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REVIEW

Recent developments in benzotriazole methodology for construction of pharmacologically important heterocyclic skeletons

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Abstract Benzotriazole methodology, nowadays recognized as a versatile, useful, and most successful synthesis protocol, has grown from an obscure level to very high popularity, since benzotriazole can easily be introduced into a molecule by a variety of reactions, activates it toward numerous transformations, is sufficiently stable during the course of reactions, and finally can easily be removed at the end of the reaction sequence. In this review, we briefly describe the way benzotriazole methodology has grown to its present height, the opportunities and its potentiality in the synthesis of diverse pharmacologically important heterocyclic skeletons.

Keywords Heterocycles · Benzotriazole · Cyclization · Ylide

Introduction

Heterocyclic compounds, a main class of pharmacologically active agents, are the basis of life and their synthesis has always been full of excitement and challenges. Nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities due in part to the similarities with many natural and synthetic molecules with known biological activities. Development of novel, economically viable, and efficient synthesis protocols for attractive heterocyclic scaffolds is perhaps the ultimate goal of synthetic organic chemists in search of new pharmaceutical lead structures. Hence they have strived to achieve novel and simple synthesis methods resulting in the development of benzotriazole methodology, offering many well-known versatile synthetic tools in organic synthesis during the past few decades [1–14]. This methodology has attracted growing attention from synthetic organic chemists due to several advantages over other methodologies. Benzotriazole is inexpensive, non-toxic, highly stable, and easy to introduce into molecules through a variety of reactions, activates molecules toward numerous transformations, remains sufficiently stable during the course of the reactions, and finally can be removed easily at the end of the reaction sequence. Moreover, because of the operational simplicity, benzotriazole has been drawing enormous attention and is being explored in organic synthesis as a synthetic auxiliary and catalyst as well in several reactions, such as the Baylis–Hillman reaction [15] and various coupling reactions [16, 17].

All the above features have heightened the interest of chemists and given enormous impetus to develop new benzotriazole-mediated heterocyclic skeletons. Several review articles have reported benzotriazole-based reagents as ideal synthesis auxiliaries for efficient organic synthesis [1–6], in which authors deal mainly with the chemistry of N-substituted benzotriazoles with emphasis on the many useful types of reactions including benzotriazole-mediated arylalkylation, heteroalkylation [7, 8], heterocyclization [9, 10], and benzannulations [11], conjugate addition [12], non-stabilized α-aminocarbanions [13], and acylation reactions [14]. Despite the tremendous development in benzotriazole chemistry, there is still a dearth of recent and concise reports on synthesis applications of benzotriazole for the development of heterocyclic compounds of great

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biological value. Therefore, the aim of this review is to give an instructive and concise report on the latest development in synthesis applications of benzotriazole methodology for the construction of pharmacologically important heterocyclic skeletons.

Activation and comparison of benzotriazole with other groups

Benzotriazole, a most useful synthetic auxiliary, confers many interesting types of activation to groups it is attached to, as shown in Scheme 1. Being a good leaving group, benzotriazole generates a cation which can further react with a variety of nucleophiles. Benzotriazole is known to act as a proton activator too, which can activate and abstract the attached α-proton by stabilizing the resultant anion, thus allowing reaction with a variety of electrophiles. Benzotriazole may donate electrons to stabilize the cation formed by the loss of any other leaving group, if both are attached to the same carbon. It is also known as a radical precursor via a single electron transfer (SET) mechanism, for example, in the presence of SmI_2. Moreover the bond between benzotriazole and a carbon atom can be cleaved by transfer of two electrons from a metal (e.g., Li) to generate a carbanion. Benzotriazole-based dianions obtained through lithiation of substituted benzotriazole (e.g., 1-vinylbenzotriazole) are well documented where the nitrogen of the triazole ring participates in cyclization. Despite the greater stability of benzotriazole several reactions are known due to disruption of the benzotriazole ring.

In comparison to many other substituents such as halogens, cyano, phenylthio, phenylsulfonyl, phenyl, vinyl, etc., benzotriazole is well known for its comparable leaving group ability along with its better proton activation efficiency, which makes it more preferable than any other groups. Benzotriazoles attached to a carbon atom that is a part of amino or ether functionality (X, NR_2, OR) are stable, non-volatile, versatile, and easy to prepare, whereas their halogen analogues are physiologically dangerous and often too reactive to be conveniently used as reagents [18–24]. Therefore, because of the stability of benzotriazole synthons their use is more efficient than other methodologies.

Benzotriazole-based biologically active heterocycles

Vorozole (**1**), a nonsteroidal aromatase inhibitor, and alizapride (**2**), an antiemetic drug for the treatment of nausea and vomiting, contain a benzotriazole skeleton (Fig. 1) [25, 26]. Recently, 1-substituted benzotriazole carboxylic acids have been identified as the first reported example of selective small-molecule agonists of the human orphan G-protein-coupled receptor GPR109b (HM74) [27]. Several novel benzotriazole derivatives also have their inhibitory properties against different kinases [28]. A class of stable benzotriazole esters has been reported as mechanism-based inactivators for severe acute respiratory syndrome (SARS) 3CL protease [29].

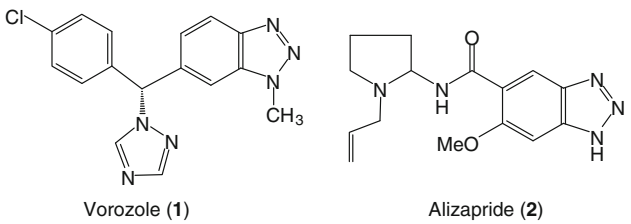
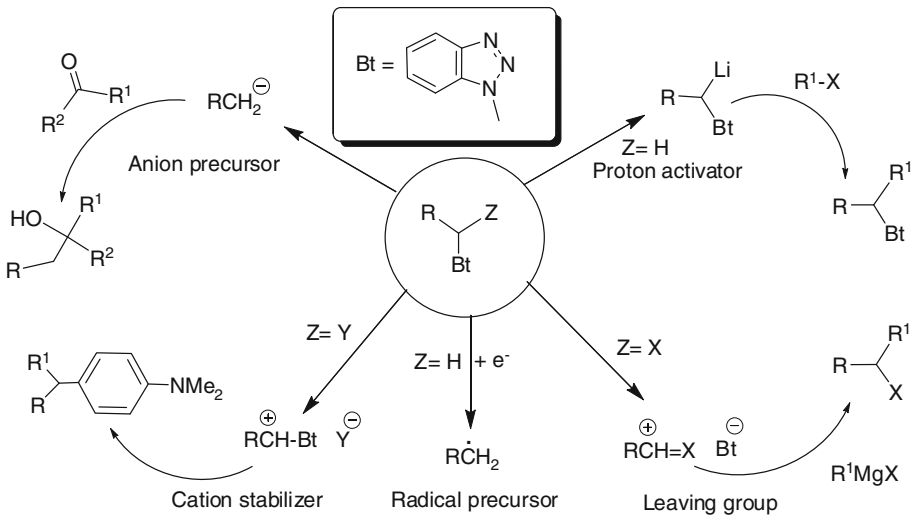


Fig. 1 Biologically active heterocycles

Scheme 1



Additionally, benzotriazole has been applied as a light-activated DNA-cleaving agent [30]. Therefore, there is a surging interest in developing benzotriazole-containing molecules, especially coupled with a heterocyclic system, and then to explore the possibility of searching for new chemical entities with a novel mode of action against frontline diseases.

Synthesis of three-membered heterocyclic rings through benzotriazole methodology

The Katritzky group developed the synthesis of 2-benzotriazolyl-substituted aziridines using benzotriazole methodology [31, 32]. 1-(Triphenylphosphorylideneaminomethyl)benzotriazole (BETMIP) [31], a convenient equivalent to CH_2NH_2, on reaction with a Grignard reagent displaces the benzotriazolyl moiety and results in an iminophosphorane intermediate, which on further reaction with epoxides afforded aziridines in good yields [32]. Carbenoids resulting from lithiation of **3** were captured by a diaryl imine and afforded aziridines **4** as a mixture of *cis*- and *trans*-isomers. Alternatively, compound **5** obtained by bromination of 2-vinylbenzotriazole on alkylamine substitution of the terminal bromide and subsequent intramolecular cyclization under basic conditions gave a similar aziridine system, 2-(benzotriazol-2-yl)aziridines **4**, in good yields (Scheme 2) [32].

The Katritzky group found 2-(benzotriazolyl)aziridine (**4**, if $R^3 = H$) not to be sufficiently thermally stable and upon heating it became converted to azomethine ylide **6**, which on polar [2+3] cycloaddition with acetylenedicarboxylic esters and subsequent aromatization by loss of benzotriazole afforded poly-substituted pyrroles **7** or **8** depending on the nature of R^1 in aziridines **4** [33].

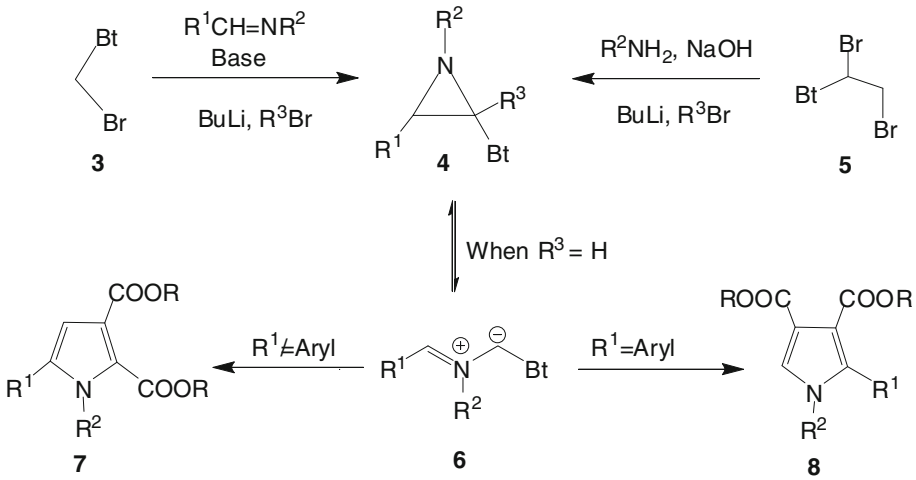
2*H*-Azirines are important for their versatile chemical and biological behavior and occur in natural antibiotics [34–37]. Synthesis of 2-(benzotriazol-1-yl)-2*H*-azirines **11** has been achieved in good yield by reacting **9** with hydroxylamine and then with tosyl chloride followed by cyclization through a Neber reaction. On treatment with a Grignard reagent in the presence of zinc chloride the product afforded azirines **13**. The sodium salt of benzenethiol and potassium phthalimide facilitated the clean conversion of **11** into novel 2*H*-azirines **12** and **14** in good yields (Scheme 3) [38].

Synthesis of epoxides has also been achieved by using benzotriazole methodology. *N*-(α-Ethoxyallyl)benzotriazole (**15**) was obtained almost in quantitative yield from benzotriazole and the corresponding acetal on a large scale. Upon lithiation followed by the reaction with a variety of ketones and Lewis acid (e.g., $ZnBr_2$), 2-vinyl-2-alkoxyepoxides **16** were obtained in good yields (Scheme 4) [38].

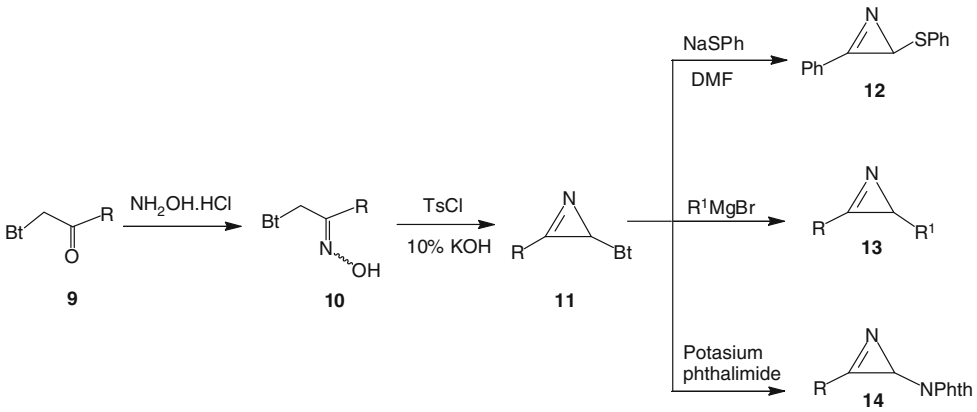
Synthesis of four-membered heterocyclic rings

A survey of the literature revealed that the development of four-membered heterocyclic rings using benzotriazole methodology is not known yet. Inspired by the utility and potential versatility of benzotriazole methodology in organic synthesis, we have recently developed a facile and highly stereoselective novel chiral approach to spiro-β-lactams **18** using benzotriazole methodology. 3-*O*-Benzyl-1,2-*O*-isopropylidenealdopentos-5-ulose, obtained from commercially available D-(+)-glucose in four steps on oxidation using hypervalent iodine chemistry, provides the desired chiral acid in good yield, which on further treatment with thionyl chloride in anhydrous dichloromethane and in situ coupling with BtH afforded acylbenzotriazole **17** as a white crystalline solid in 94% yield. Compound **17** has successfully been used to overcome the selectivity problem in the Staudinger [2+2] cycloaddition reaction for the synthesis of spiro-β-lactams **18** and **19** (as major and

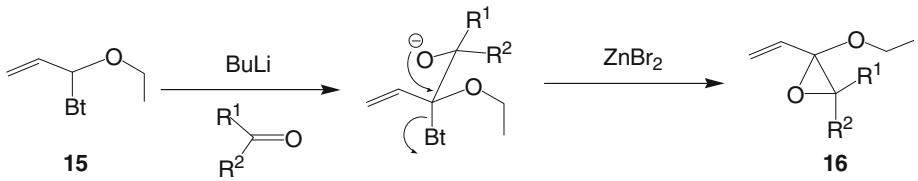
Scheme 2



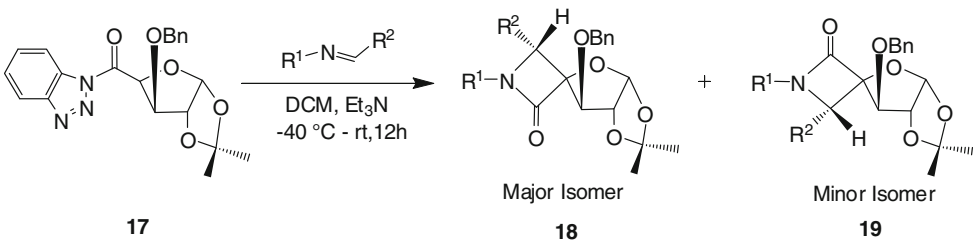
Scheme 3



Scheme 4



Scheme 5



minor isomer) through the coupling with different imines (Scheme 5) [39, 40]. Benzotriazole stereochemically plays an important role in obtaining the major isomer **18** with high yield and better stereoselectivity compared to the reported synthesis [40].

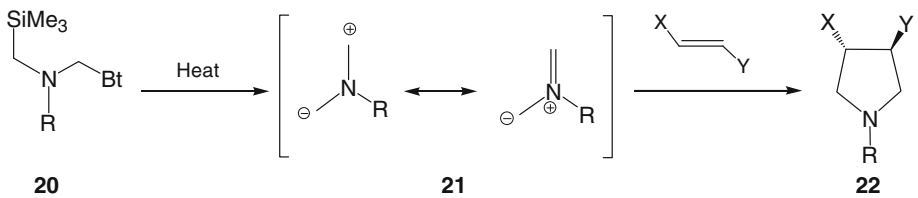
Synthesis of five-membered heterocyclic rings

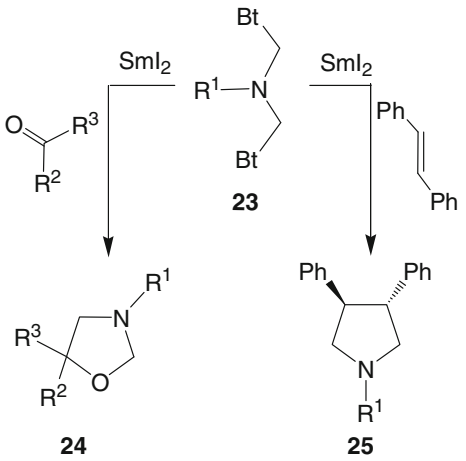
Thermal desilylation of benzotriazolylmethylaminosilanes resulted in azomethine ylide **21**, which on 1,3-dipolar cycloaddition with dipolarophiles yielded pyrrolidines **22** (Scheme 6). This method is stereospecific and has an edge over the previous route as it avoids the use of catalysts like AgF, CsF, etc. [41].

Search for easy access to diverse 3,5-substituted 1,3-oxazolidines in good yields has been of paramount importance in heterocyclic chemistry. When different types of *N*,*N*-bis(benzotriazolylmethyl)alkyl/aryl amines **23** were treated with ketones in the presence of samarium diiodide in tetrahydrofuran (THF)/hexamethylphosphoramide (HMPA) they afforded oxazolidines **24** in 39–81% yields, whereas similar reaction with (*E*)-stilbene afforded pyrrolidines **25** in 81% yield (Scheme 7) [42].

A series of electron-rich 3-functionalized-2-aminothiophenes and 1,3-disubstituted 2-(methylthio)pyrroles were successfully synthesized using benzotriazole methodology. Reaction of substituted allyl benzotriazoles with *n*-BuLi followed by condensation with isothiocyanates afforded a mixture of thioamide derivatives **26a** and **26b**, which

Scheme 6





Scheme 7

finally on Lewis acid promoted cyclization resulted in the formation of 3-substituted 2-aminothiophenes **28** in 25–80% yields (Scheme 8). Similarly, 1,3-disubstituted 2-(methylthio)pyrroles were also synthesized from allyl benzotriazoles through methyl protection of sulfur anion obtained from thioamide **26** followed by Lewis acid promoted cyclization [43].

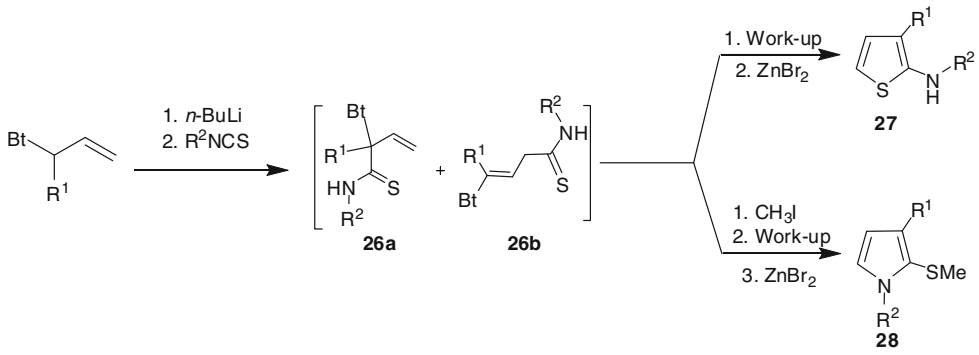
Transition-metal-catalyzed intramolecular amination of α-substituted allyl benzotriazoles **29** regioselectively gave five-membered 2-vinylpyrrolidines **30** (Scheme 9). Being a simple and high yielding methodology it was successfully applied to the synthesis of six-membered nitrogen heterocycles such as 2-vinylpiperidines **31** and may be useful for the synthesis of pyrrolidine and piperidine alkaloids [44].

Aryl benzotriazoles are useful synthons in thermal and photochemical Graebe–Ullmann reactions which lead to formation of carbazoles, pyridoacridines, carbolines, benzocarbolines, and fused tetraazapentalenes. The Katritzky group developed an efficient one-pot synthesis of N-substituted 2-(benzotriazol-1-yl)pyrroles **32** and isoindoles **33** by Mannich condensation of benzotriazole and primary amines with 2,5-dimethoxy-2,5-dihydrofuran or *o*-phthalaldehyde. However, similar treatment of 2,5-dimethoxy-2,5-dihydrofuran with benzotriazole in the presence of acetic acid facilitated the formation of 2-methoxy-5-benzotriazolyl-2,5-dihydrofuran (**34**, Scheme 10) [45].

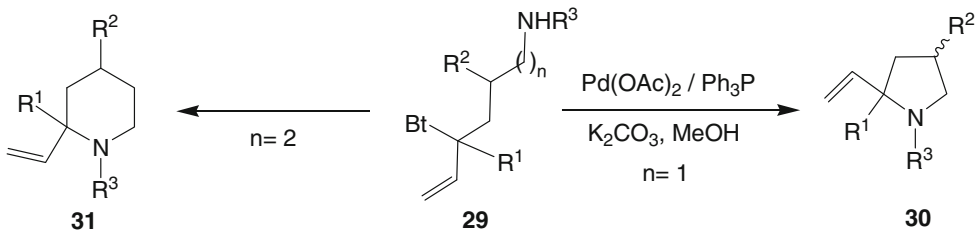
S-Methyl thioimidate **35** obtained from *N*-(benzotriazol-1-ylmethyl)thiobenzamide in 87% yield on reaction with a Michael acceptor afforded 2,3,4-trisubstituted pyrroles **36** in 75–93% yields. The reaction proceeded regiospecifically without formation of any isomer. Similarly, the treatment of 4-vinylpyridine or 2-vinylpyridine with **35** afforded 2-phenyl-3-(4-pyridyl)pyrrole (**37**) or the corresponding 2-pyridinyl isomer in good yield (Scheme 11) [46].

Furthermore (*E*)-1-ethoxy-3-(benzotriazol-1-yl)propenes **38** on reaction with butyl lithium and then with diarylimines at −78 °C afforded intermediates **39**, which on heating in the presence of $ZnBr_2$ furnished 1,2-diarylpyrroles **40** in good yields through intramolecular S_N2 reaction followed by elimination (Scheme 12) [47]. Similarly, the reaction of 1-(3-morpholinoprop-2-enyl)benzotriazole and imines provided the expected pyrroles in good yields [47]. The use of **38** as a C_3-fragment via [3+2] annulation afforded an attractive alternative route to 1,2-diarylpyrroles and 2,3-disubstituted furans [47, 48].

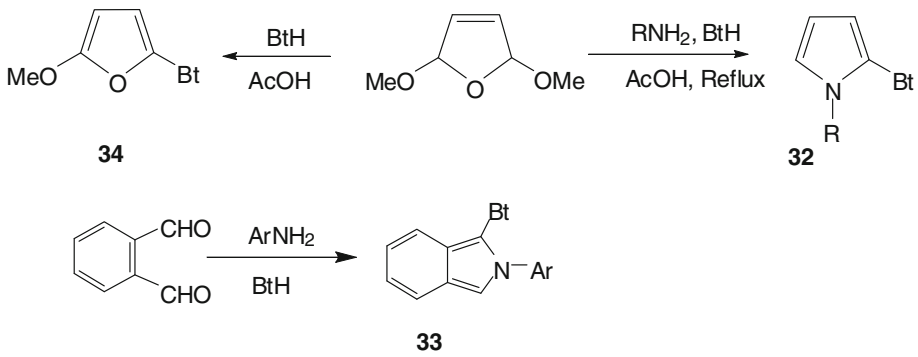
Scheme 8



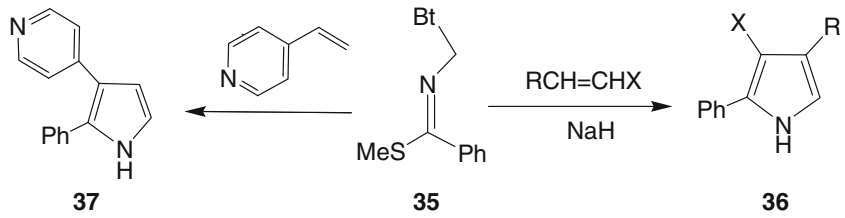
Scheme 9



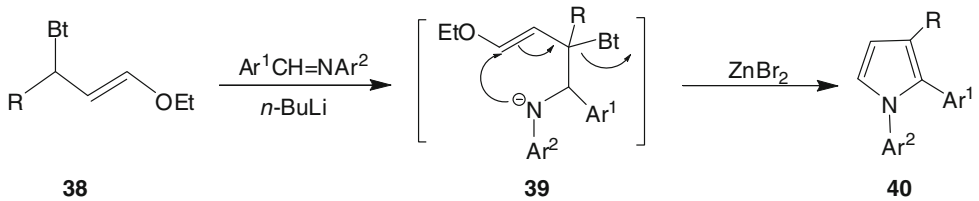
Scheme 10

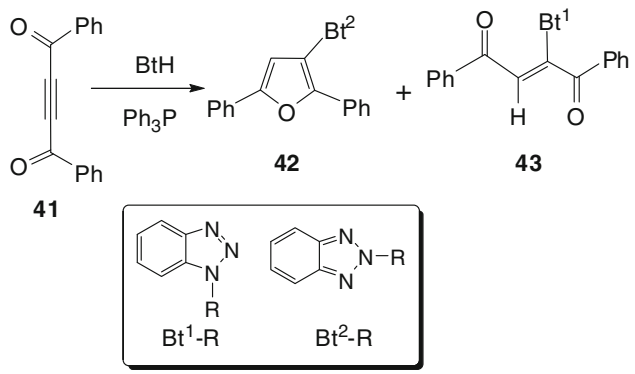


Scheme 11



Scheme 12





Scheme 13

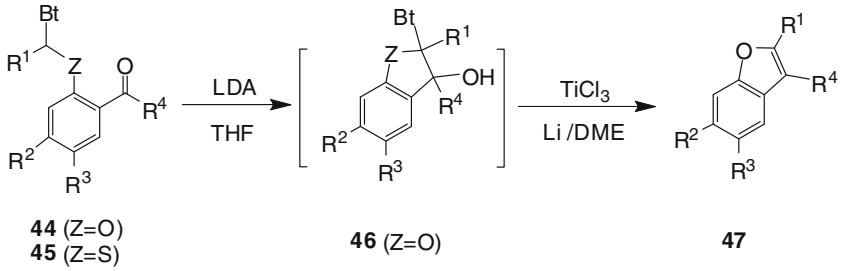
Yavari et al. reported a facile synthesis protocol for trisubstituted furan derivatives through benzotriazole methodology under neutral conditions at room temperature. A PPh_3-catalyzed reaction of benzotriazole with dibenzoylacetylene (**41**) led to the formation of two different products, 2,3,5-trisubstituted furan derivative **42** and the enamino ketone **43** (Scheme 13) [49].

The Katritzky group developed an efficient and simple route to benzofurans by reaction of α-benzotriazolylalkyl chlorides and *o*-hydroxyphenyl ketones. Compound **44** on abstraction of a proton from the α-position of benzotriazole followed by $TiCl_3$-promoted aromatization gave the 2,3-disubstituted benzofurans **47** in excellent yield (Scheme 14). However, $ZnBr_2$-catalyzed rearrangement of compound **46** gave 2,3-dihydrobenzofuran-2-ones as the major product. Similar reaction of (1-benzotriazolylalkylsulfanyl)benzophenones **45** with lithium diisopropylamide (LDA) followed by $ZnBr_2$-catalyzed rearrangement was complicated and gave a mixture of products including 2-alkyl-2-aryl-2,3-dihydrobenzothiophen-3-ones, 3-alkyl-3-aryl-2,3-dihydrobenzothiophen-2-ones, or benzothiophenes depending upon the reaction conditions and substituents [50, 51].

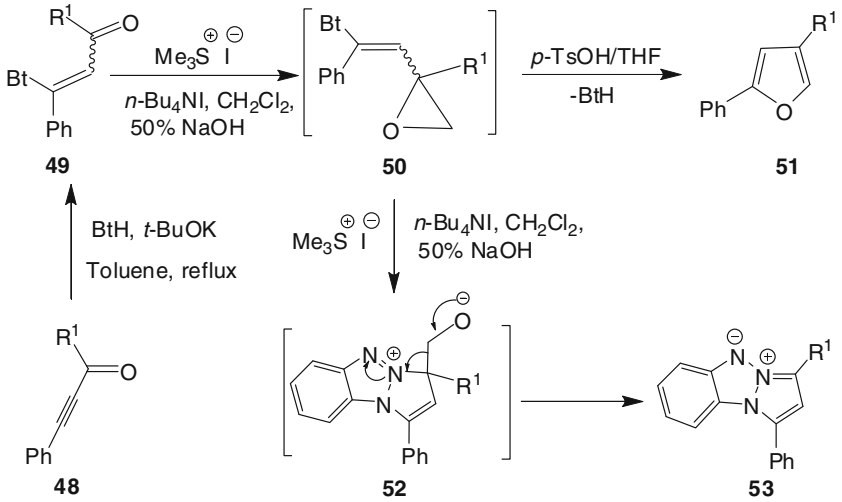
2,4-Disubstituted furans **51** and 4,6-diaryl-substituted 2,3-benzo-1,3a,6a-triazapentalenes **53** have been obtained from acylacetylenes **48** in good yield (Scheme 15). Compound **49** resulted from the reaction of benzotriazole and *t*-BuOK with trimethylsulfonium iodide to give intermediate oxiranes **50** which further on acid-catalyzed rearrangement furnished 2,4-disubstituted furans **51** along with 2,3-benzo-1,3a,6a-triazapentalenes **53** depending on substituents [52].

Synthesis of 2,4-diarylthiazoles, potent cytotoxic agents, has been achieved by several methodologies but very few efforts have been made for 2,4-diaryl-5-aminothiazoles. Rare availability and low stability of the starting materials (e.g., azirene and ω-chloro-ω-acylamidoacetophenones)

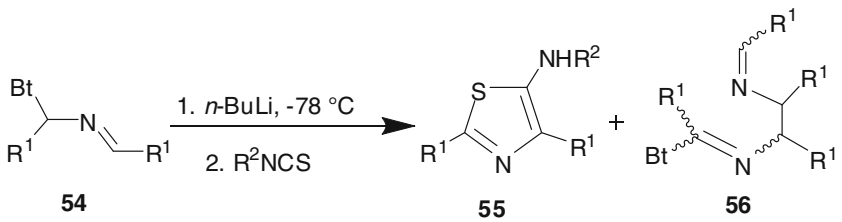
Scheme 14



Scheme 15



Scheme 16

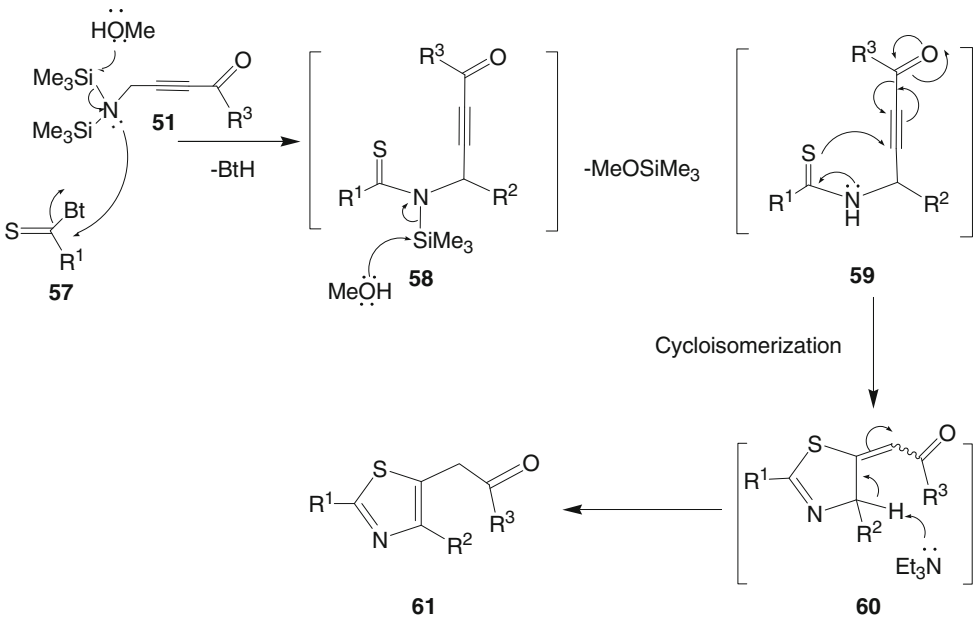


are major limitations. An efficient synthesis of 2,4-diaryl-5-aminothiazoles from easily available starting materials has been achieved through a simple reaction as compared to earlier methods [53]. Thiazoles **55** were successfully constructed in moderate to good yields by reacting *N*-arylmethylene[(benzotriazole-1-yl)arylmethyl]amines **54** with a variety of isothiocyanates. The side product **56** was obtained in less than 10% yield (Scheme 16) [53].

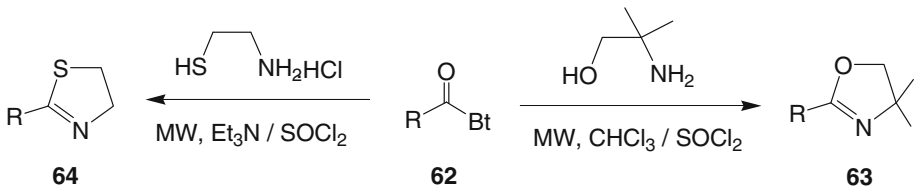
Sasmal et al. introduced an efficient one-pot facile protocol for the synthesis of a thiazole ring via N-desilylation followed by thioacylation and then cycloisomerization in an intramolecular thia-Michael fashion [54]. The treatment of benzotriazolylthiones **57** with different silyl-protected amines gave diverse thiazoles **61**. In all cases, cycloisomerization was spontaneous and the corresponding thiazoles were obtained in fairly good yields. A plausible reaction mechanism reported by the authors is presented in Scheme 17. Initial intermediate **58** obtained from **57** after N-desilylation generates intermediate **59** that subsequently undergoes cycloisomerization-aromatization in the presence of a base to give thiazoles **61** via **60**. Intermediate **59** was observed in TLC and in some cases the authors successfully isolated it by column chromatography, whereas **58** and **60** were not observed even by TLC. The method has wide applicability to introduce various oxo- or thio-functionalities including aliphatic and aromatic moieties especially at the C-2 position of thiazoles [54].

Synthesis of a variety of 2-substituted oxazolines and thiazolines has been achieved from readily available *N*-acylbenzotriazoles under mild reaction conditions. Thus microwave irradiation of 2-amino-2-methyl-1-propanol and 2-aminoethanethiol with readily available *N*-acylbenzotriazoles **62** in the presence of $SOCl_2$ furnished 2-substituted 2-oxazolines **63** in 84–98% yields and 2-substituted thiazolines **64** in 85–97% yields. By employing this method chiral oxazoline, bis-oxazoline, bis-thiazoline, and 5,6-dihydro-4*H*-1,3-oxazines have also been prepared in 82–96% yields (Scheme 18) [55].

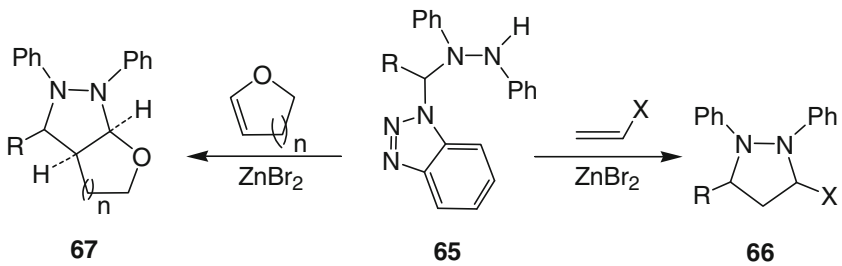
Scheme 17



Scheme 18



Scheme 19



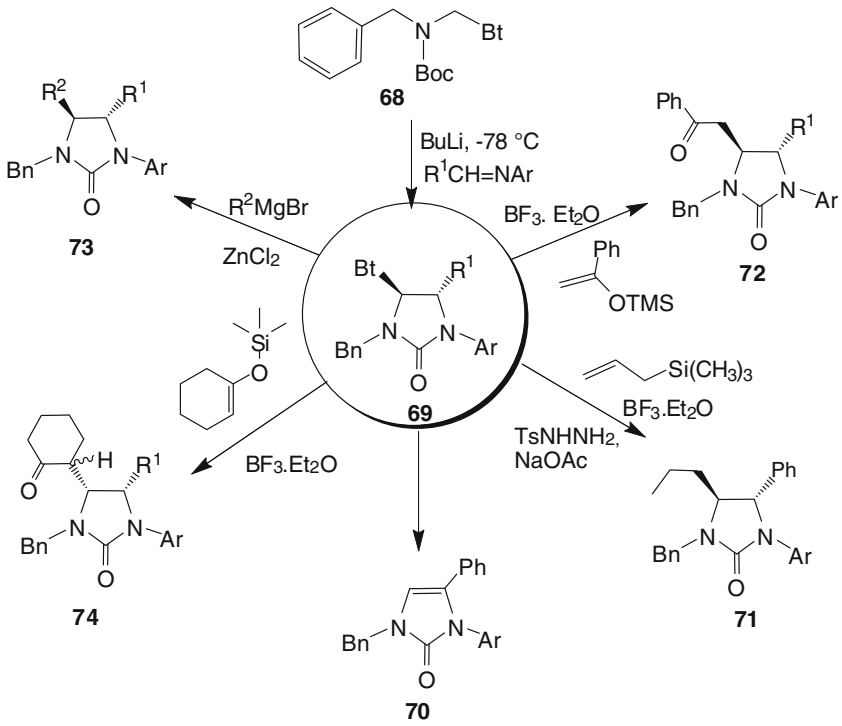
N-(1-Benzotriazolylalkyl)-*N*,*N*′-diphenylhydrazines **65**, easily accessible from *N*,*N*-diphenylhydrazine, benzotriazole, and an aldehyde in CH_2Cl_2 as mixtures of benzotriazol-1-yl and benzotriazol-2-yl isomers in a ratio of 8:1, on treatment with electron-rich alkenes in the presence of Lewis acid gave N,N-disubstituted pyrazolidines **66** exclusively in moderate to good yields (Scheme 19). The strategy has been applied to the preparation of various *cis*-fused bicyclic compounds **67** using **65** and cyclic vinyl ethers [56].

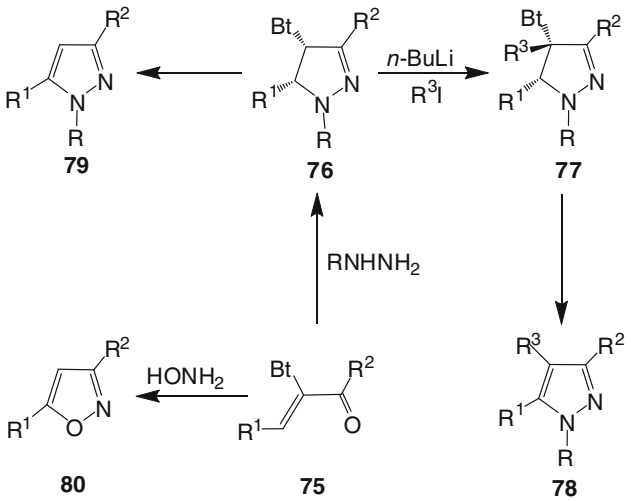
N-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine (**68**) was successfully used as a 1,1-dipole equivalent for 4,5-disubstituted imidazolidin-2-ones **69** which on treatment with various nucleophiles in the presence of a Lewis acid catalyst such as $ZnCl_2$ or $BF_3{\cdot}Et_2O$ gave diverse imidazolidin-2-ones **70**–**74** [57]. All reactions were smooth, high yielding, and stereoselective (Scheme 20).

A regioselective and clean synthesis of biologically important polysubstituted pyrazoles and isoxazoles has been achieved through benzotriazole methodology. Reaction of α-benzotriazolyl-α,β-unsaturated ketones **75** with monosubstituted hydrazines followed by alkylation at the 4-position of the pyrazoline **76** and then treatment with base furnished 1,3,4,5-tetrasubstituted pyrazoles **78** in excellent yields. Similar reaction with hydroxylamine afforded exclusively 3,5-disubstituted isoxazoles **80** in good yields (Scheme 21) [58].

Reported methods for the solid-phase synthesis of 1,2,3-triazoles are associated with some limitations [59, 60]. Synthesis of 3,5-bis(benzotriazol-1-yl)triazole is known

Scheme 20





Scheme 21

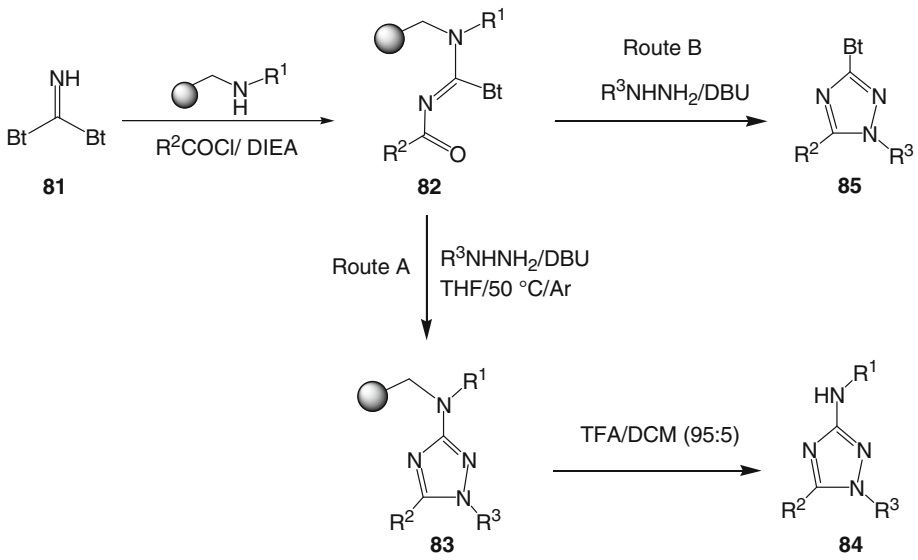
through the condensation of 1-cyanoalkylbenzotriazoles with hydrazine hydrate followed by deamination with sodium nitrite. A solid-phase synthesis of trisubstituted 3-alkylamino-1,2,4-triazoles has been developed by using benzotriazole methodology. Base-mediated cyclization of immobilized *N*-acyl-1*H*-benzotriazole-1-carboximidamides **82** with substituted hydrazines under mild conditions regioselectively furnished the 3-alkylamino-1,2,4-triazoles **84** in good yields and high purity. Amidine base-catalyzed reaction of resin-bound **82** with different hydrazines followed by cyclo-release strategy resulted in an ensemble of traizoles **85** in high yield with high purity (Scheme 22) [61].

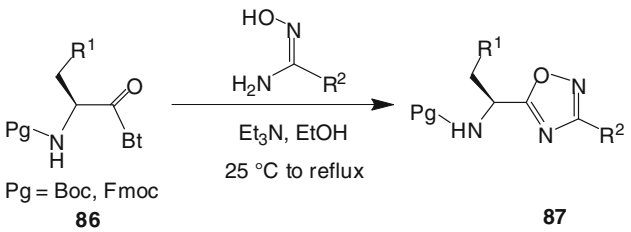
Katritzky et al. described the high yielding convenient methodology of chiral 1,2,4-oxadiazoles **87** from N-protected (α-aminoacyl)benzotriazoles **86** and aromatic *N*-acylbenzotriazoles (Scheme 23) [62].

Many reactions are reported for the synthesis of 1,5-disubstituted tetrazoles, such as (i) reaction of amides with phosphorus pentachloride or triflic anhydride and hydrogen azide or sodium azide [63–67]; (ii) reaction of thioamides with trimethylsilyl azide [68]; (iii) reaction of imidoyl chlorides with sodium azide, although in this reaction low stability of imidoylchlorides is a serious concern [69]; (iv) reaction of ketones with sodium azide [70–72] or trimethylsilyl azide [73, 74]; (v) treatment of oximes with hydrogen azide [75]; (vi) reaction of nitriles with alkyl chlorides and trimethylstannyl azide [76] or with alkyl azides [77–79]; (vii) reaction of nitrilium triflates with sodium azide [80]; and (viii) reaction of amidrazones with dinitrogen tetroxide or nitrous acid (Scheme 1) [81, 82]. Synthesis of 5-substituted tetrazoles is achieved from reaction of 1-cyanoalkylbenzotriazoles with sodium azide followed by Grignard reagent. However, all these methods or reactions have been associated with some serious drawbacks. Recently, 1,5-disubstituted tetrazoles **89** were obtained from imidoylbenzotriazoles **88** through simple, short, and mild reaction conditions with high yield (Scheme 24) [83].

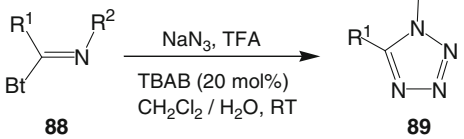
The strategy described in Scheme 22 with slight modification has recently been applied by us to the synthesis of

Scheme 22





Scheme 23



Scheme 24

glycosyl tetrazole, which is supposed to be more stable toward enzymatic degradation than natural N-nucleoside because of a C–C linkage between sugar and heterocyclic ring instead of a C–N linkage.

Bicycles with fused five-membered heterocyclic rings

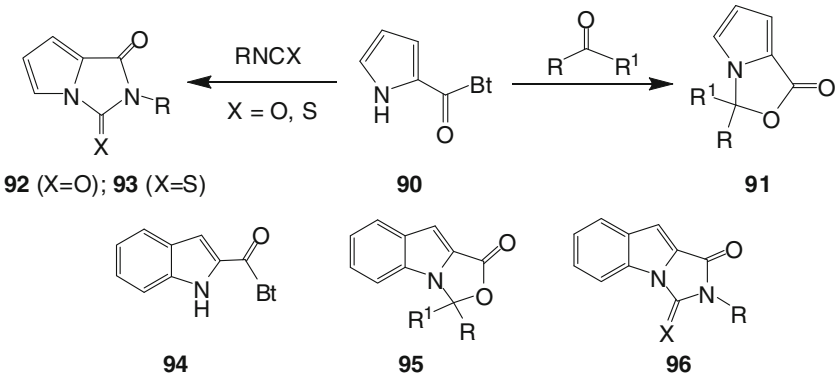
Benzotriazol-1-yl-(1*H*-pyrrol-2-yl)methanone (**90**) on reaction with different ketones, isocyanates, and isothiocyanates in the presence of a non-nucleophilic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished pyrrolo[1,2-*c*]oxazol-1-ones **91** and pyrrolo[1,2-*c*]imidazoles **92**, **93** in a simple one-step method [84, 85]. This method was useful for the synthesis of oxazolo[3,4-*a*]indol-1-ones **95** and related imidazo[1,5-*a*]indoles **96** from benzotriazol-1-yl-(1*H*-indol-2-yl)methanone (**94**) in one step (Scheme 25) [86].

A series of benzo-fused and styryl-substituted heteroaromatic systems were prepared by using chemistry similar to the Hantzsch method. 1-(1*H*-Benzotriazol-1-yl)-3-chloroacetone (**97**) was successfully converted into some interesting benzannelated and 2-arylethen-1-yl-substituted heterocycles including benzothiazoles, pyrido[1,2-*a*]indoles, styryl-substituted indolizines, and imidazo[1,2-*a*]-pyridines **98**–**100** [87]. The method is short, efficient, and high yielding (Scheme 26).

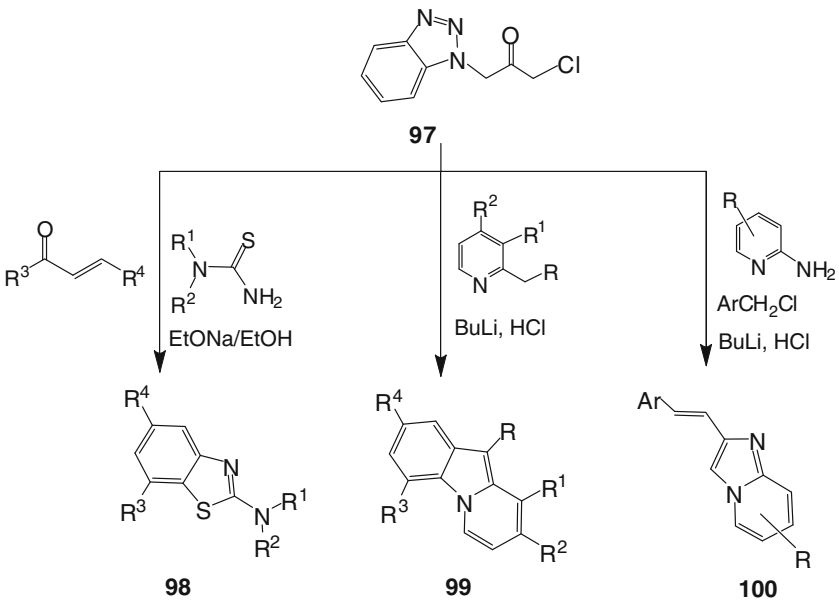
The Katritzky group developed an efficient and regiospecific approach for the formation of 3-substituted imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, and imidazo[1,2-*c*]pyrimidines **104** by one-pot reactions of 2-aminopyridines **101** or 2-(4-)aminopyrimidines **102** with 1,2-bis(benzotriazolyl)-1,2-(dialkylamino)ethanes **103**. Cyclization of 2-aminopyridines **101** with **103** proceeded only under reflux, whereas the cyclization of 2-(4-)aminopyrimidines **102** with **103** proceeded smoothly in the presence of Lewis acid such as $ZnBr_2$ (Scheme 27) [88].

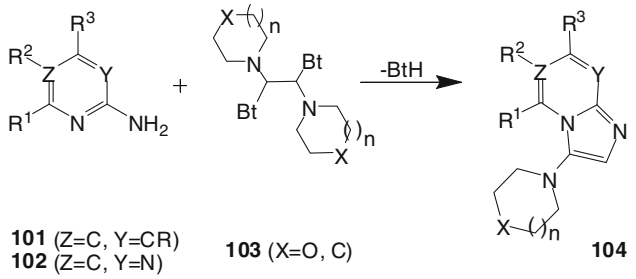
A series of modified motifs of imidazoles and octahydroimidazo[1,2-*a*]pyridines were prepared by using benzotriazole chemistry. When various nucleophiles such as Grignard reagents, allylsilanes, silyl ethers, and triethylphosphite reacted with benzotriazole intermediate **106** the desired 1-phenyl-5-substituted hexahydro-1*H*-pyrrolo-[1,2-*a*]imidazoles and 1-phenyl-5-substituted octahydroimidazo[1,2-*a*]pyridines **107** were obtained in good to excellent yields after the cleavage of benzotriazole (Scheme 28) [89]. A similar reaction of glutaraldehyde and benzotriazole with phenylglycinol gave a quantitative yield of (3*S*)-5-benzotriazolyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (**105**) which further on reaction with Grignard reagent and then reduction with $NaBH_4$ and/or hydrogenation with Pd/C gave the single diastereomeric chiral 2-substituted or 2,6-disubstituted piperidines in good yields [90].

Scheme 25

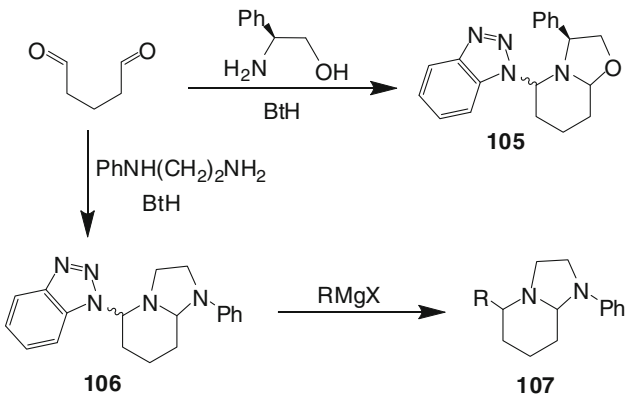


Scheme 26





Scheme 27



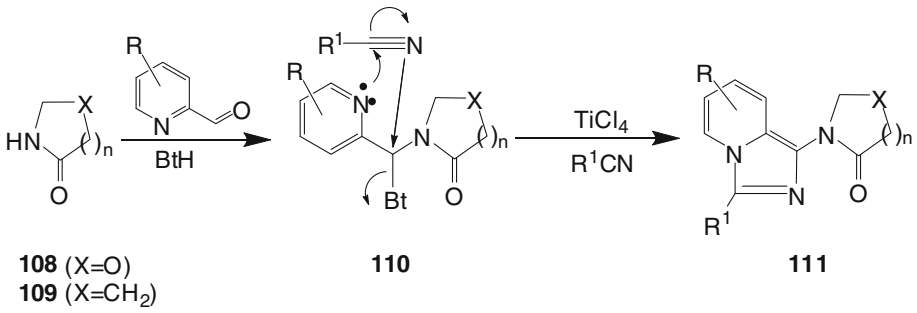
Scheme 28

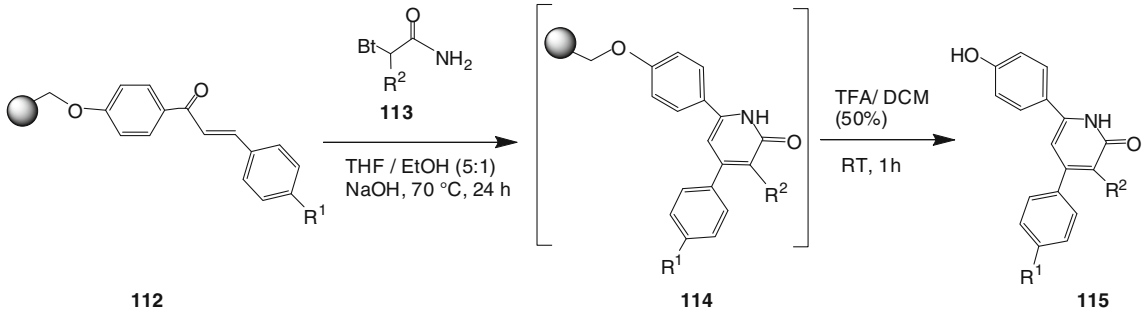
Pyridin-2-yl intermediates **110**, Mannich adducts obtained from the condensation of 2-oxazolidinone **108** or 2-pyrrolidinones **109** with 2-pyridinecarboxaldehydes and benzotriazole, on treatment with several functionalized cyanides in the presence of $TiCl_4$ gave excellent yields of 1-amido-3-aryl- and 1-amino-3-alkylimidazo[1,5-*a*]pyridines **111** (Scheme 29) [91].

Six-membered heterocyclic systems

Pyridone scaffolds are considered as valuable pharmacophores in medicinal chemistry [92–94]. Four general

Scheme 29





Scheme 30

methods reported for the solid-phase synthesis of pyridones are (i) the reactions of Danishefsky's diene with imine resins [95], (ii) acylation of pyridines followed by the condensation with Grignard reagents [96, 97], (iii) reacting 4-pyridones and acetylketene with polymer-bound enamines [98], and (iv) the reaction of resin-bound chalcones with 1-(methoxycarbonylmethyl)pyridinium bromide and ammonium acetate (Scheme 30) [99].

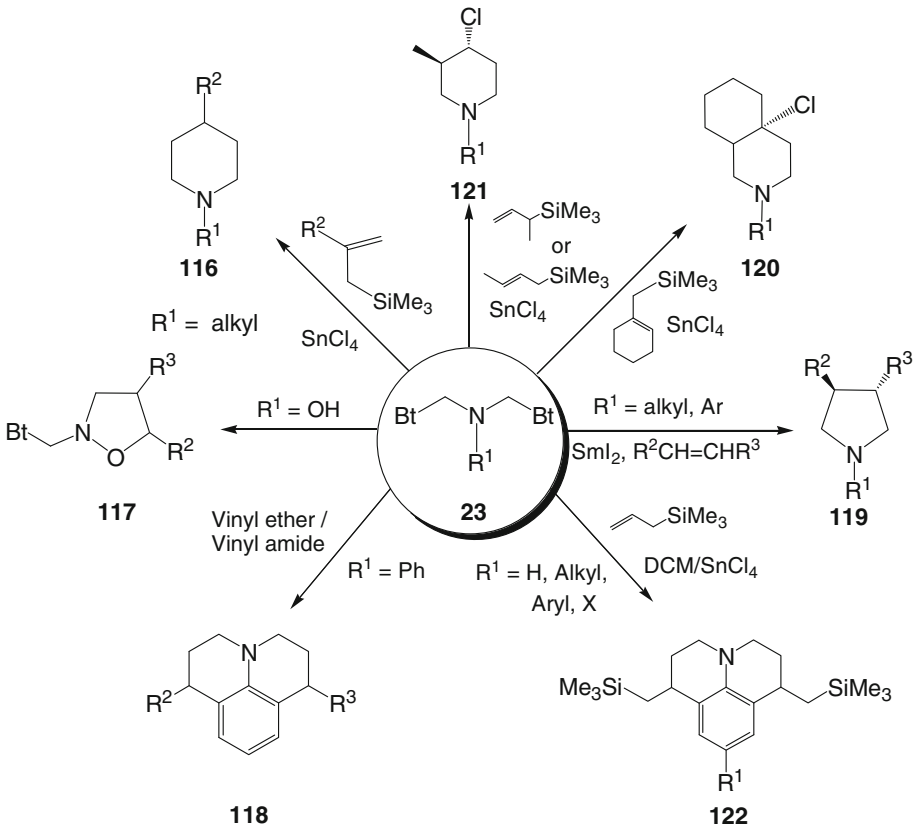
The serious drawbacks associated with these methods, such as rare availability of starting materials, harsh reaction conditions, etc., stimulated interest in searching for an alternative facile route. Recently, Katritzky et al. introduced a combinatorial ensemble of 4,6-disubstituted and 3,4,6-trisubstituted 2-pyridones **115** using Wang resin-bound chalcones **112** with 2-(benzotriazol-1-yl)acetamides **113** in excellent yields (Scheme 30) [100]. *N*,*N*-Bis-[(benzotriazol-1-yl)methyl]amines **23** can easily be accessible from 1-(hydroxymethyl)benzotriazole and amines or from benzotriazole, aqueous formaldehyde, and amines [101, 102]. Different derivatives of *N*,*N*-bis-[(benzotriazol-1-yl)methyl]amines **23** were treated with allyltrimethylsilanes to yield substituted piperidines **116**, whereas other *N*,*N*-bis[(benzotriazol-1-yl)methyl]anilines gave julolidines **122**. Application of *N*,*N*-bis-[(benzotriazol-1-yl)methyl] amines for the construction of other biologically important heterocycles **116–122** is summarized in Scheme 31 [103].

3,4-Dihydro-2*H*-1,3-benzoxazines **123** or corresponding benzothiazines **124** were synthesized from **23** through directed *o*-lithiation of phenols or thiophenols in a one-pot reaction. The method was also successful for constructing larger heterocyclic rings including 2,3,4,5-tetrahydro-1,3-benzothiazepines **125** through side-chain lithiation of substituted thiophenols (Scheme 32) [104].

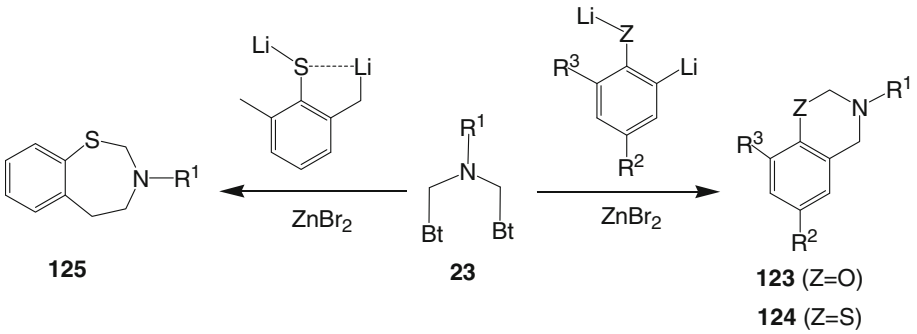
1-(Benzotriazol-1-yl)-1-phenoxyalkanes **126** and 1-(benzotriazol-1-yl)-1-thioether **128** on treatment with BuLi followed by trimethylchlorosilane gave the trimethylsilylbenzotriazoles **127** and **129**. Thioacylsilanes obtained from **127** or **129** on reaction with hexamethyldisilathiane (HMDST) in the presence of TfOTMS or $CoCl_2{\cdot}6H_2O$ were trapped with 2,3-dimethyl-1,3-butadiene to lead to 2-methyl-2-trimethylsilyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyrans **130** in good yields. This method was very useful for the easy synthesis of diverse 2*H*-thiopyrans (Scheme 33) [105].

The quinazolinone synthesis has become the cornerstone for synthesis chemists and gained extensive importance in medicinal chemistry because of the diverse pharmacological activities of the products. Moreover, the skeleton is found in hundreds of naturally occurring alkaloids [106, 107] and hence the exploration of this skeleton in drug discovery research is of paramount importance. Despite the growing potential of quinazolinones, their synthesis methodologies suffer various limitations like multi-step nature, use of hazardous chemicals, long reaction times, low reaction yields, limited availability of starting materials, etc. In an attempt to find an easy and convenient synthesis of quinazolines, we turned our attention to bis(benzotriazolyl)-methanethione (**131**), a crystalline solid derived from benzotriazole in high

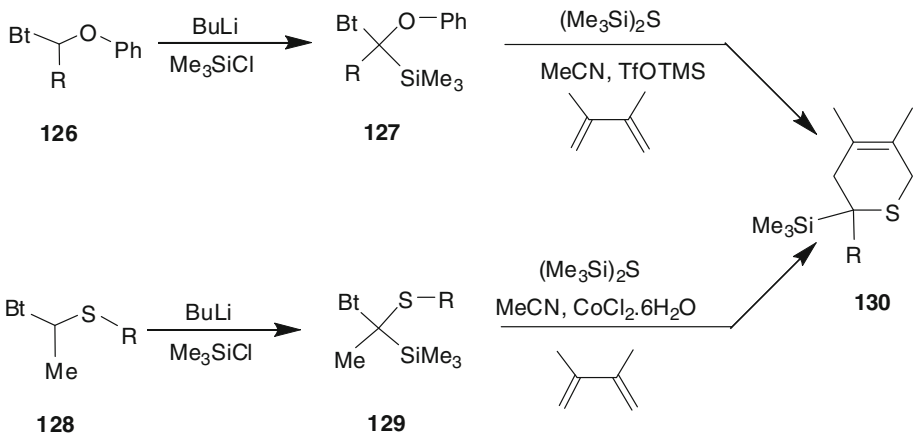
Scheme 31

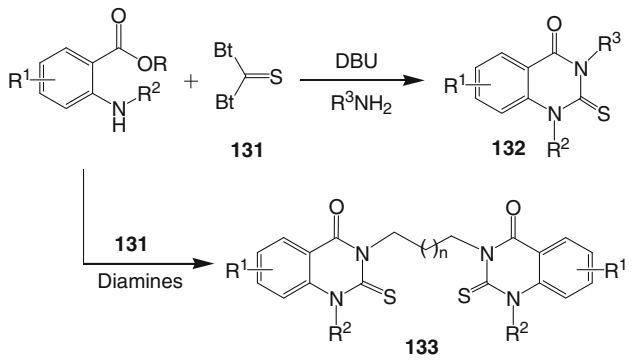


Scheme 32



Scheme 33





Scheme 34

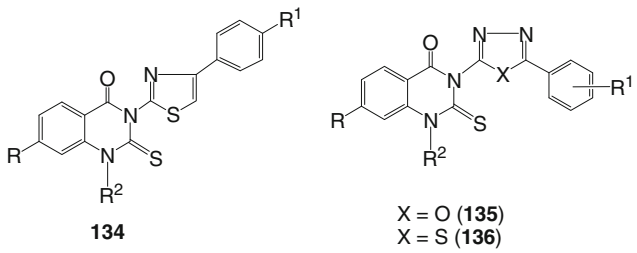


Fig. 2 Quinazolinones prepared under microwave conditions

yield, which proved to be a very effective thiophosgene equivalent in thioacylation as well as in the synthesis of different thiocarbonyl compounds. Application of **131** has been found to be more advantageous as compared to thiophosgene due to its lower toxicity, high stability, and moreover easy handling. In another study the Katritzky group reported a facile strategy for preparation of secondary and tertiary thioureas by using 1-(alkyl/arylthiocarbonyl)benzotriazoles as precursor and **131** as thioacylating agent [108]. Using the same synthon **131** we have recently developed a facile protocol for the preparation of medicinally important diverse 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **132** and **133** through one-pot reaction of anthranilic acid/esters, primary amines or diamines, and **131** in the presence of an amidine base (Scheme 34) [109, 110].

Considering the importance of tiodazosin, an antihypertensive agent and hybrid of quinazoline and 1,3,4-oxadiazole heterocycles, we synthesized new quinazolinone hybrids using different pharmacological important heterocyclic amines containing thiazole, 1,3,4-oxadiazoles, and thiadiazole skeletons. The reaction was very sluggish with low yield but under microwave irradiation was found to be clean, smooth, and fast and the resulting thioxoquinazolinones were obtained in high yields [111]. The prepared prototype quinazolinones **134–136** are shown in Fig. 2.

Very recently, we have found a convenient synthesis protocol for diverse dithiocarbamates having various substituents including alkyl, aryl, heteroaryl, and alkyl/aryl at the thiol or amine chain, or at both chains by the one-pot reaction of mercaptanes, amines, and **131** in the presence of amidine base under mild reaction conditions [112]. This method was also useful for the synthesis of glycosyl dithiocarbamate from the glycosyl thioester **137** [113], which on similar cyclative amidation as described earlier [114], (RR Kale, unpublished data) may lead to an alternative path for the development of C-nucleoside **138** in fair to good yield (Scheme 35).

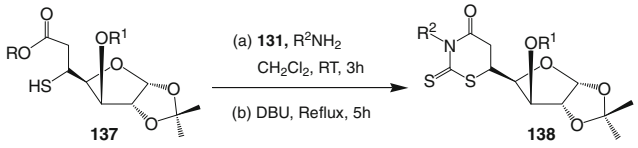
High-yielding syntheses of 2-aminoquinazoline-4-thiones **140** have been achieved by $ZnBr_2$-catalyzed condensation of N-functionalized benzotriazole-1-carboximidoyl chlorides **139** with potassium thiocyanate. The N-functionalized benzotriazole-1-carboximidoyl chlorides obtained as a mixture of Bt^1 and Bt^2 are recognized as highly stable and easily accessible novel isocyanide dichloride synthesis equivalents (Scheme 36) [115].

Base-catalyzed reactions of stable *N*-(*o*-hydroxyarylacyl)benzotriazoles **141** with various aldehydes or isocyanates afforded high yields of 1,3-benzodioxin-4-ones **142** and benzoxazine-2,4-diones **143**. This strategy was successful for other series of heterocycles including naphtho-1,3-dioxinones, naphthoxazine-1,3-diones, etc. (Scheme 37) [116].

A series of pyrido[1,2-*a*]pyrimidin-2-ones, 2*H*-quinolizin-2-ones, pyrido[1,2-*a*]quinolin-3-ones, and thiazolo[3,2-*a*]pyrimidin-7-ones were also prepared by using a similar benzotriazole strategy. These structural motifs are present in many pharmaceutical drugs, such as tranquilizer pirenperone, the antiallergic agent ramastine, etc. The reaction of 1-(benzotriazol-1-yl)-3-phenylpropynone (**144**) with substituted 2-aminopyridines, 2-picolines, and 2-methylquinoline afforded pyrido[1,2-*a*]pyrimidin-2-ones **145**, 2*H*-quinolizin-2-ones **146**, and pyrido[1,2-*a*]quinolin-3-ones **147** in good yields (Scheme 38) [117].

Abonia et al. reported the reaction of 5-amino-4-(benzotriazol-1-ylmethyl)-3-*t*-butyl-1-phenylpyrazole (**148**) with some unactivated electron-rich alkenes under solvent-free conditions and facilitated the formation of hydropyrazolopyridines **149** or **150** in high yields through benzotriazole-mediated heterocyclization (Scheme 39) [118].

Another novel work by the Katritzky group is the development of an efficient route for the synthesis of biologically important 1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazines through benzotriazole chemistry. When benzotriazole and 2-(pyrrol-1-yl)-1-ethylamine (**151**) reacted with formaldehyde they afforded intermediate **152** which on subsequent nucleophilic substitution gave a series of related pyrrolo-pyrazines. Similarly the reaction of **151** with BtH and glutaric dialdehyde gave **153** with a mixture of Bt^1 and Bt^2, which further reacted with different nucleophiles to give 5,6,9,10,11,11a-hexahydro-8*H*-pyrido-



Scheme 35

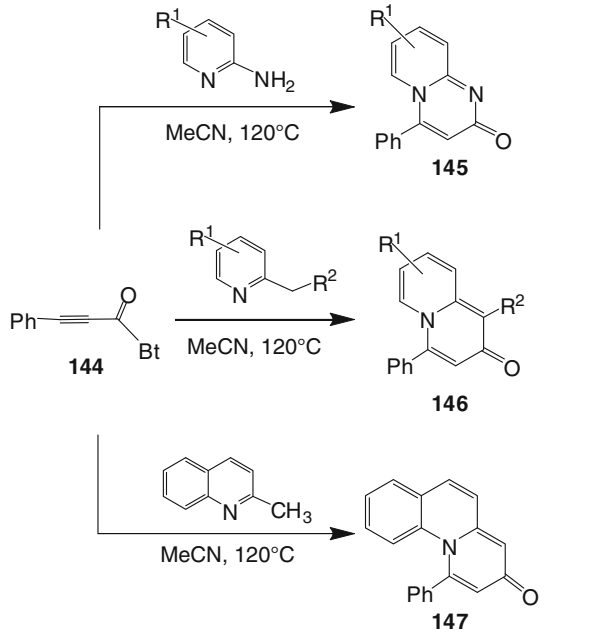
Scheme 36

[1,2-*a*]pyrrolo[2,1-*c*]pyrazines in good yields (Scheme 40) [119].

Benzotriazole-mediated cyclization for constructing larger heterocyclic rings

Synthesis of pharmacologically interesting large heterocyclic systems, such as benzazepines, tetrazolotriazepines, diazapines, 1,4-benzothiazepines, 1,4-benzooxazepines, etc., have been achieved through benzotriazole methodology [52, 53]. Khalaj et al. reported a short and efficient benzotriazole methodology to construct benzodiazepine carboxamide analogs. *N*-(2,3-Dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-carboxamides **156** were successfully prepared in high yields by coupling 2-aminobenzophenones with (benzotriazol-1-yl)-*N*-acylglycines **154** followed by displacement of the benzotriazole with ammonia and finally cyclization of the resulting monoacyl aminals using ammonium acetate in glacial AcOH (Scheme 41) [120].

5-Amino-4-(benzotriazolylmethyl)-3-*t*-butyl-1-phenylpyrazole was elegantly used for the synthesis of the interesting heterocyclic skeleton **157**. 1-(Triphenylphosphoranylideneaminomethyl)benzotriazole was treated with methylidenetriphenylphosphorane followed by deprotonation with *n*-BuLi resulting in a monoazabisphosphorus ylide, which on subsequent treatment with phthalic dicarboxaldehyde gave 3*H*-2-benzazepine (**158**). 4-



Scheme 38

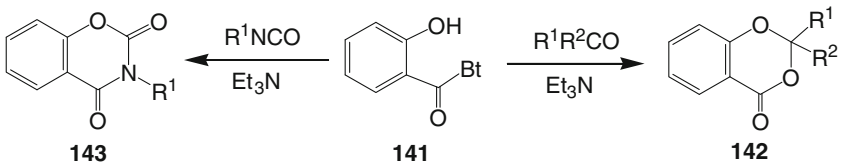
(Benzotriazol-1-yl)-6*H*-benzo[1,5-*e*][1,2,5]triazepine (**159**) was obtained by reacting 1,2-dichloro-1,2-di(benzotriazol-1-yl)ethane with NaN_3 via expansion of the triazole ring of benzotriazole by two atoms as shown in Fig. 3.

1-[2-Arylthio(oxy)ethyl]-5-benzotriazolyl-2-pyrrolidinones **160** and **161** and 3-benzotriazolyl-2-[2-arylthio(oxy)-ethyl]-1-isoindolinones **162** and **163** were prepared from the reaction of benzotriazole and 2-(arylsulfanyl)ethylamines or 2-phenoxyethylamine with 2,5-dimethoxy-2,5-dihydrofuran or 2-formylbenzoic acid. Further treatment of these intermediates with Lewis acid furnished 1,4-benzoxazepines **164** and **165** and 1,4-benzothiazepines **166** and **167** in good to excellent yields (Scheme 42) [121].

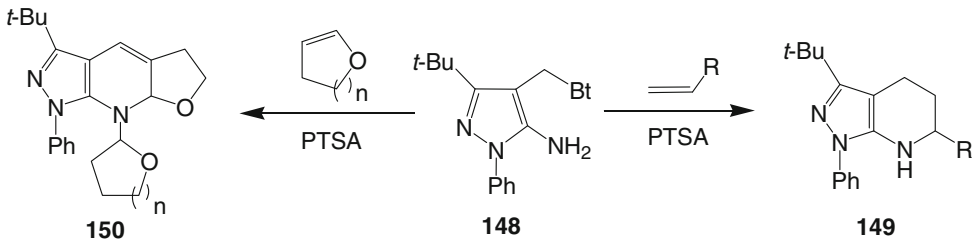
Heterocycles prepared through benzotriazole-mediated annulations

Benzotriazole-mediated ring annulations have been recognized as a most useful method for the synthesis of heterocycle[*b*]-fused carbazoles, indoles, and other related molecules [122]. Pyrrolo- and indoloisoquinolinones were easily synthesized via aromatic annulation as shown in

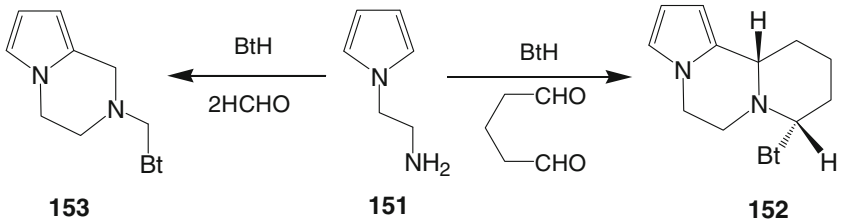
Scheme 37



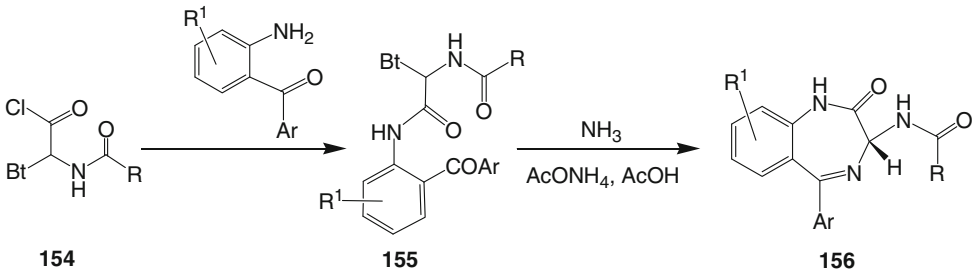
Scheme 39



Scheme 40



Scheme 41



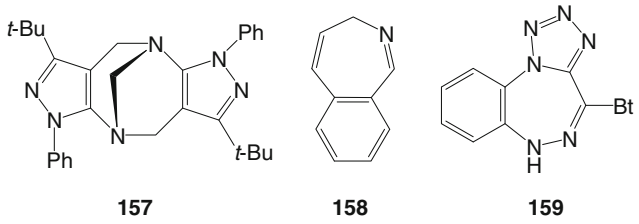
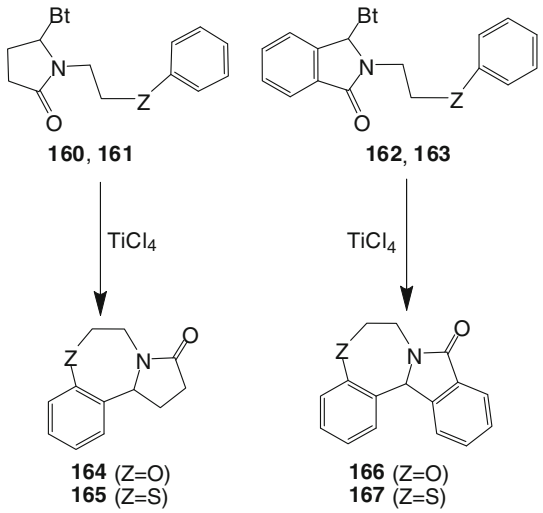


Fig. 3 Some synthetic benzoazepine derivatives



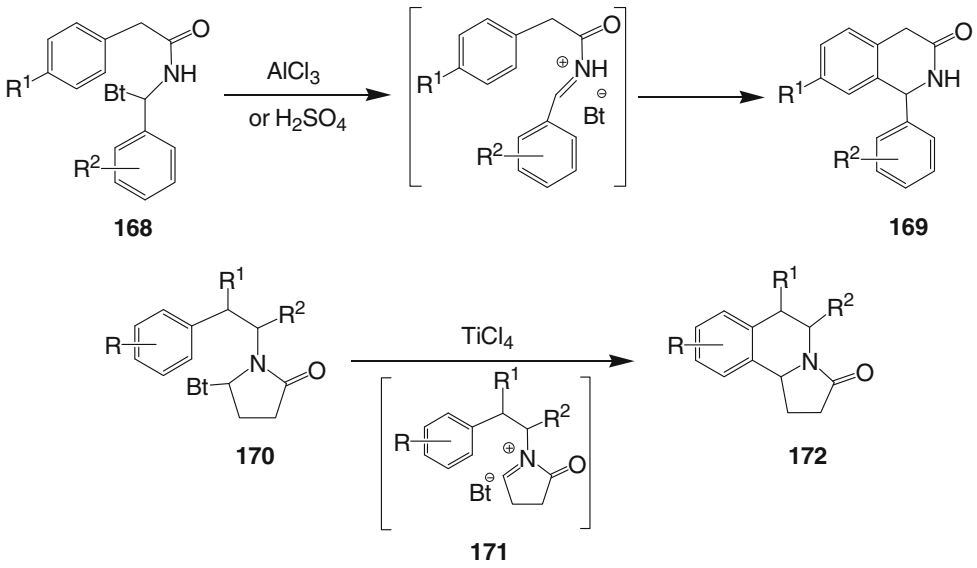
Scheme 42

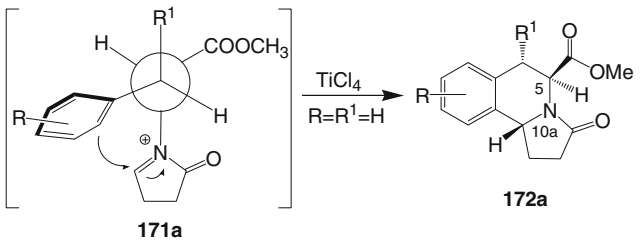
Scheme 43. 1-(2-Arylethyl)-5-benzotriazolyl-pyrrolidin-2-ones **170** were readily prepared in one step from 2-arylethylamines, BtH, and 2,5-dimethoxy-2,5-dihydrofuran, which on $TiCl_4$-induced intramolecular cyclizations gave 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones **172** with good stereoselectivities [123]. This method was found to be useful for the high-yielding synthesis of 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones (Scheme 43).

Treatment of Bt intermediate **170a** (obtained from methyl (2*S*)-amino-3-phenylpropanoate) with $TiCl_4$ leads to the formation of transition state (TS) **171a**. As a result of the repulsion between the ester and the phenyl group, the ester group prefers to be located at the *anti*-position to the phenyl group and thus stimulates the phenyl group to attack the iminium cation in TS **171a** favorably from the *anti*-direction to the ester group and furnishes the major diastereomer, i.e., methyl (5*S*,10b*R*)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-5-carboxylate **172a**. Absence of a significant NOE effect for H(5) after the irradiation of a hydrogen peak at 10b position supported the assignment of the *trans*-orientation for H(5) and H(10b) of the cyclized product **172a** (Scheme 44).

Brominated 1-methyl-3-(benzotriazol-1-ylmethyl)indole **173** on Li-X exchange followed by reaction with heteroaryl

Scheme 43





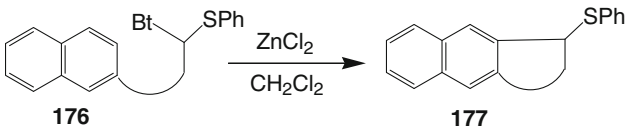
Scheme 44

aldehydes/iodomethane gave intermediate **174** that underwent ionization induced by heating resulting in ring closure, and finally on subsequent in situ aromatization afforded heterocycle [*b*]-fused carbazoles **175** (Scheme 44). An attractive feature of this benzotriazole-mediated annulation is the wide variety of fused carbazoles which can easily be prepared by changing the starting heteroaryl aldehydes, such as 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-indolyl rings (Scheme 45) [124].

Treatment of benzotriazol-1-ylphenylthiomethane with BuLi followed by reaction with a variety of electrophiles gave derivative **176**, which on Lewis acid promoted cyclization afforded fused aromatics **177**. The resistance of the phenylthio group to Lewis acid catalyzed elimination makes this procedure more attractive for aromatic annulations (Scheme 46) [125].

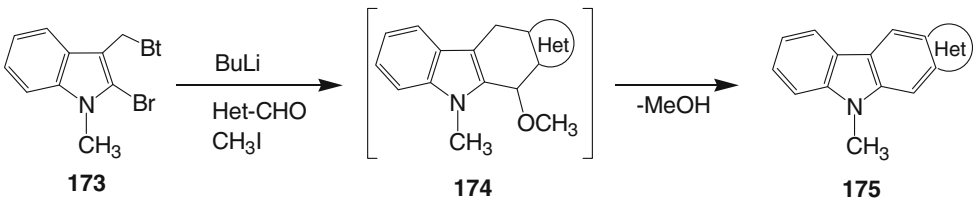
Benzotriazole-mediated substitution modification in heterocycles

Replacement of a substituent at the α-position of a heteroaromatic ring is achieved through benzotriazole methodology. The substitutions of a benzotriazole group from carbazoles, indoles, pyrroles, and benzimidazoles are some representative examples. Their presence separated by one carbon atom from a heteroaromatic ring allows the synthesis of many heterocycles with quite complex substituents. Representative examples include a brilliant synthesis of the complex heteroaromatic skeleton **180** starting from propargyl benzotriazole (**178**, Scheme 47) [126].

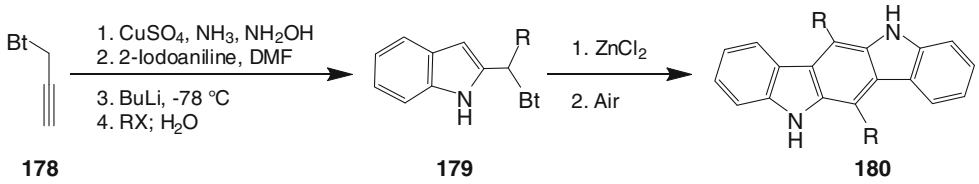


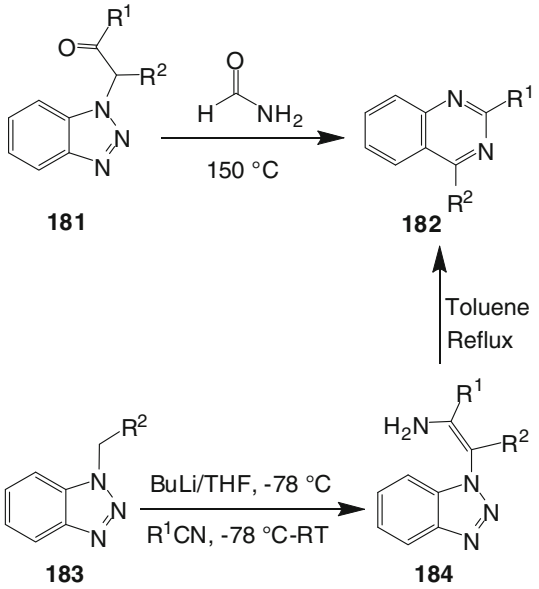
Scheme 46

Scheme 45



Scheme 47





Scheme 48

Benzotriazole-mediated insertion of alkyl substituents into heteroaromatic amines such as aminopyridine has great advantages over others classical methods.

Synthesis of heterocyclic systems through cleavage of a benzotriazole ring

Despite the high stability of benzotriazole in synthetic transformations there are few reactions reported to involve the disruption of the benzotriazole ring during the development of interesting heterocycles, for example, the synthesis of quinazolines through benzotriazole ring cleavage as depicted in Scheme 48. 2-(Benzotriazol-l-yl)-1,2-diphenylethanone **181** ($R^1 = R^2 =$ Ph) and formamide reacted at 150 °C to give 2,4-diphenylquinazoline **182** in 50% yield instead of the expected 4,5-diphenylimidazole. Enamine **184** from lithiated 1-benzylbenzotriazole on refluxing in toluene afforded product **182** (Scheme 48) [127].

The amino group of enamines **184** facilitates the opening of the triazole ring to form a betaine intermediate **185** which on loss of nitrogen provides **186**, which subsequently undergoes intramolecular cyclization to form the five-membered ring of **187** (Route A). Attack of the imine carbon by the amino group in **187** results in an aziridine intermediate **188**, which finally undergoes ring expansion to give the six-membered ring followed by aromatization to produce quinazoline **182**. However, in the case of $R^1 =$ *p*-$OMeC_6H_4$ the OCH_3 group stabilizes the iminium system **187** and further intramolecular nucleophilic attack as shown in Route B generates a new six-membered ring intermediate **190**, which finally aromatizes to form **191** and not the desired quinazoline **182** (Scheme 49).

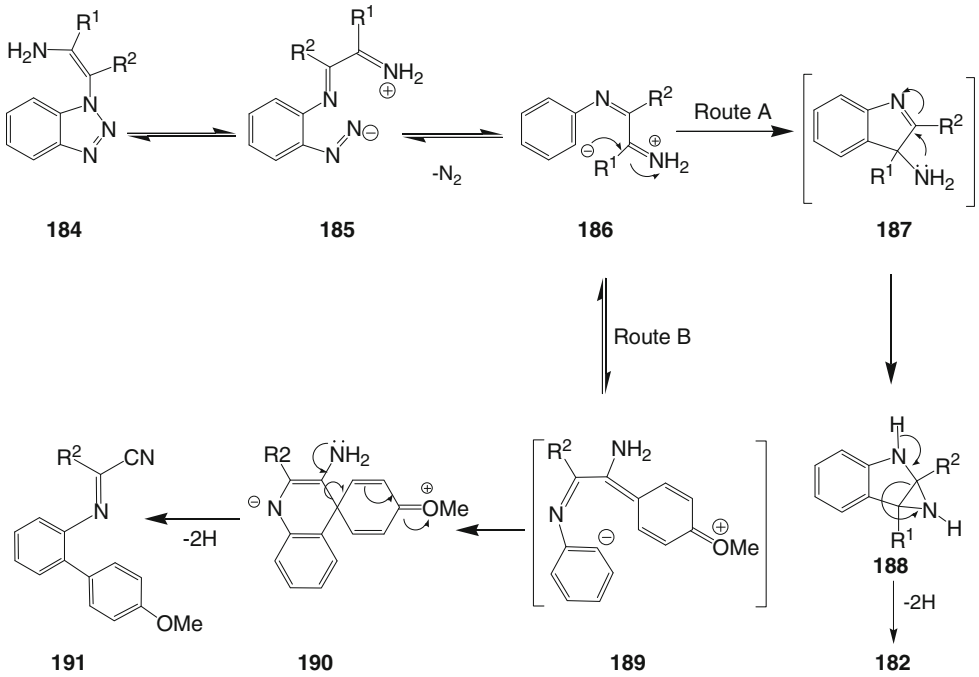
Several interesting benzoheterocycles including benzoazines, quinazolines, 3,4-dihydroquinazolines, quinazoline-4-thiones, etc. were also synthesized via disruption of the benzotriazole ring followed by spontaneous extrusion of nitrogen. The Katritzky group identified the lithio derivatives of *N*-(α-alkoxyalkyl)benzotriazoles **192**, which underwent ring opening at −78 °C and were found to be able to trap the generated *o*-iminophenyl anion intermediates **193** with a variety of electrophiles. Such ring opening of benzotriazole derivatives **192** provided an attractive way to generate a wide variety of benzoheterocycles **192–196** with the breaking of two bonds and the formation of two new bonds in a one-pot fashion (Scheme 50) [128].

In the case of halides or esters as electrophiles the loss of the alkoxy group and subsequent cyclization do not occur. Ring opening of benzotriazole has been known under mild conditions instead of pyrolysis or photolysis, extrusion of nitrogen avoiding ionic or radical fragmentation and rearrangement [128].

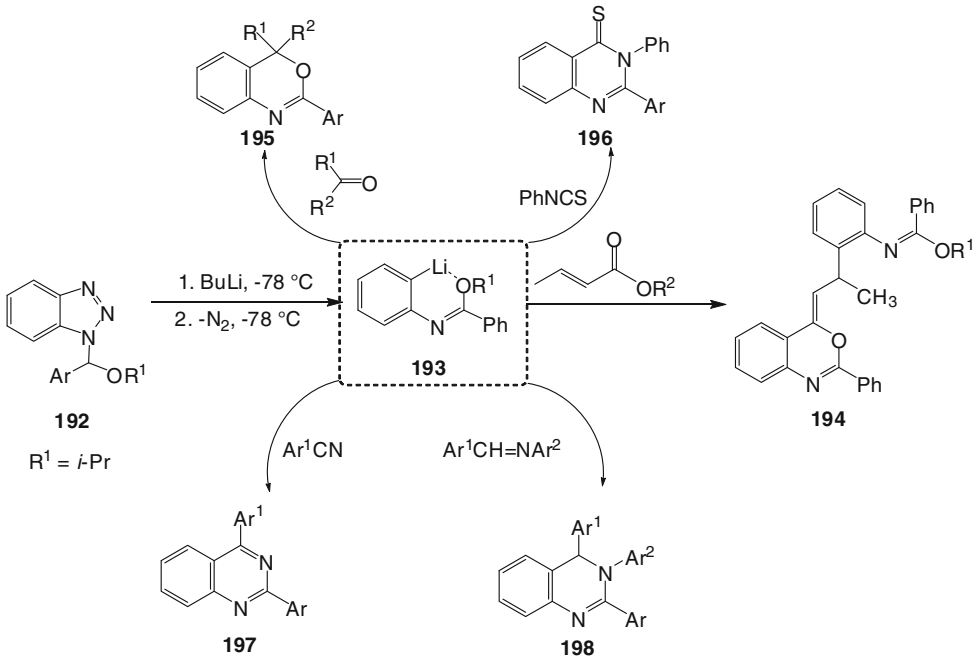
Very recently, the Nakamura group reported a highly facile palladium-catalyzed synthesis of polysubstituted indoles (Scheme 51) [129]. Reaction of *N*-aroylbenzotriazoles **199** with alkynes in the presence of 10 mol% of $Pd(PPh_3)_4$ under neat reaction conditions at 130 °C provided the polysubstituted indoles **200** in excellent yields.

Here benzotriazole acts as a synthetic equivalent of 2-haloanilides of Larock's indole synthesis and the obtained polysubstituted indoles were free from by-products with atomic economy. The plausible mechanism of the reaction proposed by the authors is presented in Scheme 51. Palladium(0) oxidatively inserts into a C–N bond of the 2-iminobenzenediazonium species **201** obtained from thermal decomposition of benzotriazole **199** at higher temperature leading to intermediate **202**, which on further insertion of the internal alkyne into the C–Pd bond results in the formation of palladacycle species **203**. Reductive elimination of Pd(0) from intermediate **203**

Scheme 49



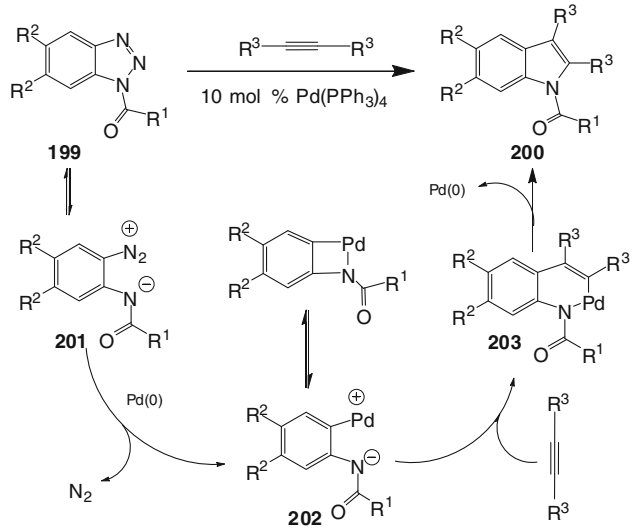
Scheme 50



gives an excellent yield of polysubstituted indoles **200** (Scheme 51) [129].

In other examples of benzotriazole ring disruptions, ring expansion predominates prior to the elimination of nitrogen, for instance the synthesis of 1,2,4-triazolo[1,5-*a*]-quinoxalines (Scheme 52). Base-catalyzed reaction of *N*-(benzotriazol-1-ylmethyl)furylimidoyl chloride prepared in situ from the corresponding benzotriazolyl amide **204** with benzyl cinnamate or benzyl bromide gave the expected pyrrole **205** in moderate yield (49%) along with 2-furyl-4-phenyl-1,2,4-triazolo[1,5-*a*]quinoxaline (**206**) as a minor product (2%) [130]. A plausible reaction mechanism involves the benzylation of *N*-(benzotriazol-1-ylmethyl)-substituted imidoyl chlorides under basic conditions, which induces an unusual rearrangement accompanied by benzotriazole ring opening with the formation of 1,2,4-triazolo[1,5-*a*]quinoxaline derivative **206** (Scheme 52).

Beside the disruption of the benzotriazole ring for development of a variety of heterocyclic skeletons as described above few examples are known where the

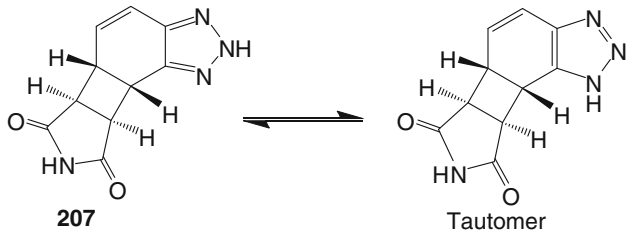


Scheme 51

triazole ring remained intact but the benzene ring is involved in the reaction. Booker Milburn et al. investigated the intermolecular photochemical [2+2] cycloaddition of benzotriazole which proceeded selectively via the 2*H*-tautomer. Benzotriazole irradiated with maleimide using a 125-W medium-pressure Hg lamp as a UV source in a Pyrex immersion well ($\lambda > 290$ nm) gave [2+2] cycloadduct **207**; however, irradiation in a quartz immersion well ($\lambda > 200$ nm) resulted in intractable tar. Tautomeric forms of the product are shown in Scheme 53 [131].

Benzotriazole dianion strategies

Knight and Little [132] reported the dilithiation of certain N-substituted benzotriazoles by deprotonation at both the α-position of the N-substituent and the 7-position of benzotriazole. Later on the Katritzky group applied the benzotriazole-based dianion strategy to the development of interesting novel heterocyclic ring systems [133]. Dianion **209** obtained through lithiation of 1-vinylbenzotriazole (**208**) was useful for the synthesis of diverse quinoline and benzazocine heterocycles, where the N-atom of triazole was involved in the cyclization whereas benzotriazole remained intact. Several 1,2-, 1,3-, and 1,4-dielectrophiles



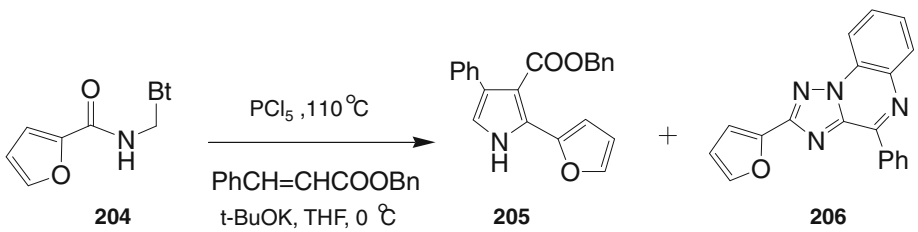
Scheme 53

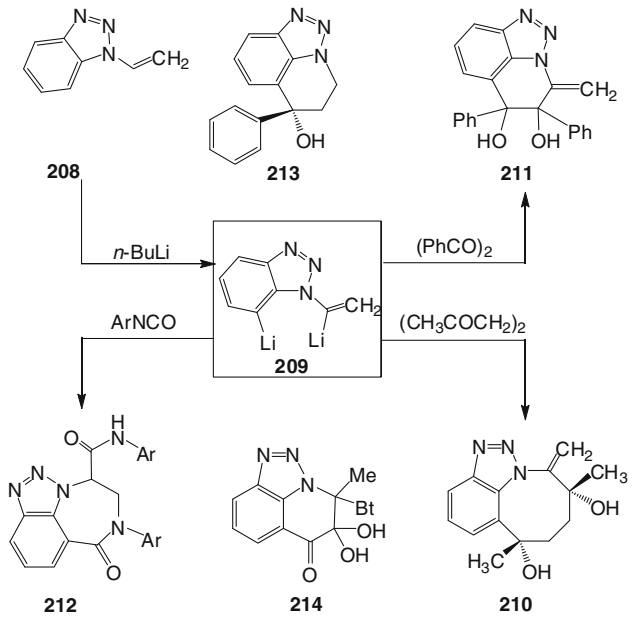
(e.g., 1,2-diphenylethane-1,2-dione, 1,3-diphenyl-1,3-propanedione, hexane-2,5-dione, etc.) on treatment with dianion **209** resulted in good yields of different bicyclic heterocyclic skeletons, such as 4*H*-[1,2,3]triazolo-[4,5,1-*kl*]-[1]benzazocine-5,8-diol **210**, 4*H*-[1,2,3] triazolo[4,5,1-*ij*]-quinoline-5,6-diol **211**, and 4*H*-[1,2,3]triazolo[4,5,1-*ij*]-quinolin-6-ol **213**. Similarly, the reaction of **209** with different aryl isocyanates led to the formation of *N*,6-diaryl-4,5,6,7-tetrahydro-7-oxo[1,2,3]triazolo[4,5,1-*jk*][1,-4]benzodiazepine-4-carboxamides **212** by Michael-type intramolecular addition of the amide nitrogen to the vinyl bond. Furthermore, this strategy was elegantly used to construct the attractive heterocyclic skeleton triazoloquinolinone **214** in good yield from the dianion obtained from 1,2-dibenzotriazolyl and reaction with diethyl oxalate (Scheme 54) [134].

Benzotriazole as an efficient ligand in heterocyclization

Benzotriazole is known to catalyze some useful functional group conversions, e.g., the Baylis–Hillman reaction, one of the most important atom economic reactions [15]. Verma et al. successfully used benzotriazole as a catalyst in various coupling reactions [16, 17] and very recently introduced a efficient one-pot facile protocol for the synthesis of pharmaceutically important heterocyclic skeletons, such as polycyclic indolo- and pyrrolo[2,1-*a*] isoquinolines **218**, **219** using benzotriazole as a ligand. The reaction of **216** with **217** in the presence of 10 mol% of CuI and KO*t*Bu at 110 °C for 24 h in DMF failed to afford the desired heterocyclic skeleton **218**. However, the addition of 20 mol% of benzotriazole to the reaction mixture led to the formation of the desired product **218** in high yield.

Scheme 52





Scheme 54

Benzotriazole (BtH) and hydroxymethyl benzotriazole (**215**) were verified to be useful ligands for the heterocyclization reaction, but the latter was found to be more effective [135].

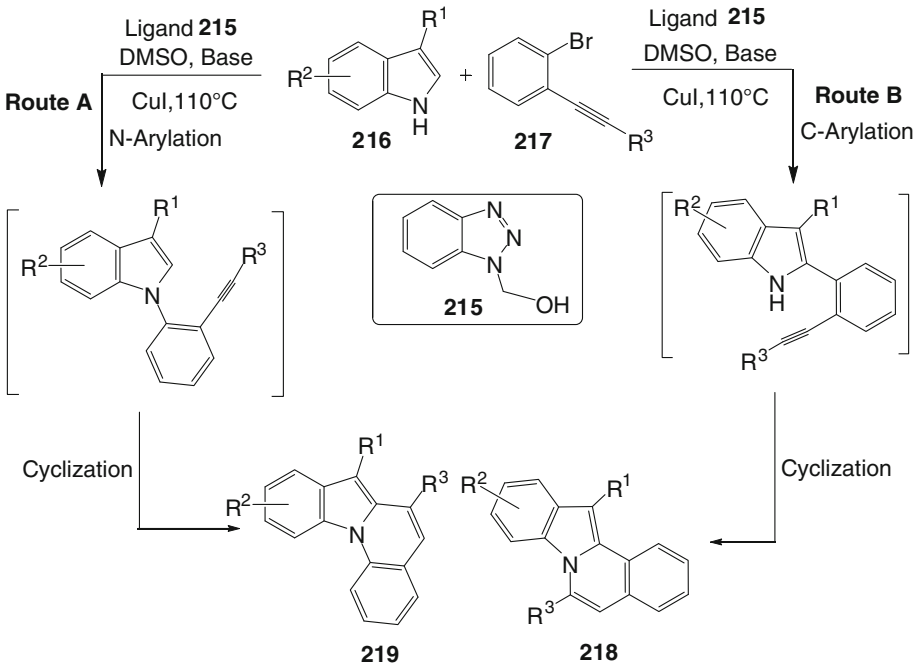
Mechanistically the reaction proceeds through the preferential nucleophilic addition of indoles or pyrroles onto the *ortho*-haloarylalkynes and gives **218** as a major product through N-arylation of the aryl halide via route A and **219** through C2-arylation via route B. The method is high yielding, regioselective, and useful for the direct synthesis of pharmaceutically important diverse polycyclic heteocyclic skeletons, such as indolo- and pyrrolo[2,1-*a*]-isoquinolines and hence is expected to find new applications in the synthesis of novel pharmacophores in medicinal chemistry (Scheme 55).

Furthermore, a similar strategy was extended for N-arylation of indole heterocycles using benzotriazole as an efficient ligand where selective mono N-arylation with *ortho*-dihaloarenes has successfully been achieved in good yields [136].

Concluding remarks and future perspectives

In the present review we have tried our best to describe concisely the present status, recognition, attractions, opportunities, and challenges of benzotriazole methodology with emphasis of its versatile roles in the development of diverse pharmacologically important heterocyclic skeletons ranging from small to large-membered ring systems. The subject is very demanding and undoubtedly has a very bright future and wide scope in heterocyclic synthesis, which will provide a new horizon to benzotriazole strategies. The methodology is not limited to heterocyclization only but was also successful for polynuclear hydrocarbons of small carbocyclic systems. In addition, several medicinally interesting molecules which contain the benzotriazole core, e.g., vorozole, alizapride, and many other novel benzotriazole derivatives, have been reported to exhibit inhibitory properties against different kinases. Therefore, there is a considerable interest in developing benzotriazole-

Scheme 55



containing molecules coupled with a heterocyclic skeleton of great biological value and searching for new chemical entities with a novel mode of action against frontline diseases. We hope and anticipate that this review will provide additional stimulus for the further development of benzotriazole chemistry.

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