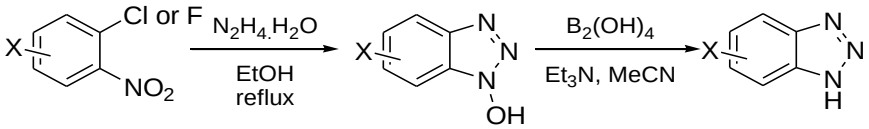
Scheme 33: Synthesis of tetrazolomethylbenzo[d][1,2,3]triazole derivatives

Chinh and co-workers[53] have synthesized new 1*H*-benzotriazol-1-ylmethyl-substituted chalcones starting from 2-hydroxyacetophenone (Scheme 34) and tested for their antimicrobial activity. Most of the benzotriazole derivatives were found to be active against gram-positive and gram-negative bacteria.

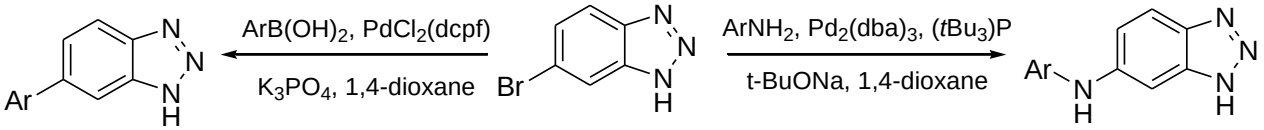


Scheme 34: Synthesis of 1*H*-benzotriazol-1-ylmethyl-substituted chalcones

A new, broadly applicable method to diverse 1*H*-benzotriazoles via a mild diboron reagent-mediated deoxygenation of 1-hydroxy-1*H*-benzotriazoles was demonstrated (Scheme 35, 36) by Gurram and group.[54] Further, diversification of the benzotriazole moiety was also done by Pd-mediated C-C and C-N bond formation reaction.

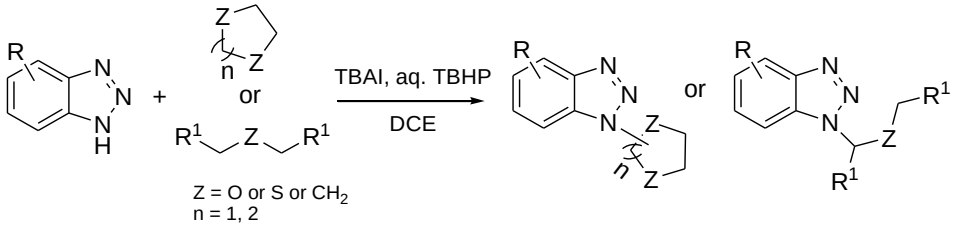


Scheme 35: Synthesis of 1-hydroxy-1*H*-benzotriazoles



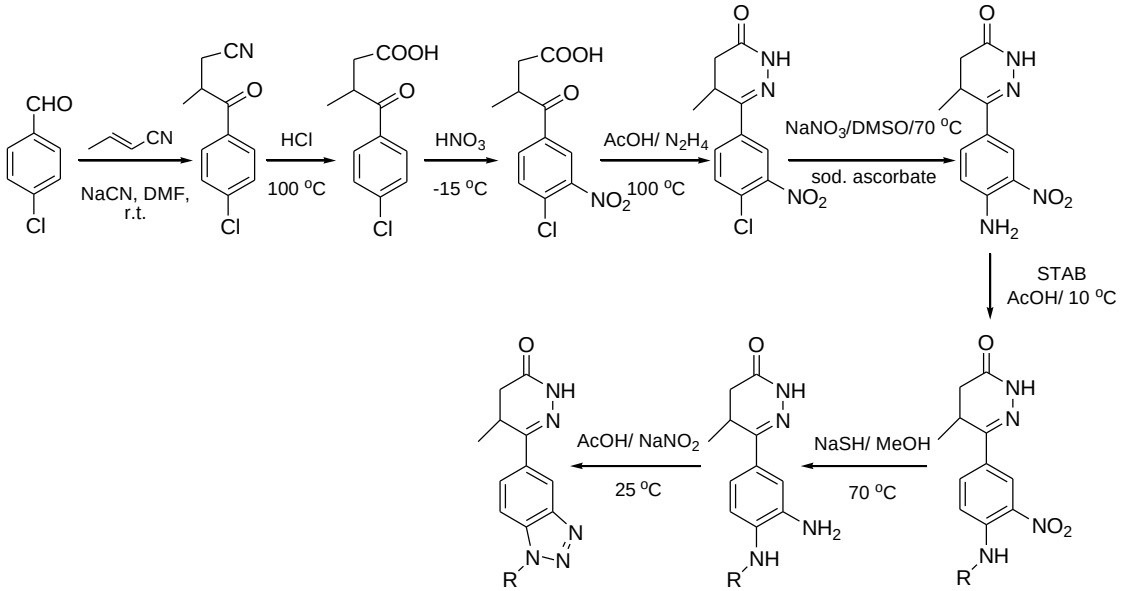
Scheme 36: Diversification Synthesis of 1*H*-benzotriazoles via Pd-catalyzed C-C and C-N bond formation

Aruri *et al.*[55] carried out a metal-free cross-dehydrogenative coupling of benzotriazole with ethers and thioethers for the synthesis of N-substituted benzotriazoles (Scheme 37).



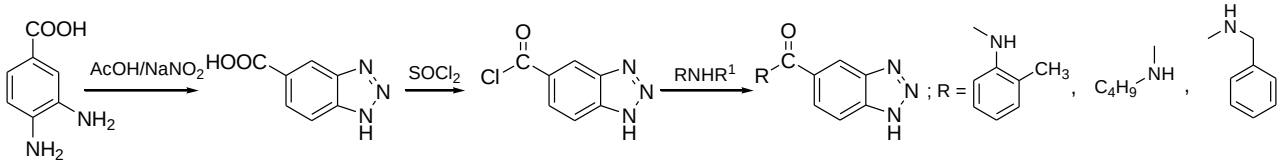
Scheme 37: Coupling of Un/substituted benzotriazoles with ethers/thioethers

A modified version of Stetter and Schreckenbeig's procedure was utilized by Reddy and group[56] for the synthesis of novel 5-methyl-6-(1-substituted 1*H*-benzotriazol-5-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives (Scheme 38).

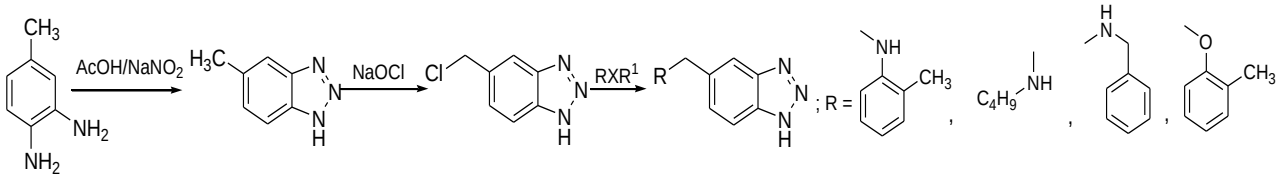


Scheme 38: Synthesis of novel pyridazinolylbenzotraizole derivatives

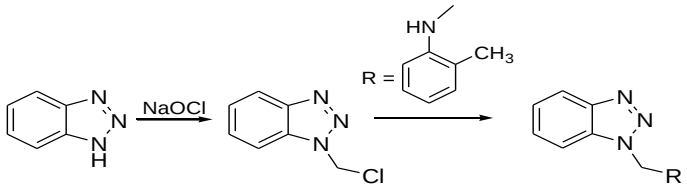
Considering the urgency for discovering new antifungal drugs with greater potency and broad spectrum of antibiotics, a new series of 5-substituted benzotriazoles were synthesized (Scheme 39-41) by Shah *et al.*[57] The molecules were evaluated for their antifungal activity against Candida albicans. Good correlation between docking scores and antifungal activity was observed.



Scheme 39: Synthesis of 5-substituted benzotriazoles amides

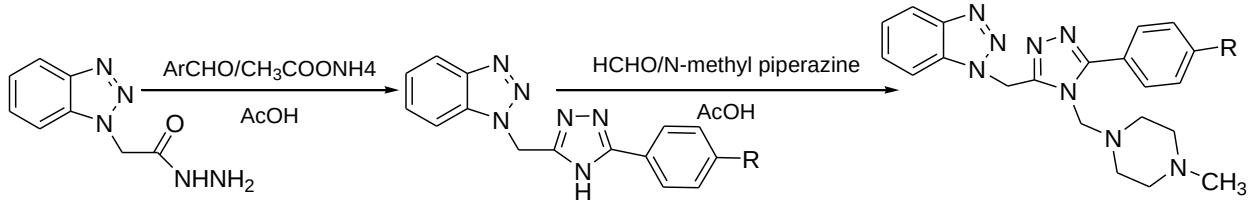


Scheme 40: Synthesis of 5-substituted benzotriazoles amines and ethers



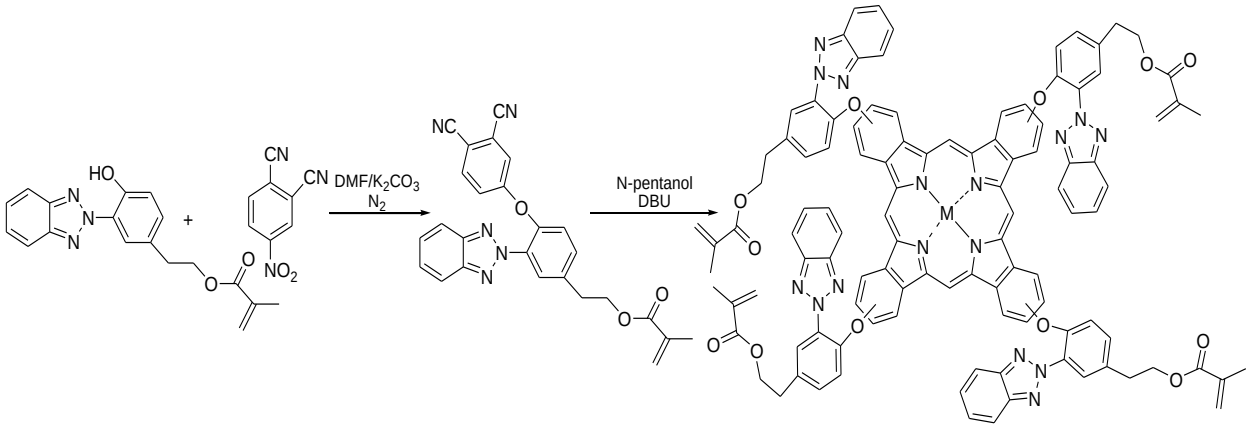
Scheme 41: Synthesis of 1-substituted benzotriazoles amines

Substituted phenyl triazolyl benzotriazoles and phenyl methyl piperazine triazolyl benzotriazoles have been synthesized from benzotriazolyl acetohydrazide (Scheme 42) by George and group.[58] Significant antimicrobial and antioxidant activity was shown by most of the synthesized benzotriazole derivatives.



Scheme 42: Synthesis of 1-substituted benzotriazoles derivatives

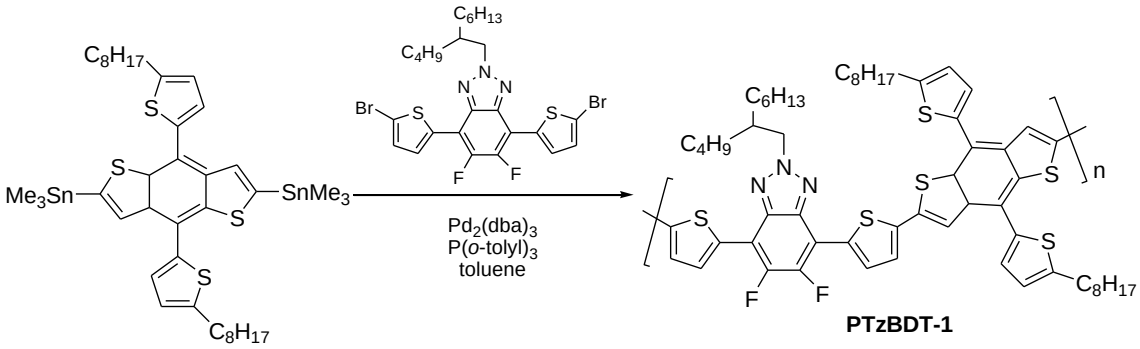
Synthesis and characterization of 3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-4-hydroxyphenethyl methacrylate substituted novel phthalonitrile and its metallo [zinc (II), lead (II) and metal-free]phthalocyanine (Pc) derivatives were performed (Scheme 43) for the first time by Demirbaş *et al.*[59] The photophysical and photochemical properties of novel Pcs were also explored in DMF for comparing the central metal effect and the substituent on these properties.



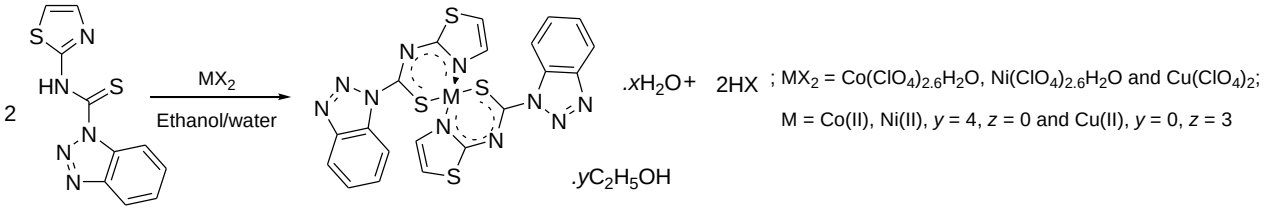
Scheme 43: Synthesis of benzotriazoles substituted phthalonitrile and phthalocyanine derivatives

Gedefaw and co-workers[60] carried out the synthesis of two high band gap benzodithiophene-benzotriazole-based polymers *via* palladium-catalyzed Stille coupling reaction (Scheme 44). To compare, the effect of the side cahins on the opto-electronic and photovoltaic properties of the

resulting polymers the benzodithiophene monomers were substituted with either octylthienyl (PTzBDT-1) or dihexylthienyl (PTzBDT-2) as side groups keeping benzotriazole uniteunaltered.



Scheme 44: Stille cross-coupling reaction for the synthesis of PTzBDT-1



Scheme 45: Synthesis of $[ML_2].yC_2H_5OH.zH_2O$ complexes, HL = N-(2-thiazolyl)-1H-benzotriazol-1-carbothioamide

Co (II), Ni (II) and Cu (II) complexes of *N*-(2-thiazolyl)-1H-benzotriazol-1-carbothioamide (HL) have been synthesized (Scheme 45) by Mansour[61] in good yield. Synthesized complexes were tested for their antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*. The experimental studies were in accordance with the quantum chemical calculations. HL coordination with Co (II) resulted in an inactive complex, but complexes with Ni (II) and Cu (II) did alter the toxicity.

CONCLUSION

Benzotriazole-based heterocycles have diverse biological and synthetic potential. Several pharmaceutically important molecules having benzotriazole core (alizapride, vorozole) and variety of other benzotriazole heterocycles are known which possess inhibitory activities against various kinases. Undoubtedly, there is a great deal of interest in developing new benzotriazole bearing compounds having novel mechanism of action that will be used in clinic for the betterment of human's health. We would also like to apologize to those researchers and scientists whose contribution may not have appeared in this review either due to the limited description of the review or oversight.

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