Applications of Benzotriazole Methodology in Heterocycle Ring Synthesis and Substituent Introduction and Modification

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Applications of benzotriazole methodology for the preparation of heterocyclic compounds are reviewed. The characteristic advantages of benzotriazole as a synthetic auxiliary are first briefly considered. This is followed by a summary of its use in ring synthesis in which the construction of small; five-membered; six-membered; and larger heterocyclic rings using benzotriazole methodology are each examined separately. Finally, consideration of the use of benzotriazole in the ring annulation - particularly benzannulation - of heterocycles. Subsequent sections deal with the introduction of substituents into aromatic heterocycles; the ring substitution of saturated heterocycles; and benzotriazole assisted modification of heterocyclic substituents.

The present review supplements a recent comprehensive review of benzotriazole chemistry [1] which covers the literature through 1996.

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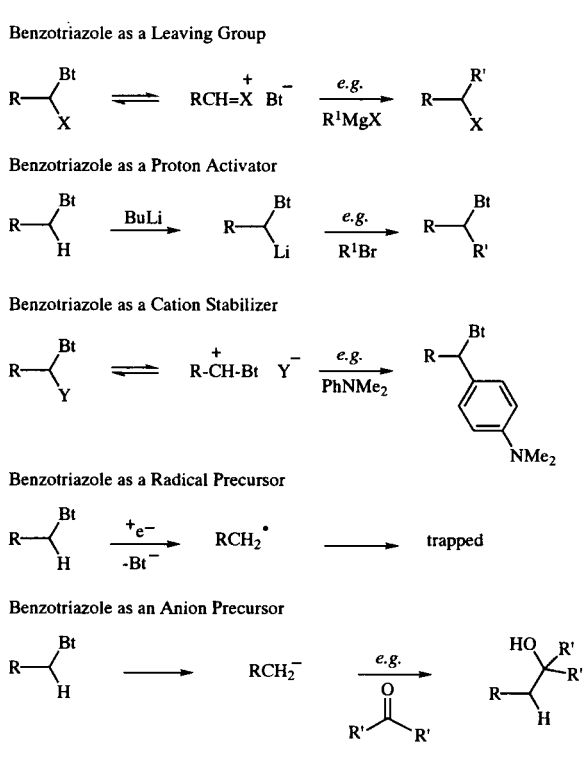
1. Introduction.

Applications of benzotriazole chemistry in synthesis have recently been reviewed [1], although this review is already seriously out of date (for some significant applications not included in [1], see [2-13]). The purpose of the present overview is to collect together the main applications of benzotriazole methodology used up to the present for the synthesis of heterocyclic compounds.

Benzotriazole is a most useful synthetic auxiliary because it confers at least five different types of reactivity to groups to which it is attached. These different types of activation are summarized in Scheme 1: (i) Benzotriazole is a good leaving group, generating a cation which can react further with, for example, a Grignard reagent; (ii) Benzotriazole activates an attached α-CH group to loss by stabilizing the resultant anion, allowing the introduction of an electrophile; (iii) When a benzotriazole residue and another leaving group are attached to the same carbon, benzotriazole can donate electrons to stabilize the cation formed by loss of the other leaving group. Furthermore, the bond between benzotriazole and a carbon atom can be cleaved by (iv) single electron transfer (*eg.* with SmI_2), generating a carbon-centered radical, and (v) by the transfer of two electrons from lithium metal to generate a carbanion.

In this overview we first consider the uses of benzotriazole in the formation of small heterocyclic rings, and then go on to consider the construction of five-membered, six-membered, and larger heterocyclic rings. In further sections, we consider the use of benzotriazole in the ring annulation of heterocycles, and in the ring substitution of aromatic heterocycles. This is followed by an overview of the ring substitution of saturated heterocycles and the review ends by considering the way in which benzotriazole can help to modify heterocyclic substituents.

Scheme 1

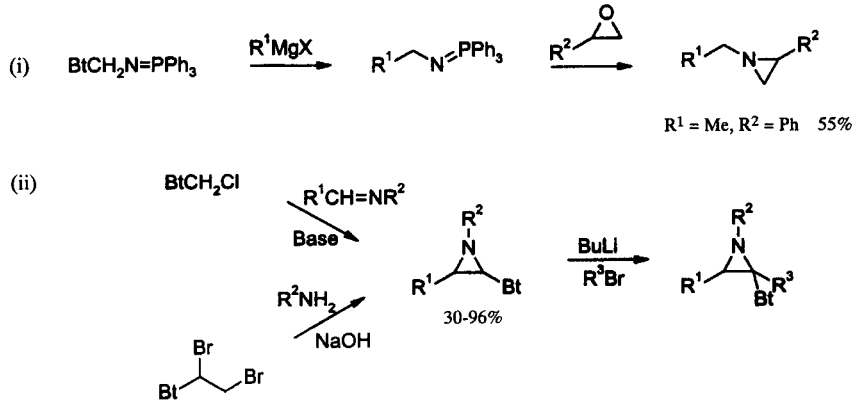


2. The Construction of Small Heterocyclic Rings.

We have demonstrated that benzotriazole mediated synthesis of aziridines is possible from 1-(triphenylphosphoranylideneaminomethyl)benzotriazole - a convenient $^+CH_2NH_2$ equivalent synthon and a crystalline solid, prepared from benzotriazole in four steps on a large scale and in high yield [14]. Treatment of 1-(triphenylphosphoranylideneaminomethyl)benzotriazole with Grignard

reagents displaces the benzotriazolyl moiety to give the an iminophosphorane intermediate. Further reaction with epoxides forms aziridines as shown in Scheme 2 (i) [15]; the only side-product is triphenylphosphine oxide.

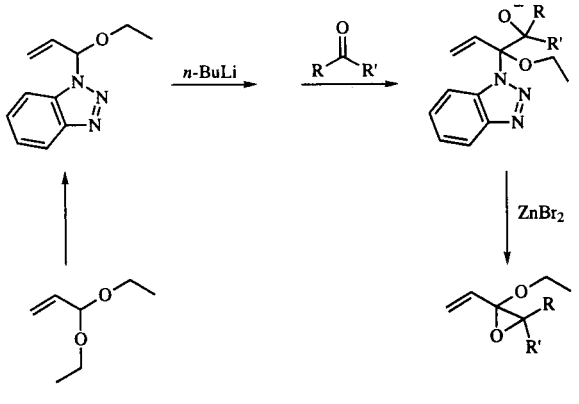
Scheme 2



More recently, 2-benzotriazolyl-substituted aziridines have been prepared as in Scheme 2 (ii) [16]. Lithiation of 1-chloromethylbenzotriazole forms a carbenoid which can be captured by a diaryl imine to form aziridines in high yields, but as mixtures of *cis* and *trans* isomers (Scheme 2). This is the first report of an α-nitrogen substituted carbenoid. The use of lithium bis(trimethylsilyl)amide gives superior yields compared with *s*-butyllithium. Only imines derived from aromatic aldehydes and aniline reacted satisfactorily with the carbenoid thus limiting the aziridines made in this way to 1,3-diaryl substituted derivatives. Alternatively, bromination of 2-vinylbenzotriazole followed by alkylamine substitution of the terminal bromide and intramolecular cyclization, under basic conditions, gave 2-(benzotriazol-2-yl)aziridines (Scheme 2).

2-Vinyl-2-alkoxyepoxides can advantageously be obtained using benzotriazole chemistry (Scheme 3). *N*-(α-Ethoxyallyl)benzotriazole was prepared in a quantitative yield on a large scale from the reaction of benzotriazole with the corresponding acetal using performance fluid as an inert medium with a reversed Dean-Stark trap. Lithiation of *N*-(α-ethoxyallyl)benzotriazole followed by the reaction with ketones and zinc bromide at 20° gave epoxides in 65-72% yields [17,18].

Scheme 3



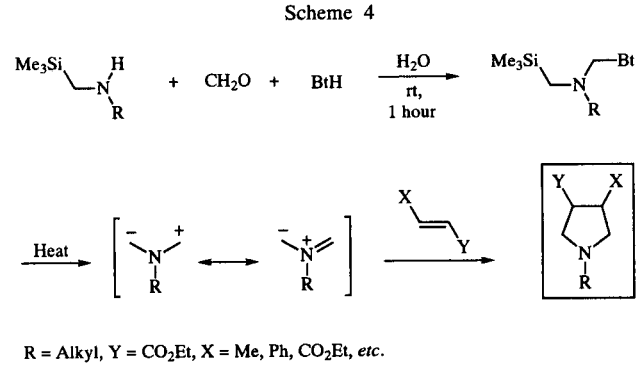
3. The Construction of Five-Membered Heterocyclic Rings.

3.1. With One Heteroatom.

a. One Nitrogen Atom: Pyrrolidines, Dihydropyrroles, Pyrroles.

Pyrrolidines have been prepared by 1,3-cycloadditions as shown in Scheme 4. Thermally induced desilylation of benzotriazolylmethylaminosilanes - easily prepared from benzotriazole, an aldehyde, and an (aminomethyl)silane - provides a novel route to azomethine ylide equivalents. In the presence of a dipolarophiles, the azomethine ylide undergoes stereospecific 1,3-dipolar cycloadditions to give substituted pyrrolidines [19]. This thermally induced method is an alternative to the previous routes that require catalysis (*eg.* Silver fluoride, Cesium fluoride, *etc*).

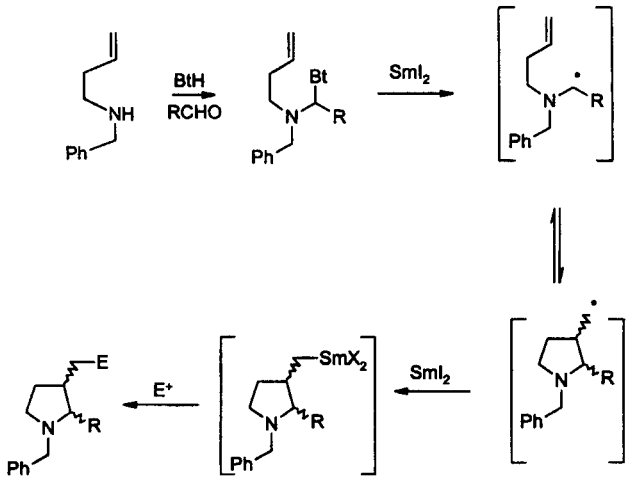
Scheme 4



R = Alkyl, Y = CO_2Et, X = Me, Ph, CO_2Et, *etc*.

In a recently reported novel reaction sequence, an α-aminoalkyl radical - generated by samarium diiodide cleavage of benzotriazole - undergoes intramolecular cyclization by regioselective addition to an unactivated C=C bond [20]. The cyclic radical is reduced further to a carbanion which is trapped by an electrophile to give 1,2,3-trisubstituted pyrrolidines (Scheme 5).

Scheme 5



The cyclization of an α-aminoalkyl radical onto an unactivated C=C bond is generally difficult because (i) the amino substituent partly losses the ability to stabilize the radical in the transition state; (ii) the radical is nucleophilic; and (iii) the radical tends to dimerize. As the open-chain and cyclic radicals exist in equilibrium, it was reasoned that further reduction of the radical to a carbanion and subsequent trapping with an electrophile would provide a driving force that favored the formation of cyclized products [20]. This was found to be the case. Using aldehydes or symmetrical ketones as the electrophile gave a mixture of *cis* and *trans* pyrrolidines, whereas unsymmetrical ketones gave four racemates due to the additional chiral center in the side-chain. The product of carbanion protonation is always formed as a by-product.

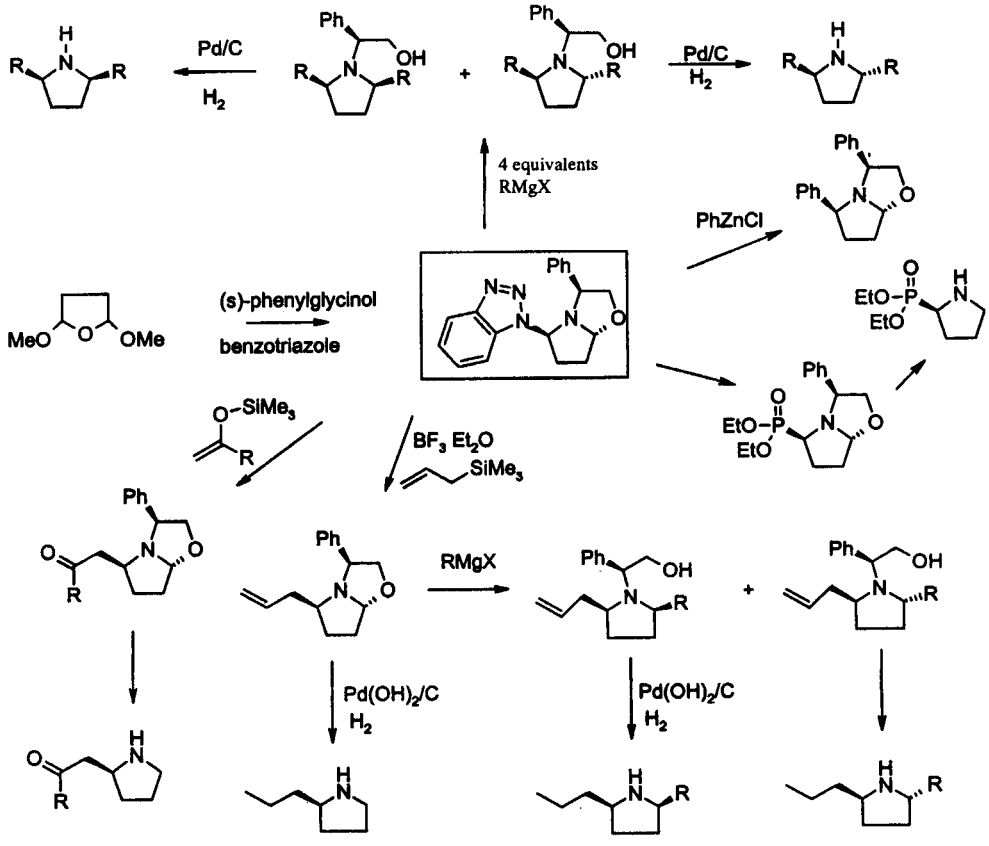
We recently demonstrated the preparation of 2-substituted, and unsymmetrically 2,6-disubstituted pyrrolidines *via* a Bt-method. Benzotriazole, (*S*)-phenylglycinol and hydrolyzed 2,5-dimethoxytetrahydrofuran (the equivalent of succindialdehyde), gave crystalline 3*S*,5*R*-5-(benzotriazol-1-yl)-3-phenylhexahydropyrro[2,1-*b*][1,3]oxazole at room temperature in 80% yield. The ^{1}H and ^{13}C nmr spectra of the crude product both showed only one diastereoisomer, which structure was proved by X-ray crystallography. 3*S*,5*R*-5-(Benzotriazol-1-yl)-3-phenylhexahydropyrro[2,1-*b*][1,3]oxazole reacted with allyltrimethylsilane in the presence of boron trifluoride to give the chiral 2-substituted product, converted by direct hydrogenation into 2-substituted pyrrolidines, or by reaction with Grignard reagent to form chiral 2,6-disubstituted pyrrolidines. Similarly, 3*S*,5*R*-5-(benzotriazol-1-yl)-3-phenylhexahydropyrro[2,1-*b*][1,3]oxazole reacted with (i) (α-substituted-vinyloxy)trimethylsilanes in the presence of boron trifluoride-diethyl etherate at 0° to produce *C*-allylpyrrolidines; (ii) with triethyl phosphite to give the expected 2-substituted-pyrrolidine phosphonate, or (iii) with Grignard reagents at 0° giving mixtures of *cis*- and *trans*-2,5-disubstituted-pyrrolidines [21,22] (Scheme 6).

Dihydropyrroles were prepared from: (i) 1,3-dipolar cyclization of electron poor double bonds with *N*-arylmethylene[(benzotriazol-1-yl)aryl]amines (obtained from benzotriazole, aromatic aldehyde and ammonia) [23]. The structures of these products were confirmed by X-ray [24]; (ii) 1,3-dipolar cyclization of benzotriazolylmethylaminosilanes and acetylenic dipolarophile, benzotriazolylmethylaminosilanes was formed from the condensation of benzotriazole, formaldehyde and (trimethylsilylmethyl)-amine [19], and (iii) 1-allenylbenzotriazole and imines [25] (Scheme 7).

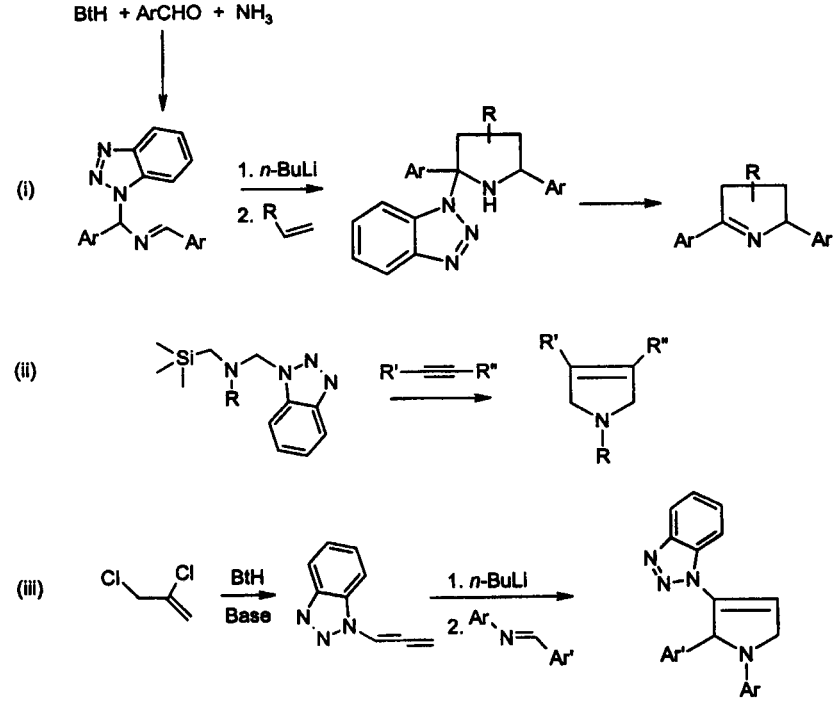
Pyrroles have been made using 1-(triphenylphosphoranylideneaminomethyl)benzotriazole as shown in Scheme 8 [26]. The nucleophilic reaction of 1-(triphenylphosphoranylideneaminomethyl)benzotriazole with methylidenetriphenylphosphorane followed by deprotonation with butyllithium gave the first reported monoazabisphosphorus ylide - an analog of both 1,3-bisylides and 1,3-bisazaylides [27]. Double Wittig/aza-Wittig reactions of the monoazabisylide with symmetrical bisaryl 1,2-diketones gave 2,3-disubstituted pyrroles in good yields. 1-Phenyl-1,2-propanedione (an unsymmetrical diketone) formed an approximately 1:1 mixture of the two isomeric 2,3-disubstituted pyrroles.2-Benzotriazolylaziridines (discussed in the previous section) react with acetylenedicarboxylic esters to give poly-substituted pyrroles (Scheme 9) [16]. This reaction presumably proceeds *via* the formation of an azomethine ylide followed by a polar [2+3] cyclization and aromatization by benzotriazole loss.

2-Arylpyrroles are prepared using 1-propargylbenzotriazole as a three-carbon annulation unit (Scheme 10) [28]. (i) Lithiated 1-propargylbenzotriazole reacted cleanly with *N*-tosylarylimines to give acetylenes. Treatment with ethanolic sodium hydroxide gave 2-aryl- and 2-heteroarylpyrroles in moderate yields. The mechanism for this novel transformation probably involves an acetylene-allene isomerization followed by cyclization to 2,5-dihydropyrroles. Elimination of benzotriazole and *p*-toluenesulfonic acid yields pyrroles [28]. (ii) Lithiated 1-propar-

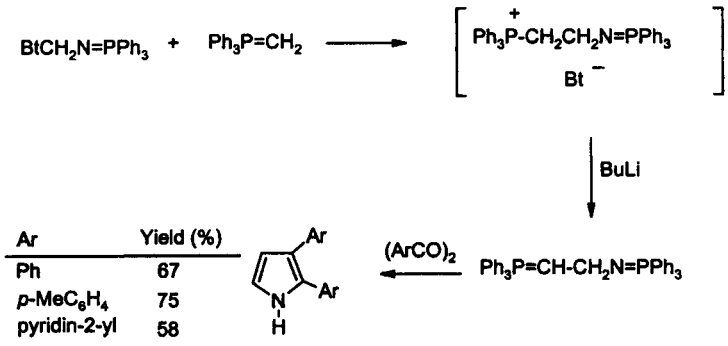
Scheme 6



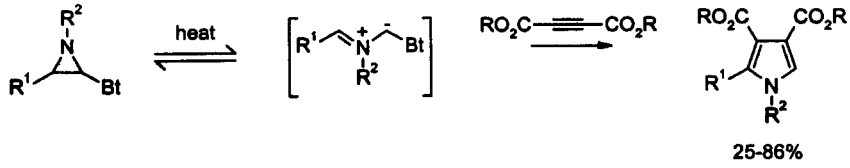
Scheme 7



Scheme 8

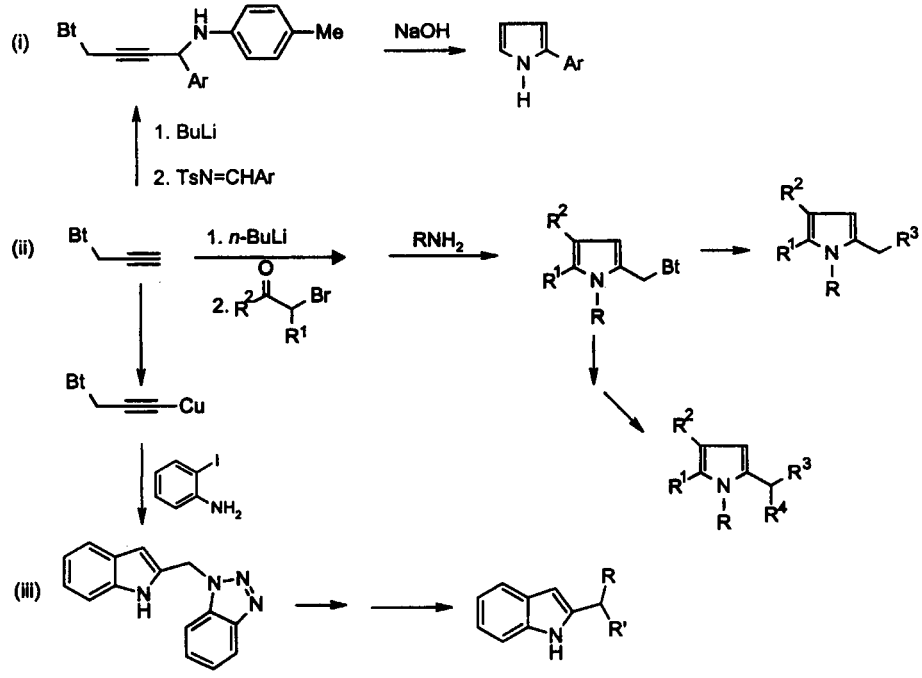


Scheme 9



gylbenzotriazole and α-bromoketones and primary amines give substituted 2-benzotriazolylmethylpyrroles which react further with Grignard reagents to form polysubstituted pyrroles [29,30]. (iii) A similar method was applied for indole synthesis [31] (Scheme 10).

Scheme 10



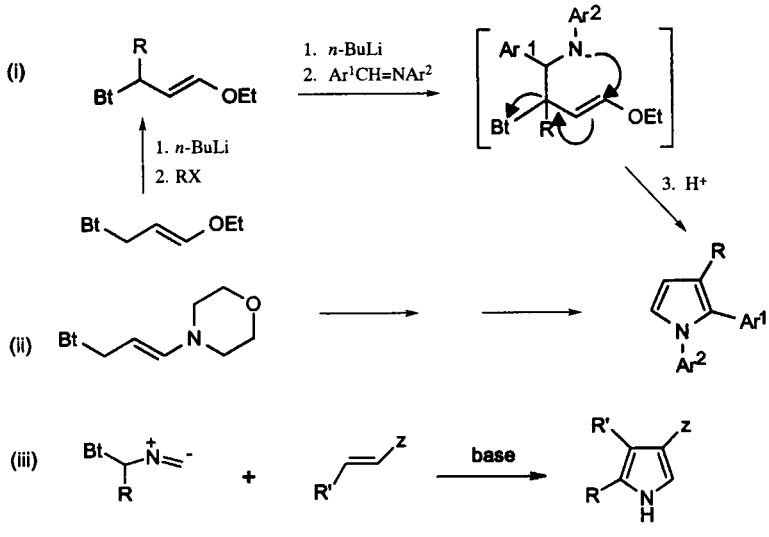
Further methods for preparation of pyrroles are shown in Scheme 11: (i) 1-Ethoxy-3-(benzotriazol-1-yl)propene [32] is treated with zinc bromide in dry tetrahydrofuran at 20° to give *E*-1-ethoxy-3-(benzotriazol-1-yl)propene in 95% yield, followed by butyllithium at -78°, addition of diarylimines, and heating in the presence of zinc bromide yielded 1,2-diarylpyrroles in 55-63% yields, presumably *via* intramolecular S_N2' nucleophilic substitution and elimination of ethanol. This use of 1-ethoxy-3-(benzotriazol-1-yl)propene as a C_3-fragment *via* [3 + 2] annulation provides an attractive alternative approach to 1,2-diarylpyrroles. (ii) 1-(3-Morpholinoprop-2-enyl)benzotriazole [33], prepared from benzotriazole, acrolein and morpholine, and imines showed transformations similar as those in (i) to give the expected pyrroles. (iii) From benzotriazol-1-ylmethyl isocyanide and electron-deficient alkenes [34]. Benzotriazol-1-ylmethyl isocyanide was generated from condensation of benzotriazole, formaldehyde and formamide, followed by dehydration with phosphoryl oxychloride [35]. α-Metallation of benzotriazol-1-ylmethyl isocyanide reacted with electron deficient alkenes to form pyrroles in a similar fashion to its analog *p*-toluenesulfonylmethyl isocyanide, but with better yields.

b. With One Oxygen Atom: γ-Lactones, Dihydrofurans, Furans and Benzofurans.

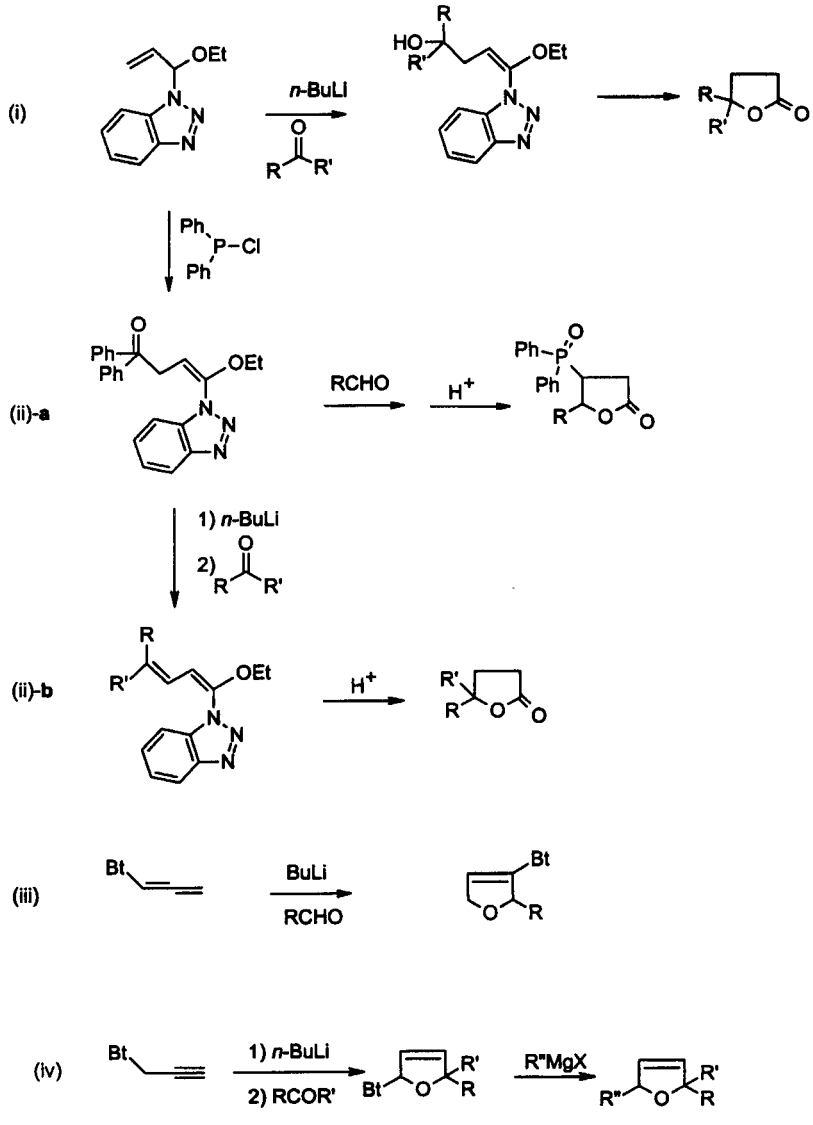
γ-Lactones were prepared as shown in Scheme 12: (i) from the reactions of lithiated *N*-(α-ethoxyallyl)benzotriazole and ketones followed by hydrolysis under acidic condition [36]. (ii) Reaction of lithiated *N*-(α-ethoxyallyl)-benzotriazole with chlorodiphenylphosphine then hydrogen peroxide gave 1-(benzotriazol-1-yl)-3-(diphenylphosphoranyl)-1-ethoxy-1-propene, which was lithiated and then reacted; a) with aldehydes followed by hydrolysis under acidic conditions to form β-(diphenylphosphoranyl-substituted γ-lactones; b) with ketones and acidic hydrolysis to generate γ,γ-disubstituted, γ-lactones [37].

Dihydrofurans were synthesized: (iii) from lithiated 1-allenylbenzotriazole and aldehyde in 60% yield [25], (1-allenylbenzotriazole was obtained as described in Scheme 7); (iv) by reaction of lithiated 1-propargylbenzotriazole and ketones followed by substitution of benzotriazole by Grignard reagents [38] (Scheme 12).

Scheme 11

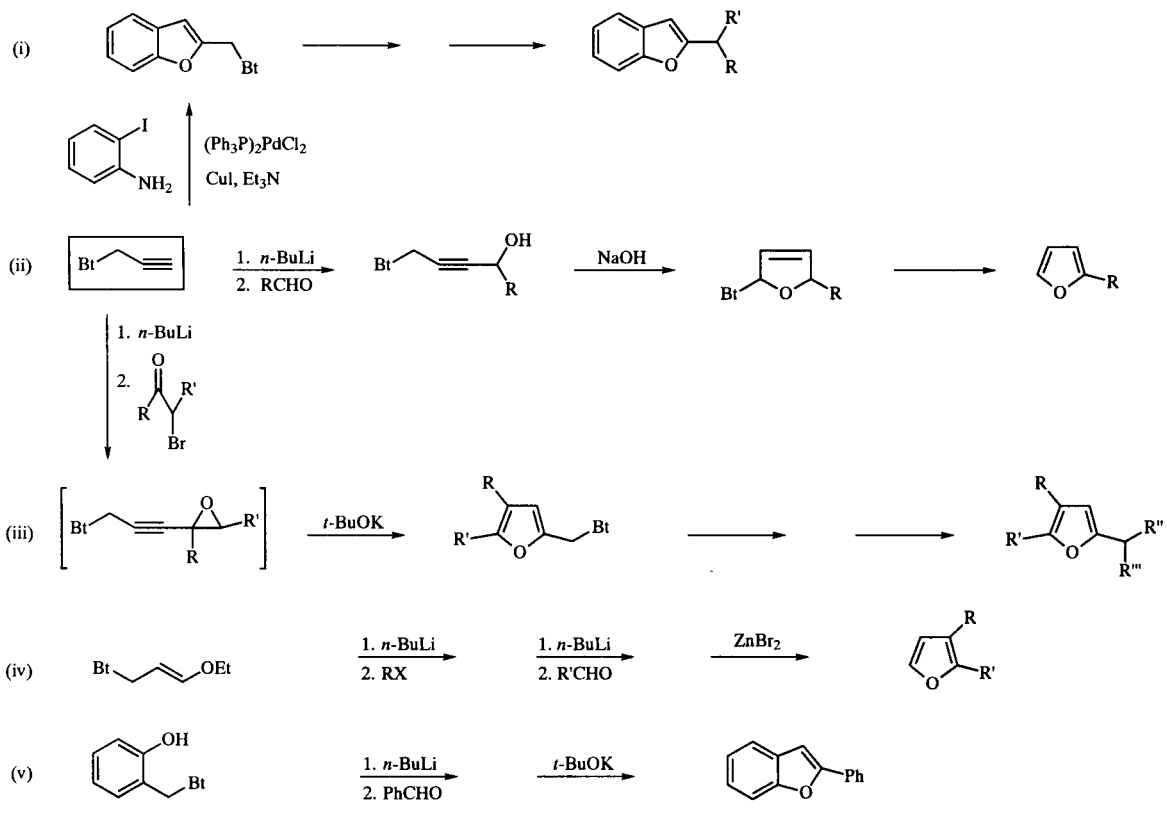


Scheme 12



Furans and benzofurans were prepared from following several methods (Scheme 13): (i) Reaction of lithiated 1-propargylbenzotriazole and *o*-iodoaniline [39] (to give benzofurans); (ii) Reaction of lithiated 1-propargylbenzotriazole and aldehydes [38]; (iii) Reaction of lithiated 1-propargylbenzotriazole and α-bromo ketones, followed by treatment with base potassium *tert*-butoxide, gave 2-benzotriazol-1-ylmethyl-substituted furans [40]; (iv) Lithio 1-ethoxy-3-(benzotriazol-1-yl)propene reacted with an alkyl halide to form intermediates 1-ethoxy-3-(benzotriazol-1-yl)-3-alkylpropene which, without separation, were treated with *n*-butyllithium followed by aldehydes to yield adducts, cyclized by zinc bromide to 2-substituted furans in 46% to 52% overall yields [32]; (v) Reaction of α-lithiated *o*-(α-benzotriazolylalkyl)phenol and an aldehyde, followed by elimination of benzotriazole and one molecule of water [41].

Scheme 13



3.2. With Two Heteroatoms.

a. With Two Nitrogen Atoms: Pyrazolines, Pyrazoles, Imidazolidines, Imidazoles and Benzoimidazoles.

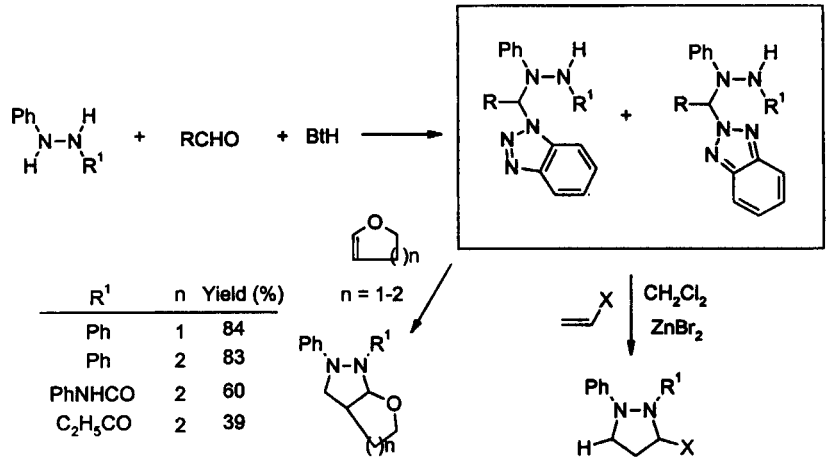
It is also possible to prepare five-member rings with two heteroatoms. Methods for the preparation of pyrazolines, both monocyclic and condensed are shown in Scheme 14 [42]. The reaction of *N,N'*-disubstituted-hydrazines, an aldehyde, and benzotriazole under dehydrating conditions gave the *N*-benzotriazolylalkyl substituted *N,N'*-disubstituted hydrazine intermediate. This key intermediate reacts with electron-rich olefins, in the presence of zinc bromide, to give pyrazolidines in moderate to good yields.

Pyrazoles were generated following the three methods of Scheme 15: (i) the reaction of 2-benzotriazolylmethyl-1,3-diketones and hydrazine gave 4-benzotriazolylmethyl-3,5-disubstituted-pyrazoles, which further reacted with Grignard reagents to offer 3,4,5-trisubstituted-pyrazoles [43]; (ii) condensation of 2-(1-benzotriazolyl)vinamidinium salt with a variety of substituted phenyl hydrazines in an ethanol/sodium carbonate gave 1-substituted-4-benzotriazolylpyrazoles [44]; (iii) 1,3-dipolar reactions of electron-rich 1-ethoxy-3-(benzotriazol-1-yl)propene or 1-morphorine-3-(benzotriazol-1-yl)propene or 1,3-dibenzotriazolylpropene with *N*-(2,4-dibromophenyl)phenylnitrilimine followed by elimination gave 1,3-disubstituted-4-(benzotriazolylmethyl)pryazoles [45].

The preparation of imidazolidines by condensation of benzotriazole with formaldehyde ethylenediamine is shown in Scheme 16 [46]. Nucleophilic displacement of the benzotriazolyl moieties by Grignard reagents or cyanide ion opens up access to a large variety of imidazolidines, of which a few are shown in Scheme 16.

Imidazoles can be obtained as shown in Scheme 17: (i) by the reaction of lithio *S*-methyl-*N*-(benzotriazol-1-ylmethyl)thioimidate and imine followed by treatment of heating or with zinc bromide to eliminate benzotriazole [47]; (ii) by the reaction of benzotriazol-1-ylmethyl isocyanide (preparation of benzotriazol-1-ylmethyl isocyanide was described in Scheme 11) and imines [34].

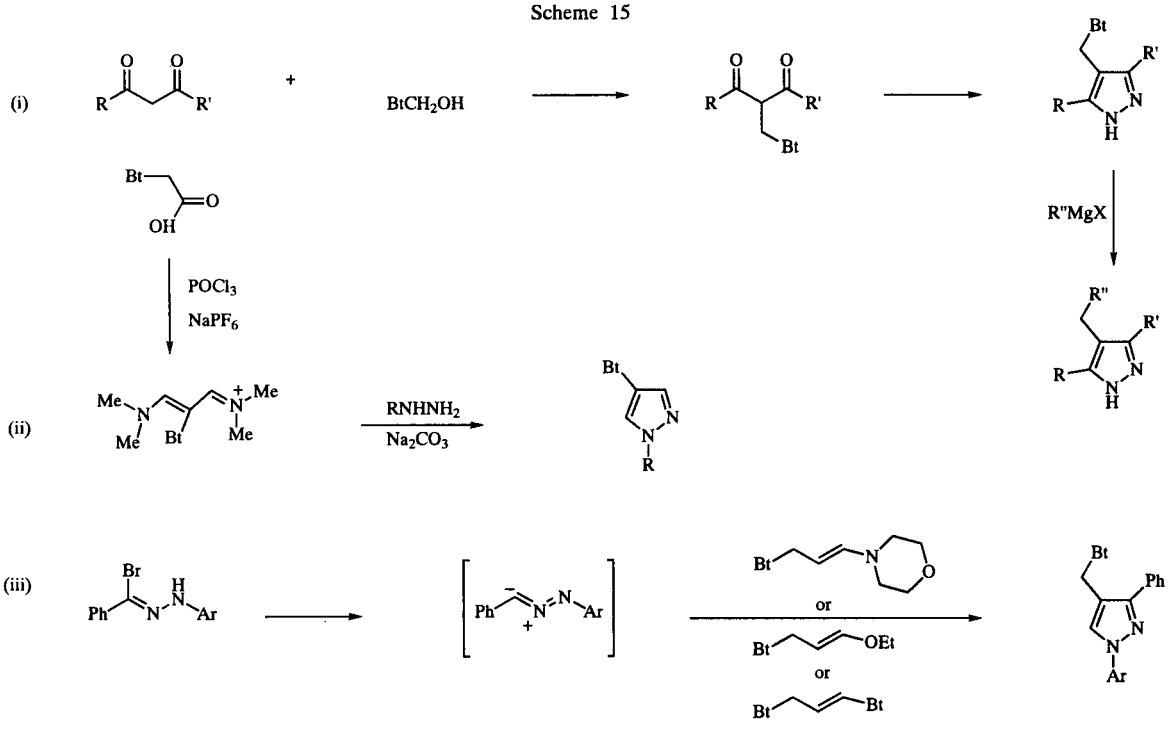
Scheme 14



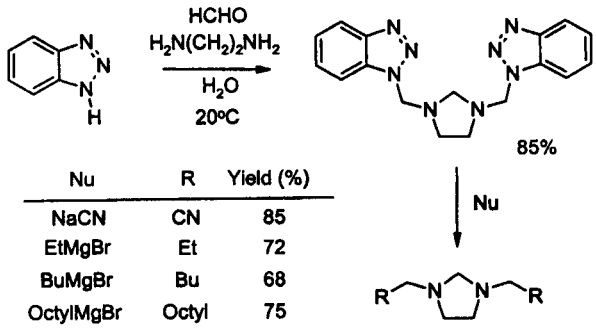
R^1	n	Yield (%)
Ph	1	84
Ph	2	83
PhNHCO	2	60
C_2H_5CO	2	39

R^1	X	Yield (%)
Ph	2-pyrrolidonyl	53
Ph	*N*-methylacetamidyl	43
PhNHCO	OEt	60

Scheme 15



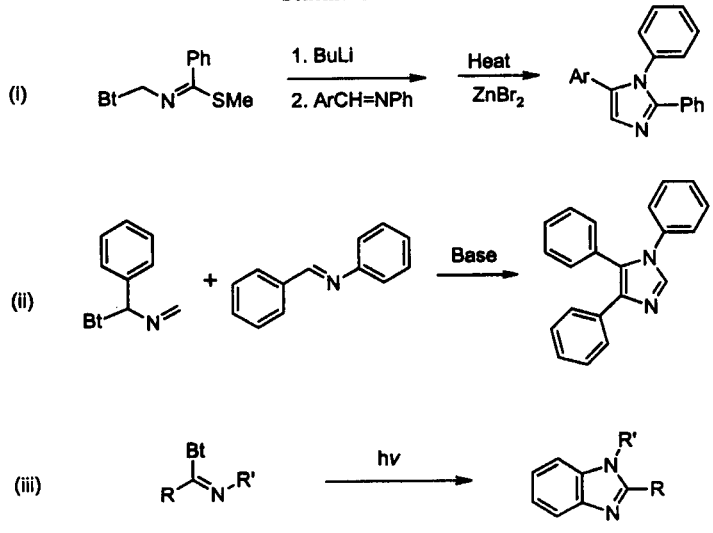
Scheme 16



Nu	R	Yield (%)
NaCN	CN	85
EtMgBr	Et	72
BuMgBr	Bu	68
OctylMgBr	Octyl	75

Benzoimidazoles were obtained from photolysis of imidoylbenzotriazoles. Irradiation of the imidoylbenzotriazole gives the diradical which followed by loss of nitrogen, isomerization and cyclization to form benzoimidazoles [48] [Scheme 17 (iii)].

Scheme 17



b. With One Nitrogen and One Oxygen: Isoxazolidines, Oxazoles.

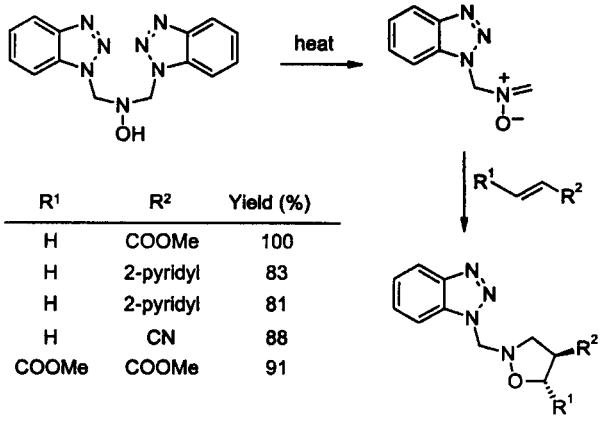
Scheme 18 shows 1,3-dipolar cycloadditions leading to isoxazolidines [49]. The key nitrone 1,3-dipole is obtained by the elimination of benzotriazole from *N*-bis-(benzotriazol-1-ylmethyl)hydroxylamine. This 1,3-dipole reacts regio- and stereo-specifically with dipolarophiles to furnish 2-(benzotriazolylmethyl)isoxazolidines.

Oxazoles were prepared from heating of 1,2-diacylamino-1,2-di(benzotriazol-1-yl)ethanes in *N,N*-dimethylformamide in the presence of sodium hydride. The starting materials were generated from amides and 1,2-di(benzotriazol-1-yl)ethane-1,2-diol, which itself was obtained in almost quantitative yield from glyoxal and two equivalents of benzotriazole [50] (Scheme 19).

c. With One Nitrogen and One Sulfur Atom: Thiazoles.

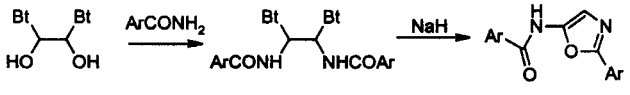
Heating (benzotriazol-1-yl)thioacetamide with α-bromoketones in ethanol provided 2-(benzotriazol-1-ylmethyl)-4,5-disubstituted-thiazoles. Lithiation of 2-(benzotriazol-1-ylmethyl)-4,5-disubstituted-thiazoles followed by addi-

Scheme 18



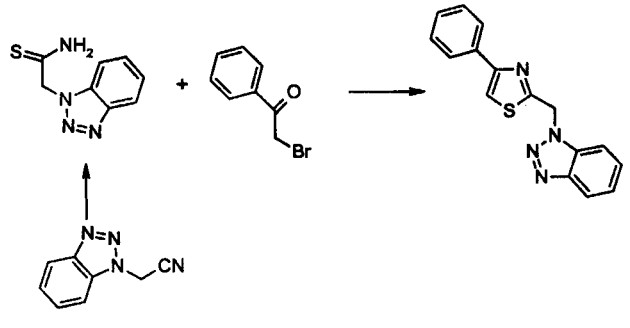
R^1	R^2	Yield (%)
H	COOMe	100
H	2-pyridyl	83
H	2-pyridyl	81
H	CN	88
COOMe	COOMe	91

Scheme 19



tion of alkyl halides generated alkylation products which reacted with Grignard reagent to give polysubstituted-thiazoles (see late section, Scheme 56). Starting (benzotriazol-1-yl)thioacetamide is readily available from 1-(cyanomethyl)benzotriazole [51] (Scheme 20).

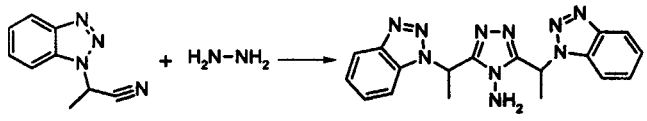
Scheme 20



3.3. With Three Heteroatoms: 1,2,4-Triazoles.

Condensation of 1-cyanoalkylbenzotriazoles with hydrazine hydrate gave 4-amino-3,5-bis(benzotriazol-1-yl)-triazoles which underwent deamination with sodium nitrite to yield 3,5-bis(benzotriazol-1-yl)triazole [52] (Scheme 21).

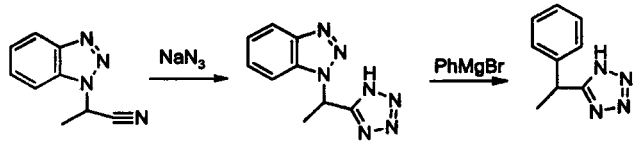
Scheme 21



3.4. With Four Heteroatoms: Tetrazoles.

Reaction of 1-cyanoalkylbenzotriazoles with sodium azide gave 5-(benzotriazol-1-yl)alkyltetrazoles, which reacted with Grignard reagents to yield 5-substituted-tetrazoles [53] (Scheme 22).

Scheme 22



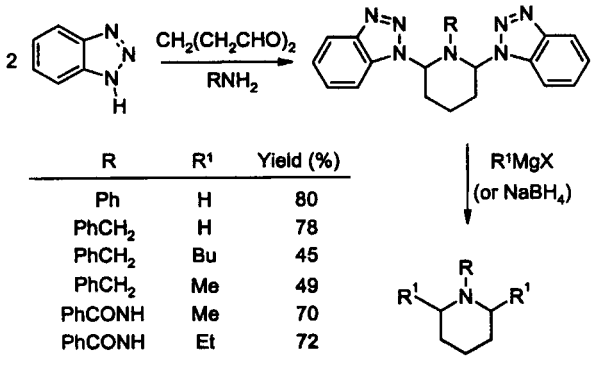
4. The Construction of Six-Membered Heterocyclic Rings.

4.1. With One Heteroatom.

a. With One Nitrogen Atom.

A simple yet versatile method for the preparation of 1-substituted and 1,2,6-trisubstituted-piperidines is given in Scheme 23 [54]. Previous methods of preparing 1,2,6-trisubstituted-piperidines are limited by the availability of starting materials and sometimes the use of severe reaction conditions. Our method involves the double condensation of amines (or hydrazines) with benzotriazole and glutaraldehyde to give *N*-substituted-*cis*-2,6-bisbenzotriazolylpiperidines. The products are isolated by filtration in high yields and are essentially pure. Displacement of the benzotriazolyl moieties by sodium borohydride or Grignard reagents gave 1-substituted and 1,2,6-trisubstituted-piperidines, respectively [54]. This method was later applied to the preparation of polyhydroxypiperidines [55].

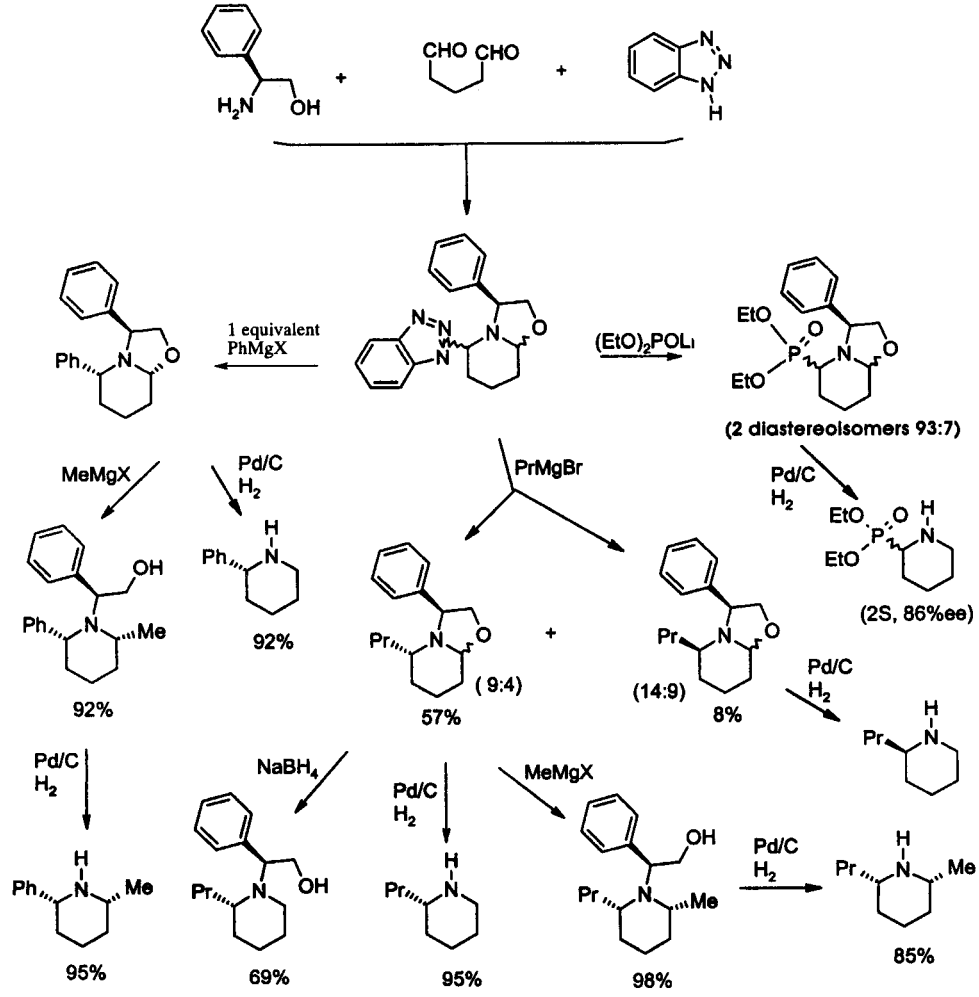
Scheme 23



R	R^1	Yield (%)
Ph	H	80
$PhCH_2$	H	78
$PhCH_2$	Bu	45
$PhCH_2$	Me	49
PhCONH	Me	70
PhCONH	Et	72

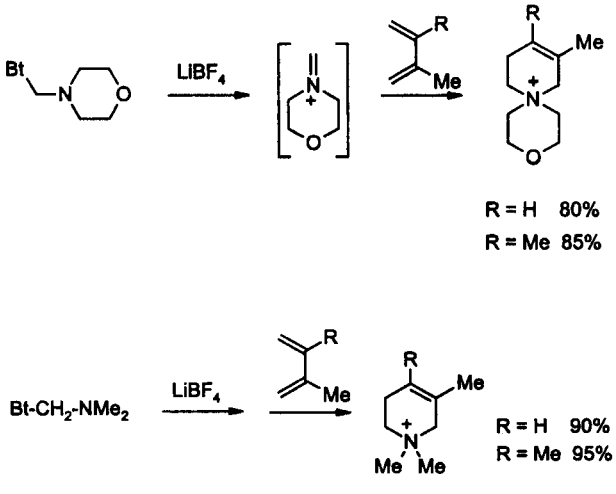
More recently this work has been extended to asymmetric syntheses of 2- and 2,6-disubstituted-piperidines as shown in Scheme 24 [56]. (3*S*)-5-Benzotriazolyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole - a novel and convenient chiral 1,4-dihydropyridine equivalent - was prepared from *S*-2-phenylglycinol, aqueous glutaraldehyde, and benzotriazole in 95% yield. Displacement of the benzotriazolyl moiety by phenylmagnesium bromide results in the formation of a new chiral center. By contrast, the use of propylmagnesium bromide gave a mixture of both isomers at this center which were separated by column chromatography as two pairs of diastereoisomers. Removal of the phenylglycinol residue from the piperidine ring by hydrogenation gave 2-substituted-piperidines. Alternatively, cleavage of the oxazole ring with a Grignard reagent prior to hydrogenation gave 2,6-disubstituted-piperidines. These syntheses are higher yielding and shorter than those previously reported [56].

Scheme 24



A preparation of tetrahydropyridinium salts by cycloaddition of iminium intermediates derived from *N*-(α-aminoalkyl)benzotriazoles is given in Scheme 25 [57]. Lithium tetrafluoroborate is used to generate the benzotriazolate anion/iminium cation ion pair from *N*-(α-aminoalkyl)benzotriazoles. The iminium cation undergoes hetero Diels-Alder cycloadditions with 1,3-dienes to give 1,2,5,6-tetrahydropyridinium salts under mild conditions, as shown in Scheme 25 [57]. Although benzotriazol-1-yl and benzotriazol-2-yl derivatives easily interconvert *via* the benzotriazolate anion/iminium cation ion pair [58,59], the iminium cation does not react with 1,3-dienes in the absence of lithium tetrafluoroborate. The regioselectivity of this reaction is the same as for hetero Diels-Alder reactions of Eschenmoser's salt, but the readily available, stable, crystalline *N*-(α-aminoalkyl)benzotriazoles are more convenient starting materials than α-haloamines or iminium salts [57].

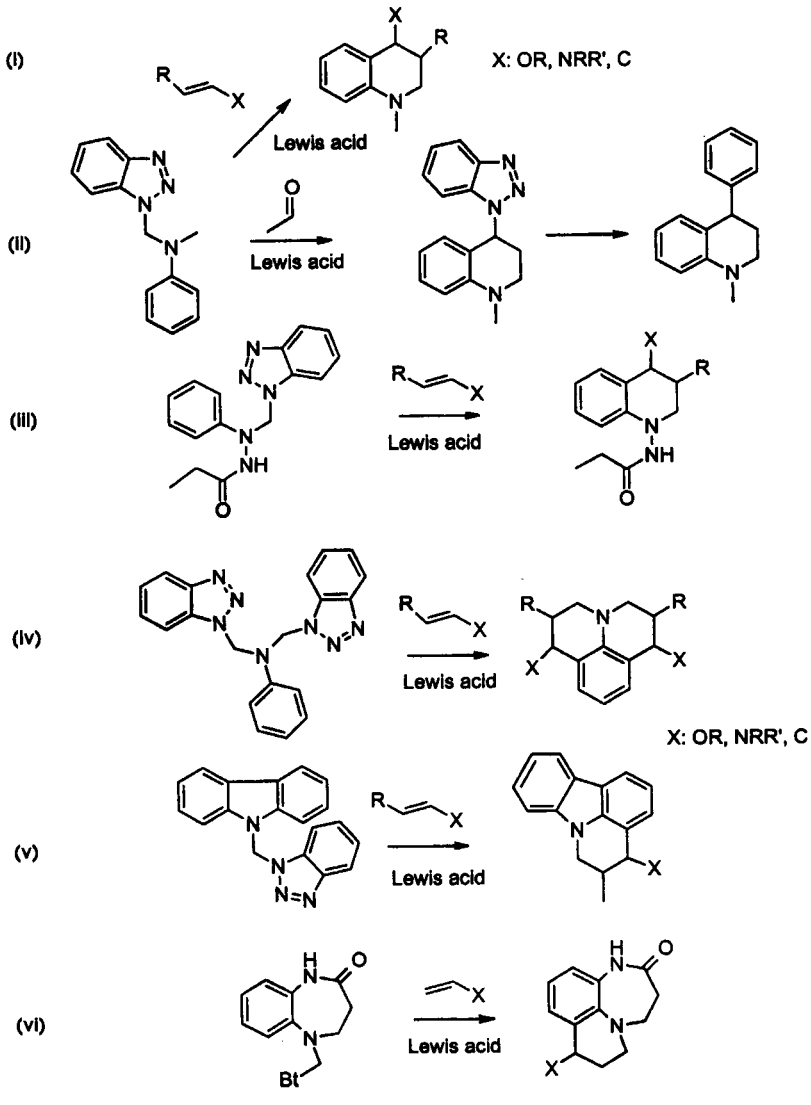
Scheme 25



The benzotriazolate anion/iminium cation ion pair methodology has also been used to prepare tetrahydroquinolines as shown in Scheme 26: (i) Electrophilic attack of *N*-aryliminium cations on electron-rich olefins [60-62], olefins [63] or 1,3-dienes [57] forms a new cationic species which reacts intramolecularly with the aromatic moiety to give tetrahydroquinolines; (ii) reactions of such *N*-aryliminum cations with enolizable aldehydes lead to 4-(benzotriazol-1-yl)tetrahydroquinolines, which with Grignard reagents yield substituted tetrahydroquinolines [64]; (iii) *N*-acyl-*N'*-(benzotriazol-1-yl)-*N'*-phenylhydrazines react with electron-rich olefins to give 1-acylaminotetrahydroquinolines [42].

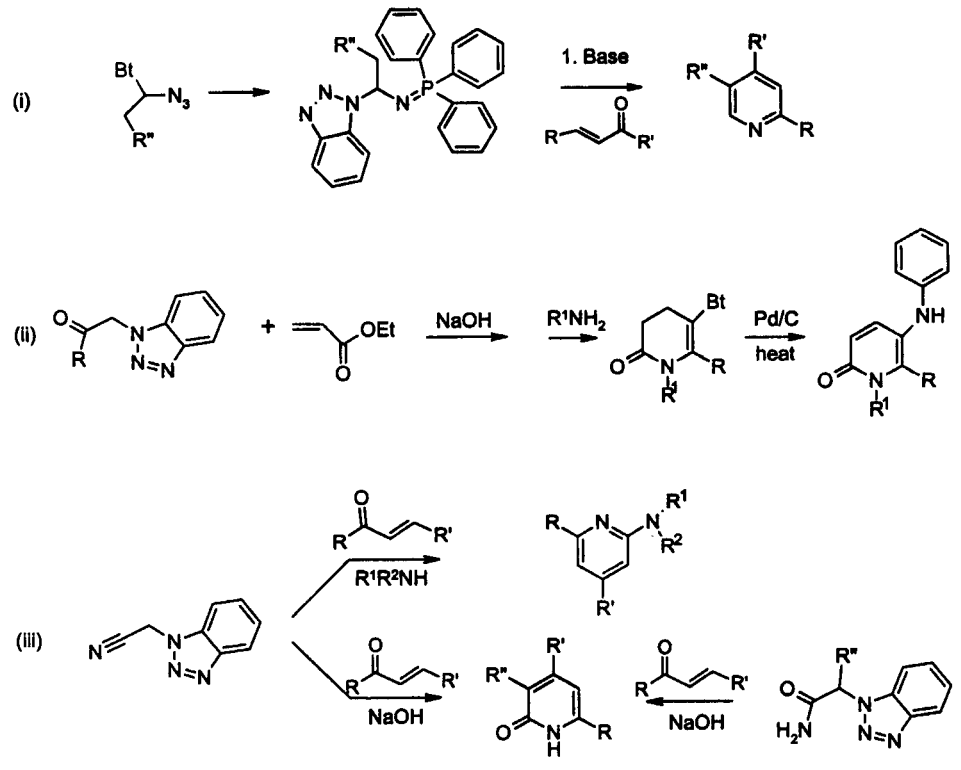
Similar methods were applied for the syntheses of julolidines [65] [Scheme 26 (iv)], 5,6-dihydro-4*H*-pyrido-[3,2,1-*jk*]carbazoles [66] [Scheme 26 (v)] and 3,4,7,8-tetrahydro-6*H*-pyrido[1,2,3-*ef*]-1,5-benzodiazepin-2(1*H*)-ones [67] [Scheme 26 (vi)].

Scheme 26



Pyridines were constructed *via* the routes as shown in Scheme 27: (i) α-(benzotriazol-1-yl)alkyl azides were treated with triphenylphosphine in a Staudinger phosphenimide-forming reaction to yield 1-[α-(phosphoranylideneamino)alkyl]benzotriazoles, which, after deprotonation by sodium hydride, reacted with chalcone to give the corresponding 2,4-diphenylpyridines [68]; (ii) reaction of α-benzotriazol-1-yl ketones with ethyl acrylate under phase-transfer catalysis followed by *in situ* hydrolysis of ester group gave δ-oxocarboxylic acids, which treated with a primary amine formed result 5-(benzotriazol-1-yl)-3,4-dihydropyrid-2-ones. Dehydrogenation of 5-(benzotriazol-1-yl)-3,4-dihydropyrid-2-ones in the presence of 10% palladium on carbon gave pyrid-2-ones [69]; (iii) by one-pot regioselective syntheses of 2-aminopyridines and pyrid-2-ones *via* Michael addition, dehydration, and debenzotriazolylation reactions [70], while allows access to 3-unsubstituted pyridine derivatives difficult to obtain by previous methods.

Scheme 27

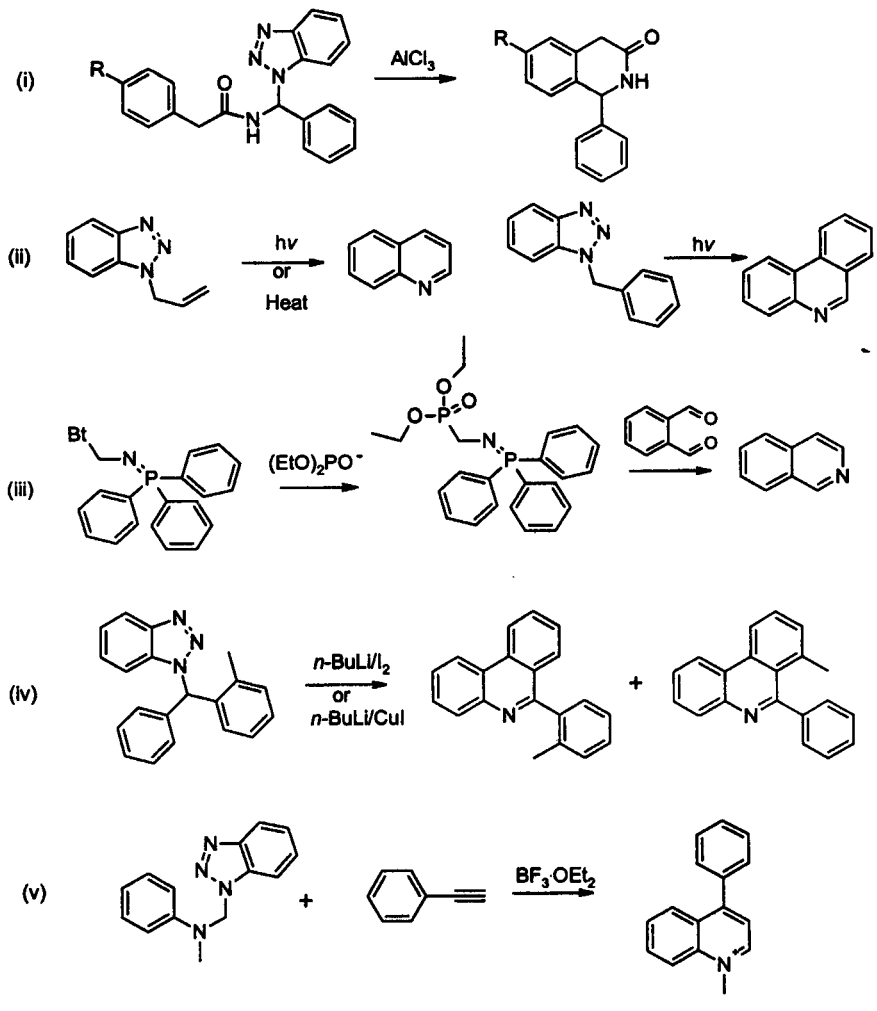


Routes to polycyclic pyridines are collected in Scheme 28: (i) *N*-(α-benzotriazolylalkyl)arylacetamides (readily available from an arylacetamide, aldehyde and benzotriazole) undergo intramolecular cyclization under acidic conditions to give 1,4-dihydro-3(2*H*)-isoquinolinones [71]; (ii) photolysis of 1-allylbenzotriazoles gave quinolines derivatives [72], photolysis of 1-benzylbenzotriazole similarly yielded phenanthridine [73]; (iii) reaction of 1-(triphenylphosphoroylideneaminomethyl)benzotriazole with the lithium salt of diethyl phosphite generated diethyl [(triphenylphosphoranylidene)aminomethyl]phosphonate, which reacted with phthalic 1,2-dicarboxaldehyde to give isoquinoline [27,74]; (iv) the lithiation of diaryl(benzotriazol-1-yl)methanes followed by addition of iodine generated phenanthridines and dimers [75]. The reaction of lithiated diaryl(benzotriazol-1-yl)methanes with copper(I) iodide gave same phenanthridines as products [76]. Both reactions involve radical intermediates.

b. With One Oxygen Atom: Naphtho[2,1-*b*]pyrans, Benzopyrans.

1-[α-(Benzotriazol-1-yl)alkyl]-2-napthols and 2-[(benzotriazol-1-yl)methyl]phenols to lose a molecule of benzotriazole to generate *o*-quinone methides, which was trapped with electron-rich olefins to afford 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans and 3,4-dihydro-2*H*-1-benzopyrans, respectively [77] (Scheme 29).

Scheme 28

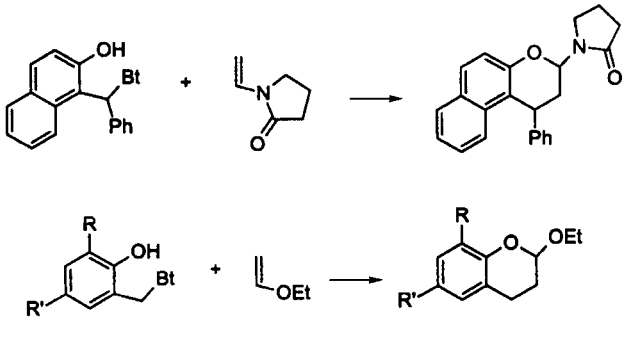


4.2. With Two Heteroatoms.

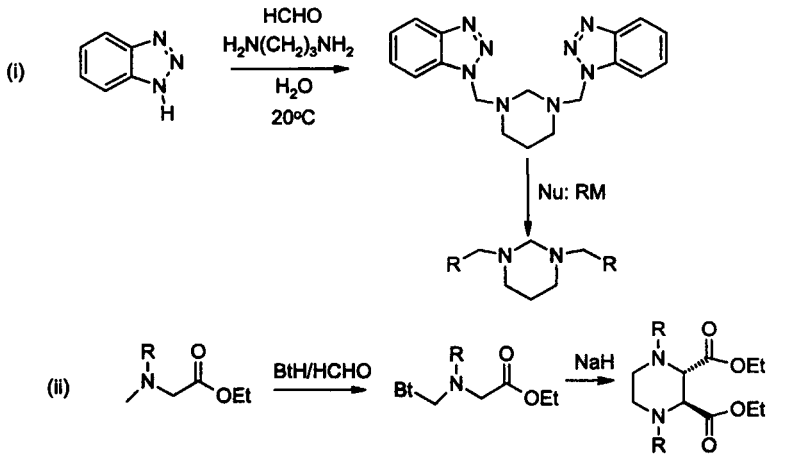
a. With Two Nitrogen Atoms: Pyrimidines, Pyridazines, Pyrido[1,2-*a*]pyrimidinium Salts, Quinazolines, Quinoxalines.

Scheme 30 showed the preparation of hexahydropyrimidines [46]: a procedure similar to that described in the previous section for the preparation of imidazolidines, but using 1,3-diaminopropane as the diamine [Scheme 30 (i)]. Heating *N*-(benzotriazolylmethyl)glycine ethyl ester, which was obtained from the condensation of glycine ethyl ester, formaldehyde and benzotriazole, in tetrahydrofuran in the presence of excess of sodium hydride gave diethyl *trans*-2,3-piperazinedicarboxylates. The reaction involves an aziridine intermediate, which could form diradicals upon heating and dimerization to give diethyl *trans*-2,3-piperazinedicarboxylates [78] [Scheme 30 (ii)].

Scheme 29

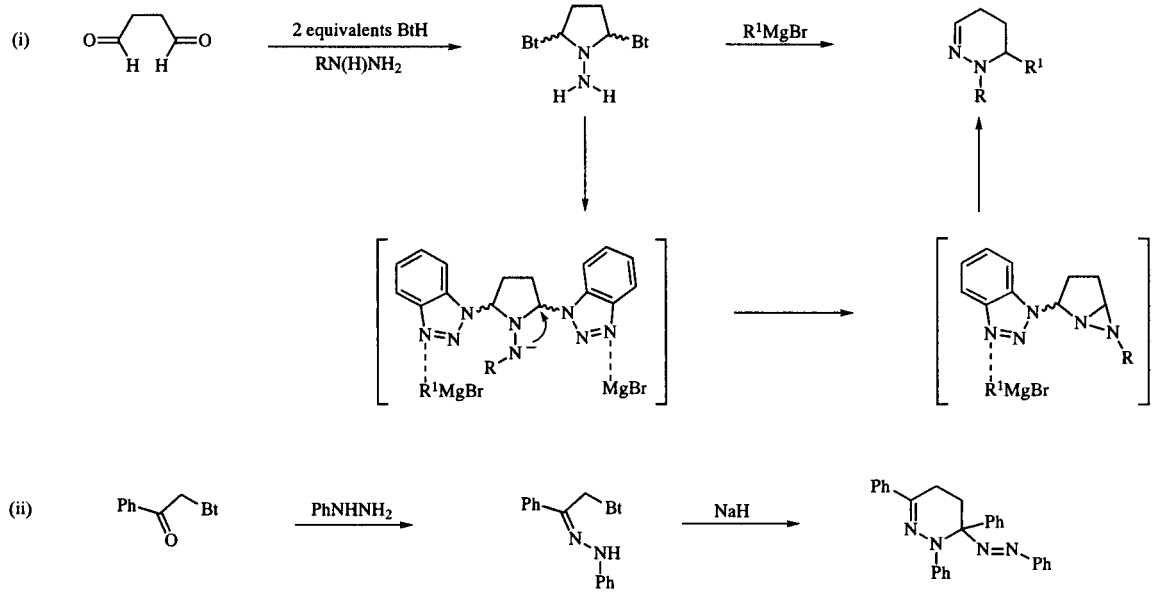


Scheme 30



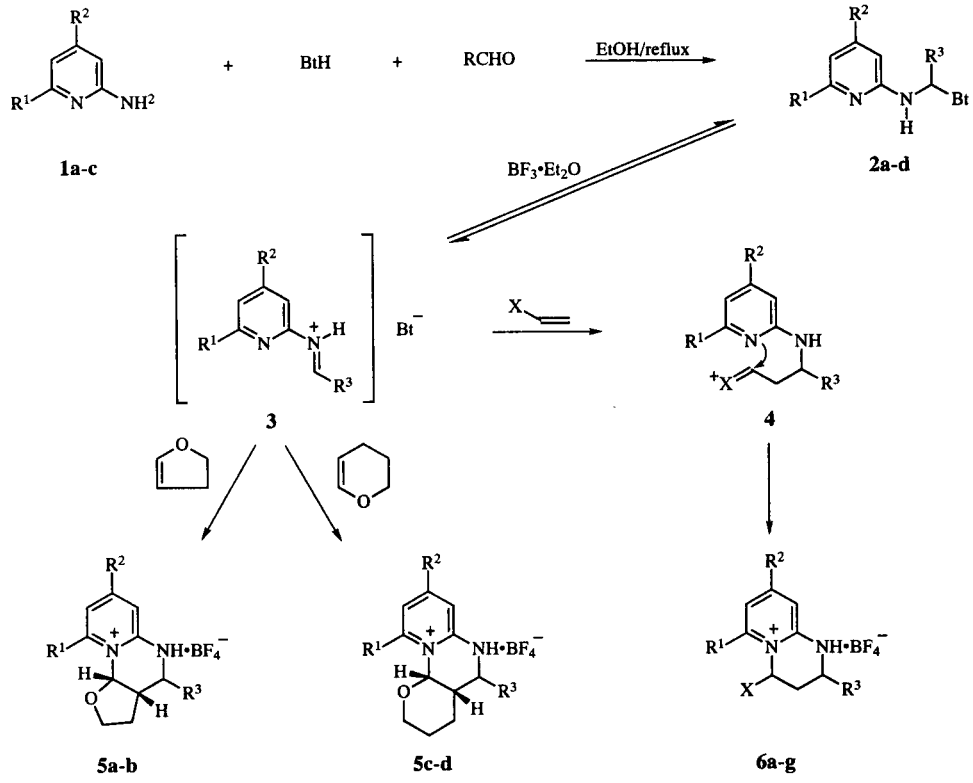
Approaches to tetrahydropyridazines are shown in Scheme 32 [79]: (i) One-pot condensation of benzotriazole, succinic dialdehyde, and an arylhydrazine gave bis-benzotriazolyl derivatives, while upon treatment with excess Grignard reagent, undergo ring enlargement to form tetrahydropyridazines in good to high yields [79]. The Grignard reagent is believed to act initially as a base and complex with the benzotriazolyl moieties. Intramolecular attack of the nitrogen anion displaces one benzotriazolyl moiety to form an aziridine, ring enlargement is driven by the elimination of the second benzotriazolyl moiety. The resultant iminium intermediate is quenched by Grignard reagent to yield the product 1,6-disubstituted 1,4,5,6-tetrahydropyridazines in a procedure which compares favorably with previous alternatives. (iii) α-(Benzotriazol-1-yl)acetophenone, prepared from α-bromoacetophenone and sodium benzotriazolide, reacted with hydrazine to form an hydrazone. On treatment with sodium hydride this gives α-(phenylazo)styrene, which spontaneously underwent Diels-Alder dimeration to yield the 1,4,5,6-tetrahydropyridazine [80].

Scheme 31



2-(Benzotriazol-1-ylalkyl)aminopyridines, readily available from 2-aminopyridine, aldehydes and benzotriazole, react with electron-rich alkenes to give good yields of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidinium salts [81] (Scheme 32).

Scheme 32

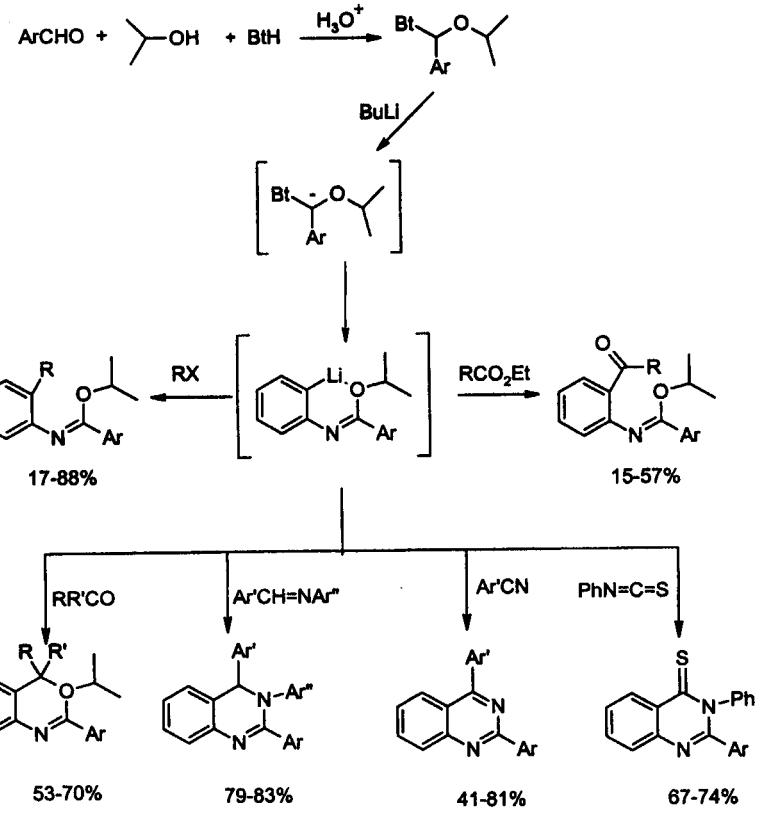


In an exception to the general rule that the benzotriazole ring remains intact thoughout the synthetic transformations, various benzoxazine and quinazoline derivatives can be prepared by a reaction involving disruption of the benzotriazole ring as shown in Schemes 33 [82] and 34 [83].

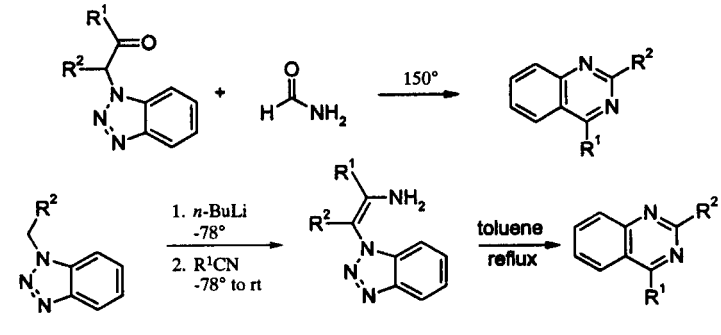
The key *o*-iminophenyl anions were generated at -78° by lithiation of *N*-(α-propoxyalkyl)benzotriazoles and spontaneous extrusion of nitrogen. Treatment of the anion with electrophiles and ring closure results in the preparation of benzoheterocycles. The addition of ketones results in the formation of benzoxazines; arylamines gave 3,4-dihydroquinazolines; nitriles yielded quinazolines; whereas isothiocyanates gave quinazoline-4-thiones (Scheme 33) [82]. In the case of halides and esters, the loss of the isopropoxy group and subsequent cyclization do not occur.

Further benzotriazole ring cleavages to prepare quinazolines are shown in Scheme 34 [83]. Heating 2-(benzotriazol-1-yl)-1,2-diphenylethanone and formamide at 150° gave 2,4-diphenylquinazoline instead of the expected 4,5-diphenylimidazole. The postulated enamine intermediate, prepared from lithiated benzylbenzotriazole and benzonitrile, was indeed transformed to the same quinazoline product. A number of other enamines were prepared in this way but the use of a nitrile with an a proton was unsuccessful. Cross-over experiments concluded that the mechanism for quinazoline formation does not involve reverse scission of enamines into benzylbenzotriazole and a nitrile. The intramolecular process shown at the bottom of Scheme 34 is proposed for this thermolytic rearrangment. Initially the amino group assists the opening of the triazole ring to form a betaine. Loss of nitrogen forms an intermediate which undergoes intramolecular ring closure to form a five-membered ring. Attack of the imine carbon by the amino group gives an aziridine intermediate which undergoes ring expansion and aromatization to form quinazoline derivatives [83].

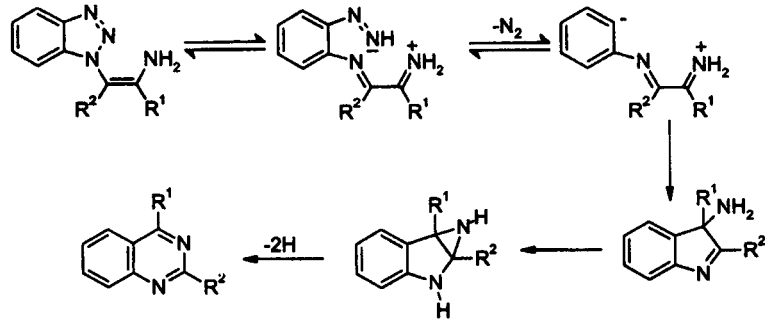
Scheme 33



Scheme 34



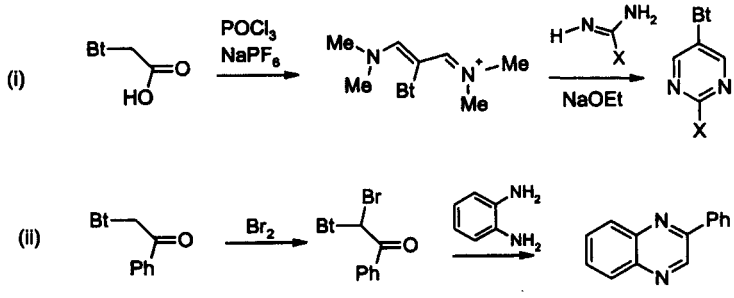
Postulated Mechanism:



Condensation of 2-(1-benzotriazolyl)vinamidinium salt with a variety of substituted amidines in an ethanol/sodium ethoxide gave a series of 2-substituted-4-benzotriazolylpyrimidines in excellent yields [44] [Scheme 35 (i)].

α-(Benzotriazol-1-yl)-α-bromoacetophenone, prepared from α-(benzotriazol-1-yl)acetophenone and bromine, reacted with *o*-phenylenediamine to afford 2-phenylquinoxaline [80] [Scheme 35 (ii)].

Scheme 35

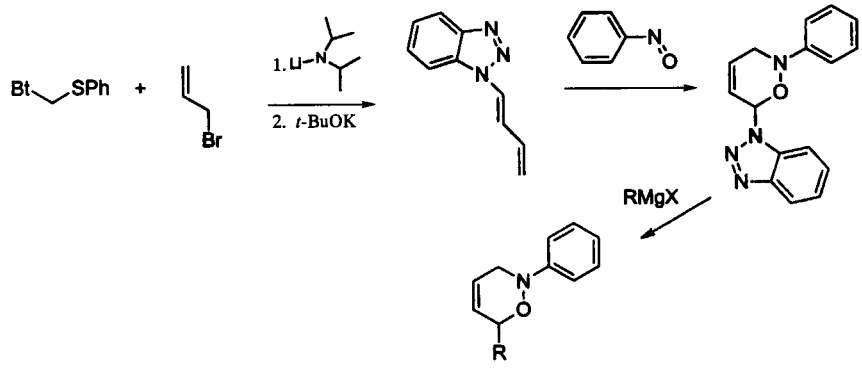


b. With One Nitrogen and One Oxygen: Benzoxazines, 1,2-Oxazines.

As already shown in Scheme 33, benzoxazines were obtained in 53-70% from *N*-(α-propoxyalkyl)benzotriazoles and ketones.

1-(1,3-Butadien-1-yl)benzotriazole, obtained from reaction of α-lithio 1-[α-(phenylthio)methyl]benzotriazoles and allyl bromide followed by treatment with potassium *tert*-butoxide, readily reacted with nitrosobenzene under mild conditions to give the substituted dihydro-1,2-oxazine in high yield [84] (Scheme 36).

Scheme 36



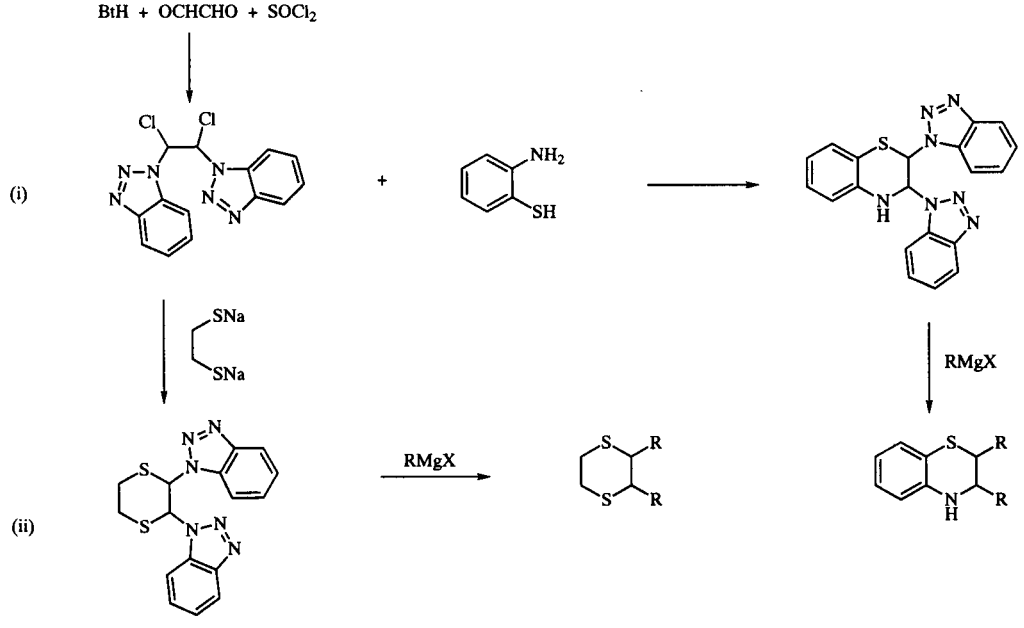
c. With One Nitrogen and One Sulfur Atoms: 1,4-Thiazines.

1,2-Dichloro-1,2-di(benzotriazol-1-yl)ethane, prepared from 1,2-di(benzotriazol-1-yl)ethan-1,2-diol and thionyl chloride, reacted with *o*-aminothiophenol in the presence of base sodium ethoxide to yield 2,3-di(benzotriazol-1-yl)-1,4-thiazine, which further treated with Grignard reagents to give 2,3-disubstituted-dihydro-1,4-thiazines [85] [Scheme 37 (i)].

d. With Two Sulfur Atoms: 1,4-Thiins.

In similar manner, 1,2-dichloro-1,2-di(benzotriazol-1-yl)ethane reacted with 1,2-ethanedithiol dissodium salt to produce 2,3-di(benzotriazol-1-yl)-1,4-thiin, which could then react with Grignard reagents to give 2,3-disubstituted-1,4-thiin [85] [Scheme 37 (ii)].

Scheme 37



4.3. With Three Heteroatoms: 1,2,4-Benzotriazines.

α-(Benzotriazol-1-yl)hydrazones, prepared from α-(benzotriazol-1-yl) ketones and *p*-tosyl hydrazide, underwent rearrangement under base conditions to give 3-aryl-1,2,4-benzotriazines [86] (Scheme 38).

5. Construction of Larger Rings: Benzazepines, Tetrazolotriazepines.

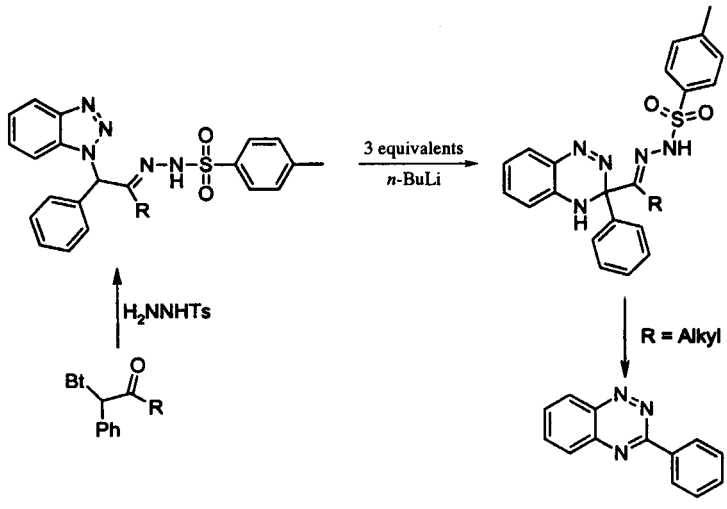
1-(Triphenylphosphoranylideneaminomethyl)benzotriazole has been used to prepare a benzazepine, (Scheme 39) [26] by a route analogous to that used for the preparation of pyrroles as described above. The nucleophilic reaction of 1-(triphenylphosphoranylideneaminomethyl)benzotriazole with methylidenetriphenylphosphorane followed by deprotonation with butyllithium gave a monoazabisphosphorus ylide. Treatment with phthalic dicarboxaldehyde at room temperature gave 3*H*-2-benzazepine in good yield.

Reaction of 1,2-dichloro-1,2-di(benzotriazol-1-yl)ethane and sodium azide gave 4-(benzotriazol-1-yl)-6*H*-benzo[*c*]tetrazolo[1,5-*e*][1,2,5]triazepine, the first example of this tricyclic system, and the first expansion of the triazole ring of benzotriazole by two atoms [87] (Scheme 40).

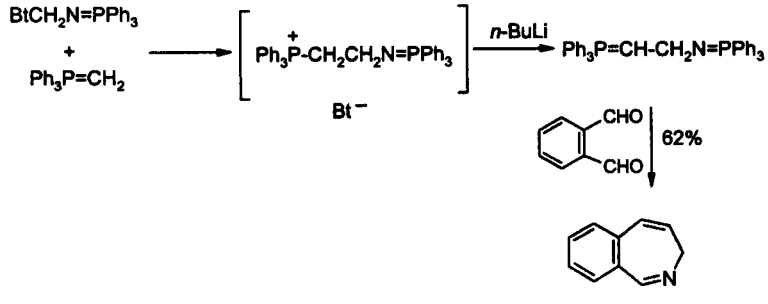
6. The Ring Substitution of Aromatic Heterocycles.

Electron rich heteroaromatics can be aminoalkylated (as shown in Scheme 41 (i)) [88]. The Mannich reaction to *C*-aminoalkylate electron rich heterocycles usually involves reacting an amine hydrochloride salt and formaldehyde with the heterocycle. Preparation of our reagents from benzotriazole, formaldehyde and a primary or secondary amine proceeds smoothly, in high yields. Further reaction with electron rich heteroaromatics then gave secondary or tertiary amines respectively.

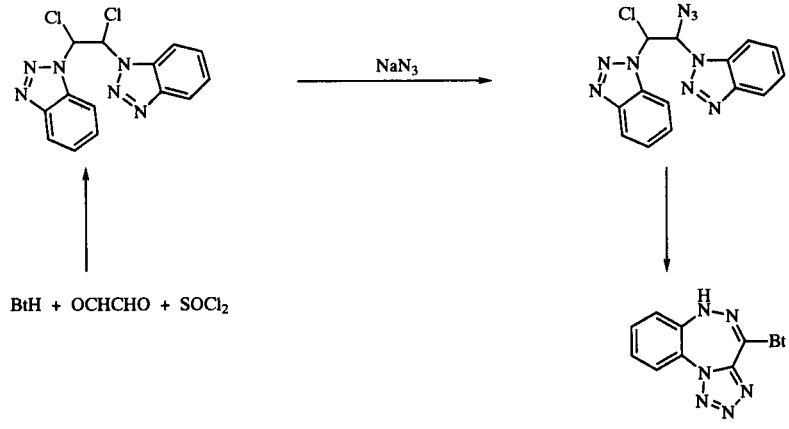
Scheme 38



Scheme 39

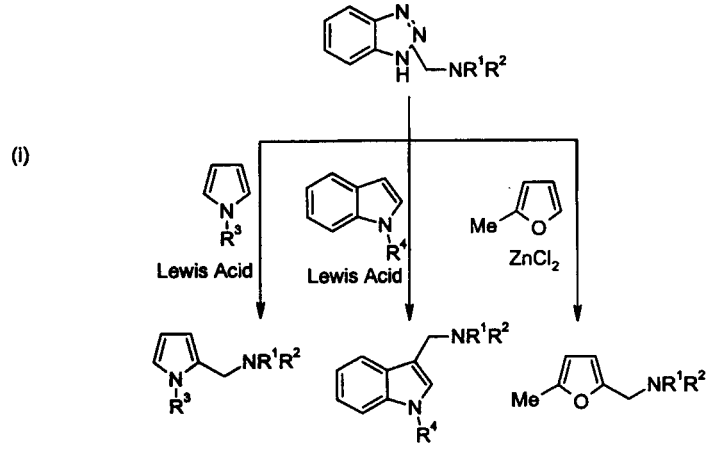


Scheme 40

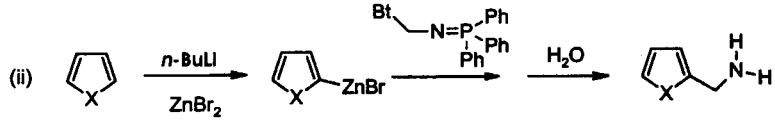


Primary aminomethyl groups were introduced to the 2-position of electron rich heterocycles in moderate to good yields by a one-pot sequence involving lithiation, transmetalation into an organozinc reagent and treatment with 1-(triphenylphosphoranylideneaminomethyl)benzotriazole [89] [Scheme 41 (ii)].

Scheme 41



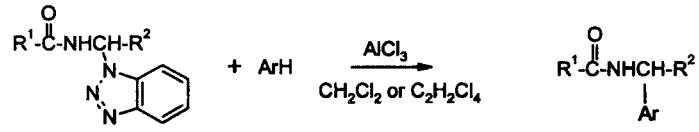
Amine	Lewis Acid	Yield (%)	Lewis Acid	Yield (%)	Lewis Acid	Yield (%)
3°	$AlCl_3$	70-96	$AlCl_3$	70-96	$AlCl_3$	70-96
2°	$ZnCl_2$	62-82	$ZnCl_2$	62-82	$ZnCl_2$	62-82



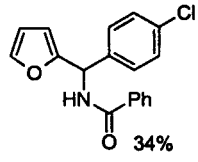
X: N, O, S

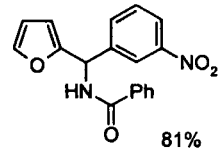
Aminobenzylations with our benzotriazolylalkylamides reagents, simply prepared from benzotriazole, amides, and aldehydes [90], convert electron-rich heteroaromatics in the presence of aluminum chloride in dichloromethane at reflux [91] into the amidoalkylated products shown in Scheme 42. Similar reaction are shown in Scheme 43 [92].

Scheme 42

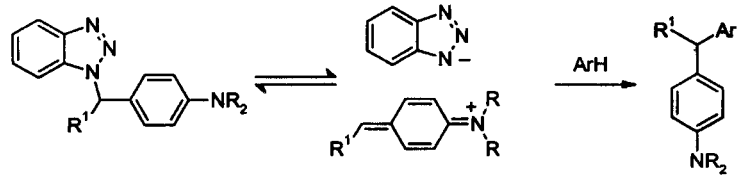


Amidoalkylation Products and their Yields

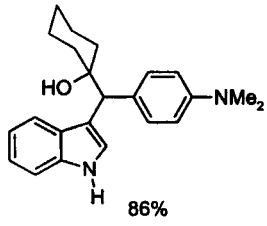


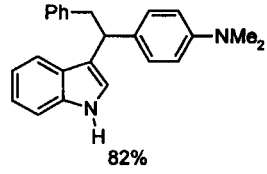


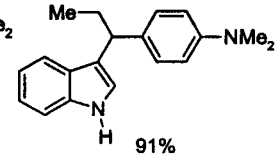
Scheme 43

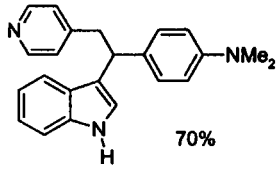


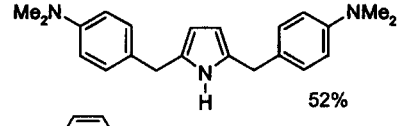
Examples:

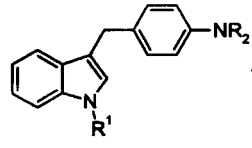








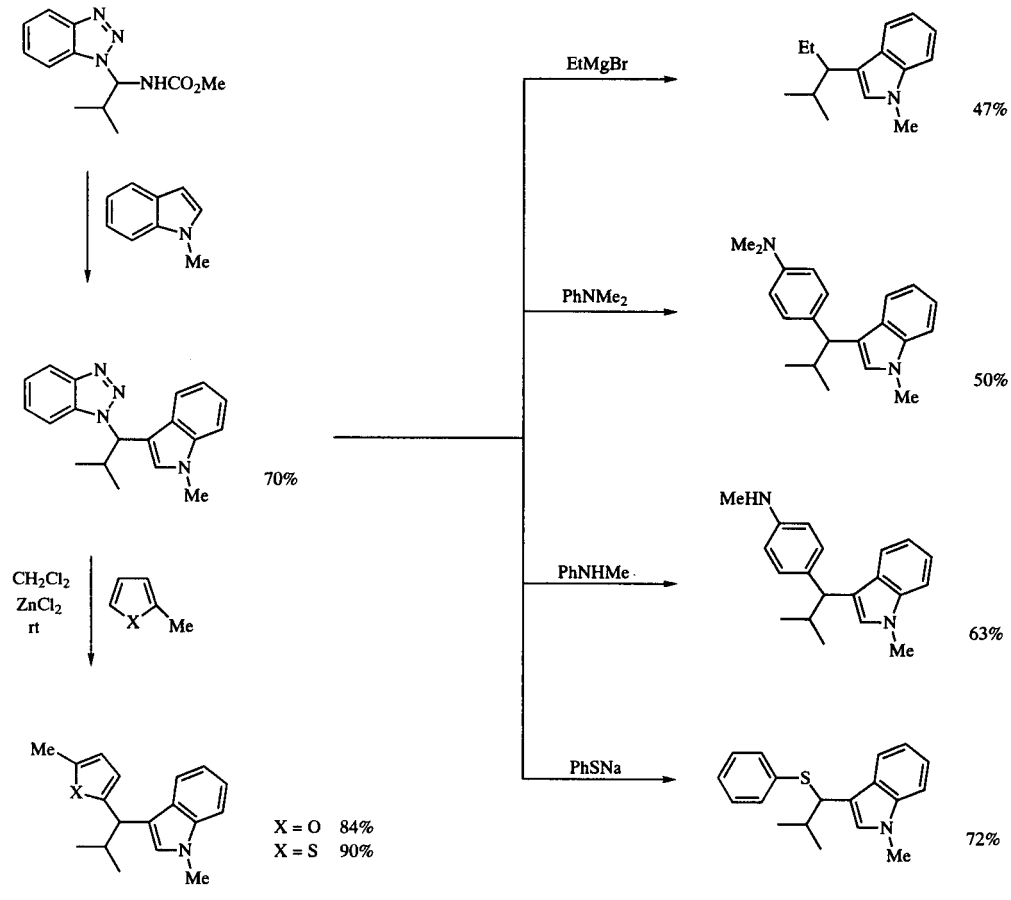




R	R¹	Yield (%)
H	H	92
Me	H	96
Me	Me	98

In a different type of transformation, although mechanistically related, benzotriazolylalkylations may be carried out. Examples are shown in Scheme 44 which also illustrates the use of the product in the preparation of further substituted indoles [93,94]. Other examples of the utilization of compounds containing benzotriazole groups separated by one carbon atom from an aromatic or heteroaromatic ring are illustrated in later sections.

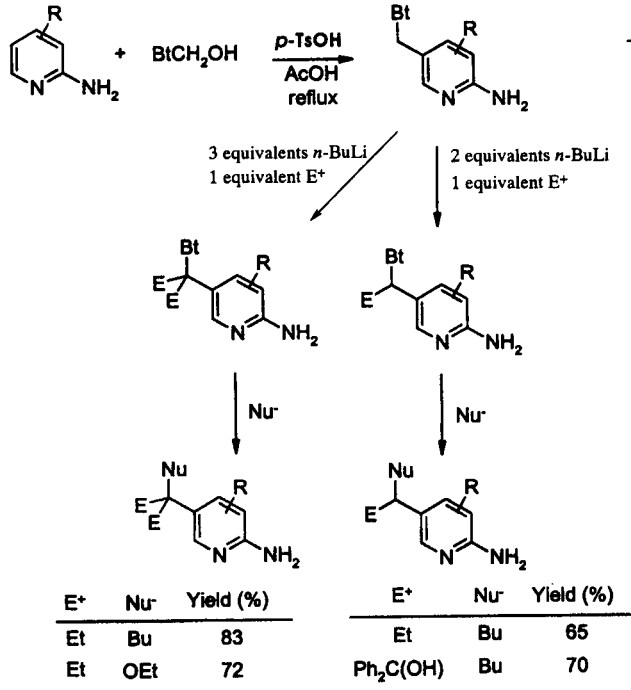
Scheme 44



Heating 2-aminopyridines with 1-(hydroxymethyl)benzotriazole gives regiospecifically the corresponding 5-(benzotriazol-1-ylmethyl)-2-aminopyridines (Scheme 45) [95]. Mono- or di-lithiation at the methylene group and treatment with electrophiles followed by displacement of the benzotriazolyl moiety allows the synthesis of many novel 5-substituted-2-aminopyridines. A few examples are shown in Scheme 45.

A completely different type of reaction which comprises the benzotriazole-mediated electrophilic substitution of electron-deficient rings is shown in Scheme 46 [96,97]. Here nucleophilic addition of the benzotriazolyl anion to the pyrylium salt allows it to be deprotonated *para* to the heteroatom, to give a reactive anion which can be trapped with alkyl halides. Removal of the benzotriazolyl auxiliary by treatment with mineral acid gives various substituted pyrylium cations. This is the first report of a general method for the electrophilic substitution of electron deficient *O*-heterocycles [97]. The procedure has also been carried out successfully on benzo[*b*]pyrylium salts and heteroniumanthracene cations or the corresponding carbinols bases [96].

Scheme 45

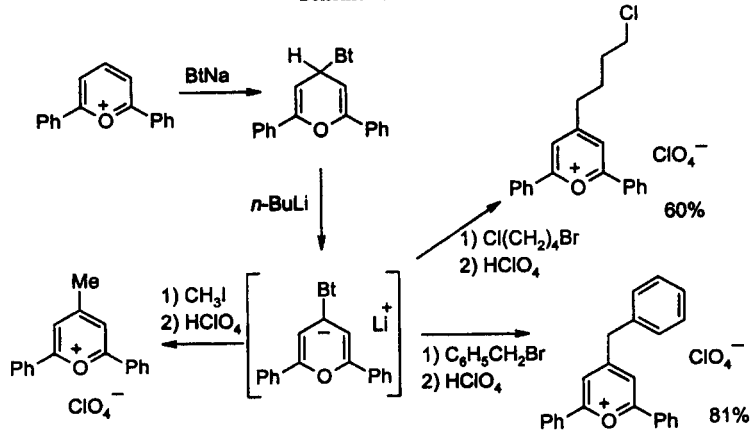


R	Yield (%)
H	53
3-Me	73
4-Me	60
6-Me	62
4,6-diMe	61

E^+	Nu^-	Yield (%)
Et	Bu	83
Et	OEt	72

E^+	Nu^-	Yield (%)
Et	Bu	65
$Ph_2C(OH)$	Bu	70

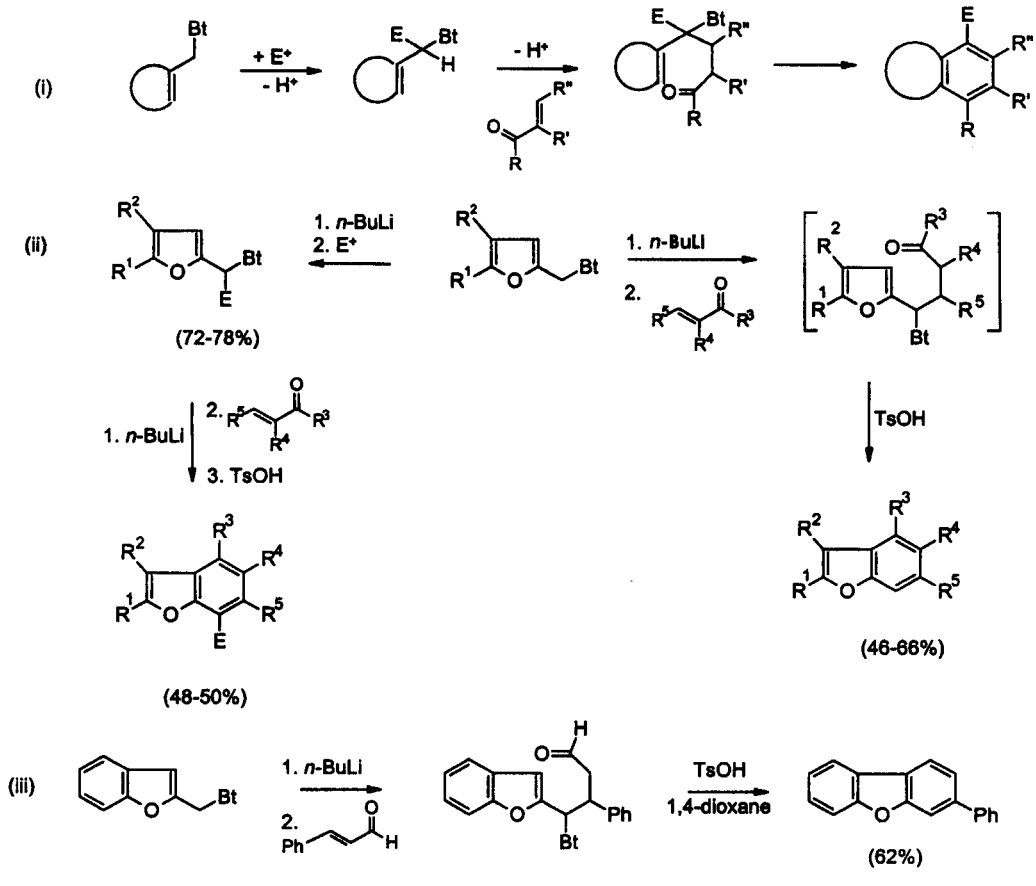
Scheme 46



7. Ring Annulations of Heterocycles.

Scheme 47 shows: (i) The principle of the benzotriazole-mediated benzannulation; (ii) examples for the conversion of furans into benzofurans, and (iii) of benzofurans into dibenzofurans [39]. Most syntheses of benzo[*b*]-furans involved the intramolecular cyclization of a suitably substituted benzene, the present method is one of the few alternatives starting with the furan ring intact. Lithiation of the 2-(benzotriazolylmethyl)furan derivatives and reaction with α,β-unsaturated carbonyl compounds gives the 1,4-addition intermediates. Heating under acidic conditions, these intermediates undergo intramolecular cyclization followed by spontaneous elimination of benzotriazole and water to give benzo[*b*]furans. Similarly, 2-(benzotriazolylmethyl)benzo[*b*]furan derivatives give dibenzofurans.

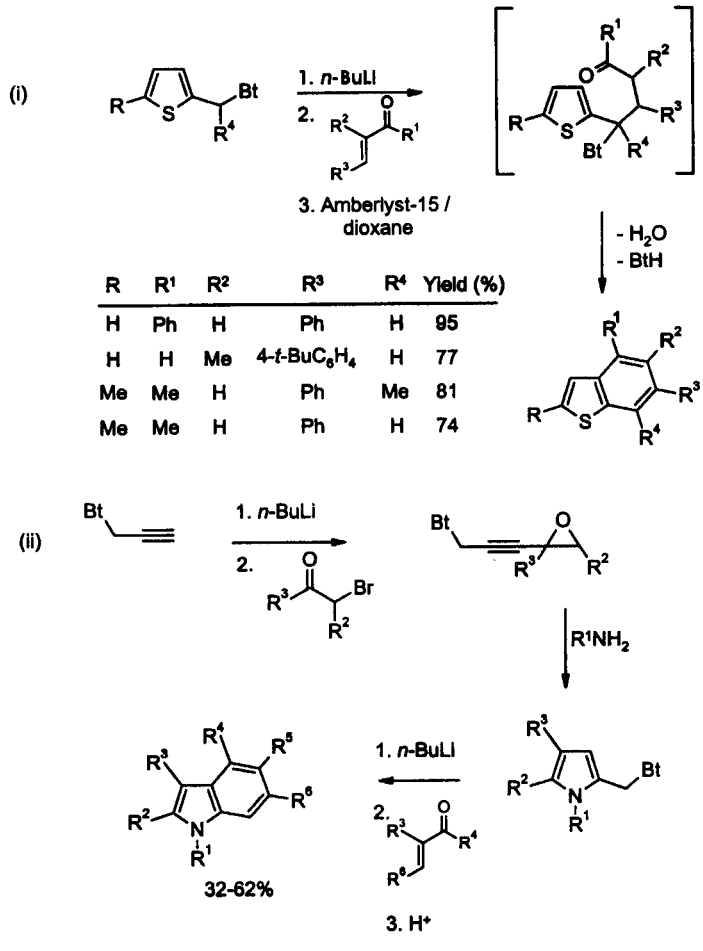
Scheme 47



Scheme 48 shows (i) the ring annulations of thiophenes [98] and (ii) of pyrroles [29] to give benzothiophenes and indoles respectively. The procedure is the same as shown in Scheme 48 for the synthesis of benzofurans. While the classical methods of starting with the substituted benzene ring and building on the heterocycle are of great utility, the new methods offer advantages for cases where several substituents are required in the benzene ring.

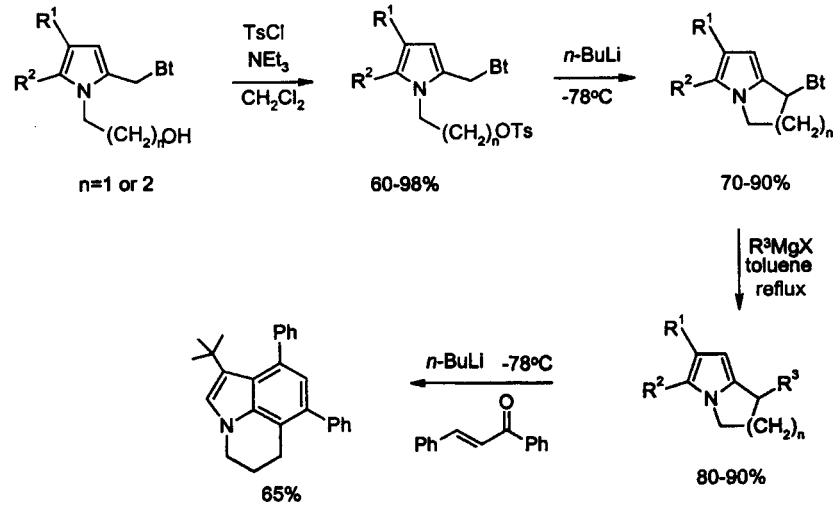
Related work leading to [1,2-*a*]fused pyrroles and indoles [99] is shown in Scheme 49.

Scheme 48



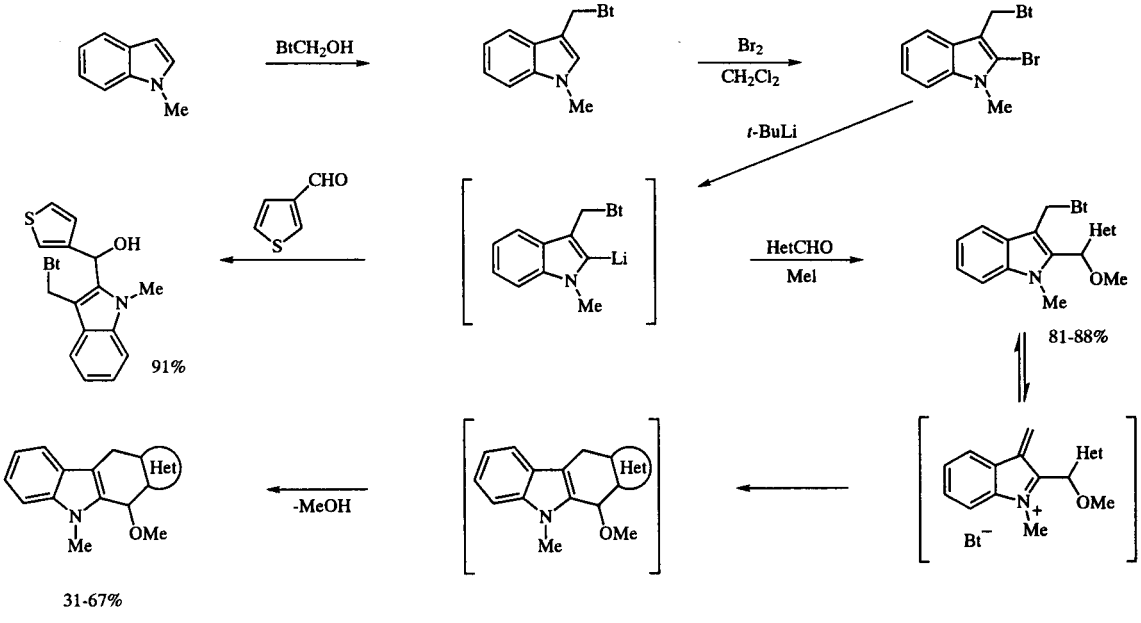
R	R¹	R²	R³	R⁴	Yield (%)
H	Ph	H	Ph	H	95
H	H	Me	4-*t*-BuC$_6$H$_4$	H	77
Me	Me	H	Ph	Me	81
Me	Me	H	Ph	H	74

Scheme 49



Benzotriazole mediated ring annulations have been used as shown in Scheme 50 for a general synthesis of heterocycle[*b*]fused carbazoles [100]. Brominated 1-methyl-3-[(benzotriazol-1-yl)methyl]indole undergoes lithium/-halogen exchange followed by reaction with heteroaryl aldehydes and methyl iodide/hexamethylphosphoramide to give the protected intermediates. Such intermediates are known [101] to undergo reversable ionization to yield small quantities of benzotriazolate anion and the corresponding carbocations. The ionization is induced by heating the intermediates at *ca.* 216° for two days causing ring closure. Subsequent aromatization by loss of methanol, *in situ*, gave heterocyclo[*b*]fused carbazoles. An attractive feature of this method is the wide variety of heterocyclo[*b*]-fused carbazoles that can be prepared easily by changing the starting heteroaryl aldehydes.

Scheme 50



Het: thien-3-yl, furan-3-yl, thien-2-yl, furan-2-yl, 1-methylindol-3-yl

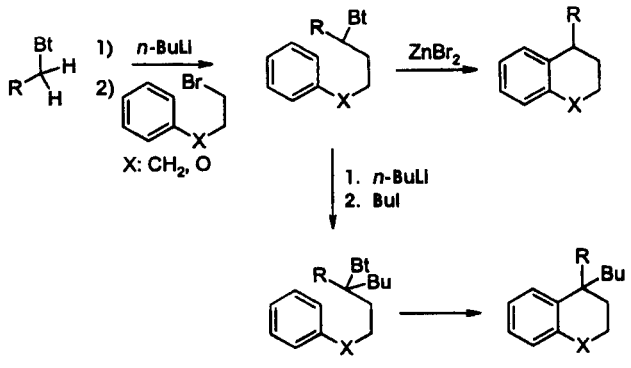
Scheme 51 shows a variety of further annulations: in these cases it is now a heterocyclic ring that is being built onto a benzene ring. The formation of the new heterocyclic ring is in each instance mediated by the benzotriazole [102].

8. Ring Substitutions Leading to Saturated Heterocycles.

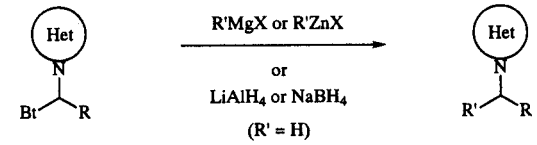
The conversion of unsaturated cyclic ethers into α-alkylated saturated cyclic ethers is shown in Scheme 52 [103]. Benzotriazole reacts smoothly and cleanly with vinyl ethers to give the α-benzotriazolyl adducts. Displacement of the benzotriazolyl moiety by phenyl or alkynyl Grignard reagents give the α-substituted cyclic ethers.

It's also possible to substitute an *N*-substituent at the position *alpha* to a heteroaromatic or other cyclic nitrogen using benzotriazole chemistry. The substitution of a benzotriazole group is illustrated for carbazoles, indoles, pyrroles, and benzamidazoles in Scheme 53: Grignard or organozinc reagents give di-α-substituted-heterocycles [104,105]. This reaction is regioselective.

Scheme 51

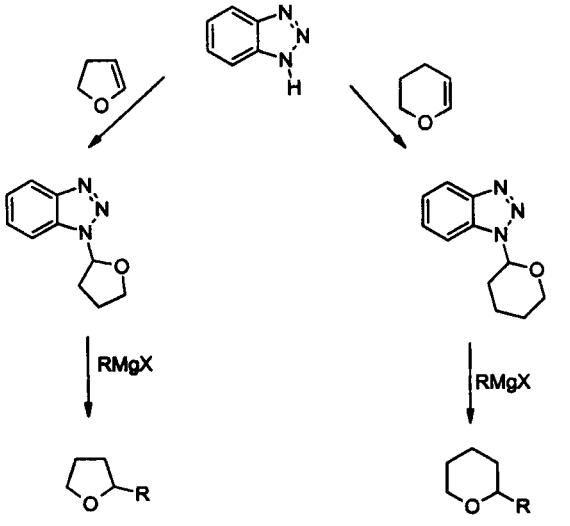


Scheme 53



Heterocyclic Group	R	R'	Yield
Pyrrol-1-yl	H	*n*-Bu	42
Pyrrol-1-yl	H	Ph	73
Pyrrol-1-yl	H	$PhCH_2$	72
Pyrrol-1-yl	$PhCH_2$	H	96
Pyrrol-1-yl	$(CH_2)_5CH(OH)$	Ph	50
Pyrrol-1-yl	4-$MeC_6H_4CH(OH)$	Ph	60
Indol-1-yl	H	*n*-Bu	37
Indol-1-yl	H	Ph	74
Indol-1-yl	$PhCH_2$	*n*-Bu	94
Indol-1-yl	4-$MeC_6H_4CH(OH)$	Ph	55
Indol-1-yl	Me_2(*t*-Bu)Si	Ph	81
Indol-1-yl	Me_2(*t*-Bu)Si	*t*-Bu	77
Carbazol-9-yl	H	Ph	96
Carbazol-9-yl	$PhCH_2$	Ph	45
Carbazol-9-yl	$Me_2NCH_2CH_2$	Me	76
Carbazol-9-yl	4-$MeC_6H_4CH(OH)$	Ph	50
Carbazol-9-yl	Me_3Si	Ph	85
Carbazol-9-yl	$(i\text{-}Pr)_3Si$	Ph	94
Benzimidazol-1-yl	H	H	75
Benzimidazol-1-yl	H	*n*-Bu	56
Benzimidazol-1-yl	H	Ph	86

Scheme 52



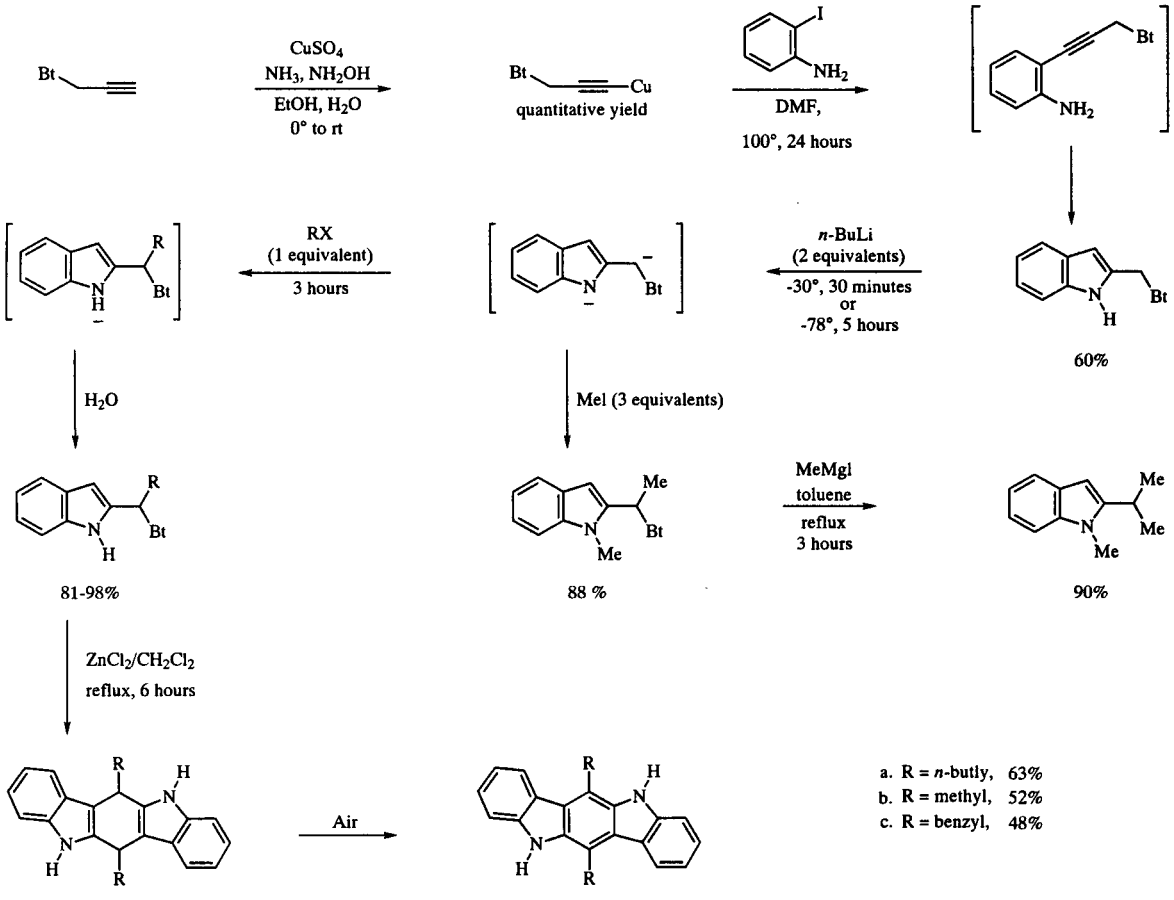
R	Yield (%)
Hexyl	59
Ph	66
PhC≡C	78
BuC≡C	90

R	Yield (%)
Ph	55
PhC≡C	84
BuC≡C	78

9. Heterocycle Substituent Modification.

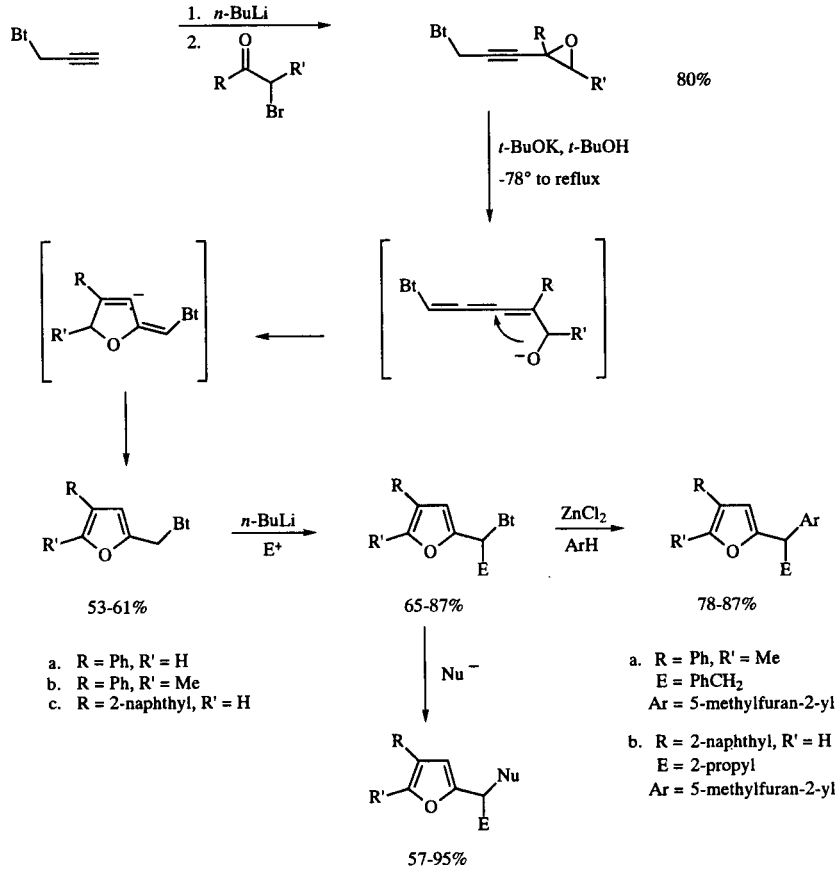
The presence of a benzotriazole group separated by one carbon atom from a heteroaromatic ring allows the synthesis of many derivatives with quite complex substituents. An example is shown for the synthesis of 2-substituted indoles in Scheme 54 [106].

Scheme 54

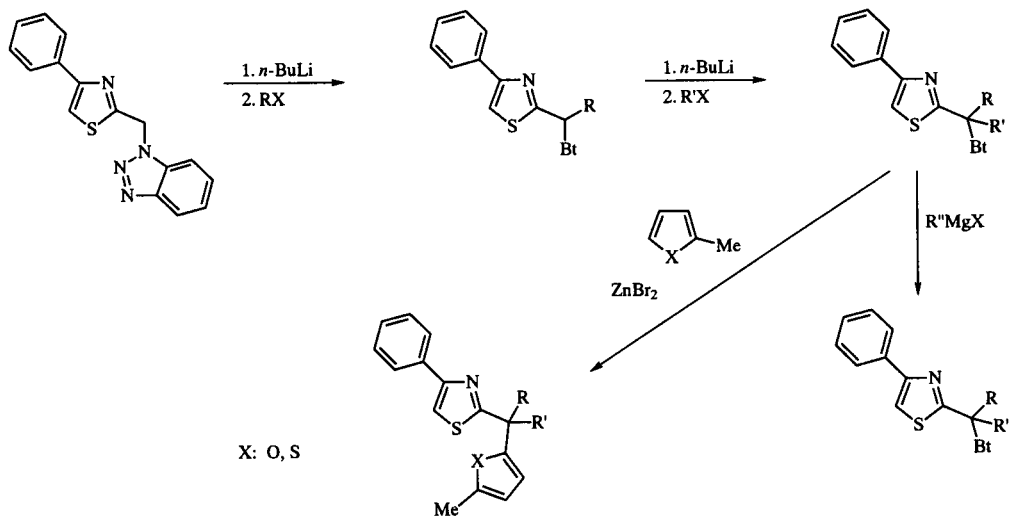


Similar reactions given in Scheme 55 lead to 2-substituted-pyrroles [40], and those in Scheme 56 afford 2-substituted thiazoles [51].

Scheme 55

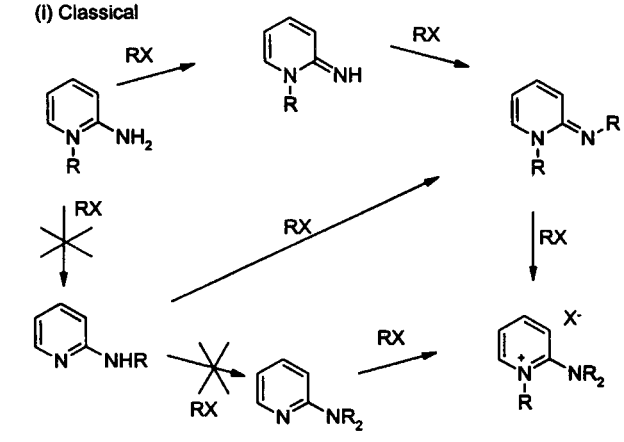


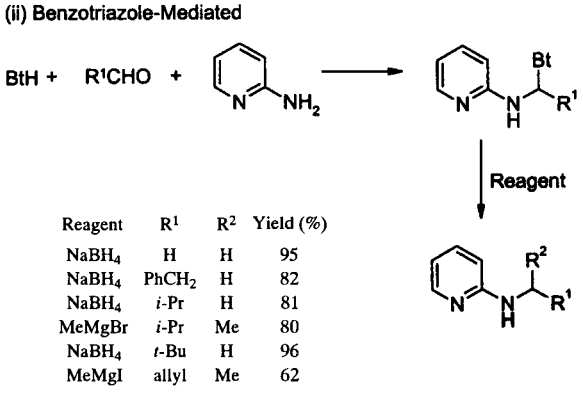
Scheme 56



Benzotriazole assisted synthesis is useful for the insertion of substituents into heteroaromatic amines. Alkylation of aminopyridines at the amino group by classical methods requires special procedures in Scheme 57 (i). By contrast such reactions is easily carried out using benzotriazole as shown in Scheme 57 (ii) [107].

Scheme 57

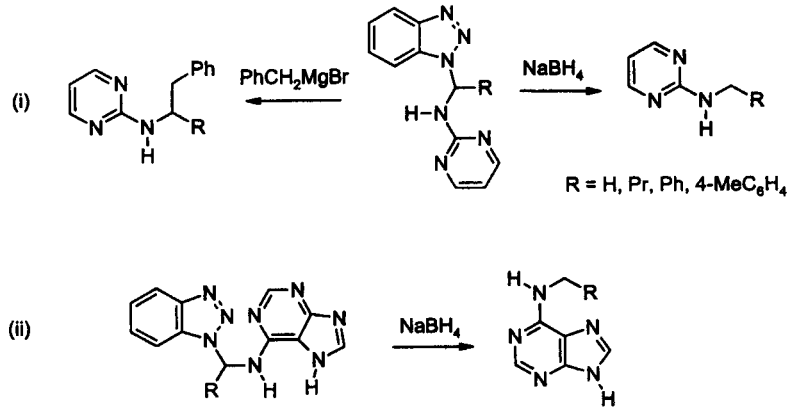




Reagent	R^1	R^2	Yield (%)
$NaBH_4$	H	H	95
$NaBH_4$	$PhCH_2$	H	82
$NaBH_4$	*i*-Pr	H	81
MeMgBr	*i*-Pr	Me	80
$NaBH_4$	*t*-Bu	H	96
MeMgI	allyl	Me	62

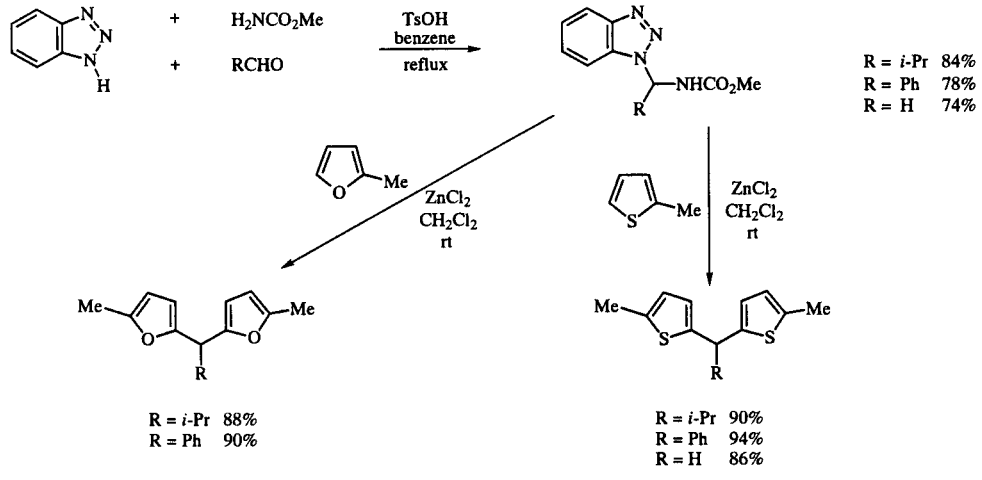
In Scheme 58, similar preparations of (i) alkylaminopyrimidines and (ii) purines are given [107].

Scheme 58

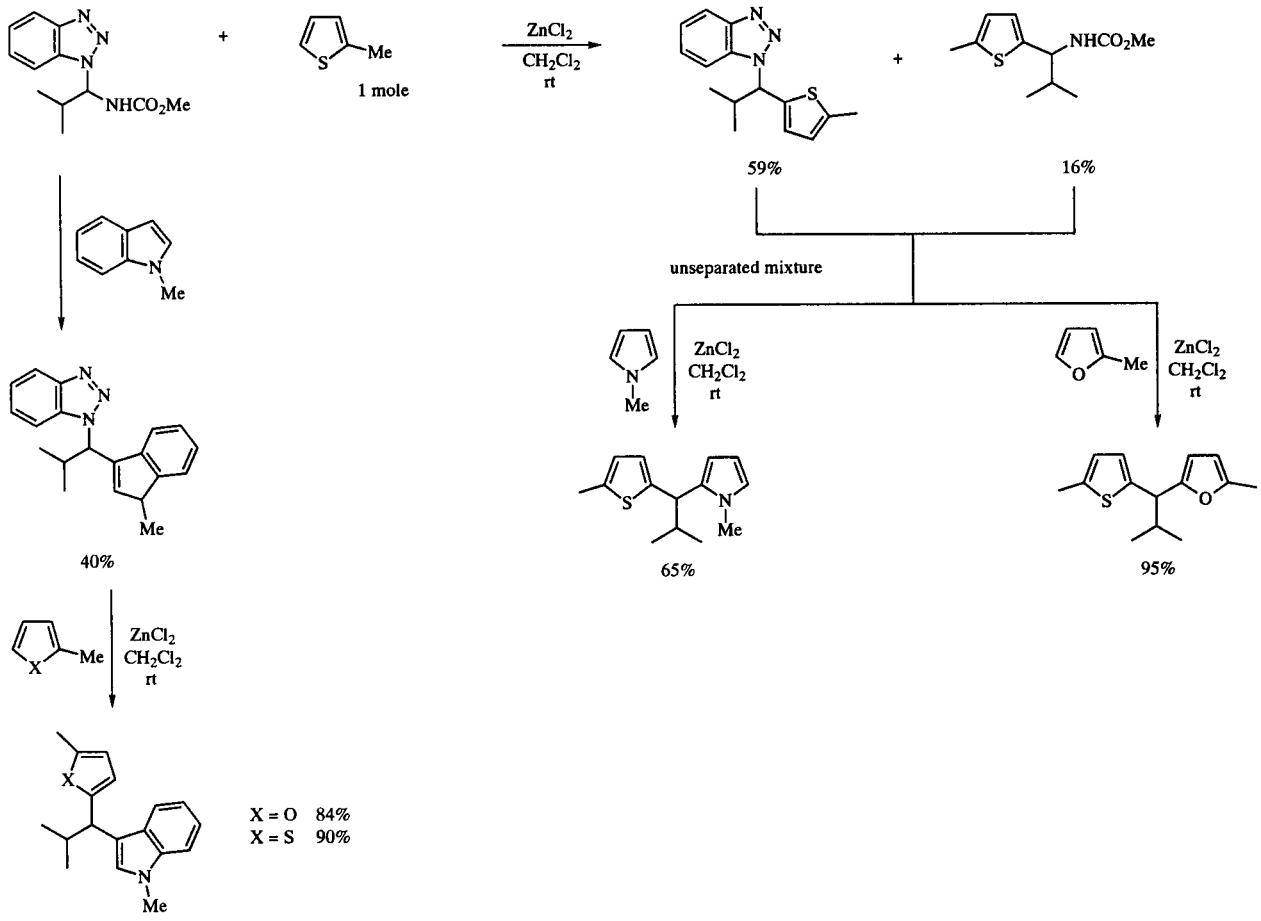


Treatment of methyl *N*-(benzotriazol-1-ylalkyl)carbamates with excess 2-methylthiophene or 2-methylfuran results in formation of the bis-heterocycles shown in Scheme 59 [93]. If only 1 equivalent of thiophene or furan used, a mixture of the carbamoyl substituted, benzotriazolyl substituted, and the disubstituted products is formed [93]. Although these products can be separated, the mixture of monosubstituted compounds can be further reacted with 2-methylfuran or *N*-methylpyrrole to give the much less well known unsymmetrical bis-heteroaryl alkanes (Scheme 60) [93].

Scheme 59



Scheme 60



10. Conclusion.

This review has attempted to illustrate some of the ways in which benzotriazole chemistry can be used for the preparation of heterocyclic compounds. The subject is ongoing and undoubtedly many further examples of both ring synthesis and substituent introduction or modification in heterocycles will become available as benzotriazole chemistry continues to develop.

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