Synthesis of Heterocycles Mediated by Benzotriazole. 1. Monocyclic Systems

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1. Introduction

Throughout the years since our first papers in the 1980s on the application of benzotriazole derivatives in organic synthesis,[1,2] tremendous progress has been achieved in the field of benzotriazole chemistry. Benzotriazole intermediates are now commonly used for introduction of a variety of functional groups into molecules. Five major functions of benzotriazole in organic transformations are illustrated in Figure 1. Many aspects of the application of benzotriazole methodology in organic synthesis have been reviewed; however, there is only one outdated review[3d] of a limited scope that is specifically devoted to the synthesis of heterocyclic molecules. With this paper, we fill this existing gap and hope to make the work of chemists who are struggling with the construction and derivatization of heterocyclic systems a bit easier.

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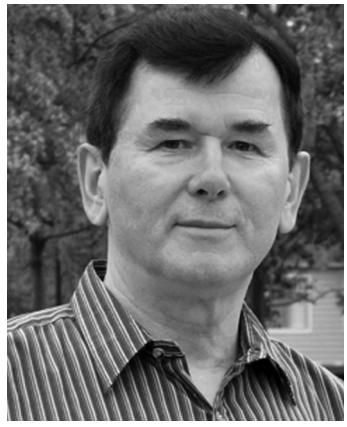
Alan R. Katritzky is Kenan Professor of Chemistry and Director for the Center of Heterocyclic Compounds at the University of Florida. He studied, researched, and taught in the United Kingdom at the Universities of Oxford, Cambridge, and East Anglia before crossing the Atlantic to take up his present post in 1980. He has researched in diverse areas of organic and physical-organic chemistry but none more deeply than in the chemistry of benzotriazole, a topic which blossomed in his group after Stan Rachwal joined him in 1983. Benzotriazole chemistry was first summarized in *Chemical Reviews* in 1998; that manuscript has since received 264 citations. It is a particular pleasure for him to have been asked by Stan to share in the authorship of the present summary, which updates part of the earlier review.



Stanislaw Rachwal was born in Jodlowka and was raised in Krakow, Poland. He received a Ph.D. in organic chemistry from Jagiellonian University in Krakow and was nominated to the position of Adjunct Professor at that university in 1980. His main research at that time was focused on the chemistry of ferrocenophanes. During a sabbatical leave in 1984, he joined Professor Alan R. Katritzky at the University of Florida to lay a foundation for application of benzotriazole in organic synthesis. He returned to the University of Florida in 1988, where as a group leader he effectively contributed to the research on derivatives of benzotriazole. His collaboration with Professor Katritzky resulted in over 40 scientific papers on benzotriazole. Since 1993, he has worked in the pharmaceutical industry specializing in CNS drugs with a primary focus on heterocyclic compounds.

The aim of this review is to provide practical guidance for synthetic chemists. Bearing in mind that the major interest in heterocycles is the synthesis of biologically active compounds, we arranged the material systematically according to the size and shape of the molecules. The nature of the heteroatoms and their number and positions in the molecule are used as secondary discriminators. This way, any chemist searching for bioisosteres of a heterocyclic scaffold or a heterocyclic substituent will find a whole range of useful structures.

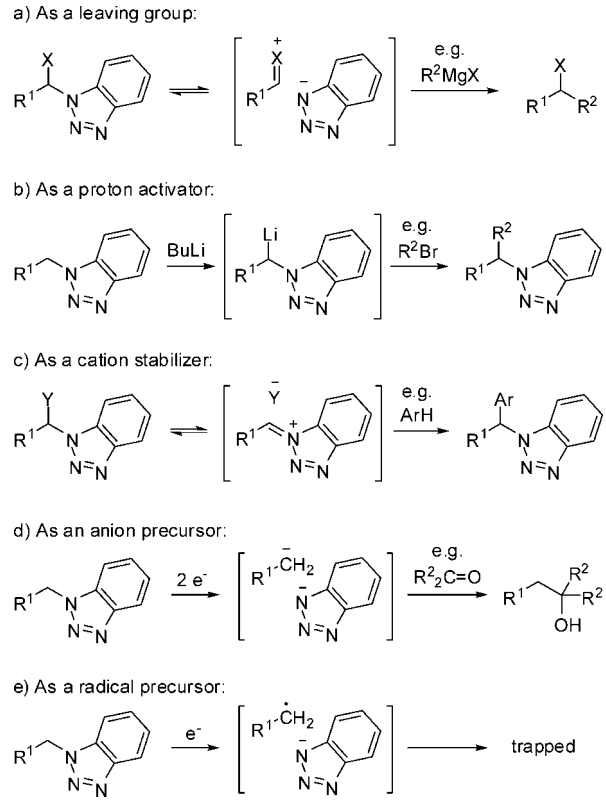
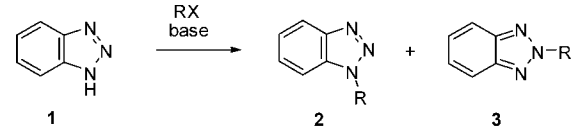


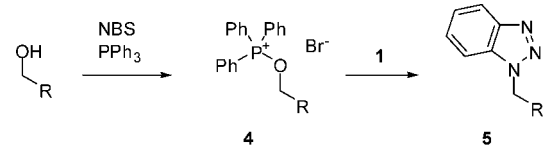
Figure 1. Reactivity profile of benzotriazole.

Scheme 1



R = Me, Et, *n*-Pr, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-$C_{10}H_{21}$ or *c*-$C_6H_{11}CH_2$

Scheme 2



R = H, *n*-C_5H_{11}, Ph, CH_2=CH, MeCH=CH, CH_2=$CHCH_2$, PhCH=CH, HC≡C, MeC≡C or EtC≡C

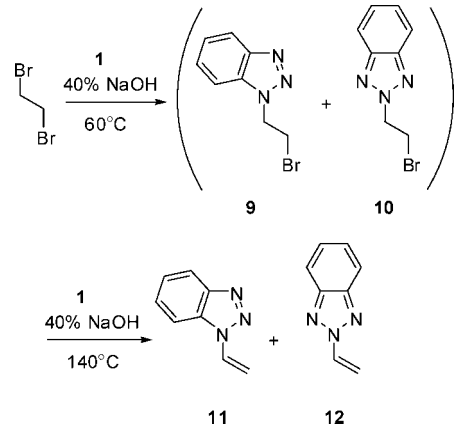
2. Preparation of Simple Derivatives of Benzotriazole Used for Heterocyclic Synthesis

2.1. By Nucleophilic Aliphatic Substitution

Alkylation of benzotriazole (**1**) with alkyl halides or sulfates in the presence of a base leads to mixtures of 1-alkylbenzotriazoles **2** and 2-alkylbenzotriazoles **3**. The ratio of product **2** to product **3** depends on the bulkiness of the alkyl group and varies from 78:22 (R = Et) to 50:50 (R = $C_6H_{11}CH_2$) (Scheme 1).[4,5]

Direct alkylation of benzotriazole with alcohols in the presence of triphenylphosphine and NBS provides some progress (Scheme 2). It is assumed that the first step is the formation of reactive intermediates **4**, which are then attacked by benzotriazole in the S_N2 fashion to give derivatives **5**. The reaction is regioselective and provides exclusively 1-alkyl-, 1-(arylmethyl)-, 1-(2-alken-1-yl)-, and 1-(2-alkyn-

Scheme 3

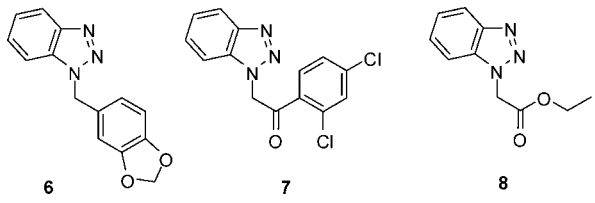


1-yl)benzotriazoles in 60−84% yields. Secondary alcohols give the corresponding alkyl derivatives in low yields, while tertiary alcohols do not alkylate benzotriazole under these conditions.[6]

In an aqueous micellar medium with cetyltrimethylammonium bromide surfactant, benzotriazole is alkylated regioselectively at N-1 with *n*-propyl and *n*-butyl bromides, but activated alkylating agents (benzyl chloride, allyl bromide, phenacyl chloride, etc.) produce mixtures of benzotrizol-1-yl and -2-yl isomers in ratios varying from 55:45 to 80:20.[7] Use of ionic liquids as media generally provides higher regioselectivity; however, the trend is opposite to that found under micellar conditions: phenacyl bromide and similar compounds provide exclusively benzotriazol-1-yl derivatives, and *n*-alkyl halides give mixtures of benzotriazol-1-yl and -2-yl derivatives in a ratio of 15:1.[8]

Microwave irradiation can facilitate the alkylation. Thus, compound **6** is cleanly prepared in 95% yield upon irradiation of benzotriazole and the corresponding benzyl bromide in DMF for 40 s.[9] Very often microwave-assisted alkylation of benzotriazole works best when no solvent is used; for example, derivative **7** is prepared in this way in 94% yield.[10] In another example, benzotriazole with ethyl chloroacetate and K_2CO_3 in ethyl acetate catalyzed by polyethylene glycol (PEG 400) gives a mixture of ethyl benzotriazol-1-ylacetate (**8**; 56%) and its benzotriazol-2-yl isomer (15%).[11]

In the presence of tetrabutylammonium bromide catalyst,

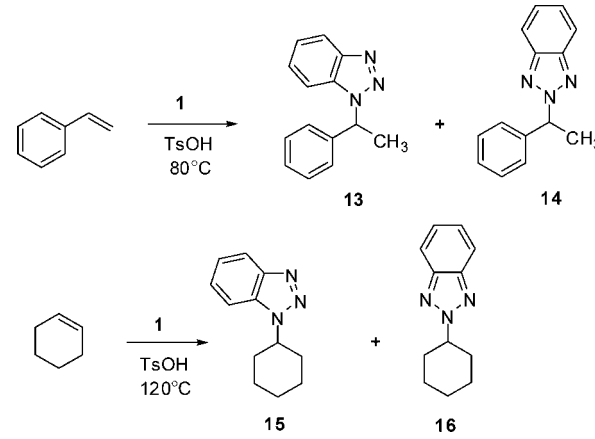


benzotriazole reacts with 1,2-dibromoethane in 40% NaOH at 60 °C to give a mixture of 2-bromoethyl derivatives **9** and **10**. When the reaction mixture is heated at 140 °C, HBr is eliminated to provide a mixture of 1-vinylbenzotriazole (**11**) and 2-vinylbenzotriazole (**12**). Column chromatography of the mixture provides **11** in 34% yield and **12** in 10% yield (Scheme 3).[12]

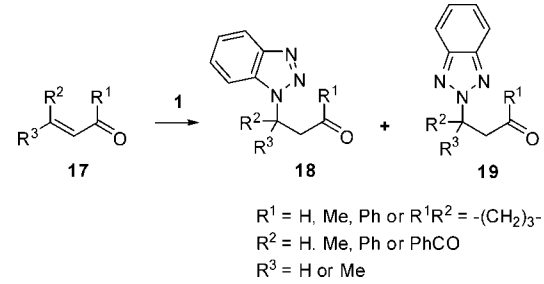
2.2. Addition to Multiple CC Bonds

Under strongly acidic conditions (10 molar equiv of TsOH), benzotriazole adds to unactivated alkenes to afford a mixture of 1-alkyl- and 2-alkylbenzotriazoles. Because

Scheme 4



Scheme 5



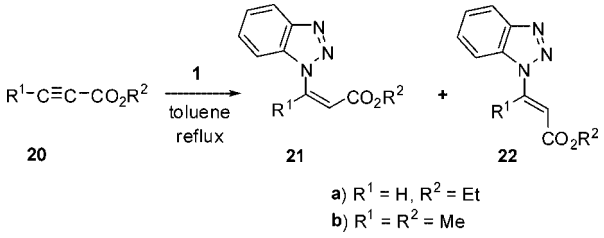
protonation of the double bond with formation of the corresponding carbocation is the first step, Markovnikov's rule is followed, and derivatives with a benzotriazolyl substituent at the terminal carbon atom are not observed. Two examples of such additions are depicted in Scheme 4. Thus, with styrene, benzotriazol-1-yl (**13**) and -2-yl (**14**) isomers are formed in a ratio of 6.5:1 in a total yield of 46%. Cyclohexene does not react with benzotriazole at 80 °C; however, at 120 °C, a mixture of derivatives **15** and **16** is obtained in a ratio of 1.1:1 and a total isolated yield of 56%.[13]

Mixing benzotriazole with acrolein (**17**) in equimolar amounts results in an exothermic reaction leading to adducts **18** and **19** ($R^1 = R^2 = R^3 = H$) in a ratio of 77:23. Addition of benzotriazole to crotonaldehyde ($R^1 = R^2 = H$, $R^3 = Me$) requires initiation by heating the reagents to 60−80 °C. A similar addition to methyl vinyl ketone gives **18** and **19** ($R^1 = Me$, $R^2 = R^3 = H$) in a 95:5 ratio. More sterically hindered mesityl oxide generates equimolar amounts of **18** and **19** ($R^1 = R^2 = R^3 = Me$). In most cases, simple recrystallization of the crude mixtures provides pure benzotriazol-1-yl derivatives **18** (Scheme 5).[14]

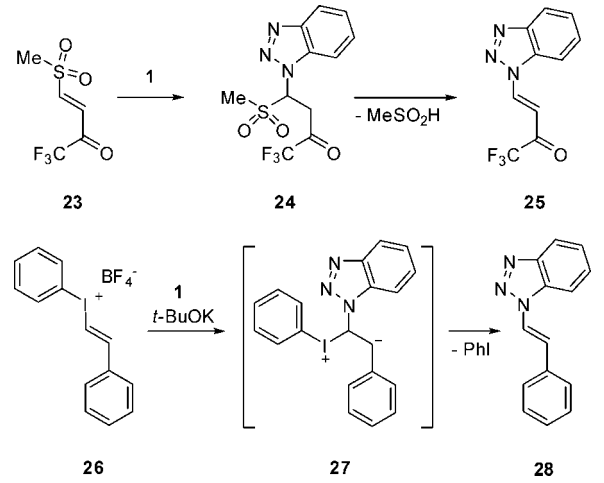
Benzotriazole with ethyl propiolate (**20**, $R^1 = H$, $R^2 = Et$) in refluxing toluene gives a mixture of adducts **21a** and **22a** in a nearly quantitative yield with a *cis*:*trans* (**21a**:**22a**) ratio of 39:61. A similar reaction with methyl 2-butynoate (**20**, $R^1 = R^2 = Me$) requires a CuI catalyst and results in a 1:1 mixture of **21b** and **21b** (Scheme 6).[15]

When the electron-deficient alkene contains a good leaving group X at the double bond, addition of benzotriazole may be followed by elimination of X (or HX) with restoration of the double bond. The total effect is a nucleophilic substitution of group X by a benzotriazolide anion. Two examples of such reactions are shown in Scheme 7. Thus, adduct **24** is obtained from a low-temperature reaction of benzotriazole with methyl 2-(trifluoroacetyl)vinyl sulfone (**23**). At slightly elevated temperature, adduct **24** eliminates spontaneously

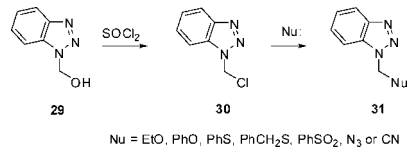
Scheme 6



Scheme 7



Scheme 8



methanesulfinic acid to give alkenone **25** in 88% yield.[16] Addition of benzotriazolide anion to the α-carbon of (*E*)-(2-phenylvinyl)phenyliodonium tetrafluoroborate (**26**) results in unstable benzyl anion **27**, which rapidly eliminates iodobenzene to afford (*E*)-1-(2-phenylvinyl)benzotriazole (**28**) in 64% yield.[17]

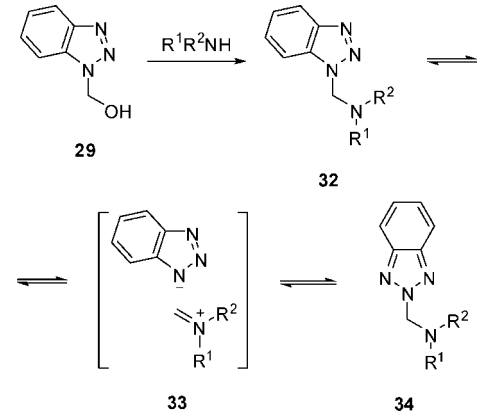
2.3. By Adducts to Carbonyl Groups of Aldehydes and Their Conversions

Benzotriazole reacts eagerly with formaldehyde, even in aqueous solutions, giving well-characterized 1-(hydroxymethyl)benzotriazole (**29**) in practically quantitative yield.[18] Treatment with thionyl chloride converts **29** into 1-(chloromethyl)benzotriazole (**30**).[18] In a more practical one-pot approach, a mixture of benzotriazole, 37% aqueous formaldehyde, and toluene is heated under a Dean−Stark trap to remove water. Thionyl chloride is then added, and the mixture is heated under reflux for 2 h to give a solution of **30** in toluene that can be directly used for further transformations.[19]

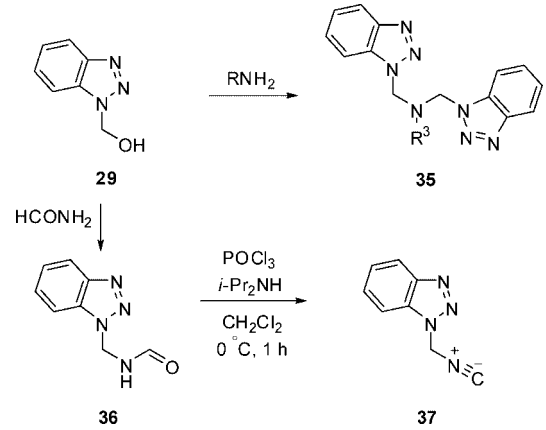
Substitution of the chlorine atom in **30** with nucleophiles is an easy process giving rise to a variety of synthetically valuable products **31**. The yields are generally good; for the examples given in Scheme 8, they vary from 44% (Nu = $PhSO_2$) to 82% (Nu = N_3).[20]

Condensation of **29** with aromatic amines proceeds rapidly in refluxing ethanol and provides crystalline 1-(aminomethyl)benzotriazoles **32** (R^1 = aryl, R^2 = H) in practically

Scheme 9



Scheme 10

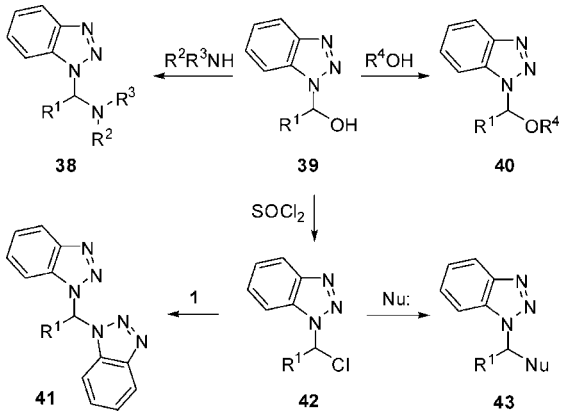


quantitative yields (Scheme 9).[21] Dialkylamines and *N*-alkylarylamines also react with **29** to give **32** (R^1 = alkyl, R^2 = alkyl or aryl).[22] In solutions, benzotriazol-1-yl derivatives **32** obtained from secondary amines are in equilibria with their benzotriazol-2-yl isomers **34**.[23−26] The intermediate iminium cations **33** can be easily trapped in reactions with nucleophiles.[1,22,27−30]

Reactions of primary aliphatic amines with 2 molar equiv of **29** provide *N*,*N*-bis(benzotriazol-1-ylmethyl)amines **35** (R^3 = alkyl), in mixtures with their benzotriazol-2-yl isomers.[21,22] Heating at reflux a toluene solution of **29** (2 molar equiv) and an aromatic amine with azeotropic removal of water allows the preparation of **35** (R^3 = aryl) as a mixture of three isomers: Bt-1/Bt-1, Bt-1/Bt-2, and Bt-2/Bt-2.[31] **29** reacts also with amides to give the corresponding *N*-benzotriazol-1-ylmethyl derivatives.[28,32] In an example in Scheme 10, reaction of **29** with formamide gives product **36** in 63% yield. It is subsequently converted into isocyanide **37** in 66% yield with phosphorus oxychloride and diisopropylamine.[32]

The reactions described in Schemes 8−10 are not limited to 1-(hydroxymethyl)benzotriazole. Higher aliphatic aldehydes and aromatic aldehydes with electron-deficient rings also give solid adducts with benzotriazole, **39**, that are stable enough to be recrystallized and their purity confirmed by CHN analysis. Condensation with alcohols further stabilizes the molecule, allowing the preparation of alkoxy compounds **40** derived from a variety of aldehydes in pure form.[33] Condensation with primary aromatic amines converts **39** into stable crystalline aminals **38** (R^2 = aryl, R^3 = H) that are isolated in 76−98% yields.[21,34] Dibenzylamine, pyrrolidine,

Scheme 11



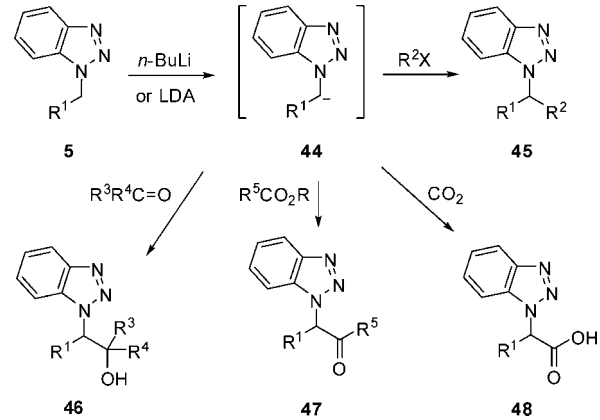
piperidine, morpholine, and thiomorpholine also give products **38** stable enough to be characterized.[22,35] Thionyl chloride converts 1-(1-hydroxyalkyl)benzotriazoles **39** into 1-chloroalkyl derivatives **42**; in the presence of excess benzotriazole, 1,1-bisbenzotriazol-1-ylalkanes **41** and their benzotriazol-2-yl isomers are formed.[36] Chlorides **42** react readily with nucleophiles to give derivatives **43** in high yields: 74% for $R^1 = t$-Bu, Nu = CN; 91% for $R^1 = n$-Pr, Nu = $PhCO_2$; 88% for $R^1 = n$-Pr, Nu = PhS; 97% for $R^1 = i$-Pr, Nu = *i*-PrO (Scheme 11).[19,36]

2.4. By Carbanions Stabilized by a Benzotriazolyl Substituent

Many synthetic applications of benzotriazole derivatives are based on the ability of the benzotriazolyl substituent to stabilize an adjacent carbanion. Even simple 1-(*n*-alkyl)benzotriazoles **5** can be converted to anions **44** (R^1 = H or alkyl) by treatment with *n*-BuLi. The consecutive treatment with alkyl halides converts **44** into 1-alkylbenzotriazoles **45** bearing secondary alkyl groups, e.g., R^1 = Me, R^2 = Et (72% yield), and R^1 = Et, $R^2 = n$-$C_{10}H_{21}$ (65% yield). Carbonyl electrophiles can be used as well to trap **44**. Thus, the anion derived from 1-methylbenzotriazole (R^1 = H) adds readily to the carbonyl groups of benzaldehyde to give alcohol **46** ($R^1 = R^4$ = H, R^3 = Ph) in 95% yield, acrylaldehyde to give **46** ($R^1 = R^4$ = H, $R^3 = CH_2$=CH) in 57% yield, or benzophenone to give product **46** (R^1 = H, $R^3 = R^4$ = Ph) in 70% yield. In a reaction of **44** with ethyl benzoate, ketone **47** (R^1 = H, R^5 = Ph) is obtained in 54% yield, whereas a reaction of **44** with CO_2 gives carboxylic acid **48** (R^1 = H) in 54% yield.[4] Reactions of lithiated 1-(arylmethyl)benzotriazoles **5** with electrophiles are even more effective; e.g., 1-benzylbenzotriazole treated with *n*-BuLi and then *n*-BuI gives **45** (R^1 = Ph, $R^2 = n$-Bu) in 82% yield,[37] 1-(2-methoxy-3-methylbenzyl)benzotriazole treated with *n*-BuLi followed by *p*-tolualdehyde gives alcohol **46** (R^1 = 2-methoxy-3-methylphenyl, $R^3 = p$-tolyl, R^4 = H) in 87% yield, and when the same **5** is lithiated and treated with ethyl benzoate, ketone **47** (R^1 = 2-methoxy-3-methylphenyl, R^5 = Ph) is obtained in 76% yield (Scheme 12).[38]

Anions **50** derived from compounds of the type $BtCH_2X$ (**49**), where X = a heteroatom or a group attached by a heteroatom, allow the generation of a variety of chemical structures. Thus, compound **49** with X = Me_3Si treated with *n*-BuLi followed by electrophiles $E(1)^+$ gives molecules **51**, in which the trimethylsilyl group also can be substituted by other electrophiles. Repeated lithiation of **51** followed by treatment with another electrophile, $E(2)^+$, generates even more complex molecules **52**.[39] Derivatives **49** with X = carbazol-9-yl readily form anions **50**, which react with electrophiles to generate derivatives **51**, in which the substituent BtCHX can be considered as a protected carbonyl group of aldehydes.[40] Their further lithiation and treatment with other electrophiles generates **52** as protected forms of complex ketones.[41] Other heterocycles, such as pyrrole, indole, benzimidazole, imidazole, and 1,2,4-triazole, can also be effective as substituents X in preparation of **51** and **52**.[42] Aryl sulfides **49** (X = ArS) are also suitable for the chemistry outlined in Scheme 13, providing interesting intermediates for further transformations.[43−45] Even alkoxy derivatives **51** (X = RO) are acidic enough to be lithiated and converted with electrophiles into **52**.[46−50] Examples of products synthesized according to Scheme 13 are given in Table 1.

Scheme 12



Scheme 13

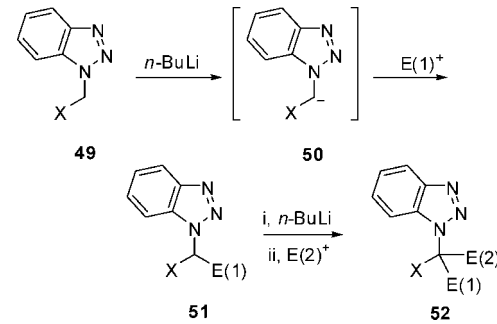


Table 1. Examples of Compounds 51 [E(2) = H] and 52 [E(2) ≠ H]

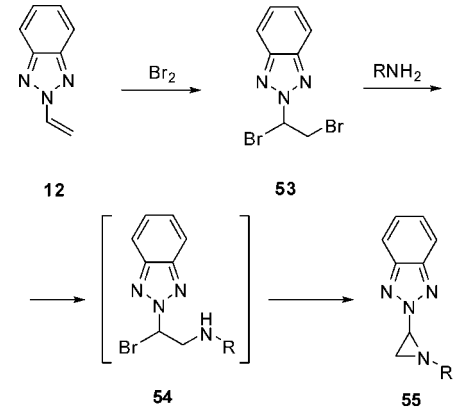
X	E(1)	E(2)	yield (%)	ref
Me_3Si	n-C_6H_{13}	H	80	39
Me_3Si	3-oxocyclohexyl	H	70	39
Me_3Si	n-C_6H_{13}	Me	80	39
carbazol-9-yl	1-hydroxycyclohexyl	H	91	40
carbazol-9-yl	$PhCH_2$	PhS	95	41
carbazol-9-yl	$PhCH_2$	CO_2Et	87	41
indol-1-yl	n-PrCO	H	95	42
PhS	$PhCH_2$	n-Bu	86	43
MeS	n-Bu	allyl	89	45
EtO	PhC≡C	PhCHOH	73	47

3. Three-Membered Rings

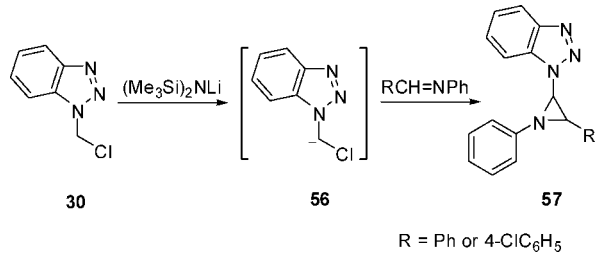
3.1. Aziridine and Azirene

Bromination of **12** provides 2-(1,2-dibromoethyl)benzotriazole (**53**) in 93% yield. Reactions with amines convert **53** into 1-alkyl-2-benzotriazol-2-ylaziridines **55**. Intermedi-

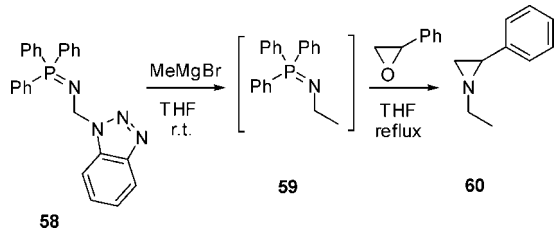
Scheme 14



Scheme 15



Scheme 16



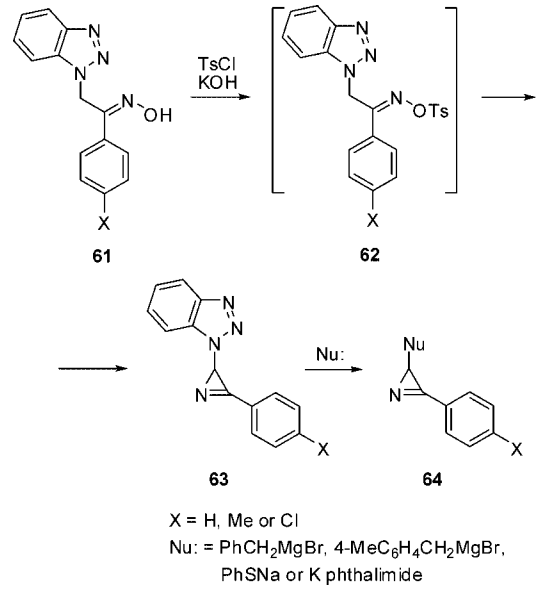
ates **54** can be observed in the reaction mixtures monitored by NMR. The yields of aziridines **55** are high (80−96%) except of that derived from benzylamine (30%) (Scheme 14).[51] The analogous reaction sequence of **11** does not give aziridines but only 1-(1-bromovinyl)benzotriazole.[51]

Treatment of **30** with lithium bis(trimethylsilyl)amide results in very unstable anion **56**, but when the reaction is carried out in the presence of Schiff bases, anion **56** can be effectively trapped, leading to aziridines **57** in high yields (85−90%) (Scheme 15).[51] Due to their reactivity, aziridines **55** and **57** are convenient starting materials for the synthesis of other heterocycles (see section 5 on pyrrole).

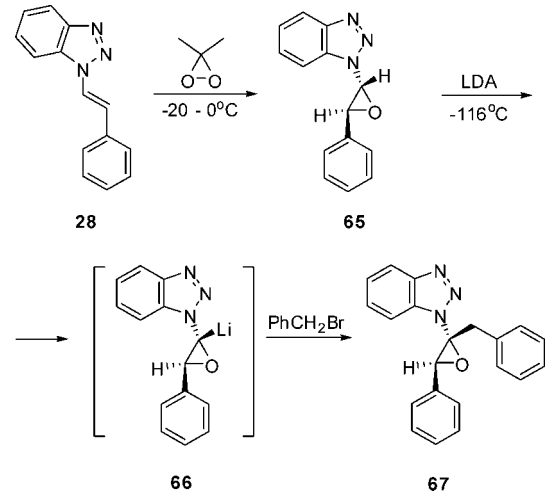
Condensation of 1-(azidomethyl)benzotriazole (**31**, Nu = N_3) with triphenylphosphine provides [*N*-(benzotriazol-1-ylmethyl)imino]triphenylphosphorane (betmip, **58**) in a practically quantitative yield. In a reaction of **58** with methylmagnesium bromide, the benzotriazolyl moiety is substituted by a methyl group to give phosphazene intermediate **59**. Using a one-pot procedure, **59** is treated with styrene oxide and heated at reflux in THF for 48 h to give aziridine **60** in 55% yield (Scheme 16).[52]

Oximes **61** are prepared in 91−93% yields from the corresponding aryl benzotriazol-1-ylmethyl ketones, hydroxylamine hydrochloride, and NaOH in refluxing ethanol/

Scheme 17



Scheme 18

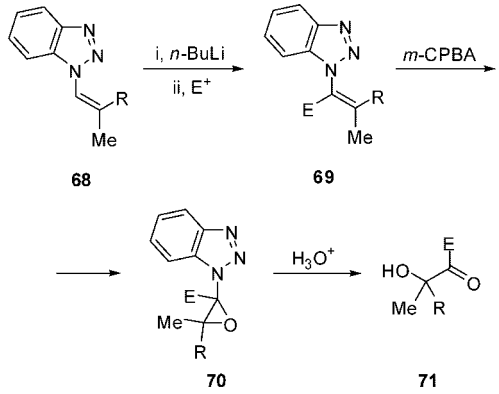


water. They can be converted into their tosylates **62**, but a large excess ofKOH converts them directly into 2*H*-azirines **63** (58−66% yields). The benzotriazolyl moiety in azirines **63** is readily substituted by nucleophiles (organomagnesium reagents, potassium phthalimide, or sodium thiophenoxide) to give disubstituted azirines **64** in 50−79% yields (Scheme 17).[53]

3.2. Oxirane

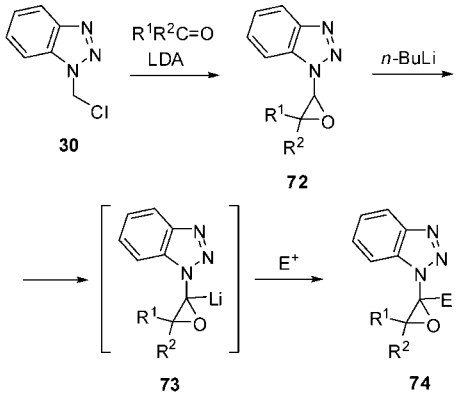
Oxiranes bearing a benzotriazol-1-yl substituent on the ring can be prepared in practically quantitative yields by epoxidation of benzotriazol-1-ylalkenes with dimethyldioxirane, e.g., conversion of alkene **28** to oxirane **65** (Scheme 18). At very low temperatures, substitution of the α-proton in oxirane **65** is possible; just its treatment with LDA at −116 °C followed by benzyl bromide leads to α-benzyloxirane **67** in 51% yield, via lithiated intermediate **66**. Using acyl chlorides or benzophenone as an electrophile in this reaction provides the corresponding oxiranes with acyl or diphenylhydroxymethyl substituents, respectively. At higher temperatures, rearrangement of lithiated oxirane **66** to the appropriate ketone is observed. The stereochemistry is preserved.[54]

Scheme 19



R = H or Me
E = octyl, 4-BrC$_6$H$_4$CH$_2$, PhCHOH, Ph$_2$COH or 1-hydroxycyclohexyl

Scheme 20



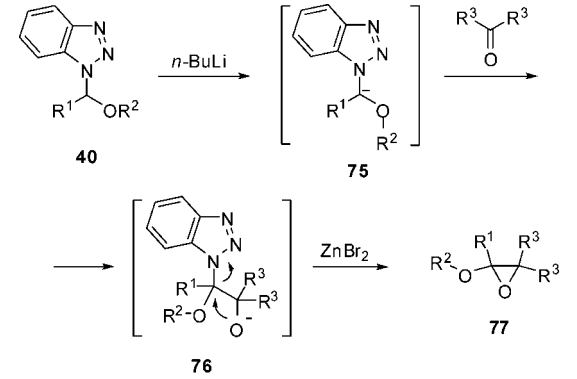
R^1 = Me, Et, Ph, 4-MeC$_6$H$_4$ or 4-ClC$_6$H$_4$
R^2 = Et or Ph or R^{1}R^2 = (CH$_2$)$_5$
E$^+$ = MeI, *n*-BuBr, Me$_3$SiCl, PhCH=NPh, PhCHO, Et$_2$CO or PhCO$_2$Et,

1-Alkenylbenzotriazoles **68** are readily prepared by isomerization of the corresponding allyl derivatives catalyzed by *t*-BuOK. Reaction of lithiated **68** with electrophiles provides α-substituted derivatives **69** in 41−80% yields. Epoxidation of the double bond with *m*-chloroperbenzoic acid converts **69** into oxiranes **70** in 43% (R = Me, E = Ph$_2$COH) to 80% (R = H, E = 1-hydroxycyclohexyl) yields. Oxiranes **70** can be hydrolyzed to α-hydroxy ketones **71** in good yields (Scheme 19).[55]

30 can be converted into its anion by treatment with LDA at −40 °C. The anion is trapped by ketones to provide a convenient synthesis of benzotriazol-1-yloxiranes **72** (68−75% yields). Treated with *n*-BuLi, oxiranes **72** give lithiated intermediates **73** that react with various electrophiles to provide tetrasubstituted oxiranes **74** in 68% (R^1 = Ph, R^2 = Et, E = PhCO) to 92% (R^1 = R^2 = Ph, E = PhCHOH) yields. Upon treatment with perchloric acid, benzoyl derivatives **74** (E = PhCO) undergo ring-opening with elimination of benzotriazole to provide 3-hydroxy 1,2-diones, which themselves are interesting starting materials for other heterocycles (Scheme 20).[56]

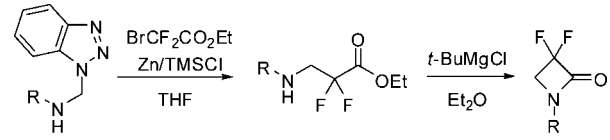
α-Benzotriazol-1-ylalkyl ethers **40** with *n*-BuLi generate anions **75** that add readily to the carbonyl group of ketones to give alkoxy anions **76**. The presence of zinc bromide promotes elimination of the benzotriazolide anion (as a zinc complex) with the formation of phenoxy- or methoxyoxiranes **77** that are isolated in 56% (**77a**), 49% (**77b**), and 71% (**77c**) yields. Several other ketones and aldehydes provided oxiranes

Scheme 21



a, R^1 = *n*-C$_5$H$_{11}$, R^2 = Ph, 2 R^3 = -(CH$_2$)$_5$-
b, R^1 = *n*-C$_5$H$_{11}$, R^2 = Ph, R^3 = Ph
c, R^1 = 4-ClC$_6$H$_4$, R^2 = Me, 2 R^3 = -(CH$_2$)$_5$-

Scheme 22



a, R = 4-MeOC$_6$H$_4$
b, R = Ph$_2$CH

77 that were unstable under the reaction conditions undergoing ring-opening and rearrangement to the corresponding α-phenoxy or α-alkoxy ketones (Scheme 21).[57]

4. Four-Membered Rings

N-Substituted 1-(aminomethyl)benzotriazoles **78** treated with ethyl bromodifluoroacetate, zinc powder, and trimethylsilyl chloride (Reformatsky-type conditions) give *N*-substituted ethyl 3-amino-2,2-difluoropropionates **79a** (89% yield) and **79b** (86% yield). Cyclization of **79** promoted by *tert*-butylmagnesium chloride furnishes *N*-protected 3,3-difluoroazetidin-2-ones **80a** (45% yield) and **80b** (65% yield) (Scheme 22). Several other attempts at the synthesis of such compounds failed.[58]

Anions generated from 1-acylbenzotriazoles **81** upon their treatment with LDA add readily to the carbonyl groups of aldehydes and ketones. Nucleophilic attack of the resultant alkoxy anion **82** on the acyl carbonyl group followed by elimination of a benzotriazolide anion results in formation of oxet-2-one **83**. This simple method allows the synthesis of oxetane derivatives **83** in 42% (R^1 = Et, R^2 = PhCH$_2$CH$_2$, R^3 = H) to 90% (R^1 = *n*-C$_6$H$_{13}$, R^2 = *t*-Bu, R^3 = H) yields (Scheme 23).[59]

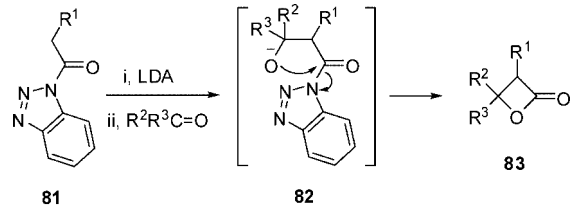
5. Pyrrole

5.1. Nonaromatic Rings

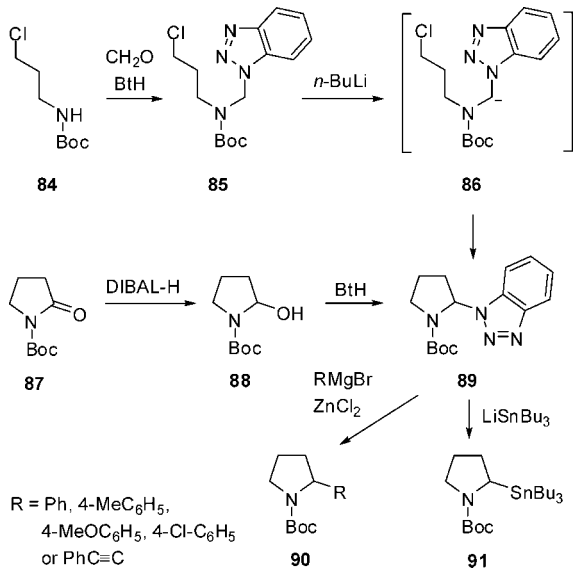
5.1.1. Pyrrolidines

Pyrrolidines monosubstituted at C-2 are easily generated from *N*-Boc-protected 3-chloropropanamine **84**. In the first step, condensation with formaldehyde and benzotriazole converts **84** into its *N*-benzotriazol-1-ylmethyl derivative **85**. In the second step, anion **86** generated from **85** and *n*-BuLi undergoes cyclocondensation to pyrrolidine **89**.[60] In another

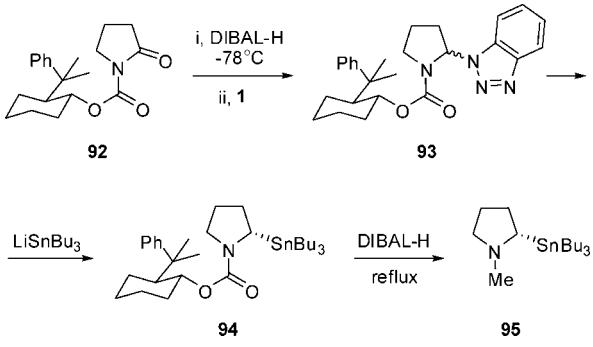
Scheme 23



Scheme 24



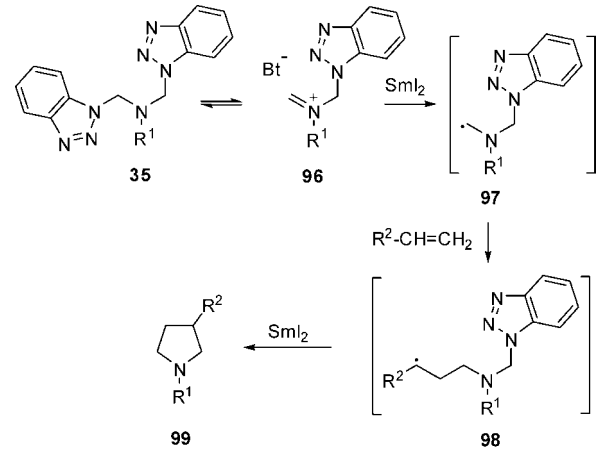
Scheme 25



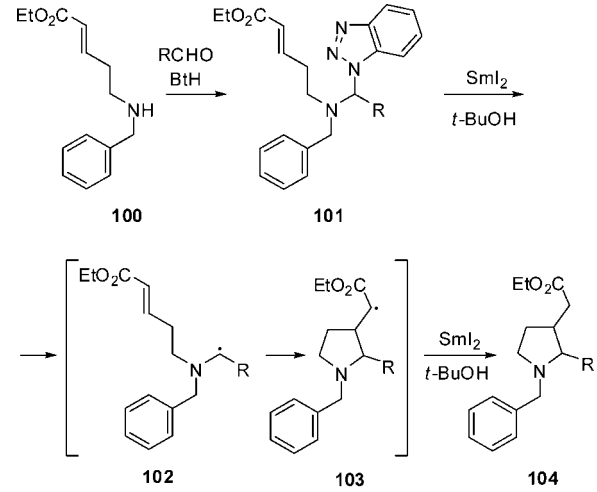
approach, pyrrolidinone **87** is reduced by DIBAL-H to 2-hydroxypyrrolidine **88**, which upon condensation with benzotriazole is converted to **89**.[61] With organomagnesium reagents catalyzed by zinc chloride, the benzotriazolyl moiety in **89** is readily substituted by an aryl or a phenylethynyl group to furnish 2-substituted pyrrolidines **90** in 62−86% yields.[60] Treatment of **89** with (tributylstannyl)lithium affords 2-stannylpyrrolidine **91** in 78% yield (Scheme 24).[61]

The reaction can be carried out enantioselectively using a chiral auxiliary instead of Boc. One such possibility is depicted in Scheme 25. Derivative **92**, obtained from 2-pyrrolidinone and 1*S*,2*R*-*trans*-2-cumylcyclohexyl chloroformate, is reduced with DIBAL-H at low temperature and then treated with benzotriazole to give compound **93**. In a reaction with (tributylstannyl)lithium, the benzotriazolyl moiety is replaced by a tributylstannyl group to give predominantly 2-(tributylstannyl)pyrrolidine **94** with the

Scheme 26



Scheme 27

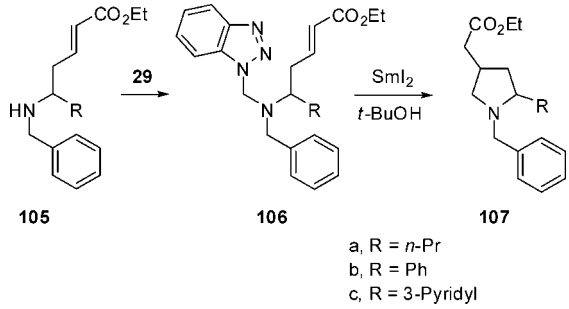


predominant *S* configuration (80:20). The diastereomers can be readily separated by chromatography. With DIBAL-H at elevated temperature, derivative **94** is converted into (*S*)-1-methyl-2-(tributylstannyl)pyrrolidine (**95**).[61]

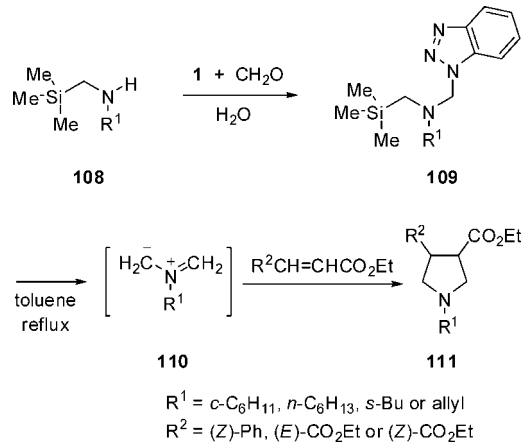
N,*N*-Bis(benzotriazol-1-ylmethyl)amines **35**, with their benzotriazol-2-yl isomers, are readily prepared by condensation of **29** with primary amines.[21,62,63] In solutions, they exist in equilibria with ionic forms **96**. Such mixtures treated with samarium diiodide generate radicals **97** that are rapidly trapped by vinyl groups of styrenes or vinyltrimethylsilane to provide more stable radicals **98**. Consecutive ionization and reduction with samarium diiodide of the second benzotriazolylmethyl substituent provides a diradical that couples intramolecularly to pyrrolidine **99**. This simple process allows preparation of 1,3-disubstituted pyrrolidines **99** in 49−85% yields (Scheme 26).[64]

When one of the substituents on the amine nitrogen atom is able to trap a radical formed by treatment of *N*-(α-aminoalkyl)benzotriazole with SmI_2, the intramolecular cyclization may occur (Scheme 27). Thus, condensation of the 5-(benzylamino) derivative of *trans*-2-pentenoic ester (**100**)

Scheme 28



Scheme 29



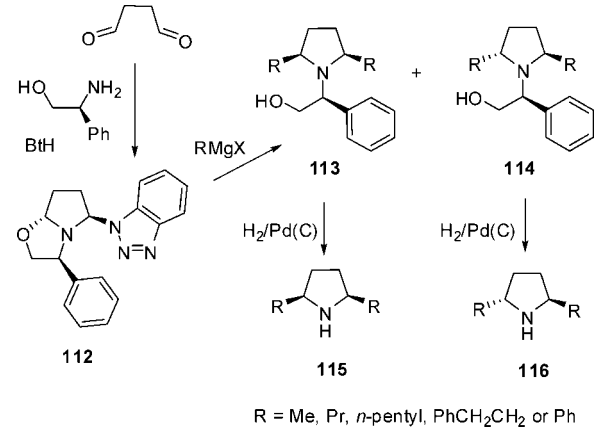
with an aldehyde and benzotriazole gives tertiary amine **101**. The α-aminoalkyl radical **102** generated by treatment of **101** with SmI_2 is intramolecularly trapped by the double bond, leading to the more stable radical **103**. Final reduction by a second molecule of SmI_2 provides 1,2,3-trisubstituted pyrrolidine **104**. Among the wide range of starting aldehydes, the yields of products **104** vary from 29% (R = $PhCH_2OCH_2$) to 74% (R = *i*-Pr). For pyridyl and aliphatic substituents, *cis* stereoisomers strongly predominate (e.g., the *cis*:*trans* ratio is 86:14 for R = *n*-$C_{10}H_{21}$), but for most aromatic substituents, the ratio is reversed (e.g., *cis*:*trans* = 1:9 for R = Ph).[65,66]

The same method is effectively used to introduce three substituents into positions 1, 2, and 4 of pyrrolidines. Thus, condensation of the 5-(benzylamino) derivative of *trans*-2-alkenoic ester **105** with **29** gives tertiary amine **106**. The aminomethyl radical generated from **106** by SmI_2 is trapped by the double bond, leading to pyrrolidine **107**. Mixtures of two stereoisomers in ratios 55:45 (**107a**), 64:36 (**107b**), and 65:35 (**107c**) are produced; however, their identities have not been established (Scheme 28).[67]

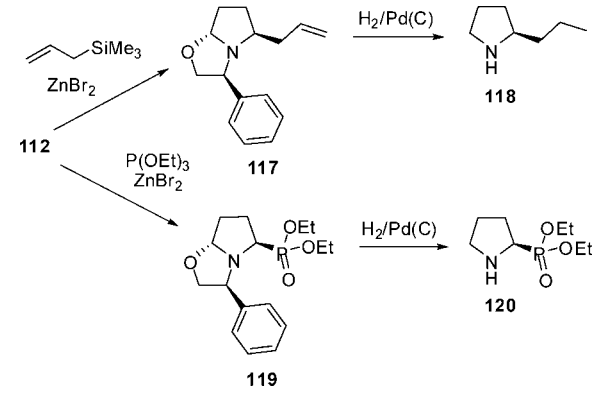
N-(Benzotriazolylmethyl)-*N*-[(trimethylsilyl)methyl]amines **109** are readily prepared by condensation of *N*-[(trimethylsilyl)methyl]amines **108** with formaldehyde and benzotriazole. Thermally induced desilylation of **109** generates azomethine ylides **110**. Electron-deficient alkenes added to the reaction mixture trap efficiently **110** to produce pyrrolidines **111** in 71−90% yields. The cycloaddition reaction proceeds stereospecifically with retention of the olefinic dipolarophile configuration (Scheme 29).[68]

Condensation of succinaldehyde (obtained by hydrolysis of 2,5-dimethoxytetrahydrofuran) with benzotriazole and (*S*)-2-phenylglycinol provides (3*S*,5*R*,7a*R*)-5-benzotriazol-1-yl-3-phenyloxazolo[2,1-*b*]pyrrolidine (**112**). Oxazolopyrrolidine **112** is a convenient synthon for asymmetric syntheses of

Scheme 30



Scheme 31



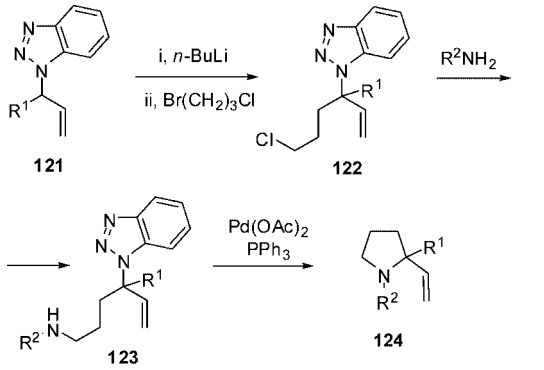
2-substituted and 2,5-disubstituted pyrrolidines. Thus, treatment with organomagnesium reagents converts **112** into mixtures of *cis* (**113**) and *trans* (**114**) pyrrolidines that can be easily separated by chromatography. For aliphatic groups R, the yields of *cis* isomers **113** vary from 53% to 60%, whereas minor *trans* isomers **114** are obtained in 17−30% yields. For R = Ph, both isomers are equally abundant. Hydrogenation of the intermediates readily removes the chiral auxiliary to provide 2,5-disubstituted pyrrolidines **115** and **116**; however, with R = Ph, such a procedure causes opening of the pyrrolidine ring (Scheme 30).[69]

In a reaction with allyltrimethylsilane, the benzotriazolyl moiety in **112** is substituted with an allyl group to provide derivative **117** in 45% yield. Hydrogenation of **117** cleaves the chiral auxiliary to give (2*R*)-2-propylpyrrolidine (**118**). Alternatively, a reaction of **112** with triethyl phosphite leads to chiral phosphonate **120**, via intermediate **119**, with 68% overall yield (Scheme 31).[69]

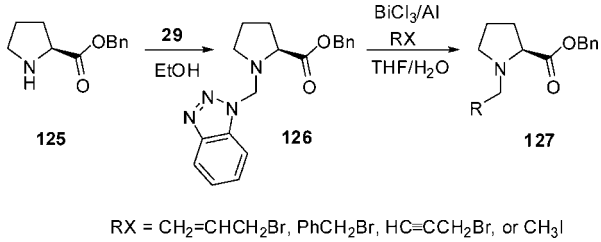
Alkylation of lithiated compounds **121** with 1-bromo-3-chloropropane gives chloropropyl derivatives **122** in good yields (80−89%). Subsequent substitution of the chlorine atom by an alkylamino group is easily accomplished by heating **122** and amine R^2NH_2 in DMF. Intramolecular substitution of the benzotriazole moiety by the amino group in amines **123** occurs at room temperature in the presence of a palladium catalyst to furnish 2-vinylpyrrolidines **124** in overall 65−85% yields for the last two steps (Scheme 32).[70]

N-Derivatization of L-proline benzyl ester (**125**) provides an example of application of benzotriazole methodology to the synthesis of biologically important structures. Thus, condensation of **125** with **29** provides intermediate **126**, which is subsequently subjected to reactions with organo-

Scheme 32



Scheme 33



bismuth reagents generated from RX and $BiCl_3$/Al. Interestingly, the reaction is carried out in aqueous solution to provide *N*-substituted proline esters **127** in 18% (R = Me) to 70% (R = allyl) yields (Scheme 33).[71]

5.1.2. Pyrrolidinones

Condensation of 2,5-dimethoxy-2,5-dihydrofuran (**128**) with benzotriazole and an amine carried out in refluxing acetic acid produces 5-benzotriazolylpyrrolidin-2-one in good yield and with strong preference for the benzotriazol-1-yl isomer **129**. Substitution of the benzotriazole moiety in **129** with nucleophiles gives 5-substituted 2-pyrrolidinones **130**−**132**. Since both benzotriazolyl isomers of **129** have similar reactivity, the isomeric mixtures can be used directly in this step. Thus, with organozinc reagents, pyrrolidinones **130** are obtained in 49−87% yields. The yields of pyrrolidinones **131** are 49−90% and those of 5-oxo-2-pyrrolidinylphosphonates **132** 49−85% (Scheme 34).[72]

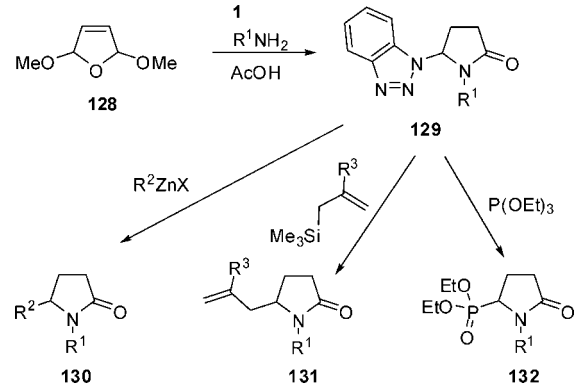
Michael addition of benzotriazole to *N*-methylmethacrylamide carried out at 150 °C provides β-benzotriazol-1-ylpropionamide **133** in 45% yield. The dianion generated from **133** by treatment with 2 molar equiv of *n*-BuLi is trapped by methyl 4-methylbenzoate to give 2-pyrrolidinone **134** in 63% yield. The stereochemistry is not determined (Scheme 35).[73]

Acylation of **1** with *N*-protected L-glutamic acid **135** in the presence of thionyl chloride readily provides derivative **136**. Condensation with L-amino acids in aqueous acetonitrile in the presence of triethylamine converts **136** into 2-pyrrolidinones **137**. Washing the crude products with 4 N HCl gives pure **137** in 58% (**a**), 88% (**b**), and 70% (**c**) yields (Scheme 36).[74]

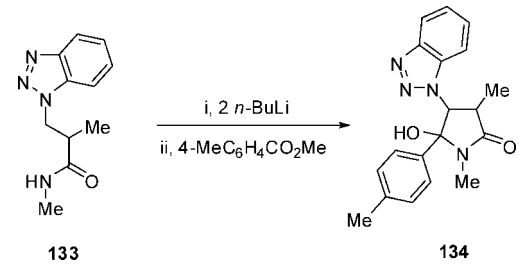
5.1.3. Pyrrolines

Condensation of benzotriazole with benzaldehyde and ammonia in ethanol provides imine **138** in 92% yield as a

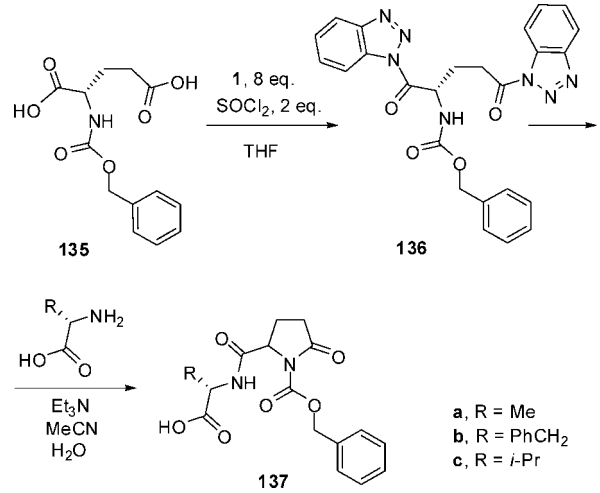
Scheme 34



Scheme 35



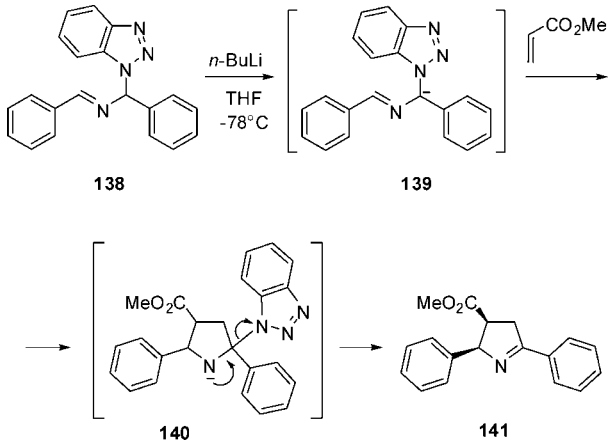
Scheme 36



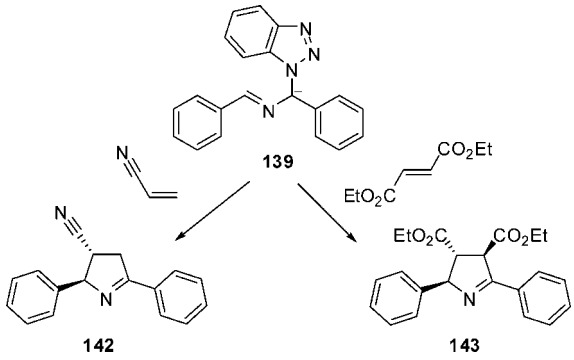
white precipitate. Anion **139** derived from imine **138** upon its treatment with *n*-BuLi adds readily to electron-deficient double bonds. In the case of methyl acrylate, pyrrolidine anion **140** resulting from such an addition eliminates spontaneously a benzotriazolide anion to give 1,2-pyrroline **141** in 96% yield (Scheme 37).[75] According to NMR data, the molecule of **141** has *cis* geometry. However, *trans* substitution is found in pyrroline **142** (63% yield) derived from a reaction of **139** with acrylonitrile. Reaction of **139** with dimethyl fumarate leads to pyrroline **143** (95% yield) with *trans*,*trans* orientation of its substituents at C-3, C-4, and C-5. A similar reaction with diethyl maleate gives a mixture of stereoisomers (Scheme 38).[75]

Alkylation of benzotriazole with 2,3-dichloro-1-propene and Na_2CO_3 in DMSO/H_2O provides 1-(2-chloropropen-3-

Scheme 37



Scheme 38



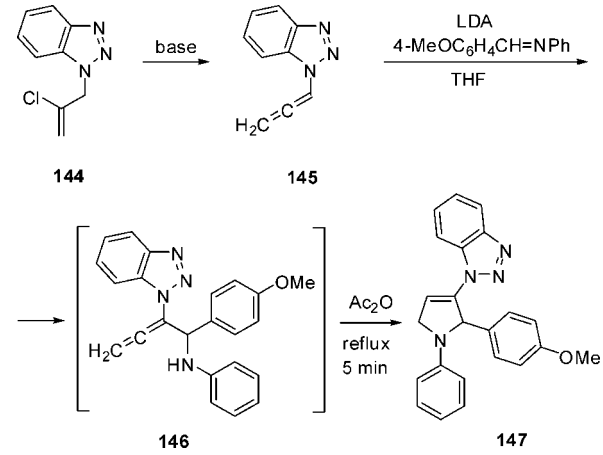
yl)benzotriazole (**144**) in 56% yield and its isomer 2-(2-chloropropen-3-yl)benzotriazole in 30% yield. Stronger bases smoothly convert **144** into 1-allenylbenzotriazole (**145**), isolated in 90% yield when 20% NaOH is used. LDA is able to remove an allenyl proton from **145**, and the resultant anion can be trapped by various electrophiles. In a useful approach, **144** is treated with 2 equiv of LDA followed by an electrophile. Several α-substituted 1-allenylbenzotriazoles are thus obtained. When *N*-(4-methoxybenzylidene)aniline is used as an electrophile, allenyl product **146** rearranges partially to its propargyl isomer, and both components can be separated by column chromatography. Heating the allenyl product in acetic anhydride results in its conversion to 3,4-pyrroline **147**, which is isolated in 30% overall yield (Scheme 39).[76]

5.2. Aromatic Ring Substituents

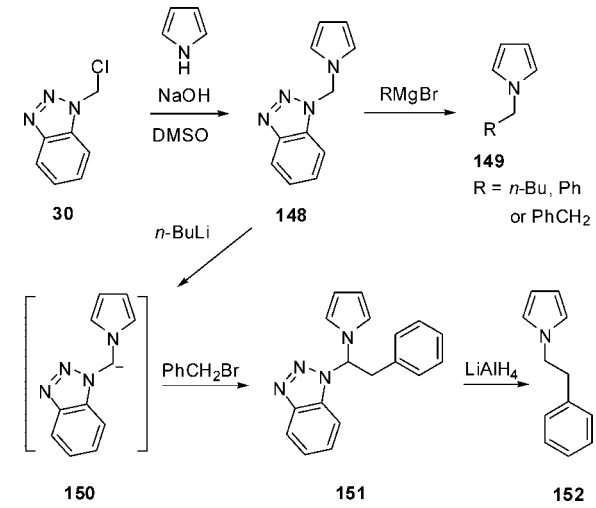
5.2.1. Substituents at the Nitrogen Atom

Introduction of a benzotriazol-1-ylmethyl substituent onto the pyrrole nitrogen atom can be easily achieved on heating a mixture of pyrrole, **30**, and powdered NaOH in DMSO. Product **148** treated with *n*-BuLi generates anion **150**, which is subsequently subjected to reactions with electrophiles. In an example of such reactions, a solution of **148** in THF is treated with *n*-BuLi at −78 °C followed by benzyl bromide and is allowed to warm slowly to room temperature. Chromatographic purification provides derivative **151** in 47% yield. The benzotriazolyl moiety can be easily removed from **151** by treatment with $LiAlH_4$ to give 1-phenethylpyrrole (**152**) in 96% yield. Reactions of **148** with RMgBr produce *N*-substituted pyrroles **149** (42−73% yields) with the groups

Scheme 39



Scheme 40



containing one carbon atom more than in the Grignard reagent (Scheme 40).[42,77]

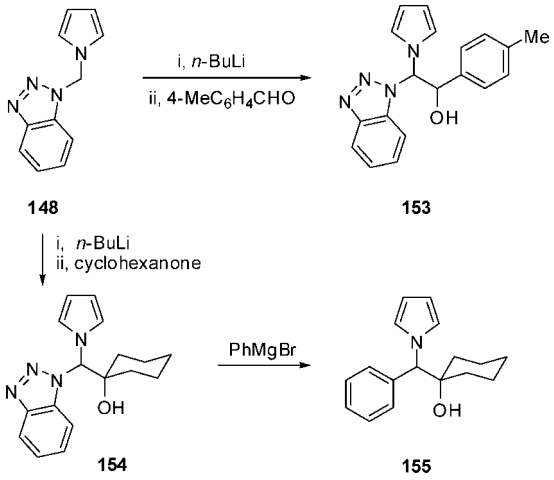
Addition of an anion generated from **148** to the carbonyl group of *p*-tolualdehyde results in alcohol **153**, which is separated in 35% yield. An analogous reaction with cyclohexanone provides alcohol **154** in 76% yield. Treatment of **154** with phenylmagnesium bromide allows a convenient removal of the benzotriazolyl auxiliary, providing alcohol **155** in 50% yield. A similar substitution of the benzotriazolyl moiety with a phenyl ring in compound **153** gives the corresponding alcohol in 60% yield (Scheme 41).[42,77]

In a reaction of lithiated benzotriazolyl derivative **148** with benzophenone, alcohol **156** is obtained in 72% yield. The use of carboxylic esters as electrophiles is exemplified by synthesis of ketone **157** (R = 4-MeC_6H_4, 53% yield). To demonstrate the removal of the benzotriazolyl auxiliary from such compounds, **157** is treated with activated zinc in acetic acid to give ketone **160** in 50% yield. In a reaction of lithiated **148** with diphenyl disulfide, disubstituted product **158** is obtained in 67% yield, whereas a reaction with trimethylsilyl chloride leads to a mixture of monosubstituted (**159**) and disubstituted products in an approximate ratio of 1:3 (Scheme 42).[42]

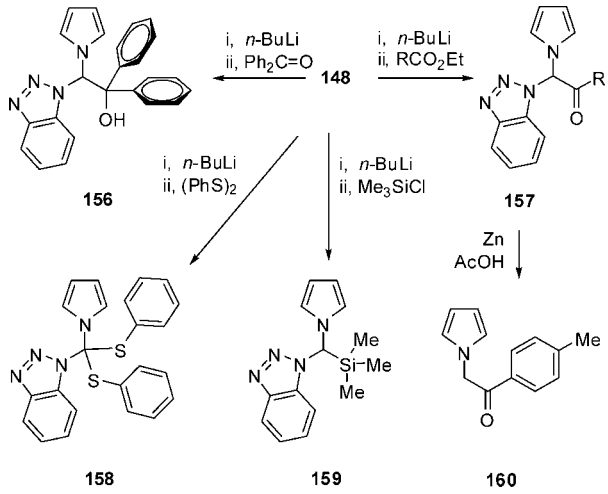
5.2.2. Electrophilic Substitution at Ring Carbon Atoms

When the condensation of benzotriazole, formaldehyde (aqueous solution), and aliphatic amines used in equimolar

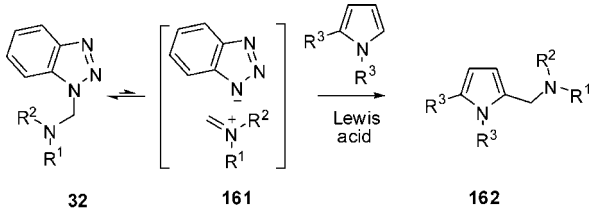
Scheme 41



Scheme 42



Scheme 43

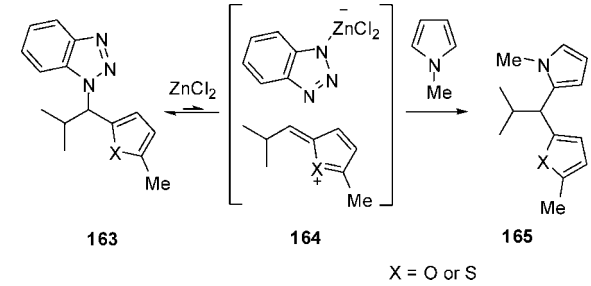


R^1, R^2 = -$(CH_2)_4$-; -$(CH_2)_5$-; *n*-Bu, H; *c*-C_5H_9, H or *c*-C_6H_{11}, H
R^3 = H or Me; Lewis acid = $AlCl_3$ or $ZnCl_2$

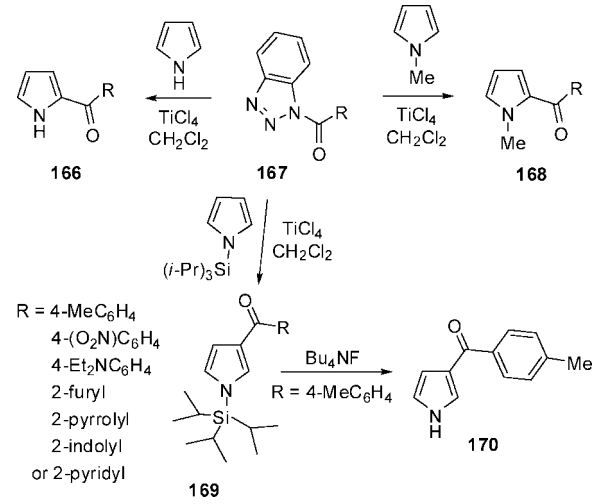
amounts is carried out in diethyl ether or dichloromethane, 1-(aminomethyl)benzotriazoles **32** are obtained in high yields (>90%). In solution, compounds **32** exist in equilibria with their benzotriazol-2-yl isomers. This equilibration is expected to proceed through iminium ion **161**, and just this cation must be involved in reactions of **32** with nucleophiles. In reactions of **32** with pyrrole or 1-methylpyrrole, 2-substituted products **162** are obtained in 62−96% yields. With tertiary amines, the reactions proceed well in the presence of $AlCl_3$; however, a milder Lewis acid, $ZnCl_2$, has to be used for secondary amines (Scheme 43).[78]

Not only amino, but also other electron-donating groups at C-α of the benzotriazolyl substituents can facilitate dissociation of the N−C bond, generating reactive carbocations as well. Thus, complexation of the benzotriazolyl

Scheme 44



Scheme 45



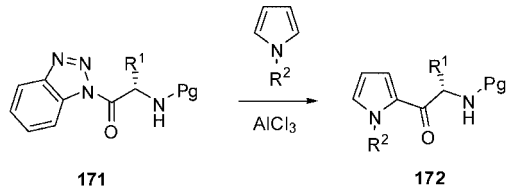
moiety in furyl and thienyl derivatives **163** with $ZnCl_2$ promotes their dissociation to cations **164** that readily attack the C-2 atom of *N*-methylpyrrole to give products **165** in 56% (X = O) and 52% (X = S) yields (Scheme 44).[79]

1-Acylbenzotriazoles **167**, readily prepared in reactions of the corresponding carboxylic acids with 1-(methanesulfonyl)benzotriazole,[80] are found to be convenient acylating agents for pyrroles. Thus, in their reactions with unsubstituted pyrrole catalyzed by $TiCl_4$, 2-acylpyrroles **166** are obtained in 21% (R = 4-$Et_2NC_6H_4$) to 91% (R = 2-furyl) yields. 1-Methylpyrrole subjected to similar reactions gives 2-acyl-1-methylpyrroles **168** in 51% (R = 4-$Et_2NC_6H_4$) to 94% (R = 2-furyl) yields. To direct the acylation reaction to C-3 of pyrrole, *N*-protection with a bulky triisopropylsilyl group is used. 3-Acylpyrroles **169** are isolated in generally good yields (54−92%). To prove the protection concept, one of the derivatives **169** (R = 4-MeC_4H_4) was deprotected using tetrabutylammonium fluoride to give 3-acylpyrrole **170** in 98% yield (Scheme 45).[81]

The benzotriazole approach allows the introduction of complex groups onto C-2 of pyrroles under mild conditions. Thus, *N*-protected 1-(α-aminoacyl)benzotriazoles **171** derived from chiral α-amino carboxylic acids can be conveniently prepared by mixing benzotriazole with thionyl chloride followed by *N*-protected α-amino carboxylic acid in a 4:1:1 ratio. Friedel−Crafts acylation of pyrrole with **171** in the presence of $AlCl_3$ provides chiral 2-(aminoacyl)pyrroles **172** in 45−82% yields (Scheme 46).[82]

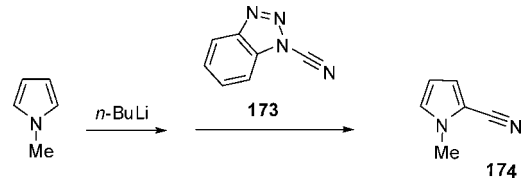
1-Cyanobenzotriazole (**173**), prepared in 92% yield from benzotriazole, NaH, and cyanogen bromide, is a convenient reagent for introduction of CN groups onto nucleophilic carbon atoms. With lithiated 1-methylpyrrole, an electrophilic attack of **173** occurs at the ring C-2 atom, providing nitrile **174** in 55% yield (Scheme 47).[83]

Scheme 46

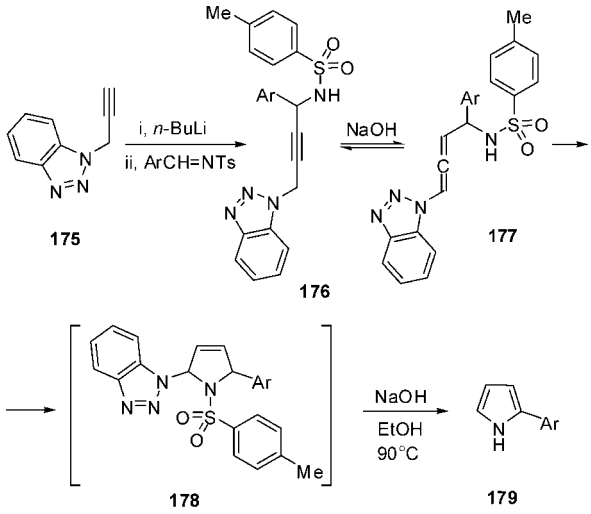


Pg = protective group: 9*H*-fluorenylmethoxycarbonyl or trifluoroacetyl
R^1 = Ph, Me, (indol-3-yl)methyl or (methylsufanyl)methyl
R^2 = H or Me

Scheme 47



Scheme 48



Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 1-naphthyl or 2-thienyl

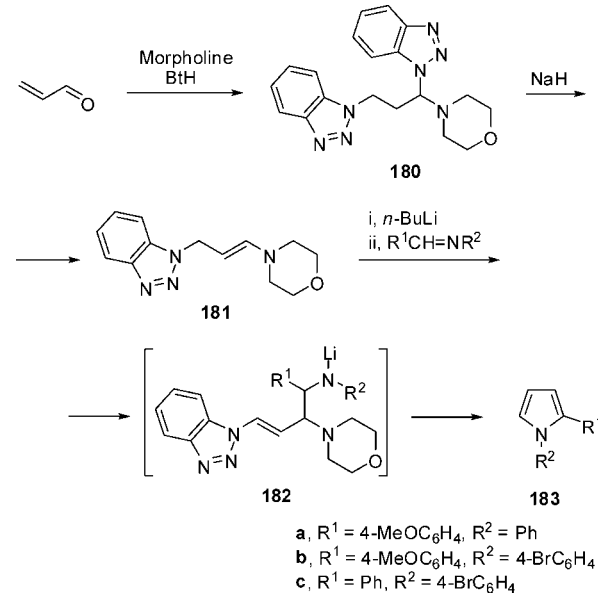
5.3. Aromatic Ring Formation

5.3.1. One Substituent at C-2

The anion delivered from 1-propargylbenzotriazole (**175**) upon its treatment with *n*-BuLi readily adds to *N*-tosylarylimines to give sulfonamides **176** in 76−92% yields. When heated with NaOH in ethanol, compounds **176** are converted into 2-arylpyrroles **179** in 47−60% yields. The proposed reaction mechanism involves isomerization of alkyne **176** to allene **177** followed by intramolecular cycloaddition to form pyrroline **178**. Finally, under basic conditions, the molecule eliminates benzotriazole and the tosylate protecting group to furnish pyrrole **179** (Scheme 48).[84]

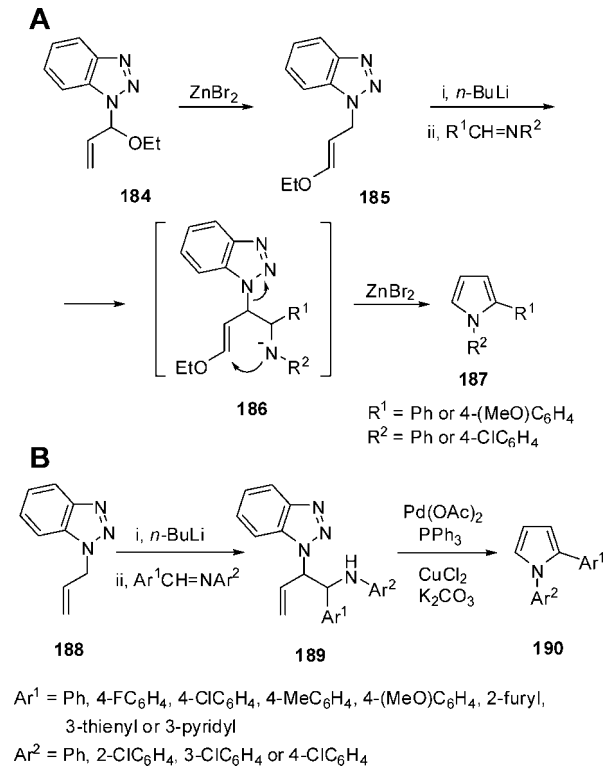
The reaction of acrolein with benzotriazole and morpholine provides product **180** in 84% yield as a mixture with its benzotriazol-2-yl isomers.[14] Upon treatment with sodium hydride, one of the benzotriazolyl substituents is eliminated to give enamine **181** in 74% yield as a stable crystalline product.[85] Additions of lithiated **181** to Schiff bases presumably give unstable intermediate diamines **182** that by cyclization and elimination of benzotriazole and morpholine

Scheme 49



a, R^1 = 4-$MeOC_6H_4$, R^2 = Ph
b, R^1 = 4-$MeOC_6H_4$, R^2 = 4-BrC_6H_4
c, R^1 = Ph, R^2 = 4-BrC_6H_4

Scheme 50



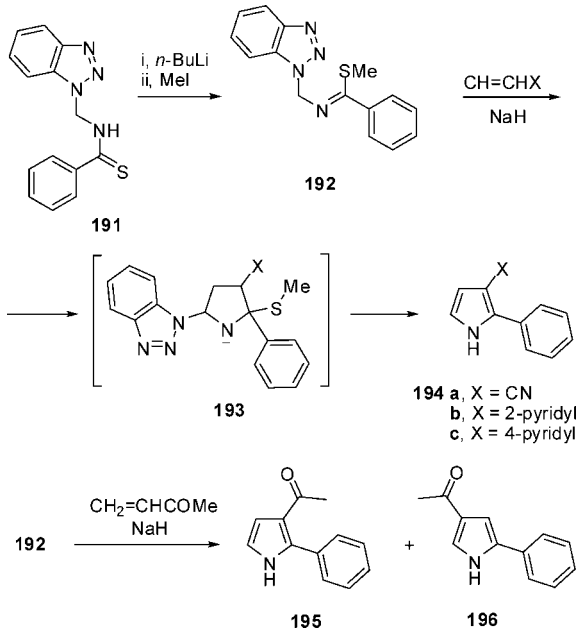
Ar^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-(MeO)C_6H_4, 2-furyl, 3-thienyl or 3-pyridyl
Ar^2 = Ph, 2-ClC_6H_4, 3-ClC_6H_4 or 4-ClC_6H_4

are converted into 1,2-diarylpyrroles **183**, isolated in 60−68% yields (Scheme 49).[86]

Alkoxy analogues of enamine **181** can be applied in such reactions as well. Thus, α-ethoxy derivative **184**, easily prepared by condensation of benzotriazole with acrolein diethyl acetal, undergoes a smooth rearrangement promoted by $ZnBr_2$ to (γ-ethoxyallyl)benzotriazole (**185**). After lithiation, the anion is trapped by Schiff bases to give anions **186**. Catalyzed by $ZnBr_2$, intermediates **186** undergo cyclization with elimination of benzotriazole and ethanol to furnish 1,2-diarylpyrroles **187** in 55−63% yields (Scheme 50A).[87]

Lithiated *N*-allylbenzotriazole (**188**) readily adds to the C=N bond of Schiff bases derived from aromatic or heteroaromatic aldehydes and amines to give amines **189** in

Scheme 51



46−85% yields. In the presence of a palladium catalyst and cupper(II) oxidizing agent, amines **189** are smoothly converted to pyrroles **190** in 46−79% yields, except **190** with Ar^1= 4-(MeO)C_6H_4 and Ar^2 = Ph where the yield is only 21% (Scheme 50B).[88]

5.3.2. Two Substituents at C-2 and C-3

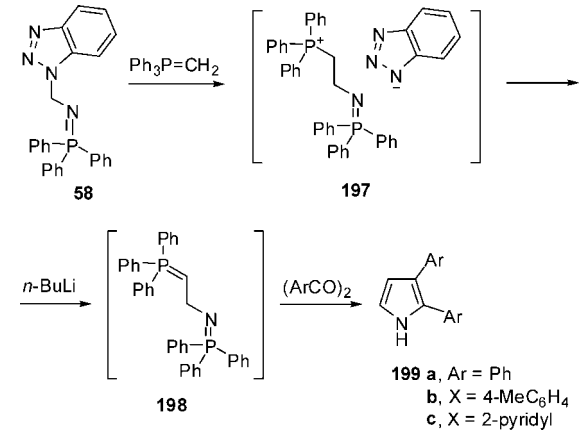
N-(Benzotriazol-1-ylmethyl)thiobenzamide (**191**) is readily prepared by condensation of benzotriazole with formaldehyde and thiobenzamide.[89,90] Treatment with *n*-BuLi followed by iodomethane converts thiobenzamide **191** into *S*-methyl thioimidate **192** in 87% yield. The anion generated from **192** adds to acrylonitrile to give pyrrolidine anion **193a**, which spontaneously eliminates benzotriazole and thiomethoxide anion to give pyrrole **194a** (88% yield). Similar reactions with 2-vinyl- and 4-vinylpyridines provide 2-phenyl-3-pyridinylpyrroles **194b** (36% yield) and **194c** (64% yield). In the case of substituents X with moderate electron-withdrawing power, the additions may occur in both modes, giving rise to mixtures of regioisomers, as demonstrated in a reaction with methyl vinyl ketone leading to 2,3-disubstituted pyrrole **195** (34% yield) and 2,4-disubstituted pyrrole **196** (18% yield) (Scheme 51).[91]

Addition of **58** to $PPh_3P{=}CH_2$ provides phosphonium salt **197**, which is easily deprotonated by *n*-BuLi to give ylide **198**. When the reaction mixture is quenched with 1,2-diaryl 1,2-diones, 2,3-disubstituted pyrroles **198a**−**c** are obtained in 67%, 75%, and 58% yields, respectively (Scheme 52).[92,93]

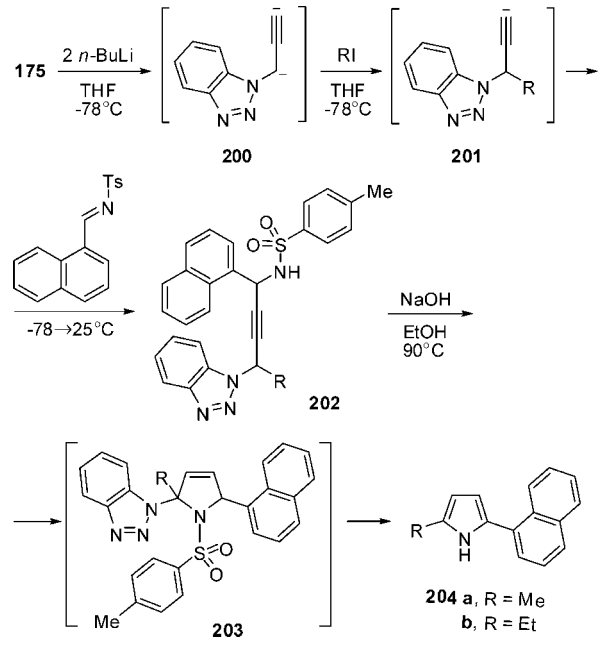
5.3.3. Two Substituents at C-2 and C-5

The synthetic method for pyrroles monosubstituted at C-2 shown in Scheme 48 can be modified for the preparation of 2,5-disubstituted pyrroles. Thus, treatment of **175** with 2 molar equiv of *n*-BuLi generates dianion **200**, which is subsequently alkylated with alkyl iodides to give alkynyl anions **201**. Consecutive addition of *N*-tosyl-1-naphthylmethyleneimine provides adducts **202** in 72−77% yields. Heated with an ethanolic solution of NaOH, compounds **202** tautomerize to their allene forms and undergo cyclization to pyrrolines **203**. Under the reaction conditions, the benzotriazole moiety is eliminated and the *N*-protection is removed to provide 2,5-disubstituted pyrroles **204a** (56% yield) and **204b** (43% yield) (Scheme 53).[84]

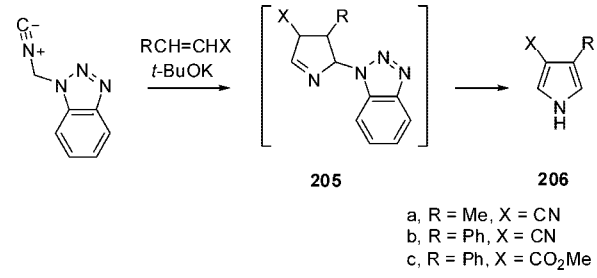
Scheme 52



Scheme 53



Scheme 54

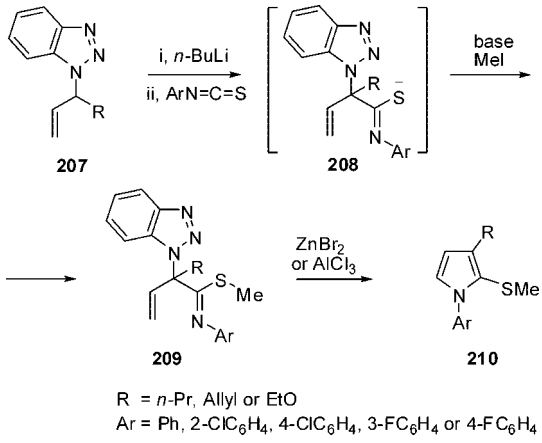


5.3.4. Two Substituents at C-3 and C-4

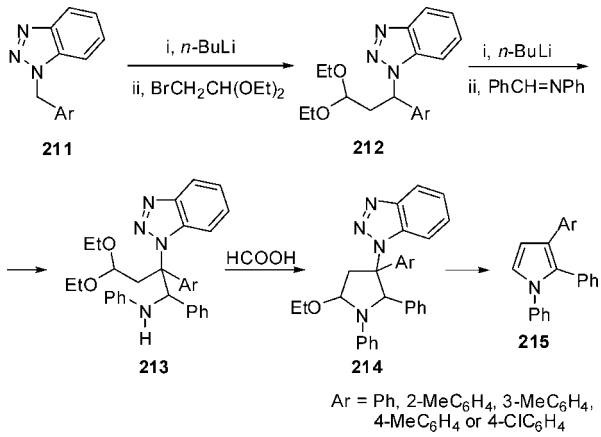
In the presence of a base, isocyanide **37** adds readily to electron-deficient double bonds, and the resultant pyrroline intermediates **205** spontaneously eliminate benzotriazole to give 3,4-disubstituted pyrroles in 92% (**206a**), 81% (**206b**), and 40% (**206c**) yields (Scheme 54).[94]

Addition of lithiated allylbenzotriazoles **207** to the C=N bond of isothiocyanates produces anions **208** that are

Scheme 55



Scheme 56



methylated in situ to provide methyl 2,2-disubstituted 3-buteniminothiates **209** in 59−80% yields. Treated with Lewis acids, compounds **209** undergo cyclization to 2-(methylthio)pyrroles **210**. Yields of **210** determined by gas chromatography are high (75−94%); however, the yields of pure materials separated by column chromatography are much lower (21−65%) due to the low stability of the electron-rich pyrroles (Scheme 55).[95]

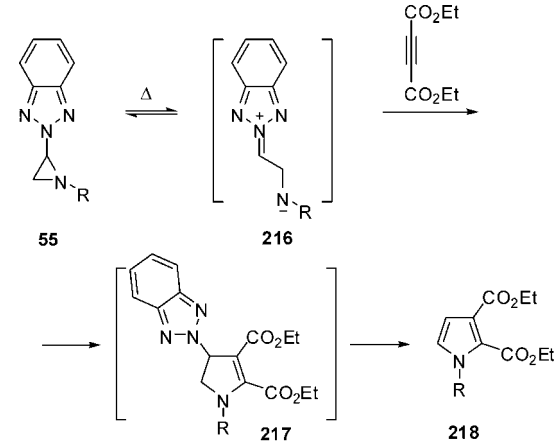
In the [1 + 2 + 2] annulation process shown in Scheme 56, alkylation of 1-benzylbenzotriazoles **211** with 2-bromoacetaldehyde diethyl acetal to give intermediates **212** is followed by a reaction with *N*-benzylideneaniline to produce adducts **213**. Subsequent treatment with formic acid causes cyclization of **213** to 5-ethoxypyrrolidines **214** that then eliminate ethanol and benzotriazole to give pyrroles **215** in 66−74% yields.[96]

Due to the high strain energy of the three-membered ring, aziridines are convenient starting materials for pyrroles. On heating to 140 °C, the C−N bond in benzotriazol-2-ylaziridines **55** is cleaved, and the dipolar species **216** undergo [3 + 2] cycloaddition to acetylenedicarboxylate to form pyrrolines **217** that aromatize to pyrroles **218** by elimination of benzotriazole (Scheme 57). The reaction is relatively slow (72 h), providing products **218** in 25% (R = *n*-$C_{10}H_{21}$) to 80% (R = *n*-C_5H_{11}) yields.[51]

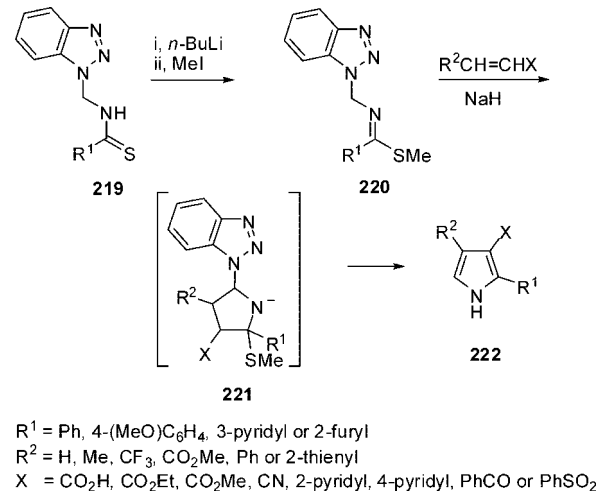
5.3.5. Three Substituents at C-2, C-3, and C-4

A 1 molar equiv of a base makes possible selective methylation of the sulfur atom in thioamides **219** to give thioimidates **220** in high yields. The anions derived from

Scheme 57



Scheme 58



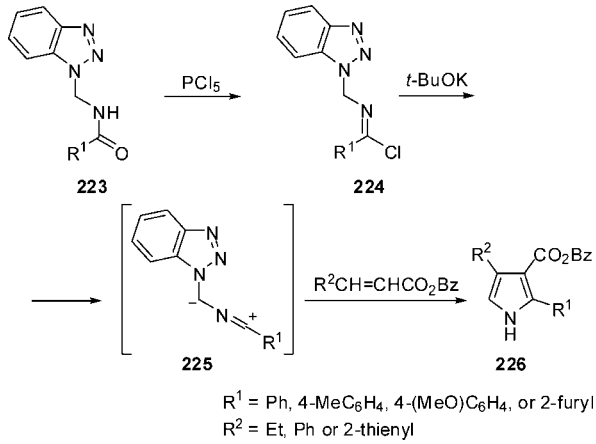
220 on treatment with sodium hydride add readily to electron-poor double bonds to create unstable anions **221** that spontaneously eliminate benzotriazole and thiomethoxide to generate pyrroles **222** (Scheme 58).[91] Both reactions, methylation and addition, can be conveniently carried out in one pot when *t*-BuOK is used as a base.[97] The yields of pyrroles **222** are generally high (60−99%), except for the case of $R^2 = CF_3$ (20%).

A similar sequence is employed for the conversion of *N*-(benzotriazol-1-ylmethyl)amides **223** into pyrroles **226**. Thus, in reactions with PCl_5, amides **223** give chloro imines **224** that on treatment with *t*-BuOK are converted to nitrile ylides **225**. Benzyl esters of α,β-unsaturated acids acting as dipolarophiles trap **225** to generate pyrroles **226** in 81−90% yield (Scheme 59).[98]

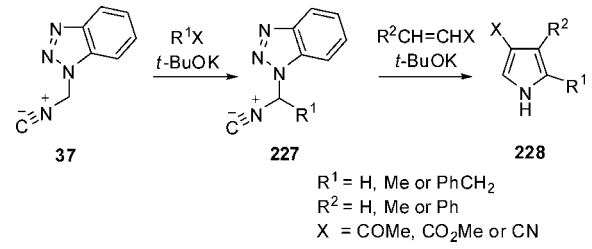
In the presence of *t*-BuOK, benzotriazol-1-ylmethyl isocyanide (BetMIC, **37**) undergoes alkylation on the methylene group to give isocyanide **227**. The anion derived from **227**, upon treatment with *t*-BuOK, adds to the electron-deficient double bonds of α,β-unsaturated ketones, esters, or nitriles to produce pyrroles **228** in 30−92% yields (Scheme 60).[94]

Benzotriazol-1-ylaziridines **229** are thermally unstable. On heating to 100 °C, the C−C bond of the aziridine ring is cleaved to give azomethine ylides **230** that can be trapped by diethyl acetylenedicarboxylate. The pyrroline intermediates that are formed in the first step spontaneously eliminate

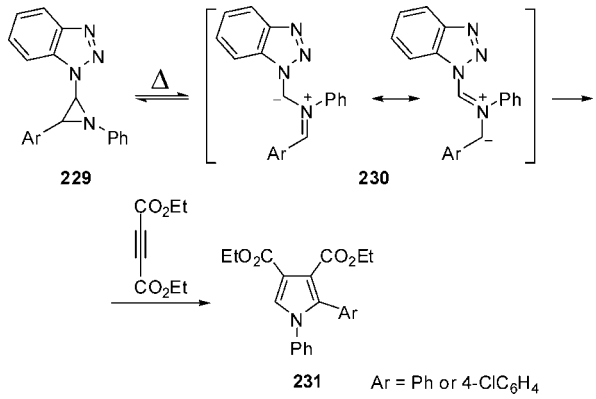
Scheme 59



Scheme 60



Scheme 61



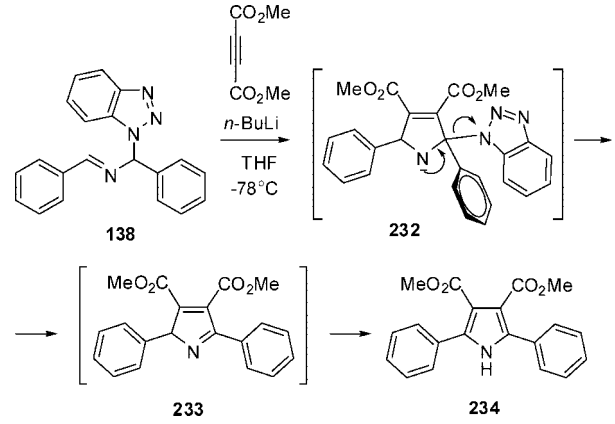
benzotriazole to furnish pyrroles **231** in 81−88% yield (Scheme 61).[51]

5.3.6. Four Substituents at Carbon Atoms

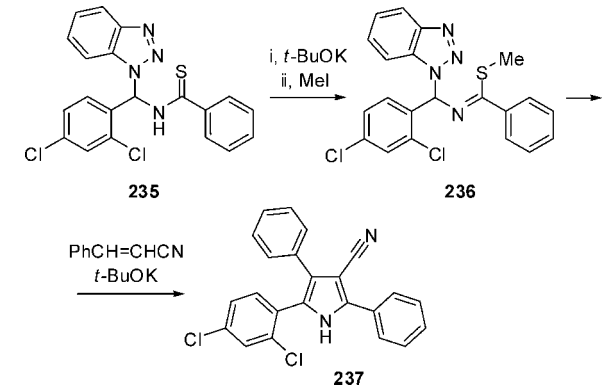
Similarly to the addition of imine **138** to dimethyl fumarate (Scheme 38), the anion generated from **138** adds readily to dimethyl acetylenedicarboxylate to give quantitatively tetrasubstituted pyrrole **234**. The reaction is believed to proceed through pyrrolinyl anion **232**, which spontaneously expels a benzotriazolide anion to generate neutral molecule **233**, which eventually rearranges to the more stable aromatic tautomer **234** (Scheme 62).[75]

The synthetic method for 2,3,4-trisubstituted pyrroles based on thioamides (Scheme 58) can be extended to 2,3,4,5-tetrasubstituted pyrroles. Thus, as given in Scheme 63, thioamide **235** is prepared in 92% yield by condensation of thiobenzamide with 2,4-dichlorobenzaldehyde and benzotriazole. *S*-Methylthioimidate **236**, obtained by methylation of **235** with iodomethane in the presence of *t*-BuOK, is treated in one pot with cinnamonitrile to give tetrasubstituted pyrrole **237** in 63% yield.[97]

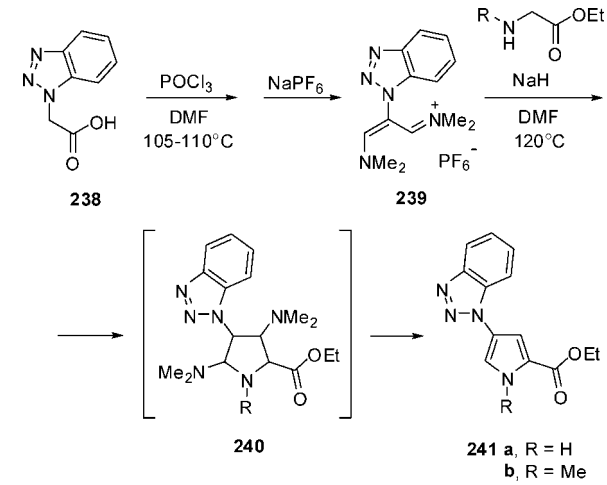
Scheme 62



Scheme 63



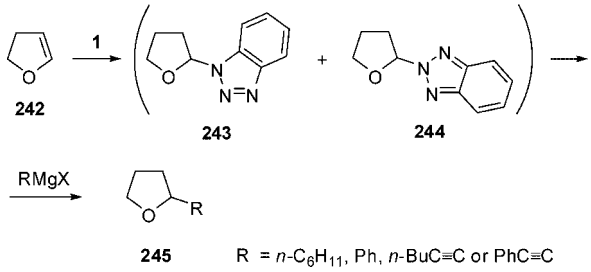
Scheme 64



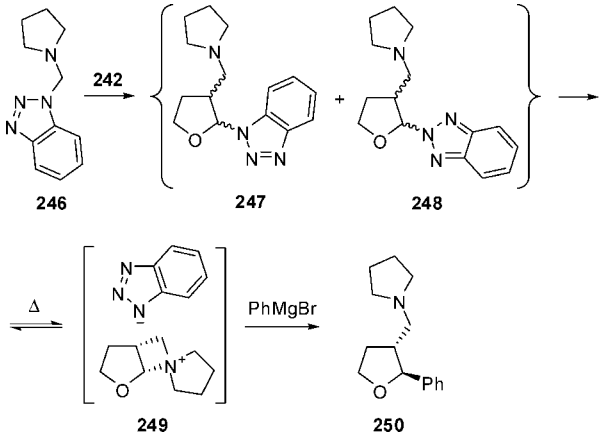
5.3.7. Benzotriazolyl Substituent at the Ring

For most of the synthetic methods described in this paragraph, pyrrole ring formation involves cycloaddition or cyclocondensation reactions leading to unstable intermediate pyrrolines or pyrrolidines that then spontaneously eliminate benzotriazole and, in the case of pyrrolidines, also another group to generate an aromatic system. However, under special circumstances, the benzotriazolyl substituent may be retained, and other groups leave. Thus, in Scheme 64, vinamidinium salt **239**, obtained in a reaction of benzotriazol-1-ylacetic acid (**238**) with DMF and $POCl_3$, reacts with ethyl esters of glycine and its *N*-methyl analogue to give 4-benzotriazol-1-ylpyrrole derivatives **241a** (89% yield) and **241b** (91% yield). Here, the presumed intermediate pyrrolidines

Scheme 65



Scheme 66



240 preferentially eliminate two molecules of dimethylamine, leaving the benzotriazolyl substituent unaffected. The only role for the benzotriazolyl group in this conversion is activation of α-protons, making the condensation and elimination easier.[99]

6. Furan

6.1. Nonaromatic Rings

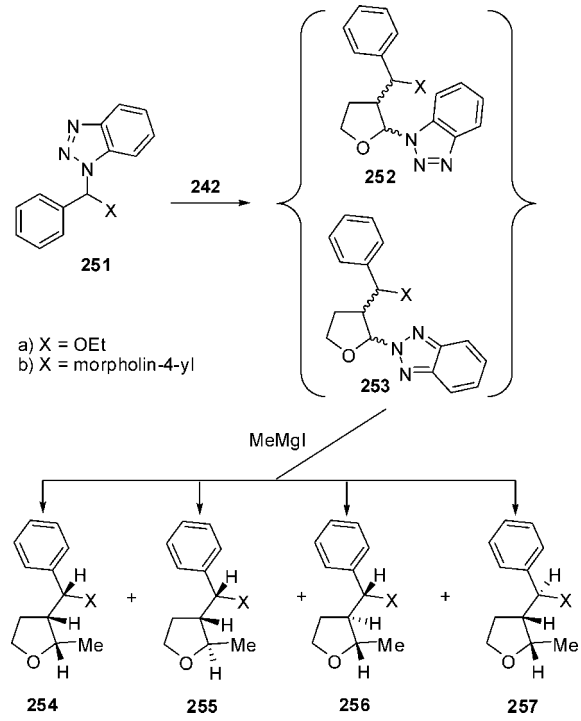
6.1.1. Tetrahydrofurans

Addition of benzotriazole to 1,2-dihydrofuran (**242**) produces a mixture of regioisomers **243** and **244** in a 7:1 ratio, respectively. The mixture can be separated by chromatography. Treatment with organomagnesium reagents smoothly converts the mixture of **243** and **244** into 2-substituted furans **245** in 59−90% yields (Scheme 65).[100]

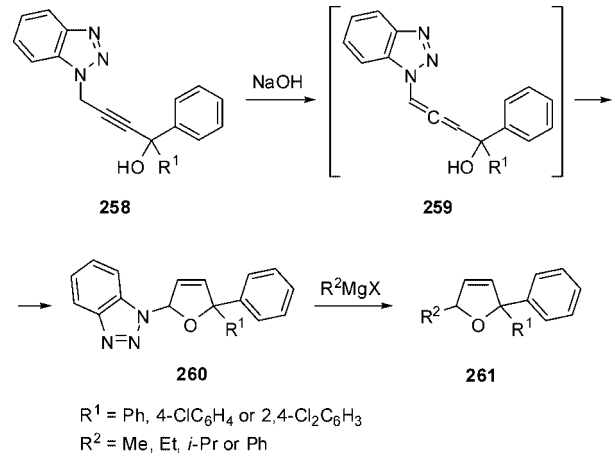
Addition of *N*-(pyrrolidin-1-ylmethyl)benzotriazole (**246**) to **242** results in a mixture of stereoisomers and regioisomers **247** and **248**. The mixture can be separated by chromatography; however, when treated with phenylmagnesium bromide at elevated temperature, it is converted exclusively into *trans*-1,2-disubstituted furan **250** in 75% yield. The stereochemistry of **250** can be explained by formation of tricyclic ionic intermediate **249** (Scheme 66).[101]

The method depicted in Scheme 66 can be extended to relatively complex substituents at C-3. Thus, compound **251a**, readily available from a reaction of benzotriazole with benzaldehyde acetal, adds to **242** in the presence of an acidic catalyst to produce a complex mixture of regio- and stereoisomers **252a** and **253a**. Treatment with methylmagnesium iodide allows the substitution of benzotriazole to provide 2-methyl-3-(1-ethoxybenzyl)tetrahydrofurans **254a**−**257a**. Isomers **254a**−**257a** (each as a pair of enantiomers) are separated by column chromatography.[101] Addition of morpholin-4-yl derivative **251b** to **242** provides isomers

Scheme 67



Scheme 68



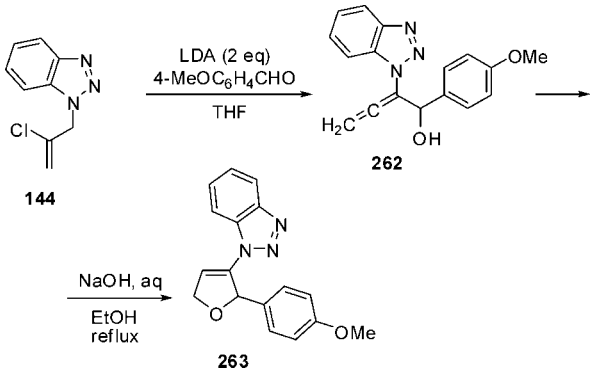
252b and **253b**. The separation of the four stereoisomers of **252b** by chromatography is described. Conversions of the individual stereoisomers **252b** with methylmagnesium iodide allows assignment of stereochemistry to the resultant derivatives **254b**−**257b** (Scheme 67).[102]

6.1.2. 2,5-Dihydrofurans

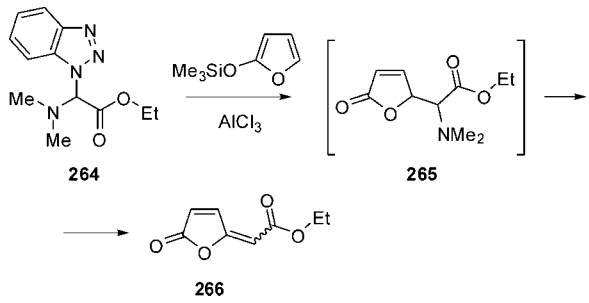
The anion generated from **175** readily adds to diaryl ketones to produce alcohols **258** in high yields. Treatment with NaOH in ethanol at 60−80 °C allows the rearrangement of alkynes **258** into allenes **259**, which, under the reaction conditions, undergo cyclization to 2,5-dihydrofurans **260**, isolated in 68−90% yields. On heating of **260** with Grignard reagents in toluene, the benzotriazolyl moiety is replaced by an alkyl or aryl group to provide 2,2,5-trisubstituted 2,5-dihydrofurans **261** in 82−95% yields (Scheme 68).[103]

The 1,1-disubstituted analogue of allene **259**, product **262** (90% yield), forms on treatment of **144** with 2 molar equiv of LDA followed by *p*-anisaldehyde. The first equivalent of LDA is used to generate 1-allenylbenzotriazole, which is

Scheme 69



Scheme 70



deprotonated with the second equivalent of LDA, and the resulting anion is finally trapped by the aldehyde. Similarly to **259**, allene **262** undergoes cyclization under basic conditions to give 2,3-disubstituted 2,5-dihydrofuran **263** in 60% yield (Scheme 69).[76]

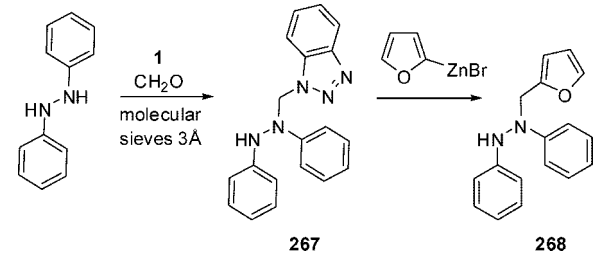
The iminium cation generated from ethyl α-(dimethylamino)-α-benzotriazol-1-ylacetate (**264**) upon treatment with $AlCl_3$ adds to C-5 of 2-[(trimethylsilyl)oxy]furan with elimination of the (trimethylsilyl)oxy group to give unstable 2,5-dihydrofuran-2-one **265**. Spontaneous elimination of dimethylamine from **265** in refluxing acetonitrile provides ethyl (5-oxo-5*H*-furan-2-ylidene)acetate **266** in 83% yield. The isomer ratio *Z*:*E* is 77:23. The isomers are readily separated by column chromatography (Scheme 70).[104]

6.2. Electrophilic Substitution of the Aromatic Ring

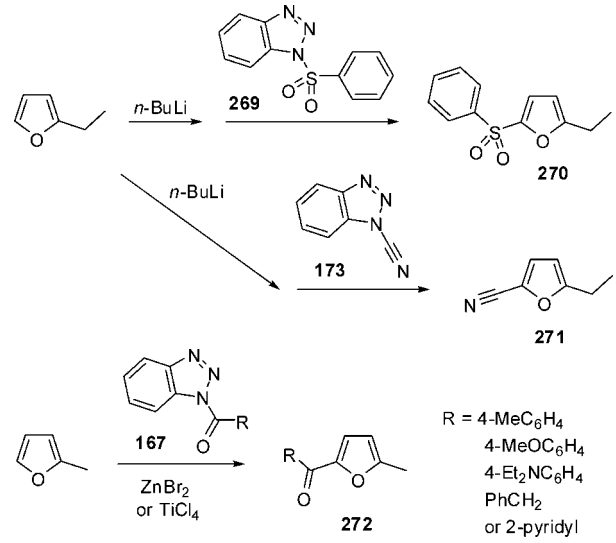
Furan can be lithiated at C-2 using *n*-BuLi in the presence of TMEDA. The following treatment with $ZnBr_2$ converts the lithiated furan into 2-furylzinc bromide, a convenient reagent for the preparation of furans monosubstituted at C-2. Thus, condensation of *N*,*N*′-diphenylhydrazine with formaldehyde and benzotriazole provides trisubstituted hydrazine **267**. In solutions, **267** exists in equilibrium with its benzotriazol-2-yl analogue, but both isomers are equally reactive. With 2-furylzinc bromide, the benzotriazolyl moiety in **267** is substituted by a furyl group to give 2-[(*N*,*N*′-diphenylhydrazino)methyl]tetrahydrofuran (**268**) in 79% yield (Scheme 71).[105]

2,5-Disubstituted furans can be readily obtained by C-5 lithiation of 2-substituted furans followed by reactions with electrophiles. As an example, 2-ethylfuran is first treated with *n*-butyllithium and then with 1-(phenylsulfonyl)benzotriazole (**269**) to give derivative **270** in 80% yield.[106] When lithiated 2-ethylfuran is treated with **173**, 5-ethyl-2-furonitrile (**271**) is obtained in 65% yield.[83] Acylation of 2-methylfuran with 1-acylbenzotriazoles **167** in the

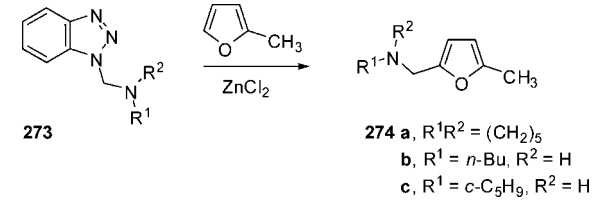
Scheme 71



Scheme 72



Scheme 73



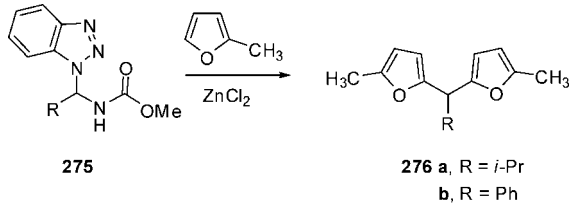
presence of a Lewis acid provides 5-acylated derivatives **272** in 54% (R^2 = 2-pyridyl) to 98% (R^2 = 4-$Me_2NC_6H_4$) yields (Scheme 72).[107]

In a Mannich-type reaction of 2-methylfuran with 1-(piperidinomethyl)benzotriazole (**273a**) catalyzed by $ZnCl_2$, 2,5-disubstituted furan **274a** is obtained in 87% yield. The reaction can also be used for the introduction of *N*-monoalkylated aminomethyl groups to C-5 of 2-methylfuran, but the yields are somewhat lower: 58% for **274b** and 47% for **274c** (Scheme 73).[78]

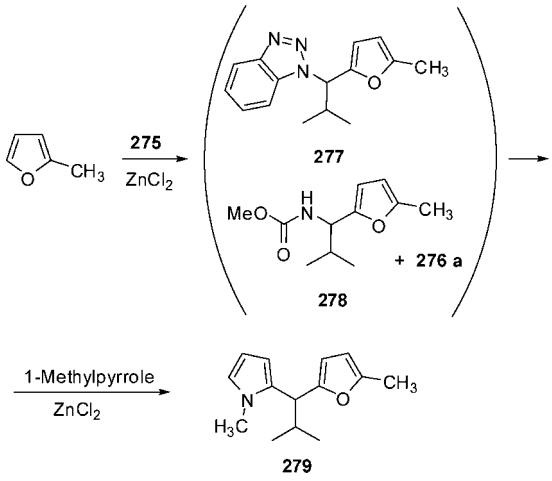
Methyl *N*-(1-benzotriazol-1-ylalkyl)carbamates **275** are conveniently prepared by condensation of aldehydes with benzotriazole and methyl carbamate.[108] With 2-methylfuran in the presence of $ZnCl_2$, both the benzotriazolyl and the carbamoyl groups in **275** are substituted to produce geminal bis(5-methylfuran-2-yl)alkanes **276** in 88−90% yields (Scheme 74).[79]

The substitution can be carried out stepwise using two different heterocyclic systems. Thus, when 2-methylfuran is subjected to a reaction with 1 molar equiv of carbamate **275a**, a mixture of compounds **277** (42%), **278** (17%), and **276a** (15%) is obtained. Treatment of the crude reaction mixture with 1-methylpyrrole and $ZnCl_2$ provides 2-[1-(1-methylpyrrol-2-yl)-2-methylpropyl]-5-methylfu-

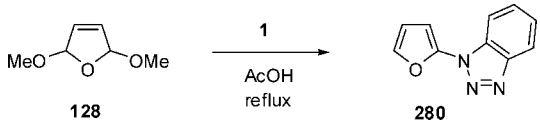
Scheme 74



Scheme 75



Scheme 76



ran (**279**) in 56% yield. Obviously, both intermediates **277** and **278** have to react with 1-methylpyrrole to give the same product (Scheme 75).[79]

6.3. Aromatic Ring Formation

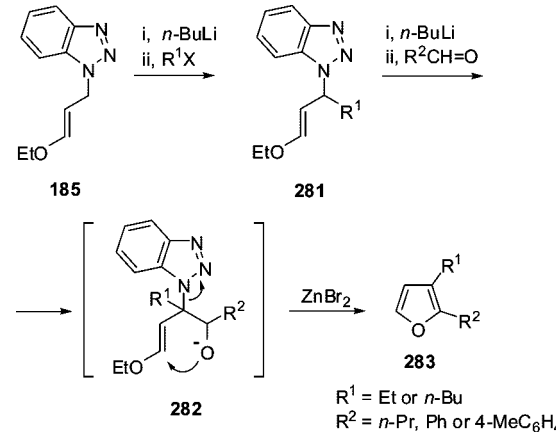
Under reflux in acetic acid, benzotriazole reacts with **128** to give 2-benzotriazol-1-ylfuran (**280**) in 67% yield (Scheme 76). In the presence of amines, *N*-substituted 2-benzotriazol-1-ylpyrroles are formed instead, but the yields are low (1−10%).[109]

Alkylation of **185** occurs exclusively at the α-C, producing derivatives **281**, which, in their lithiated forms, add readily to the carbonyl group of aldehydes. Upon treatment with $ZnBr_2$, resultant anions **282** are rapidly converted to 2,3-disubstituted furans **283** that are isolated in 46−52% overall yields (Scheme 77).[88]

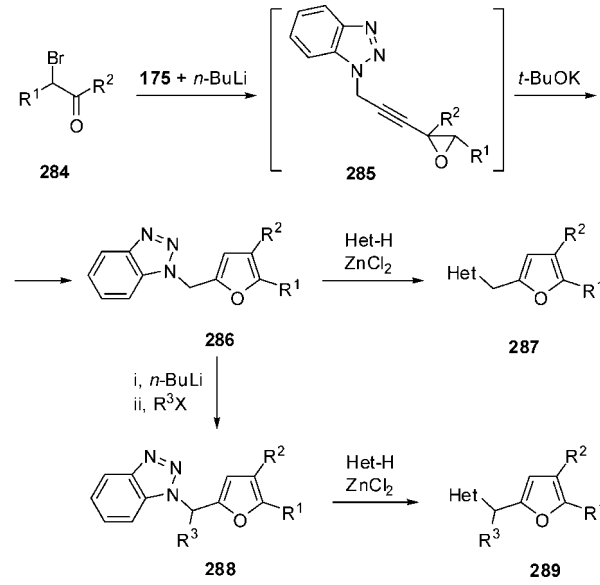
In the presence of *t*-BuOK, oxiranes **285**, obtained from lithiated **175** and α-bromo ketones **284**, undergo rearrangement to furans **286**, which are isolated in 51−61% yields. When treated with electron-rich heterocycles and $ZnCl_2$, the benzotriazolyl moiety in **286** is substituted by a heterocyclic ring to provide derivatives **287** in 57−86% yields. Alternatively, alkylation of the methylene carbon in **286** provides derivatives **288**, which in a reaction with heterocycles and $ZnCl_2$ are consecutively converted to products **289** in 55−95% yields. In this way, 2,4-disubstituted furans (R^1 = H) or 2,3,5-trisubstituted furans ($R^1 \neq$ H) are prepared (Scheme 78).[110]

Deprotonation of *N*,*N*-dimethylbenzotriazol-1-ylmethyleneiminium chloride (**290**), readily available from a reaction

Scheme 77



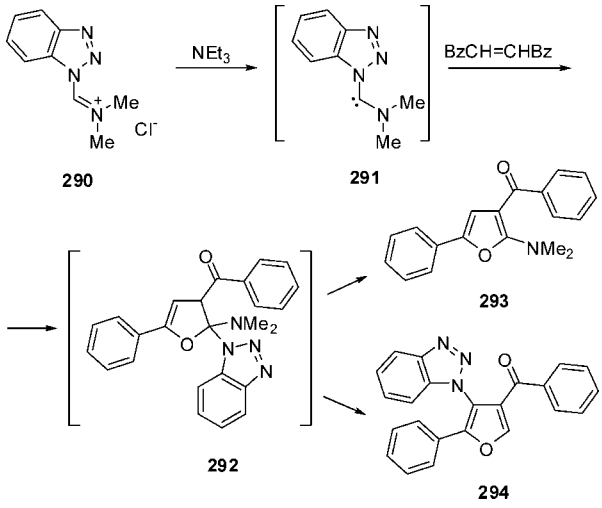
Scheme 78



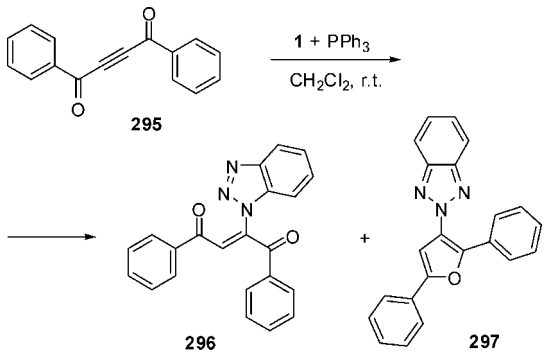
of DMF with 1-chlorobenzotriazole or 1-(trimethylsilyl)benzotriazole, by triethylamine provides (dimethylamino)benzotriazol-1-ylcarbene (**291**). In the presence of *trans*-1,2-dibenzoylethylene, 1,4-cycloaddition of the carbene provides 2,3-dihydrofuran derivative **292**, which in refluxing benzene eliminates benzotriazole to give 2,3,5-trisubstituted furan **293**, isolated in 15% yield. A more complex rearrangement process leads to a side product, furan **294**, which is isolated from the reaction mixture in 6% yield (Scheme 79).[111]

Benzotriazole with dibenzoylacetylene (**295**) and triphenylphosphine (equimolar amounts) gives a mixture of compounds **296** (40%) and **297** (45%) (Scheme 80). No open-chain benzotriazol-2-yl analogue of **296** or benzotriazol-1-yl analogue of furan derivative **297** is detected.[112] Just steric hindrance in the reaction intermediates may be responsible for that. To make the cyclization possible, the molecule **296** must first assume an *E* configuration to bring the carbonyl groups in close proximity. Isomerization between *Z* and *E* configurations in **296** can be achieved by addition of another molecule of benzotriazole to the double bond followed by its elimination, but rotation of the α-benzoyl group imposes too much strain due to the steric repulsion between its phenyl and the benzotriazolyl benzenoid ring. The less bulky

Scheme 79



Scheme 80



benzotriazol-2-yl substituent in the benzotriazol-2-yl analogue of **296** allows for such transformations without high energetic barriers.

7. Thiophene

7.1. Nonaromatic Rings

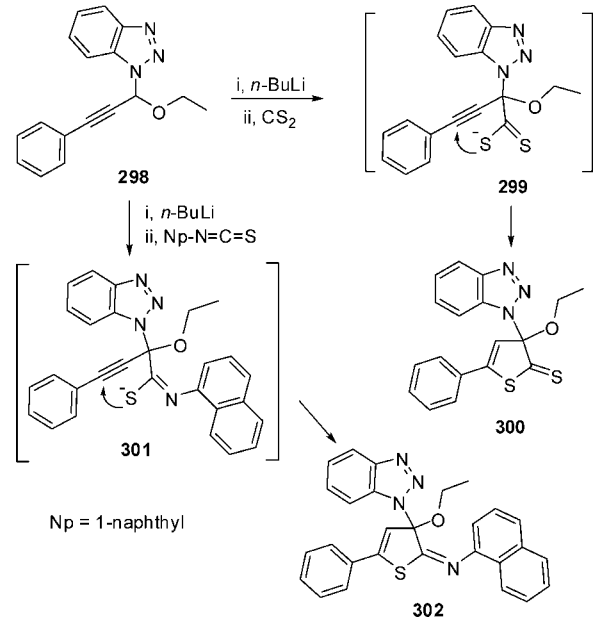
Condensation of phenylpropargylaldehyde diethyl acetal with benzotriazole readily provides 1-benzotriazol-1-yl-3-phenylpropargyl ethyl ether (**298**). Treated with *n*-BuLi, **298** forms an anion that adds to a C═S bond in CS_2 to give dithiocarboxylate anion **299**. An intramolecular attack of the sulfur nucleophile on the triple bond in **299** leads to 3,3,5-trisubstituted 2,3-dihydro-2-thiophenethione **300**, isolated in 57% yield. A similar addition of lithiated **298** to the C═S bond of 1-naphthyl isothiocyanate produces adduct **301**, which reacts further to provide 2,3-dihydro-2-(naphth-1-ylimino)thiophene **302** in 64% yield (Scheme 81).[113]

7.2. Electrophilic Substitution of the Aromatic Ring

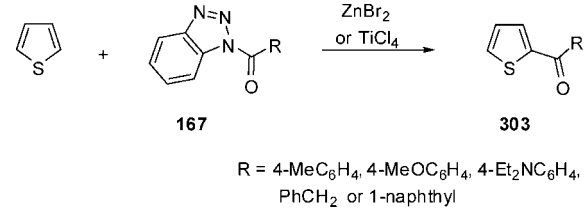
Monosubstitution of thiophene at C-2 can be achieved simply by acylation. 1-Acylbenzotriazoles **167** are efficient acylating agents under mild conditions (see section 5 on pyrrole and section 6 on furan). Thus, **167** react smoothly with thiophene in the presence of a Lewis acid catalyst to give 2-acylthiophenes **303** in 58% (R = 4-$Et_2NC_6H_4$) to 97% (R = 1-naphthyl) yields (Scheme 82).[107]

In another approach to monosubstituted thiophenes, thiophene itself is lithiated at C-2 with *n*-BuLi and TMEDA

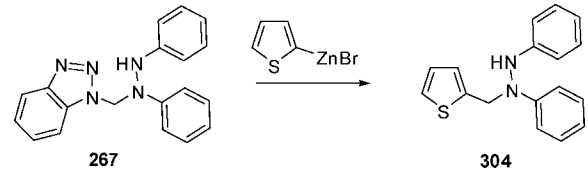
Scheme 81



Scheme 82



Scheme 83



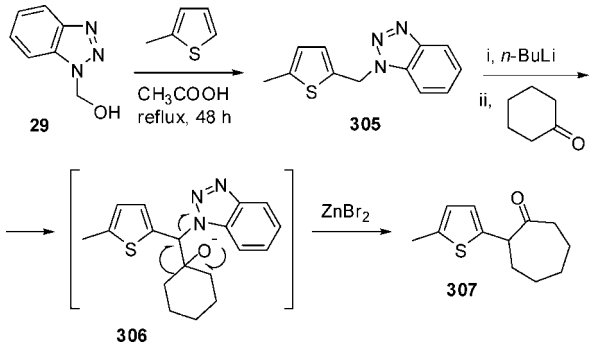
and subsequently treated with $ZnBr_2$ to give 2-thienylzinc bromide. The bromozinc group can be substituted by various electrophiles. In an example in Scheme 83, 2-thienylzinc bromide reacts with *N*-(benzotriazol-1-ylmethyl)-*N*,*N*′-diphenylhydrazine (**267**) to give product **304** in 53% yield.[105]

29 reacts with 2-methylthiophene in refluxing glacial acetic acid to give 2,5-disubstituted thiophene **305** in 50% yield. The anion derived from **305** adds to the carbonyl group of cyclohexanone to provide alkoxide anion **306**. In situ treatment with $ZnBr_2$ promotes rearrangement of anion **306** with elimination of the benzotriazolide anion and expansion of the cyclohexanone ring. 2-(5-Methylthien-2-yl)cycloheptanone (**307**) so obtained is isolated in 67% yield (Scheme 84).[114]

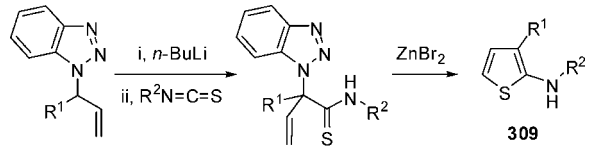
7.3. Aromatic Ring Formation

α-Substituted 1-allylbenzotriazoles **121** are readily prepared by treatment of 1-allylbenzotriazole with *n*-BuLi followed by alkylating agents. Removal of the remaining α-proton in **121** by *n*-BuLi and consecutive treatment with isothiocyanates leads to thioamides **308**. Without purification, thioamides **308** are then subjected to $ZnBr_2$, which causes cyclization and elimination of benzotriazole to provide 2-aminothiophenes **309** in 25% (R^1 = CH_2═$CHCH_2$, R^2 =

Scheme 84

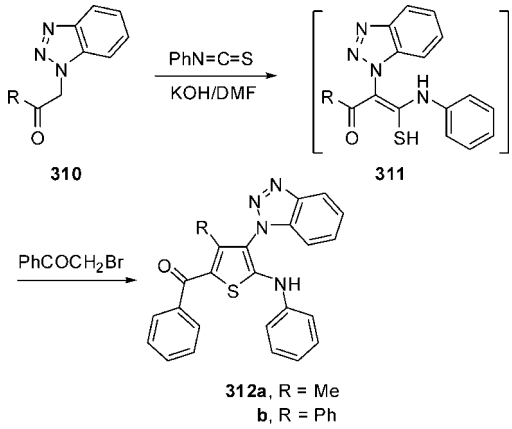


Scheme 85



R^1 = Et, *n*-C_6H_{13}, CH_2=$CHCH_2$, 2-$ClC_6H_4CH_2$ or 2-$FC_6H_4CH_2$
R^2 = Ph, 4-ClC_6H_4, 3-FC_6H_4 or 4-$MeOC_6H_4$

Scheme 86



4-ClC_6H_4) to 80% (R^1 = 2-$ClC_6H_4CH_2$, R^2 = Ph) overall yields for the two steps (Scheme 85).[95]

By a different route to 2-aminothiophenes, benzotriazol-1-ylacetone (**310**) is treated with phenyl isothiocyanate and KOH to give adduct **311**. Without separation, **311** is treated in situ with phenacyl bromide to provide tetrasubstituted thiophenes in 82% (**312a**) and 56% (**312b**) yields (Scheme 86).[115]

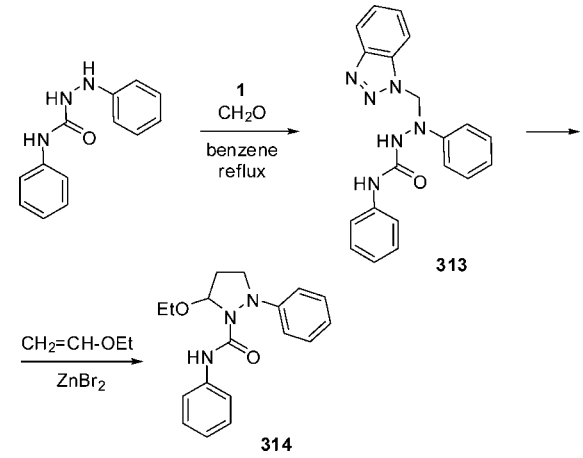
8. Five-Membered Rings with Two Heteroatoms

8.1. Pyrazole

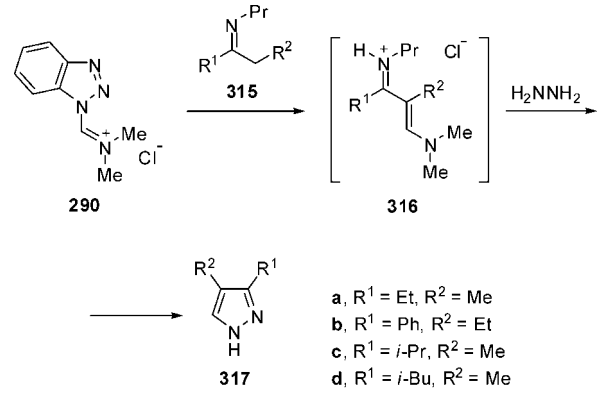
Condensation of 1,4-diphenylsemicarbazide with formaldehyde and benzotriazole carried out in refluxing benzene with a Dean−Stark trap provides 1,1,4-trisubstituted semicarbazide **313**. Using $ZnBr_2$ catalyst, the iminium ion generated from **313** by cleavage of the benzotriazolyl−C bond is trapped by a vinyl group in CH_2=CHOEt, leading to pyrazolidine **314**, separated in 60% yield (Scheme 87).[105]

The most popular method for the preparation of pyrazoles unsubstituted at the nitrogen atoms involves condensation of hydrazine with β-dicarbonyl compounds. However, such

Scheme 87



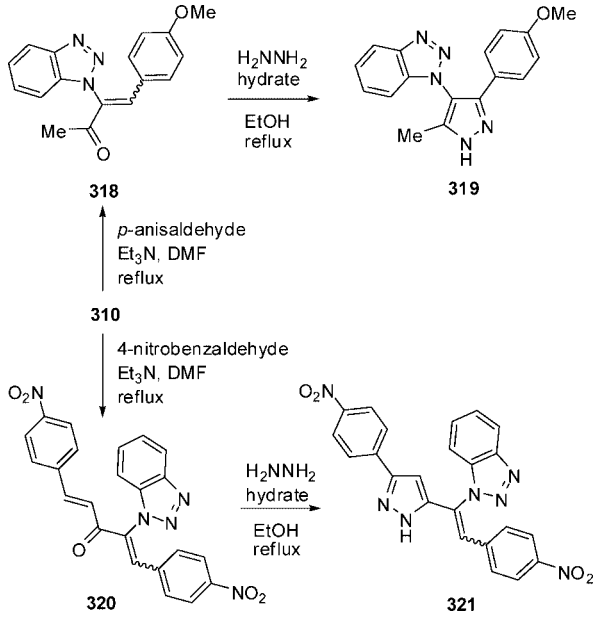
Scheme 88



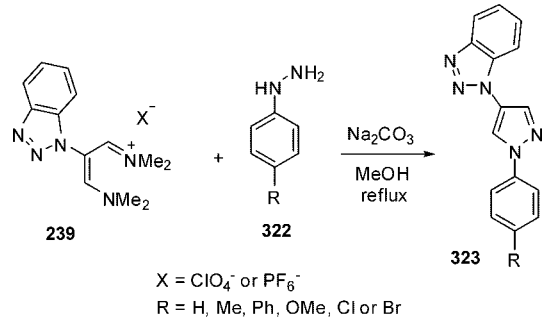
compounds are not always readily available. Various derivatives that can be considered to be synthetic equivalents of β-dicarbonyl compounds may simplify the process. An example of such reactions is given in Scheme 88. Thus, salt **290**, a Vilsmeier-type reagent, reacts with *N*-propylimines **315** generated from simple ketones to give enamino−iminium salts **316**. In situ treatment with hydrazine converts salts **316** into 3,4-disubstituted pyrazoles **317**. The synthesis proceeds well when imines **315** are derived from symmetrical ketones, when substituent R^1 is unreactive (**315b** and **315c**), or when there is a significant difference in steric hindrance between both substituents (**315d**). In the last case, pyrazole **317d** is contaminated with a minor isomer (5%) formed by condensation of salt **290** with the isobutylmethylene group. For sterically less differentiated groups, regioselectivity is poor; e.g., for **315e** (R^1 = *n*-Bu, R^2 = Et), the ratio of regioisomers in the corresponding pyrazoles **317** is 55:45. Despite these limitations and moderate yields, 31−83%, the simplicity of this method makes it an attractive alternative in pyrazole synthesis.[116]

Condensation of equimolar amounts of **310** with *p*-anisaldehyde in refluxing DMF in the presence of a catalytic amount of triethylamine gives benzotriazol-1-ylchalcone **318** in 81% yield. Chalcone **318** reacts readily with hydrazine to provide 3,4,5-trisubstituted pyrazole **319** in 73% yield. This addition/cyclocondensation process must proceed through a corresponding pyrazoline that is oxidized under the reaction conditions to pyrazole **319** without elimination of benzotriazole. When an excess of 4-nitrobenzaldehyde is used in the condensation with **310**, both the methylene and the methyl groups react to give dibenzylideneacetone **320** in 81% yield. In a reaction with hydrazine, the unsubstituted ben-

Scheme 89



Scheme 90



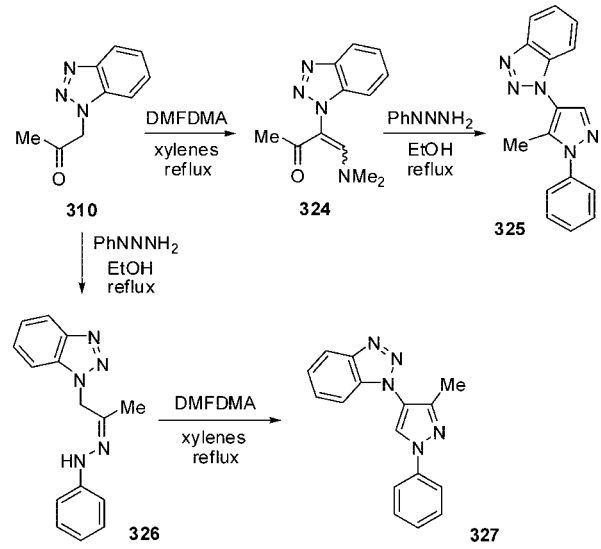
zylidene site in **320** is favored, providing pyrazole **321** in 61% yield (Scheme 89).[117]

2-Benzotriazol-1-ylvinamidinium salts **239** are convenient reagents for the preparation of pyrazoles with a benzotriazolyl substituent at C-4. In their reactions with arylhydrazines **322** and sodium carbonate in refluxing methanol, salts **239** are converted into pyrazoles **323** in 75% (R = OMe) to 91% (R = Br) yields (Scheme 90).[99]

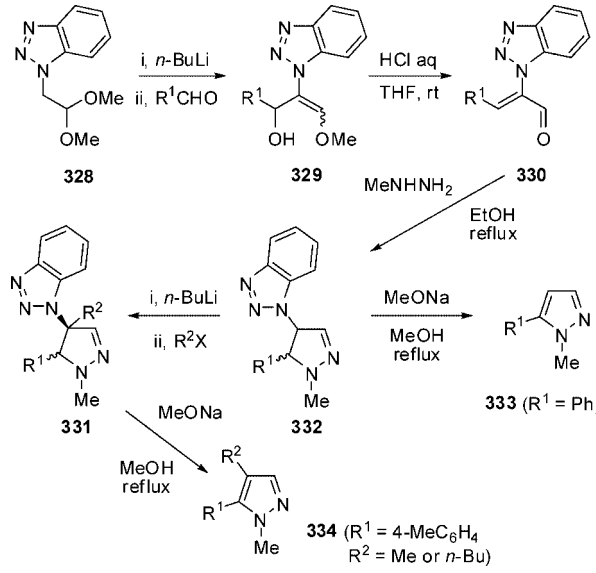
In another approach to 4-benzotriazol-1-ylpyrazoles, **310** is treated with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) to give enaminone **324** (74% yield). Cyclocondensation of **324** with phenylhydrazine provides 1,4,5-trisubstituted pyrazole **325** in 74% yield. Using the same reagents but in the reversed order converts **310** into a different regioisomer, 1,3,4-trisubstituted pyrazole **327** (70% yield), via phenylhydrazone **326** (85% yield) (Scheme 91).[115a]

When aldehydes replace ketones, pyrazoles unsubstituted at C-3 result. Thus, condensation of benzotriazole with chloroacetaldehyde dimethyl acetal provides benzotriazol-1-yl derivative **328** as the main product (60% yield) and its benzotriazol-2-yl analogue as a minor product (21% yield). Treatment of lithiated acetal **328** with aldehydes results in alcohols **329** (83−86% yields). Aqueous HCl converts alcohols **329** to α,β-unsaturated aldehydes **330** in a practically quantitative manner. Addition/cyclocondensation reactions of aldehydes **330** with methylhydrazine provide pyrazolines **332** (57−87% yields) that on treatment with bases can be converted to 1,5-disubstituted pyrazoles, e.g., **333**

Scheme 91



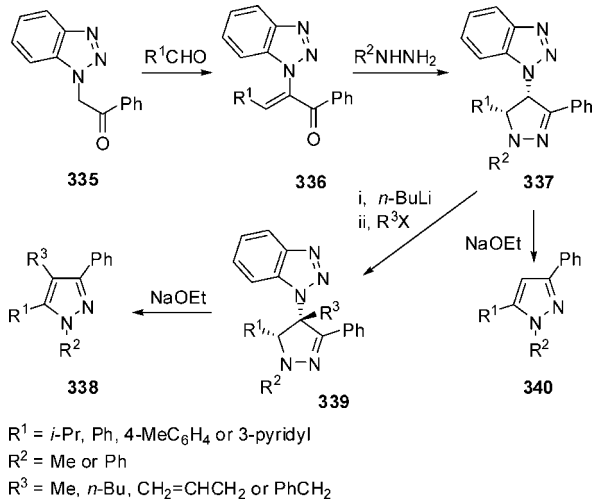
Scheme 92



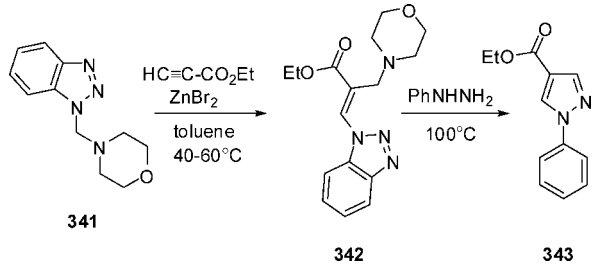
(75% yield). Alternatively, alkylation of lithiated pyrazolines **332** converts them to pyrazolines **331** that eliminate benzotriazole under basic conditions to furnish 1,4,5-trisubstituted pyrazoles **334** (52−79% yields). The process is not limited to aromatic aldehydes nor the benzotriazol-1-yl derivatives shown in Scheme 92, since similarly good results are also reported for R^1 = phenethyl and benzotriazol-2-yl analogues of compounds **328**−**332**.[118]

α,β-Unsaturated ketones with a benzotriazolyl substituent at the α-C can be easily prepared by condensation of 2-benzotriazol-1-ylacetophenone (**335**) with aldehydes in the presence of a piperidine catalyst. The *Z* isomers of α,β-unsaturated ketones **336** are formed exclusively and are isolated in 55% (R^1 = 3-pyridyl) to 71% (R^1 = Ph) yields. Treatment with hydrazines converts **336** into *cis*-substituted pyrazolines **337** that are isolated in 51% (R^1 = Ph, R^2 = Me) to 80% (R^1 = R^2 = Ph) yields. Elimination of benzotriazole from pyrazolines **337** in the presence of bases furnishes pyrazoles **340** in 81−94% yields. Lithiation of pyrazolines **337** at C-4 followed by treatment with alkylating agents provides pyrazolines **339** in 73−95% yields. Subsequent elimination of benzotriazole initiated by a base converts

Scheme 93



Scheme 94



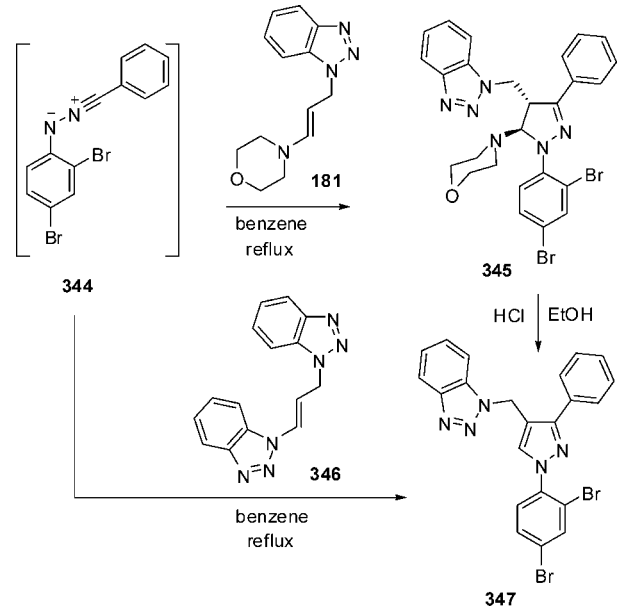
pyrazolines **339** into 1,3,4,5-tetrasubstituted pyrazoles **338** in 85−95% yields (Scheme 93).[119]

For preparation of pyrazoles substituted at C-4 and unsubstituted at C-3 and C-5, the method shown in Scheme 94 is a good option. Thus, addition of *N*-(benzotriazol-1-ylmethyl)morpholine (**341**) to ethyl propiolate catalyzed by $ZnBr_2$ provides adduct **342** in 80% yield. Apart from the *E* isomer **342**, minor benzotriazol-2-yl analogues and *Z* isomers are detected by NMR in the reaction mixture. Heating with phenylhydrazine converts **342** into pyrazole **343** in 75% yield. This step must involve oxidation by atmospheric oxygen to convert the intermediate pyrazoline, which forms first by cyclocondensation of **342** with phenylhydrazine and elimination of the benzotriazole and morpholine, into pyrazole **343** (Scheme 94).[120]

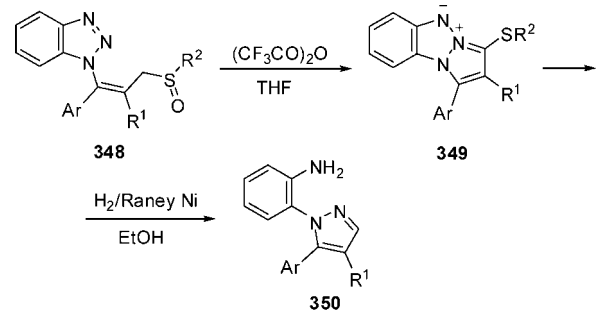
1,3-Dipolar cycloaddition of 1-(3-morpholin-4-ylallyl)benzotriazole[85] (**181**) to nitrilimine **344**, generated in situ from the corresponding phenylhydrazonyl bromide in refluxing benzene,[121] provides pyrazoline **345** in 70% yield. In the following treatment with hydrochloric acid in ethanol at room temperature, pyrazoline **345** eliminates morpholine to furnish pyrazole **347** (90% yield). 1,3-Bisbenzotriazol-1-ylpropene (**346**), prepared from epichlorohydrin and benzotriazole followed by thionyl chloride and finally sodium hydride, reacts with nitrilimine **344** to give directly pyrazole **347** in 80% yield; in this case, benzotriazole must be eliminated from an unstable 5-benzotriazol-1-ylpyrazoline intermediate (Scheme 95).[122]

In the special case shown in Scheme 96, two of the benzotriazolyl nitrogens are used to generate the pyrazole ring. Thus, treated with trifluoroacetic anhydride, sulfoxides **348** undergo conversion to triazapentalenes **349** in high yields. The process must involve acylation of the sulfoxide oxygen atom and generation of a carbocation (Pummerer

Scheme 95



Scheme 96

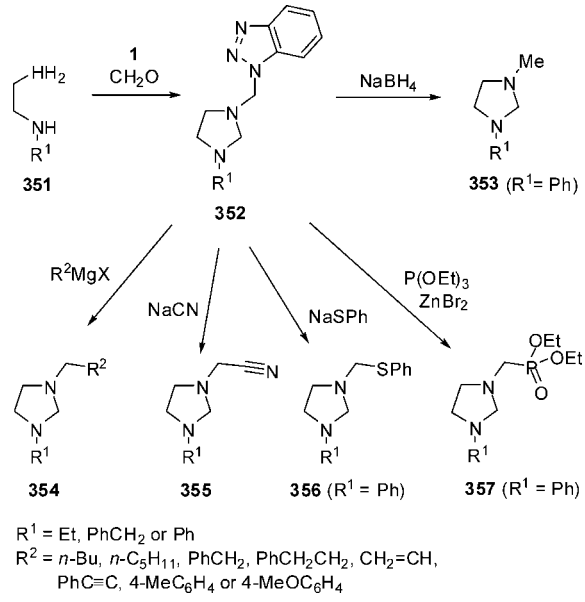


reaction) that attacks the N-2 atom of benzotriazole. Hydrogenation over Raney nickel cleaves the C−S bond and one of the N−N bonds to generate 1-(2-aminophenyl)pyrazoles **350**.[123]

8.2. Imidazole

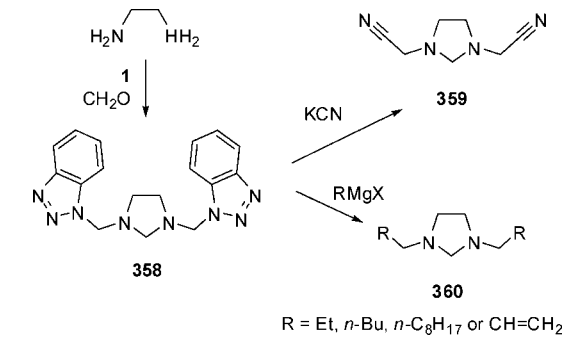
Condensations of *N*-monosubstituted ethylenediamines **351** with 2 molar equiv of formaldehyde (as a 37% aqueous solution) and 1 equiv of benzotriazole provide 1,3-disubstituted imidazolidines **352** in high yields (85−96%). For R^1 = Ph, the benzotriazol-1-yl isomer **352** is the only product; in other cases, the benzotriazol-2-yl isomers are also present as the minor components in crude product mixtures. Because there is no significant difference in their reactivity, both isomers give the same products on treatment with nucleophiles. Thus, in reactions with Grignard reagents, the benzotriazolyl moiety is replaced by an alkyl, vinyl, phenylethynyl, or aryl group to give imidazolidines **354** in 63−96% yields. Similarly, compound **352** reacts with sodium cyanide to form nitriles **355** (77−97% yields). Additional reactions of one of the imidazolidines **352** (R^1 = Ph) with sodium borohydride, benzenethiol and sodium hydride, or triethyl phosphite and $ZnBr_2$ demonstrate easy substitution of the benzotriazolyl moiety by a hydrogen atom (**353**, 96%

Scheme 97



R^1 = Et, $PhCH_2$ or Ph
R^2 = *n*-Bu, *n*-C_5H_{11}, $PhCH_2$, $PhCH_2CH_2$, CH_2=CH, PhC≡C, 4-MeC_6H_4 or 4-$MeOC_6H_4$

Scheme 98



R = Et, *n*-Bu, *n*-C_8H_{17} or $CH=CH_2$

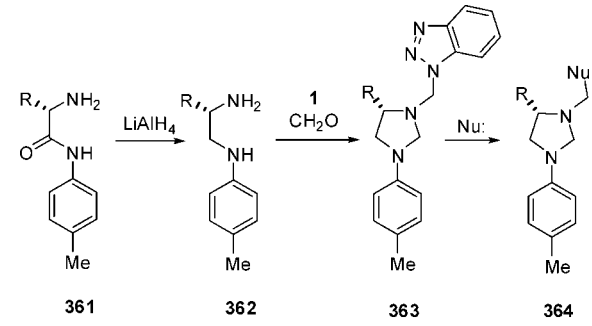
yield), a phenylthio group (**356**, 66% yield), or a phosphonate group (**357**, 70% yield) (Scheme 97).[124]

Condensation of ethylenediamine with 3 molar equiv of formaldehyde and 2 equiv of benzotriazole provides 1,3-bis(benzotriazol-1-ylmethyl)imidazolidine (**358**) together with its minor benzotriazol-1-yl/2-yl isomer. The reaction of crude **358** with KCN in refluxing acetonitrile gives dinitrile **359** in 88% yield. Treatment with Grignard reagents converts **358** into 1,3-dialkylimidazolidines **360** in 68−75% yields (Scheme 98).[63]

Commercially available *N*-Boc-protected α-amino acids can be converted in two easy steps into amides **361** by coupling with *p*-toluidine and deprotection of the amino group. Reduction of amides **361** with $LiAlH_4$ gives optically active diamines **362**. Condensation of these diamines with formaldehyde and benzotriazole provides single enantiomers of 3-(benzotriazol-1-ylmethyl)imidazolidines **363** in 85−93% yields. Subsequent reactions with nucleophiles allow substitution of the benzotriazole moiety by various functional groups, resulting in chiral 1,3,4-trisubstituted imidazolidines **364** (Scheme 99).[124]

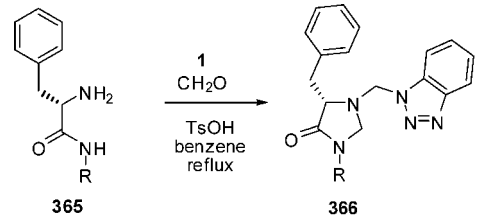
Under forcing conditions, refluxing under a Dean−Stark trap of benzene solutions, amides **365** undergo condensation with formaldehyde (generated by depolymerization of paraformaldehyde in the presence of TsOH) and benzotriazole to give 1,3,4-trisubstituted imidazolidin-5-ones **366** that are isolated as mixtures with their minor benzotriazol-2-yl isomers (isomeric ratio of 3:1 to 5:1) in 91−94% yields (Scheme 100).[125]

Scheme 99



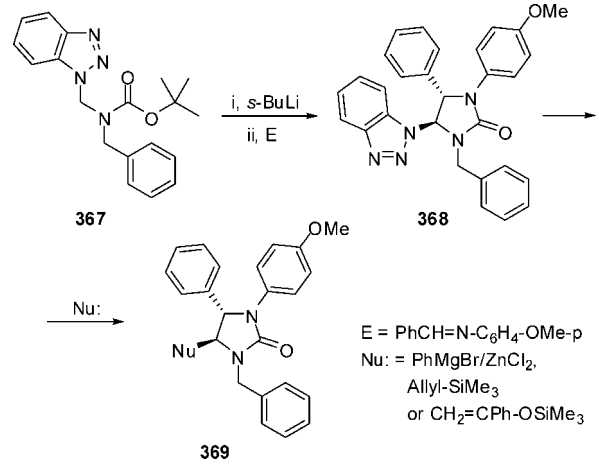
R = Me, *i*-Bu or $PhCH_2$
Nu: = $NaBH_4$, RMgX, NaCN, PhSNa, or $P(OEt)_3$

Scheme 100



R = 4-MeC_6H_4, *c*-C_6H_{11} or $PhCH_2$

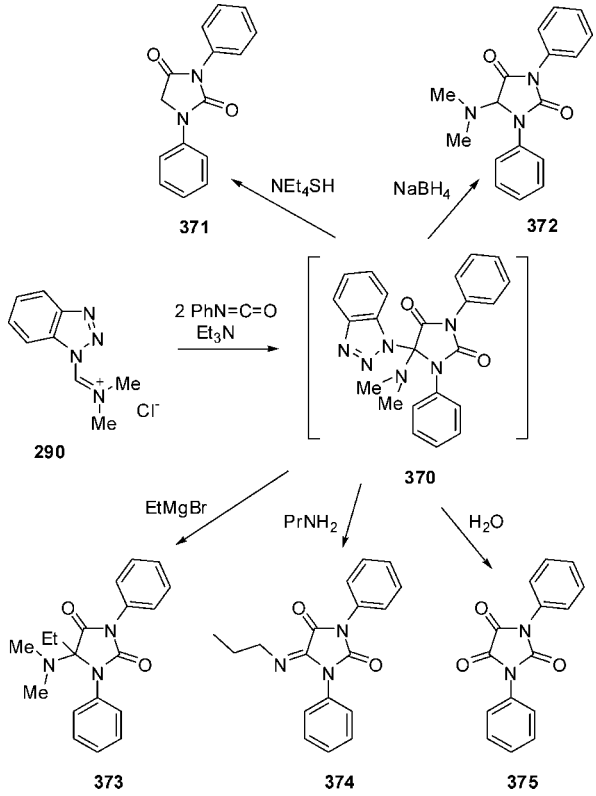
Scheme 101



N-Benzotriazol-1-ylmethyl derivatives of BOC-protected amines behave similarly to amides. Thus, treatment of the anion derived from compound **367** with *N*-benzylidene-*p*-anisidine leads to imidazolidin-2-one **368** (82% yield) with the substituents at C-4 and C-5 oriented *trans*. Subsequent treatment with nucleophiles gives products **369** stereoselectively in 64−68% yields (Scheme 101).[126]

The aminocarbene generated by treatment of iminium chloride **290** with triethylamine undergoes [1 + 2 + 2] cycloaddition with phenyl isocyanate to give imidazolidine-2,4-dione **370**. Quenching the reaction mixture with tetraethylammonium hydrogen sulfide results in reduction of the C-5 functionality to give 1,3-diphenylimidazolidine-2,4-dione (1,3-diphenylhydantoin, **371**)in 35% yield. On treatment of **370** with sodium borohydride, only the benzotriazolyl moiety is replaced by a hydride to give 5-(dimethylamino)hydantoin **372** in 51% yield. Similarly, hydantoin **373** (56% yield) is generated in a reaction of **370** with ethylmagnesium bromide. Analogous quenching of the reaction mixture with methanol or morpholine replaces the benzotriazolyl moiety by a

Scheme 102



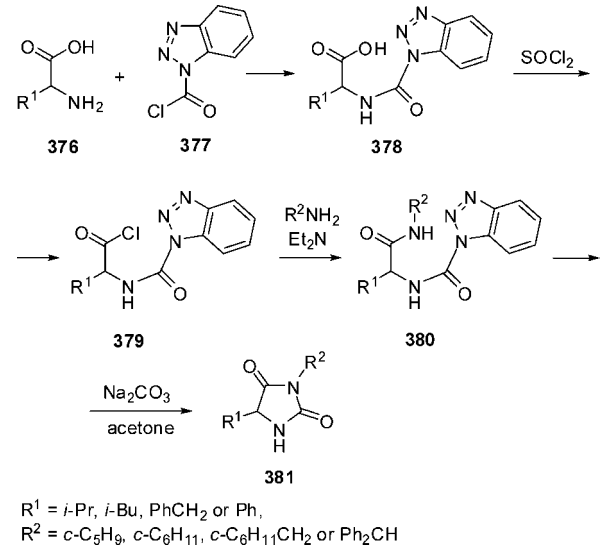
methoxy (57% yield) or morpholin-4-yl group, respectively, without affecting the dimethylamino substituent. However, when propylamine is used as a nucleophile, both the benzotriazolyl and the dimethylamino groups are eliminated to give 5-(*N*-propylimino) derivative **374** (54% yield). A simple workup of the mixture containing intermediate **370** with water results in imidazolidine-2,4,5-trione **375** in 67% yield (Scheme 102).[111]

1-(Chloroformyl)benzotriazole (**377**), prepared in a reaction of benzotriazole with phosgene[127,128] or more conveniently with triphosgene,[129] reacts with amino acids **376** to give derivatives **378**. Treatment with thionyl chloride converts acids **378** into acid chlorides **379** that are subsequently treated with amines to give amides **380**. Under mildly basic conditions, sodium carbonate in acetone, amides **380** undergo cyclocondensation with elimination of benzotriazole to furnish hydantoins **381** in 24% (R^1 = Ph, R^2 = Ph_2CH) to 88% (R^1 = Me_2CHCH_2, R^2 = Ph_2CH) yields (Scheme 103).[130,131]

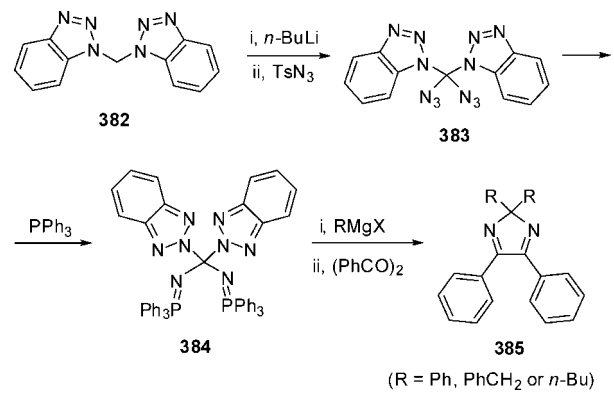
Lithiation of bisbenzotriazol-1-ylmethane (**382**) followed by treatment with tosyl azide gives diazide **383** in 22% yield. In a reaction with triphenylphosphine, diazide **383** is converted into bis(triphenylphosphoranylidene) derivative **384**. Despite the fact that **384** is not stable enough to provide an analytical sample, thorough NMR studies of the crude material reveal that the benzotriazol-1-yl substituents have rearranged to the sterically less hindered -2-yl forms. Consecutive treatments of crude **384** with Grignard reagents followed by benzil lead to 2*H*-imidazoles **385**, although the yields of isolated products are low (15−21%) (Scheme 104).[132]

The anion derived from isocyanide **227**, on treatment with *t*-BuOK, adds readily to Schiff bases to form imidazolines **386**. Under stronger basic conditions, imidazolines **386** eliminate benzotriazole to produce imidazoles **387**. This

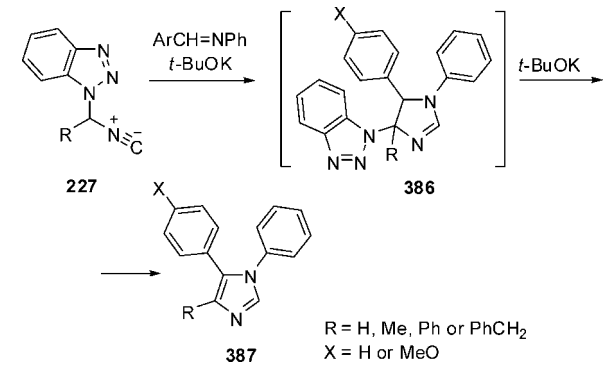
Scheme 103



Scheme 104



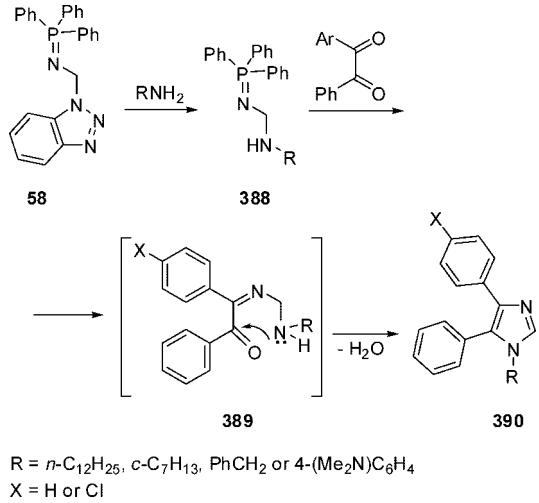
Scheme 105



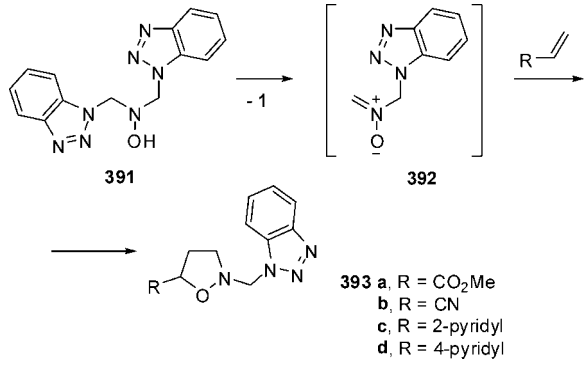
simple synthetic method provides 1,5-diarylimidazoles **387** in 23% (R = Ph) to 85% (R = H) yields (Scheme 105).[94]

Displacement of benzotriazole in **58** by primary amines provides derivatives **388** that are treated in situ with benzil to give imidazoles **390** (X = H) in 81−84% yields. With 4-chlorobenzil, the nucleophilic attack occurs primarily on the carbonyl group attached to the 4-chlorophenyl ring, leading to intermediates **389** that undergo cyclization with elimination of water to give 4-(4-chlorophenyl)imidazoles **390** (X = Cl). Identification of the substituents in a molecule of imidazole **390** with R = $PhCH_2$ and X = Cl is provided by X-ray crystallography (Scheme 106).[133]

Scheme 106



Scheme 107

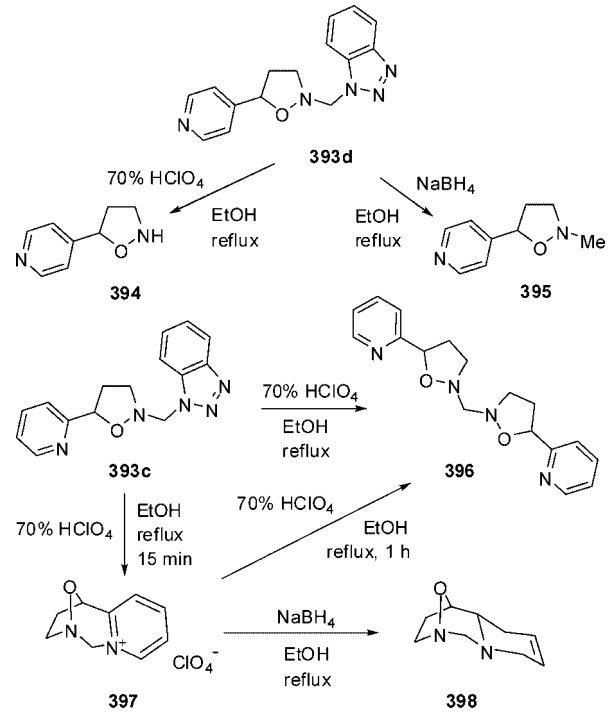


8.3. Isoxazole

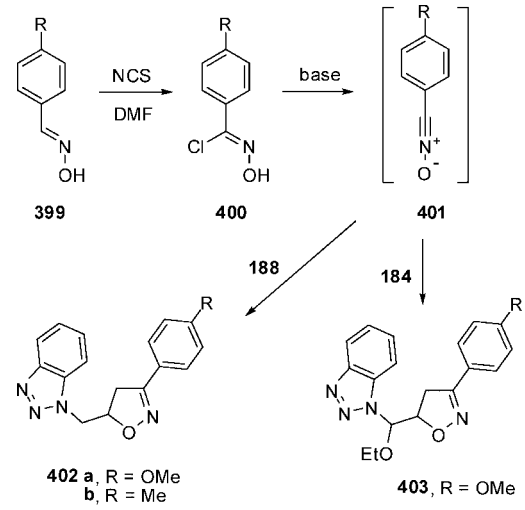
N,*N*-Bis(benzotriazol-1-ylmethyl)hydroxylamine (**391**) is easily prepared by condensation of 1-(hydroxymethyl)benzotriazole with hydroxylamine.[22] At elevated temperatures, in refluxing toluene, **391** eliminates a molecule of benzotriazole to give nitrone **392**, which can be readily trapped by 1,3-dipolarophiles. Thus, with methyl acrylate in refluxing toluene for 16 h, **391** gives isoxazolidine **393a** quantitatively and with acrylonitrile isoxazolidine **393b** in 88% yield. Pyridyl derivatives **393c** (83% yield) and **393d** (81% yield) are obtained in the same manner from the corresponding vinylpyridines. The electron-withdrawing ability of the alkene substituent R seems to be a determining factor, as no such reaction of **391** is observed with styrene. Use of 1,2-disubstituted alkenes, e.g., dimethyl fumarate or *N*-methylmaleimide, allows preparation of 1,3,4-trisubstituted isoxazolidines in this manner (Scheme 107).[134]

Removal of the benzotriazol-1-ylmethyl substituent from the isoxazolidine ring in **393** can be achieved by heating their ethanolic solutions with perchloric acid. Thus, compound **393d** undergoes straightforward hydrolysis to 5-(4-pyridyl)isoxazolidine (**394**) in 46% yield. Sodium borohydride reduces the benzotriazol-1-ylmethyl group in **393d** to a methyl group, furnishing isoxazolidine **395** in 68% yield. A similar reaction of **393c** gives the corresponding 1-methylisoxazolidine in 60% yield. However, involvement of the pyridyl nitrogen atom during hydrolysis of **393c** complicates the process, leading to bridged tricyclic system **397**, isolated in 64% yield after 15 min of reflux. To prove its structure, pyridinium salt **397** was reduced with sodium borohydride

Scheme 108



Scheme 109

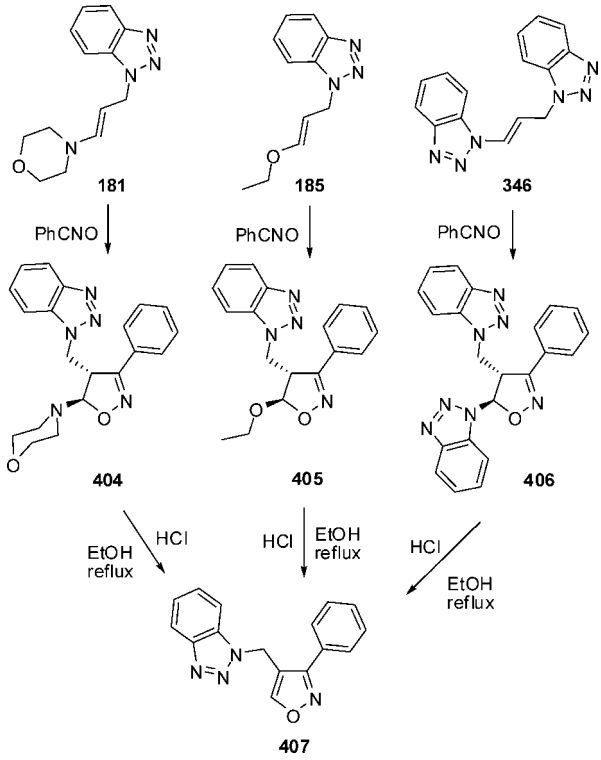


to 12-oxa-1,3-diazatricyclo[7.2.1.0^{3,8}]dodec-5-ene (**398**). Prolonged heating of **393c** with perchloric acid results in dimeric product **396** (85% yield) (Scheme 108).[134]

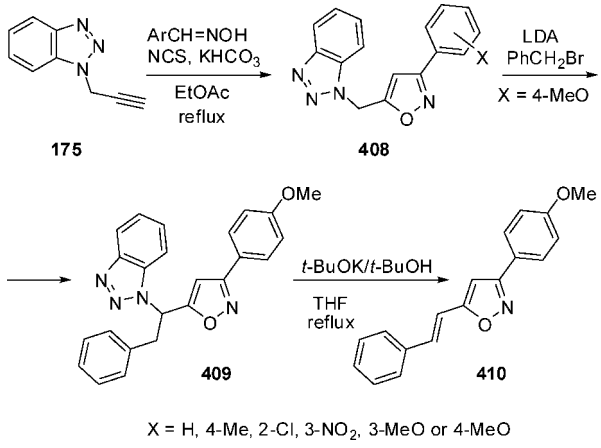
Treated with NCS, oximes **399** are readily converted into benzhydroximoyl chlorides **400**.[135,136] Exposed to mild bases, chlorides **400** eliminate HCl to give reactive benzonitrile oxides **401**.[121] When **188** is added, oxides **401** are trapped in a 1,3-dipolar cycloaddition reaction to give isoxazolines **402** in 94−100% yields. A similar reaction with ethoxy derivative **184** provides isoxazoline **403** in 81% yield. In all these products, the benzotriazol-1-ylmethyl moiety is located at C-5 of the isoxazoline ring (Scheme 109).[137]

However, an opposite orientation of the reacting molecules is required in a 1,3-dipolar cycloaddition of 1-allylbenzotriazoles bearing an electron-donating substituent at C-3. Thus, **181**[85] adds to benzonitrile oxide to provide isoxazoline **404** in 70% yield. Analogous reactions of benzonitrile oxide with **185** and **346** give isoxazolines **405** (80% yield) and **406** (65% yield), respectively. For

Scheme 110



Scheme 111

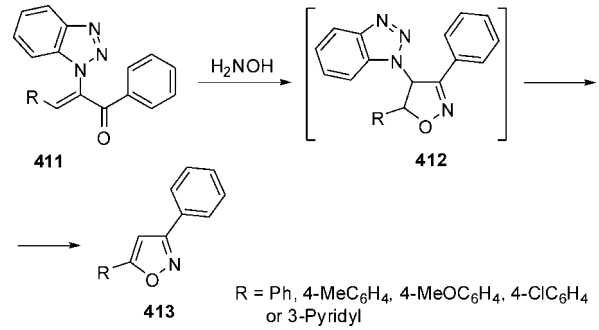


isoxazolines **404**−**406**, NMR spectra indicate a *trans* orientation of the substituents at C-4 and C-5. On treatment with hydrochloric acid in ethanol at reflux, isoxazolines **404**−**406** eliminate the substituent at C-5 to furnish isoxazole **407** in approximately 90% yield (Scheme 110).[122]

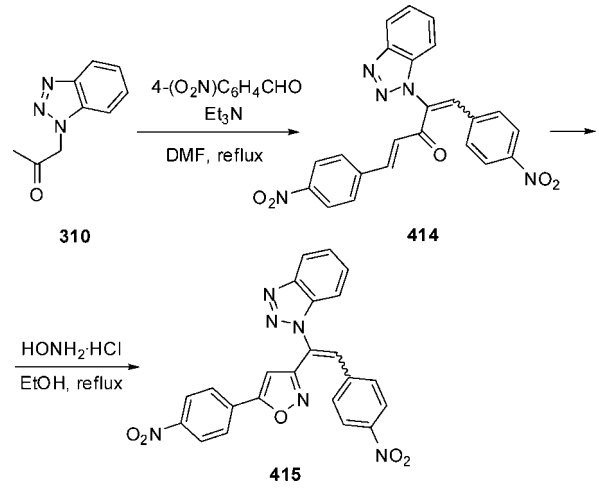
In a simplified procedure, **175** is heated with benzaldehyde oximes, NCS, and wet $KHCO_3$ to give directly in one pot 3-aryl-5-(benzotriazol-1-ylmethyl)isoxazoles **408** in 52% (X = 3-NO_2) to 100% (X = H) yields. In this conversion, the intermediate benzonitrile oxides, generated by consecutive reactions of the oximes with NCS and $KHCO_3$, undergo [3 + 2] cycloadditions with the propargyl triple bond to generate the isoxazole ring. To test possible pathways for the elimination of the benzotriazole moiety from oxazoles **408**, one of them (X = 4-MeO) is benzylated at C-α to give derivative **409**, which is subsequently treated with *t*-BuOK to furnish 4-styrylisoxazole **410** in 63% yield (Scheme 111).[137]

Condensation of **335** with aromatic aldehydes readily provides chalcones **411** bearing a benzotriazol-1-yl substituent at C-α. In a reaction with hydroxylamine, chalcones **411** are converted to 4-benzotriazol-1-ylisoxazolines **412** that spontaneously eliminate benzotriazole to provide 3,5-disubstituted isoxazoles **413** in 55−81% yields (Scheme 112).[119]

Scheme 112



Scheme 113



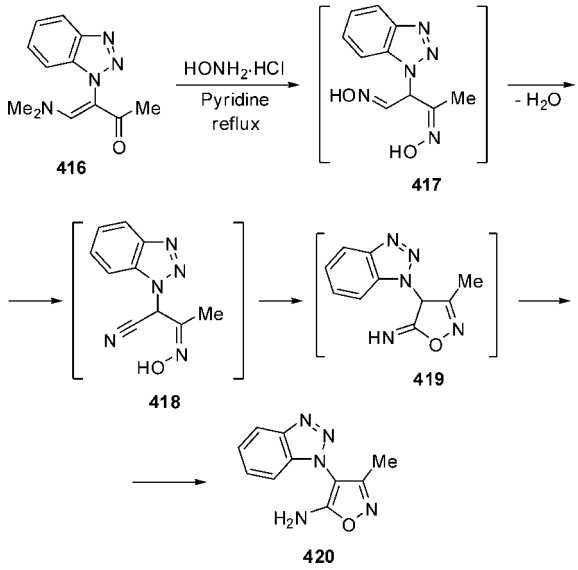
Condensation of **310** with 2 molar-equivalents of 4-nitrobenzaldehyde provides 1,4-pentadien-3-one **414** in 81% yield. In a reaction with hydroxylamine, only the double bond in derivative **414** without a benzotriazolyl substituent is affected to give isoxazole **415** in 79% yield. This process must involve an oxidation step (probably by the atmospheric oxygen) of an isoxazoline intermediate (Scheme 113).[117]

Condensation of **310** with *N*,*N*-dimethylformamide dimethyl acetal in refluxing xylene gives enaminone **416** in 74% yield. With an excess of hydroxylamine hydrochloride, enaminone **416** is converted into 5-aminoisoxazole **420** in 68% yield. The process is assumed to go through dioxime **417**, which loses a molecule of water to give α-cyanooxime **418**. An intramolecular addition of the OH to the CN group in **418** gives 5-iminoisoxazoline **419**, which is converted to the more stable tautomeric form **420** (Scheme 114).[115]

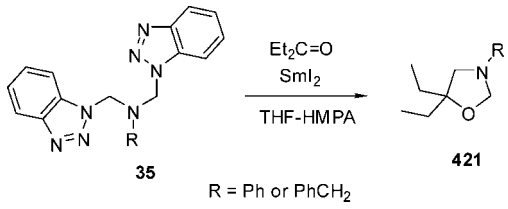
8.4. Oxazole

Similarly to the reaction shown in Scheme 26, the radicals generated by treatment of *N*,*N*-bis(benzotriazolylmethyl)amines **35** with SmI_2 are trapped by diethyl ketone, leading to oxazolidines **421**; however, the yields are low (30−38%) (Scheme 115). In this case, generally better results are obtained when *N*,*N*-bis(tosylmethyl)amines are used instead of derivatives **35**.[138]

Scheme 114



Scheme 115



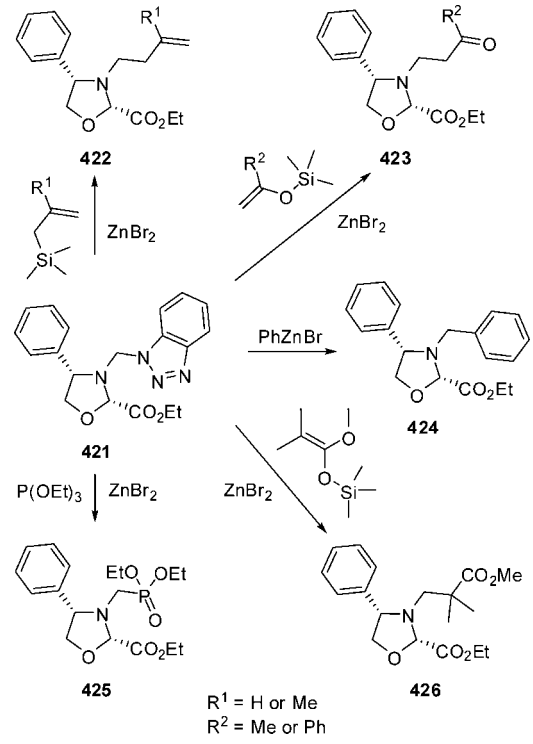
Cyclocondensation of (*S*)-2-phenylglycinol with ethyl glyoxylate, benzotriazole, and formaldehyde provides oxazolidine **421** in 80% yield. In reactions with allyltrimethylsilane and (2-methylallyl)trimethylsilane catalyzed by $ZnBr_2$, the benzotriazolyl moiety in oxazolidine **421** is readily substituted to give corresponding oxazolidines **422** in 66% and 69% yield, respectively. Similar reactions of **421** with trimethylsilyl enolates provide ketones **423** in 56% (R^2 = Me) and 70% (R = Ph) yields. Phenylzinc bromide reacts with **421** to give 3-benzyloxazolidine **424** in 57% yield; however, aliphatic organozinc reagents fail to give analogous products. In a similar manner, **421** reacts with triethyl phosphite to give phosphate **425** in 78% yield and with 1-methoxy-2-methyl-1-[(trimethylsilyl)oxy]propene to give ester **426** in 80% yield. In all these reactions, the chirality at C-2 and C-4 is preserved (Scheme 116).[139]

1-(*N*-benzylthiocarbamoyl)benzotriazole (**427**) is prepared from benzylamine and bisbenzotriazol-1-ylmethanethione in 97% yield.[140] The isothiocyanate anion generated from **427** by 2 molar equiv of potassium *tert*-butoxide adds to carbonyl groups of ketones to generate oxazolidinethiones **428**, which are isolated in 27% (R = Ph) to 51% (R = 2-thienyl) yields (Scheme 117).[141]

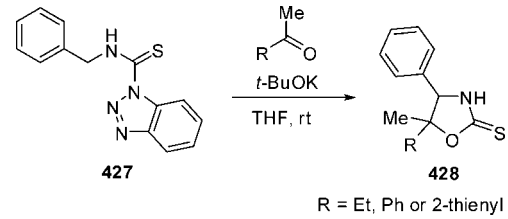
Cyclocondensation of acylbenzotriazoles **167** with 2-amino-2-methyl-1-propanol under microwave irradiation produces 2-oxazolines **429**. To prevent hydrolysis leading to side products, $SOCl_2$ is added to the mixture after initial heating at 80 °C for 10 min, and heating is then continued for an additional 2 min. In this way, high yields of oxazolines **429** (85−97%) are obtained. Use of (*S*)-2-amino-3-phenyl-1-propanol allows the preparation of chiral (*S*)-4-benzyl-2-phenyl-2-oxazoline (**430**) in 82% yield (Scheme 118).[142]

1-Imidoylbenzotriazoles **431** are prepared in a reaction of 1-acylbenzotriazoles **167** with isocyanates or a reaction of

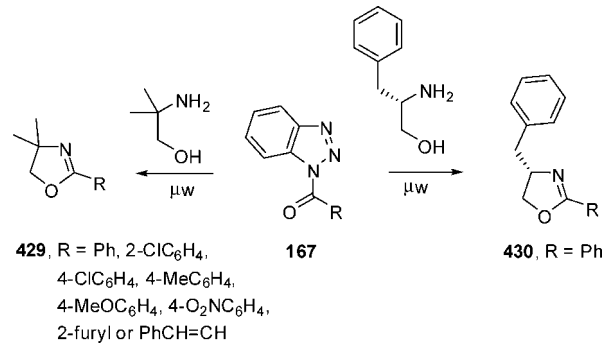
Scheme 116



Scheme 117



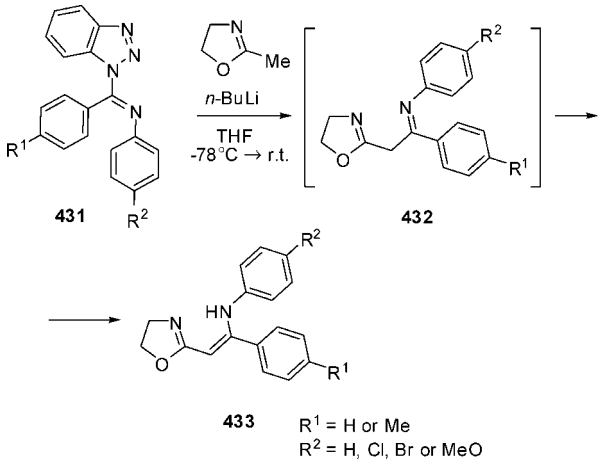
Scheme 118



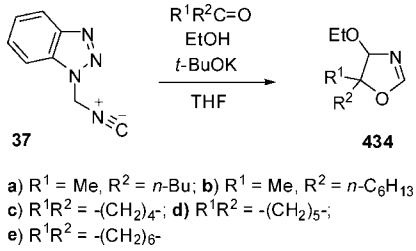
thionyl benzotriazolide with amides. Lithiated 2-methyl-2-oxazoline reacts readily with compounds **431** to give enamines **433** in 82−96% yields. Imidoyl intermediates **432** are not detected by NMR in the product mixtures due to their rapid tautomerization to forms **433** that are stabilized by strong intramolecular hydrogen bonding between their nitrogen atoms (Scheme 119).[143]

The anion derived from isonitrile **37** (BetMIC) on treatment with potassium *tert*-butoxide readily adds to the carbonyl groups of ketones. The benzotriazolyl moiety in the intermediates is substituted by an ethoxy group from the added ethanol to give 4-ethoxyoxazolines **434**. The reaction provides high yields of the products derived from acyclic ketones (93% for **434a** and 92% for **434b**) and moderate

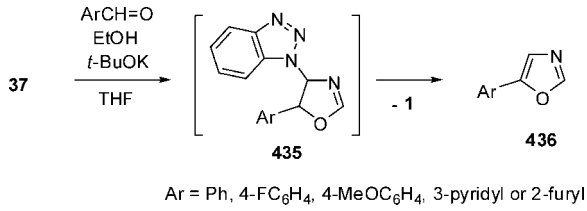
Scheme 119



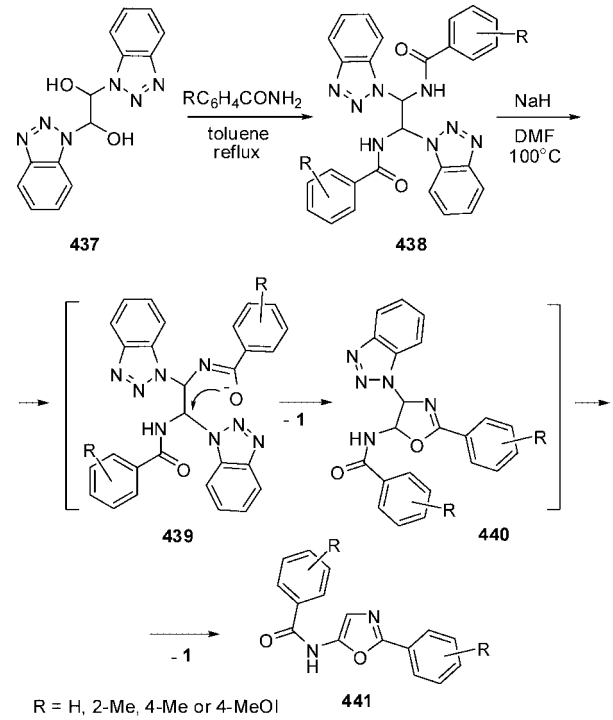
Scheme 120



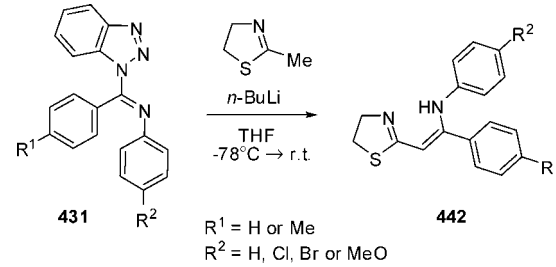
Scheme 121



Scheme 122



Scheme 123



yields for the products derived from cycloalkanones (58−65%) (Scheme 120).[144]

Addition of the anion derived from isonitrile **37** to the carbonyl group of aromatic aldehydes results in oxazolines **435** that spontaneously eliminate benzotriazole to furnish 5-aryloxazoles **436**. The reaction does not differentiate between electron-rich and electron-poor aromatic rings, as the yields of **436** obtained from benzaldehyde (69%), 4-fluorobenzaldehyde (68%), and 4-methoxybenzaldehyde (63%) are comparable, but heteroaromatic aldehydes give significantly lower yields: 35% for 2-furyl and 42% for 3-pyridyl (Scheme 121).[144]

Condensation of benzotriazole with glyoxal in aqueous acetic acid readily provides 1,2-bisbenzotriazol-1-yl-1,2-ethanediol (**437**) almost quantitatively.[33] When **437** is heated with benzamides and a catalytic amount of Amberlyst 15 ion-exchange resin in refluxing toluene with azeotropic removal of water, diamides **438** are obtained in almost quantitative yields. Deprotonation of **438** with NaH gives anions **439** that in a nucleophilic attack on C-β repel the benzotriazolide anion to provide oxazolines **440**. Under the reaction conditions, rapid elimination of the second benzotriazolyl substituent provides oxazoles **441** in 44−62% yields (Scheme 122).[145]

8.5. Thiazole

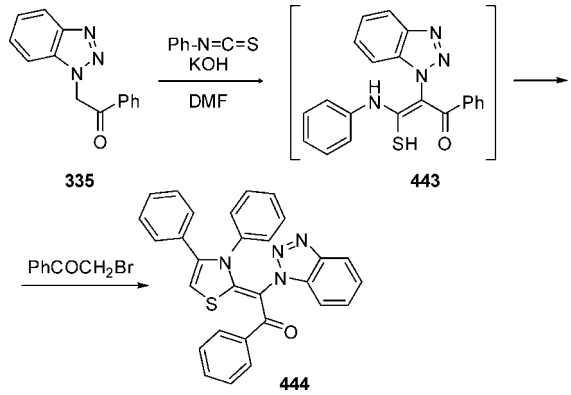
As with the analogous reaction of 2-methyl-2-oxazoline (Scheme 119), lithiated 2-methyl-2-thiazoline reacts with imines **431** to give substituted 2-(β-enamino)-2-thiazolines **442** in good yields (79−98%). Due to possible hydrolysis of the heterocyclic rings, thiazolines **442** and the previously described corresponding oxazolines **433** are considered as masked β-enamino carboxylic acids (Scheme 123).[143]

Addition of **335** to phenyl isothiocyanate provides amino thiol **443**, which is trapped by phenacyl bromide to give 2,3-dihydro-2-(1′-benzotriazol-1-yl-1′-benzoylmethylidene)-3,4-diphenylthiazole (**444**) in 85% yield (Scheme 124).[115]

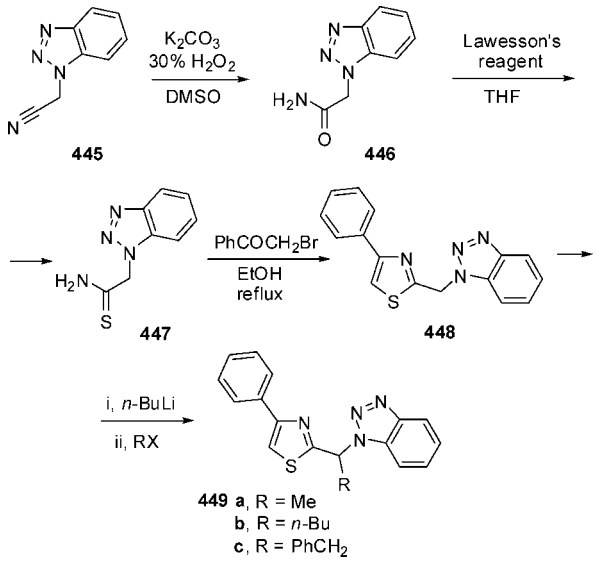
Benzotriazol-1-ylacetonitrile (**445**) is easily prepared by condensation of **30** with NaCN in DMSO.[20] Hydrolysis of nitrile **445** with $H_2O_2/K_2CO_3/H_2O$ gives amide **446** (93% yield), which is subsequently converted to thioamide **447** (83% yield) using Lawesson's reagent. Cyclocondensation of thioamide **447** with phenacyl bromide provides thiazole **448** in 84% yield. Treatment of lithiated **448** with alkyl halides allows monoalkylation of the methylene group to give derivatives **449** in 76−83% yields (Scheme 125).[146]

As is illustrated by transformation of compound **449a**, the lithiation/alkylation process can be repeated to provide thiazoles **450** (86−93% yields) with the methylene groups dialkylated with the same or different substituents. In a

Scheme 124



Scheme 125



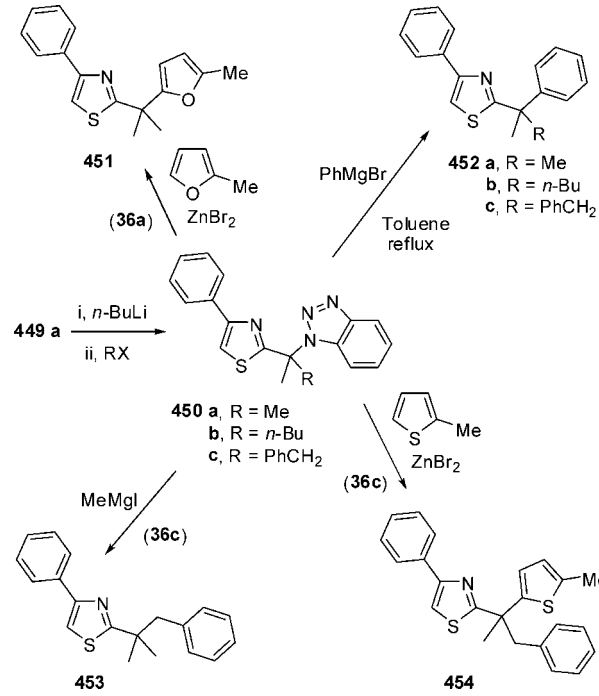
reaction with phenylmagnesium bromide in refluxing toluene, the benzotriazolyl moiety in thiazoles **450** is substituted by phenyl to furnish 2-(α,α-dialkylbenzyl)-4-phenylthiazoles **452** in 54−75% yields. Thiazole **453** is obtained in 58% yield in a similar reaction of **450c** with methylmagnesium iodide. Treatment of **450a** with 2-methylfuran and $ZnBr_2$ in refluxing 1,2-dichloroethane substitutes the benzotriazolyl moiety by furyl to provide thiazole **451** in 65% yield. 2-Methylthiophene reacts similarly with **450c** to give derivative **454** in 82% yield (Scheme 126).[146]

The anion obtained from thiazole **448** can also be trapped by other electrophiles. Thus, lithiated **448** is treated with phenyl or *tert*-butyl isocyanate to provide amides **455** in 87−96% yields. Reduction with zinc/acetic acid in refluxing ethanol removes the benzotriazolyl group to give (4-phenylthiazol-2-yl)acetamides **456** in 73−86% yields (Scheme 127).[146]

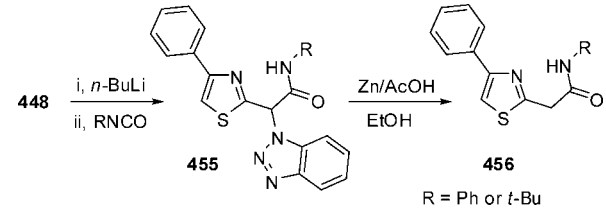
Using higher α-bromo ketones in the reaction shown in Scheme 125 allows substitution of C-5 of the ring. Thus, condensation of thioamide **447** with 2-bromopropiophenone gives thiazole **457** in 59% yield. Subsequent double lithiation/methylation furnishes thiazole **458** in 56% yield. The benzotriazolyl moiety in **458** can be substituted with a phenyl or 5-methylfuryl ring to give thiazole **459** (59% yield) or **460** (70% yield), respectively (Scheme 128).[146]

Diimines **461** are prepared as precipitates in 75−90% yields by stirring aromatic aldehydes with a 10-fold excess of an aqueous or methanolic solution of ammonia. Reactions

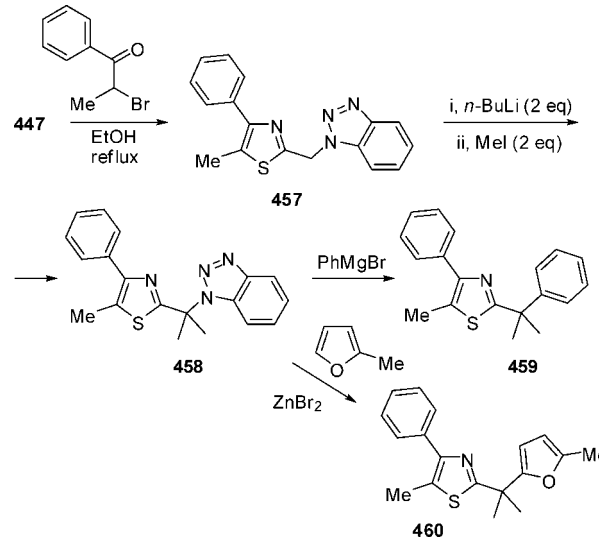
Scheme 126



Scheme 127

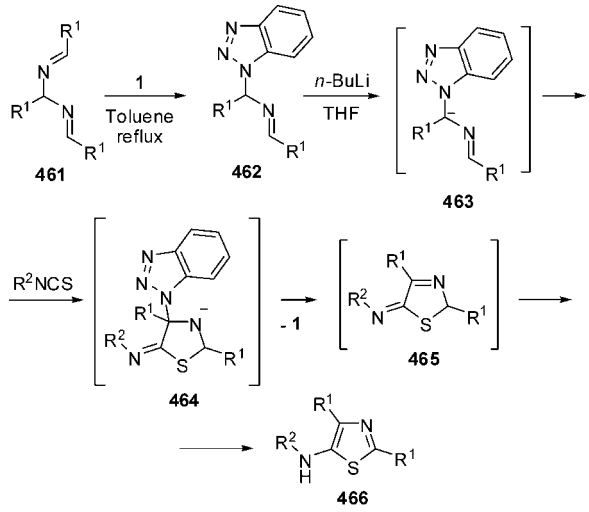


Scheme 128

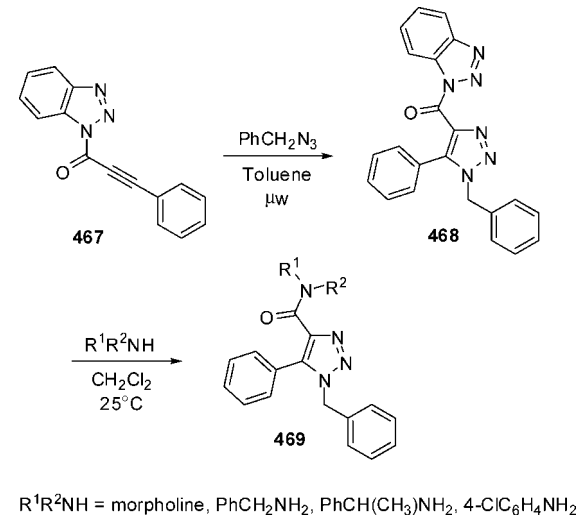


with benzotriazole in refluxing toluene or dioxane convert diimines **461** into imines **462** in 80−92% yields. Treatment of **462** with *n*-butyllithium produces anions **463** that add readily to isothiocyanates to give intermediate anions **464**. Loss of a benzotriazolide anion results in iminothiazole systems **465** that undergo tautomerization to more stable aminothiazoles **466**. This way, 5-aminothiazoles **466** bearing aryl or heteroaryl substituents at C-2 and C-4 are easily

Scheme 129



Scheme 130



prepared in 35% (R^1 = Ph, R^2 = 2-ClC_6H_4) to 81% (R^1 = R^2 = Ph) yields (Scheme 129).[147]

9. Five-Membered Rings with Three or Four Heteroatoms

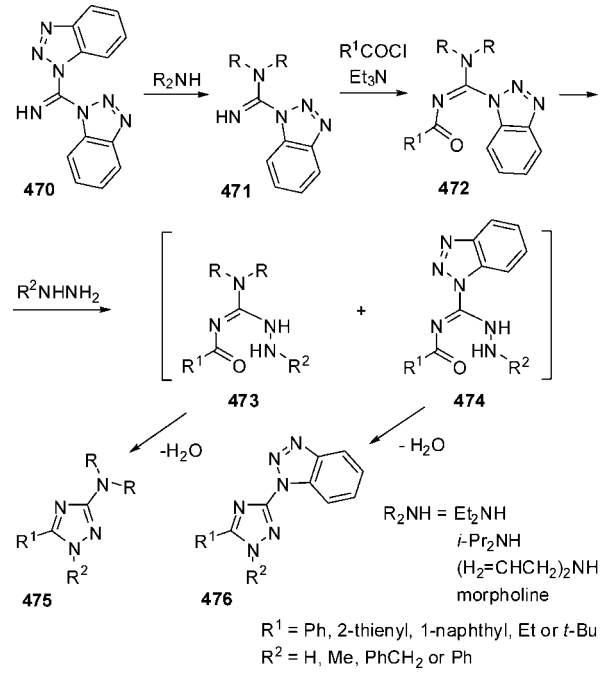
9.1. 1,2,3-Triazole

1-(Phenylpropiolyl)benzotriazole (**467**) is readily prepared by condensation of phenylpropiolic acid with 1-(methylsulfonyl)benzotriazole. Its [3 + 2] cycloaddition with benzyl azide provides smoothly substituted 4-(benzotriazol-1-ylcarbonyl)-1,2,3-triazole **468** in 75% yield. The benzotriazolyl moiety in **468** is easily substituted with amines to give 4-carbamoyl-1,2,3-triazoles **469** in 54−91% yields (Scheme 130).[148]

9.2. 1,2,4-Triazole

A reaction of benzotriazole with cyanogen bromide carried out in ethanol in the presence of NaOH provides bisbenzotriazolylmethanimine (**470**) as a mixture of benzotriazol-1-yl and -2-yl isomers.[149,150] To simplify the picture, only the

Scheme 131

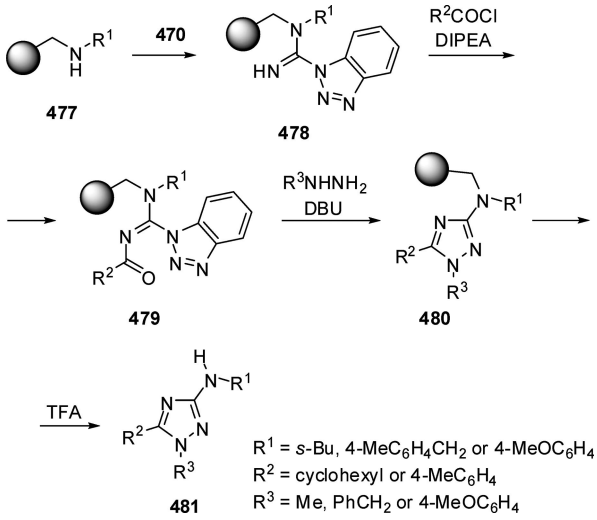


benzotriazol-1-yl isomer is shown in Scheme 131. Treatment with amines converts methanimine **470** under mild conditions into carboxyimidamides **471** as sole benzotriazol-1-yl isomers. Acyl derivatives **472** are prepared in 62−94% yields by treatment of imidates **471** with acyl chlorides and triethylamine in chloroform, and they are stable enough to be purified by column chromatography. Treatment with hydrazines substitutes the benzotriazolyl in **472** to give intermediates **473** that undergo spontaneous cyclocondensation to furnish 3-amino-1,2,4-triazoles **475**. Yields of **475** are high for R^2 = H or Me (72−95%). However, for less nucleophilic hydrazines (R^2 = Ph or $PhCH_2$), elimination of amine can compete with the elimination of benzotriazole, leading to intermediates **474**, and significant amounts of side products **476** (13−30%) are also obtained.[151]

When the reactions depicted in Scheme 131 are carried out on a solid support, no chromatographic purification of intermediates or final products is needed. Thus, amines **477** bound to StratoSpheres PL-FMP resin ((4-formyl-3-methoxyphenoxy)methyl) by a standard solid-phase protocol [$NaBH(OAc)_3$, 1% AcOH/DMF] are treated with **470** to give carboxyimidamides **478** that are washed with THF and subsequently treated with acid chlorides and DIPEA to furnish acylated products **479**. After being washed with dichloromethane and 2-propanol, the resins containing **479** are treated with hydrazines and DBU to give 3-amino-1,2,4-triazole derivatives **480**. Thorough washing after this step removes all side products including benzotriazolyl derivatives **476**. Final deprotection with TFA provides 3-amino-1,2,4-triazoles **481** in 45−65% overall yields and high purity (Scheme 132).[152]

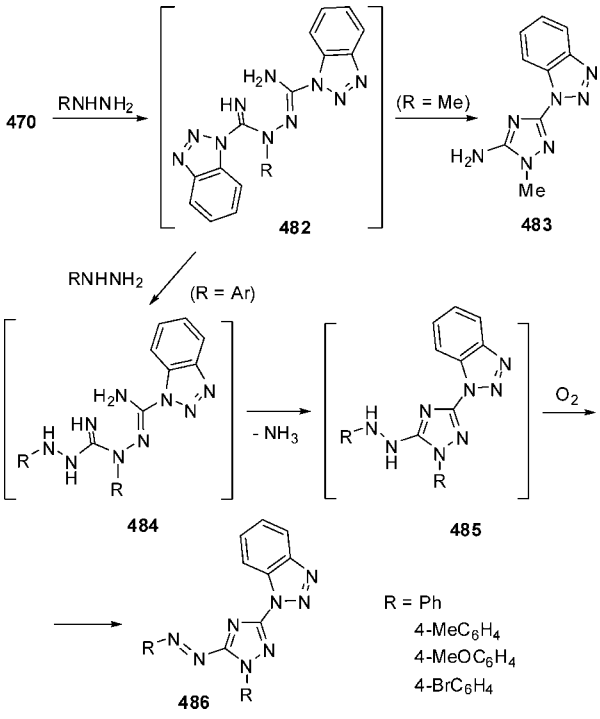
In reactions of imines **470** with hydrazines, both hydrazine nitrogen atoms are involved to give intermediates **482**. With methylhydrazine, a spontaneous cyclocondensation of **482** leads to 5-amino-1,2,4-triazole derivative **483** in 57% yield. However, for R = aryl, a reaction of **482** with the second molecule of hydrazine takes place first to form intermediate **484** before cyclocondensation to 5-hydrazino-1,2,4-triazole **485**. Spontaneous oxidation of hydrazines **485** with atmo-

Scheme 132



477 478 479 480 481

Scheme 133



482 483 484 485 486

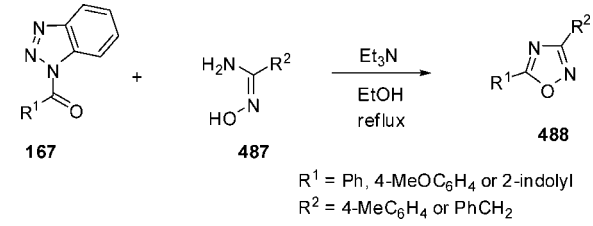
spheric oxygen furnishes orange- to red-colored azo derivatives **486**, which are isolated in 78−86% yields (Scheme 133).[153]

9.3. 1,2,4-Oxadiazole

Amidoximes **487** are prepared in 88−92% yields by refluxing the corresponding nitriles, hydroxylamine hydrochloride, and Et_3N in ethanol. Cyclocondensation of amidoximes **487** with 1-acylbenzotriazoles **167**, carried out in refluxing ethanol in the presence of Et_3N, provides 1,2,4-oxadiazoles **488** in 73−82% yields (Scheme 134).[154]

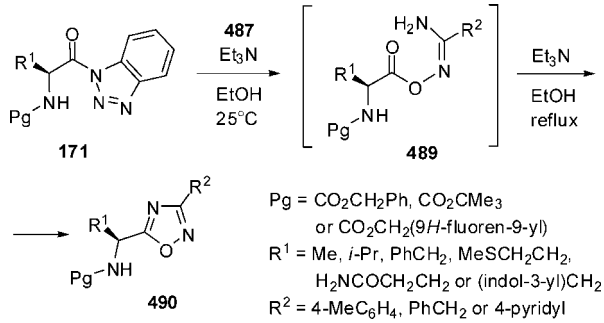
1,2,4-Oxadiazoles are valuable bioisosteres of amide groups in drug design, and benzotriazole methodology allows efficient conversion of amino acids into their 1,2,4-oxadiazole analogues. Thus, 1-acylbenzotriazoles **171** are prepared in high yields in reactions of the corresponding *N*-protected amino acids with benzotriazole and thionyl chloride. Their

Scheme 134



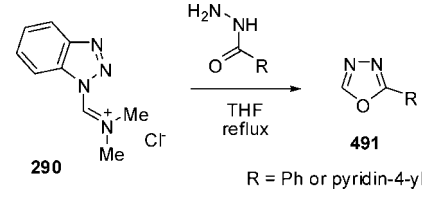
167 487 488

Scheme 135



171 489 490

Scheme 136



290 491

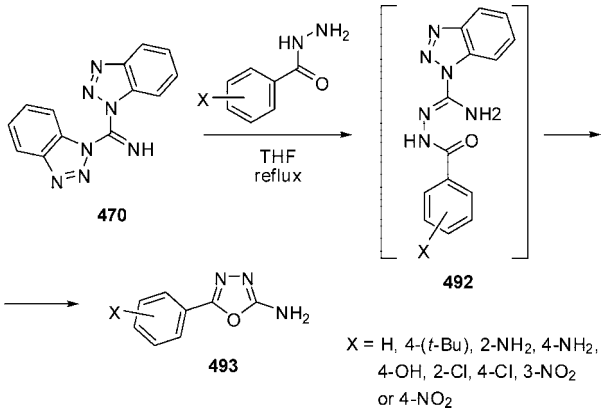
reactions with amidoximes **487** are almost instantaneous, leading to esters **489** that can be separated in stable crystalline forms. However, heating to reflux in ethanol for a few minutes in the presence of Et_3N converts **489** derived from *p*-toluic acid (R^2 = 4-MeC_6H_4) into 1,2,4-oxadiazoles **490**, which are isolated in high yields (70−94%) by crystallization. Amidoxime **487** derived from phenylacetic acid (R^2 = $PhCH_2$) is less reactive toward acyl derivatives **171** requiring reflux for 90 min, but the yields of products **490** are also high (83−89%). For **487** derived from 4-pyridinecarboxylic acid, better results are obtained when the first step is carried out under acidic conditions (10% HCl, aqueous) before cyclocondensation of the obtained intermediate **489** in the presence of Et_3N, providing corresponding 1,2,4-oxadiazoles **490** in 90−93% yields. A similar efficient conversion of several *N*-protected dipeptides into the corresponding heterocyclic derivatives **490** is also described (Scheme 135).[154]

9.4. 1,3,4-Oxadiazole

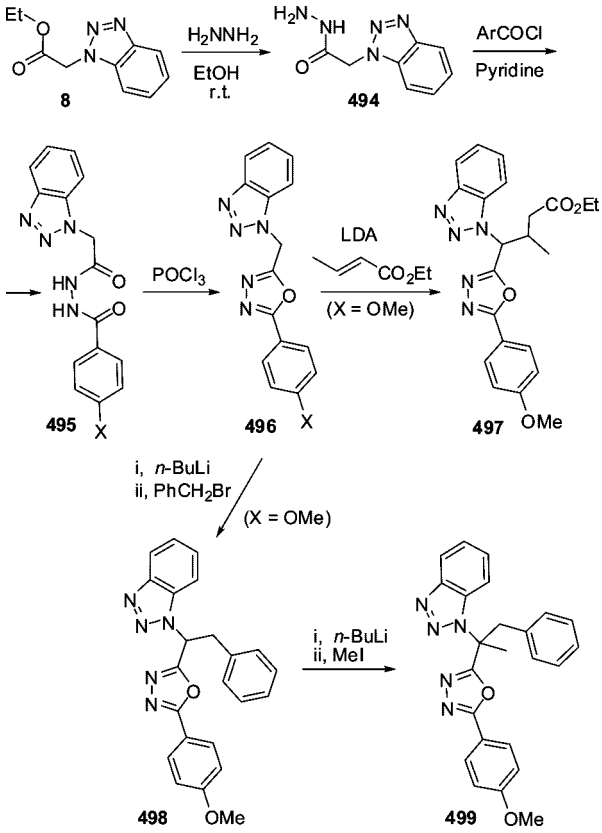
290 can readily introduce one carbon atom to a molecular sequence, and it is a convenient reagent for [4 + 1] cyclocondensations. Thus, in its reaction with benzoic hydrazide, 2-phenyl-1,3,4-oxadiazole (**491**, R = Ph) is obtained in 89% yield. A similar reaction of **290** with the hydrazide derived from 4-pyridinecarboxylic acid gives 1,3,4-oxadiazole **490** (R = 4-pyridyl) in 95% yield (Scheme 136).[155]

Substitution of one of the benzotriazolyl groups in imine **470** with hydrazides derived from benzoic acids results in intermediates **492** that spontaneously undergo cyclocondensation to 2-amino-5-aryl-1,3,4-oxadiazoles **493** with elimination of the second benzotriazolyl group. Products **493** are

Scheme 137



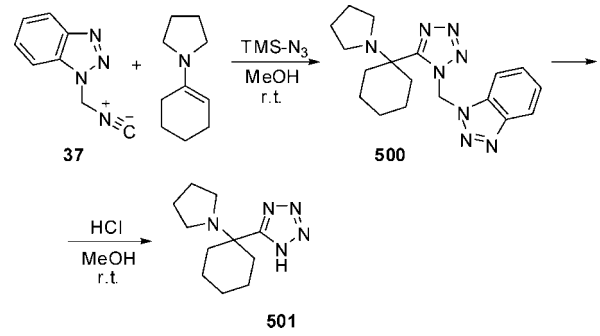
Scheme 138



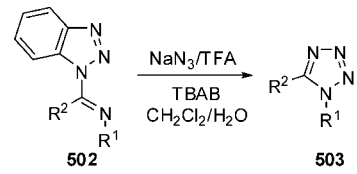
obtained in 82−97% yields. 4-Pyridinecarbohydrazide reacts similarly to give the corresponding oxadiazole in 97% yield, but acetyl hydrazide gives 1-acetyl-5-amino-3-benzotriazol-1-yl-1,2,4-triazole (42% yield) instead (Scheme 137).[153]

8 is easily prepared in a reaction of benzotriazole with ethyl bromoacetate.[156] Treatment with hydrazine converts **8** into hydrazide **494**, which is subsequently acylated with benzoyl chlorides to give *N*,*N*′-diacylhydrazines **495** in 52−95% yields.[157] Upon refluxing in phosphorus oxychloride, compounds **495** are converted into disubstituted 1,3,4-oxadiazoles **496** in 23−75% yields. Electrophilic substitution of the methylene carbon in **496** can be achieved after lithiation, as is illustrated by preparation of products **497** (70% yield), **498** (85% yield), and **499** (65% yield); however, removal of the benzotriazolyl group is difficult due to low stability of the 1,3,4-oxadiazole ring under the required conditions (Scheme 138).[158]

Scheme 139



Scheme 140



R^1 = Ph, 4-MeC_6H_4, $PhCH_2$, Me, *c*-C_6H_{11} or CH_2CO_2Et
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$(NO_2)C_6H_4$, 2-Furyl, 2-Thienyl, Me, $PhCH_2$ or $PhCH_2CH_2$

9.5. Tetrazole

In an Ugi-type reaction, **37** reacts with 1-pyrrolidin-1-yl-1-cyclohexene and trimethylsilyl azide in methanol to give tetrazole derivative **500** in 68% yield. The benzotriazol-1-ylmethyl group can be easily removed under mild acidic hydrolysis to provide tetrazole **501** in 98% yield. Examples of a few other tetrazoles bearing α-aminoalkyl substituents at their C atom obtained by this method are also reported (Scheme 139).[159]

1-Imidoylbenzotriazoles **502** are readily prepared in reactions of the corresponding amides with benzotriazole and oxalyl or thionyl chloride in yields of 62% ($R^1 = R^2 = PhCH_2$) to 90% ($R^1 = PhCH_2$, R^2 = Ph). They are stable in water and do not react with sodium azide under neutral conditions; however, TFA promotes their addition to azide anion, generating tetrazoles **503**, after elimination of benzotriazole. Phase-transfer conditions using tetrabutylammonium bromide (TBAB) accelerate the reaction, allowing its completion at 20 °C in 30 min to give a variety of 1,5-dusubstituted tetrazoles **503** in high yields (90−95%) (Scheme 140).[160]

1-Chlorobenzotriazole (**505**), a mild transfer reagent of a "positive" halogen, reacts with 1,3,5-triarylformazans **504** to give 2,3,5-triaryl-2*H*-tetrazolium chlorides **507** in 70−95% yields (Scheme 141). The reaction is believed to proceed through *N*-chloroformazans **506**. Electron-withdrawing substituents R^1 strongly facilitate formation of the product, while the substituents R^2 and R^3 have only minor effects on the reaction rate.[161]

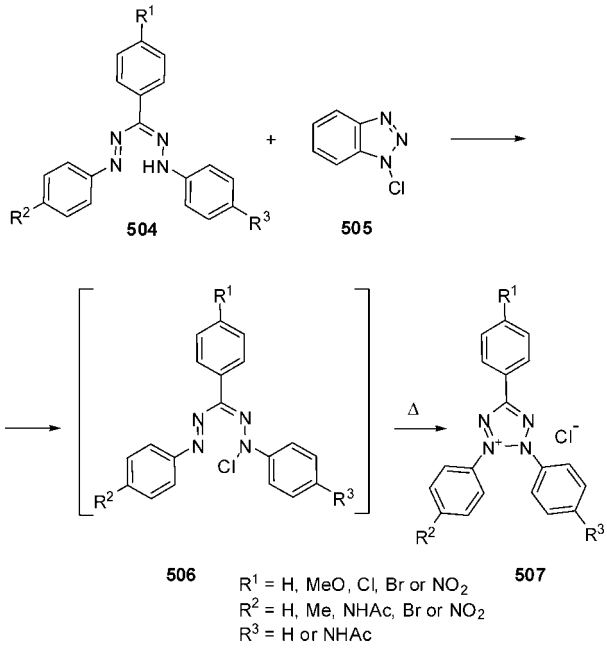
10. Pyridine

10.1. Hexahydropyridine (Piperidine)

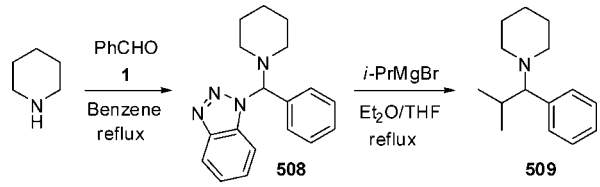
10.1.1. N-Substituent

N-Derivatization of piperidine can be easily achieved by initial condensation with an aldehyde and benzotriazole and substitution of the benzotriazole moiety by an alkyl or aryl group from organometallic reagents in the subsequent step.

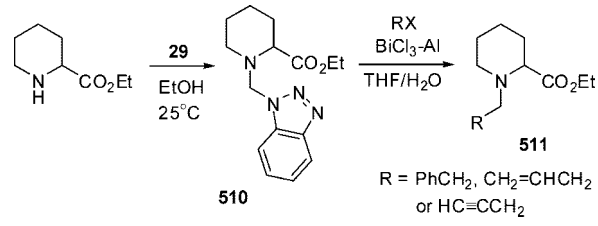
Scheme 141



Scheme 142



Scheme 143



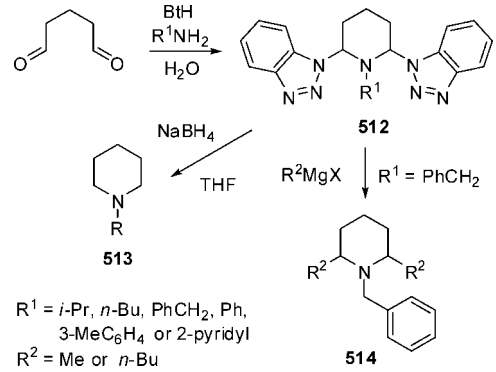
In this way more complex substituents may be introduced that are not readily available by other means. Thus, in an example given in Scheme 142, piperidine reacts with benzaldehyde and benzotriazole to give derivative **508**, which is subsequently treated with isopropylmagnesium bromide to give *N*-(α-isopropylbenzyl)piperidine (**509**) in 59% overall yield.[22]

With functional groups sensitive to Grignard reagents present in the molecule, milder acting reagents have to be used. One such option is shown in Scheme 143. Thus, the ester group in pipecolinic acid derivative **510** is not affected during its reactions with organobismuth reagents, producing derivatives **511** in 33−59% yields.[71]

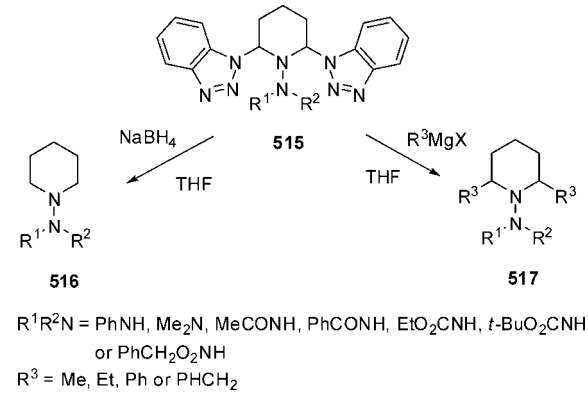
10.1.2. Ring Formation

Glutaraldehyde is a common precursor of piperidines. Its condensation with amines and benzotriazole proceeds conveniently in water, giving 2,6-bisbenzotriazolylpiperidines **512** in high yields. In fact, there are six molecular entities of products **512** present in the reaction mixtures due to *cis*/*trans* and benzotriazol-1-yl/2-yl isomerization, giving rise to complex NMR spectra. However, their reduction with

Scheme 144



Scheme 145



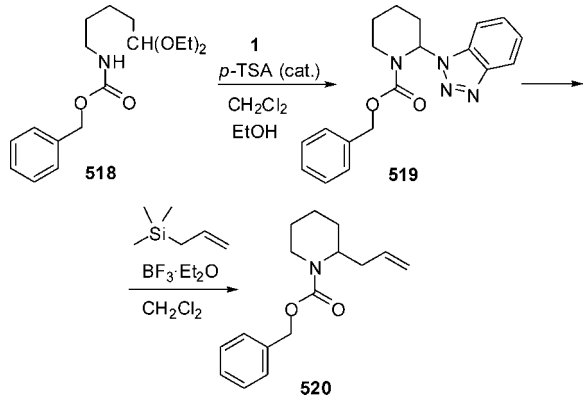
sodium borohydride removes the benzotriazolyl substituents and eliminates the chiral centers to give simple *N*-substituted piperidines **513** in 55−80% yields. Treatment of **512** with Grignard reagents allows substitution of the benzotriazolyl by alkyl groups. In Scheme 144, benzyl derivative **512** is converted into 1-benzyl-2,6-dialkylpiperidines **514** that are isolated in 45−48% yields. According to NMR data, isolated piperidines **514** have *cis* orientation of the substituents.[162]

Similarly to amines, hydrazines and hydrazides react with glutaraldehyde and benzotriazole to give derivatives **515** as mixtures of *cis*/*trans* and benzotriazol-1-yl/2-yl isomers. Treatment with sodium borohydride converts mixtures of **515** into 1-amino- or 1-amidopiperidines **516** that are isolated in 79−90% yields. Grignard reactions carried out using two hydrazide derivatives **515** (R^1R^2N = PhCONH and *t*-BuO_2CNH) give hydrazides **517** as single isomers in 49−72% yields (Scheme 145).[162]

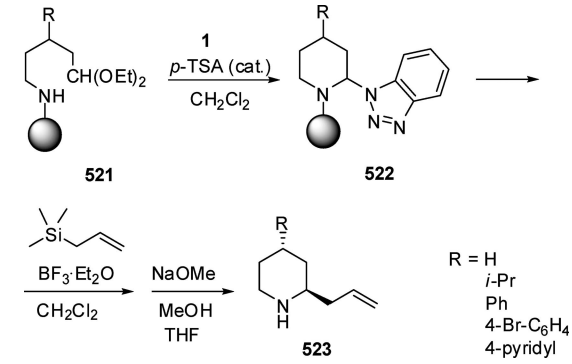
To prepare piperidines monosubstituted at C-2, a reaction of *N*-protected acetal **518** with benzotriazole in the presence of 10 mol % *p*-toluenesulfonic acid (*p*-TSA) gives piperidine derivative **519** in 88% yield. Treatment with allyltrimethylsilane and boron trifluoride etherate allows substitution of the benzotriazolyl moiety in **519** with an allyl group to provide *N*-protected 2-allylpiperidine **520** in 93% yield (Scheme 146).[163]

The reaction can be facilitated by using a solid support. In such an approach, outlined in Scheme 147, suitable amino acetals are attached to sulfonylethoxycarbonyl-modified polystyrene. The obtained resin-bound acetals **521** are treated with a solution of benzotriazole and catalytic amounts of *p*-TSA to give derivatives **522** that are subsequently subjected to a reaction with allyltrimethylsilane. Finally, the products are cleaved from the resins using sodium methoxide to furnish 2-allylpiperidines **523** in 71−86% yields. In these

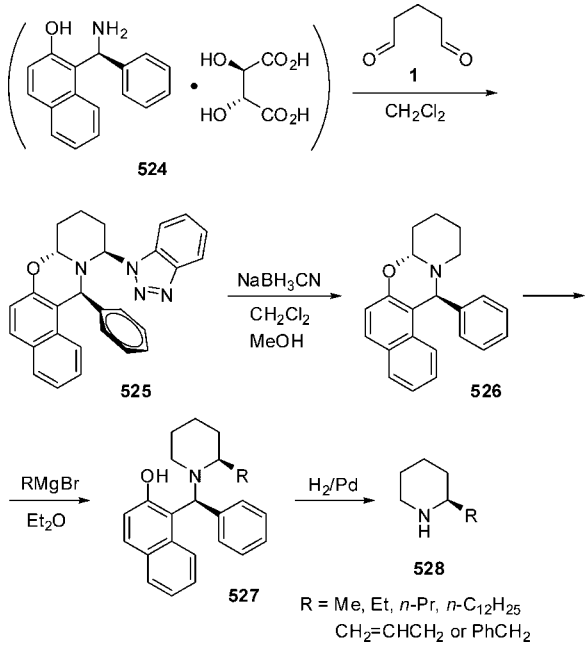
Scheme 146



Scheme 147



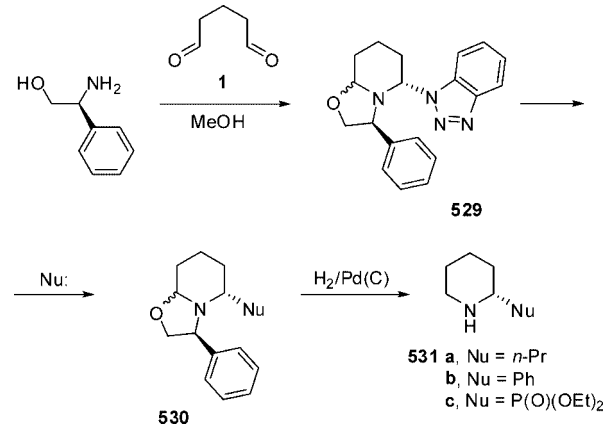
Scheme 148



reactions, when R ≠ H, only *trans*-2,4-disubstituted piperidines are isolated. High diastereoselectivity of this process is explained by a nucleophilic attack at the less sterically hindered side of the intermediate iminium ion generated from **522** (Scheme 147).[163]

Pure enantiomers of C-2-substituted piperidines can be obtained using chiral auxiliaries in the synthetic process. In one such approach outlined in Scheme 148, chiral amine **524**, as a salt with tartaric acid, is used as a template for condensation with glutaraldehyde, giving a pure diastereomer

Scheme 149



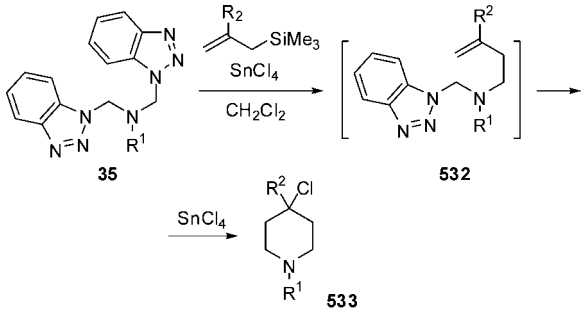
of product **525** with *R*,*R* configuration of its chiral centers, as is proved by X-ray crystal structure analysis. Treatment with sodium cyanoborohydride cleaves selectively the bond with benzotriazole, and the obtained derivative **526** is subsequently treated with Grignard reagents to give pure diastereomers of piperidines **527** in 81−92% yields. Final deprotection of the piperidine nitrogen by hydrogenolysis releases chiral piperidines **528** that are isolated in high yields (93−97%) (Scheme 148).[164]

In another approach (Scheme 149), condensation of (*S*)-2-phenylglycinol with glutaraldehyde (aqueous solution) and benzotriazole is carried out in methanol at room temperature to provide bicyclic system **529** in 95% yield as a mixture of diastereomers and benzotriazol-1-yl/2-yl isomers. Substitution of the benzotriazolyl moiety in **529** with nucleophiles (Grignard reagents and lithium diethyl phosphite) provides derivatives **530** in 57% (Nu = *n*-Pr) to 85% (Nu = Ph) yields. The reaction seems to be less stereoselective than that depicted in Scheme 147, as a minor 5-*R* enantiomer analogous to derivative **530a** (yield 8%) is also isolated from the reaction mixture. Hydrogenation over a palladium catalyst cleaves off the asymmetric auxiliary, providing 2-substituted piperidines **531a** (95% yield), **531b** (92% yield), and **531c** (68% yield).[165] A similar synthesis starting from (*R*)-2-phenylglycinol leads to the opposite enantiomers of **530** and **531**.[166]

In the preceding schemes, the piperidine ring is assembled by making C−N bonds. However, C−C bond formation can also be utilized; thus, *N*,*N*-bis(benzotriazolylmethyl)amines **35** derived from benzyl or phenethylamines undergo cyclocondensation with allylsilanes catalyzed by $SnCl_4$ to give 4-chloropiperidines **533** in 58−68% yields. This [3 + 3] cyclocondensation is assumed to proceed in two steps via intermediate **532** (Scheme 150).[167]

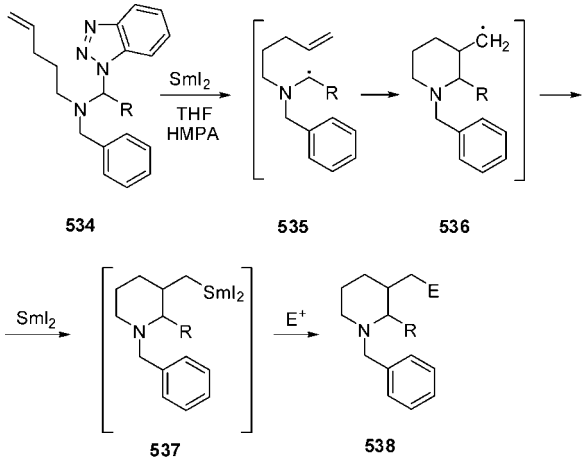
Another example of C−C bond formation in construction of the piperidine ring is depicted in Scheme 151. In this case, reduction of benzotriazolyl derivatives of 4-penten-1-ylamine **534** with SmI_2 generates radicals **535** that are subsequently rapidly trapped by the alkenyl group and converted to radicals **536**. The following reaction with excess SmI_2 gives samarium intermediates **537**. During aqueous workup, derivatives **537** are hydrolyzed to give 3-methylpiperidines **538** (E = H) in 50−56% yields. Alternatively, treatment with electrophiles converts **537** into piperidines **538** with various substituents at C-3, which are isolated in 30−50% yields. In general, slight predominance of the *cis* isomers of piperidines **538** is observed (Scheme 151).[168]

Scheme 150



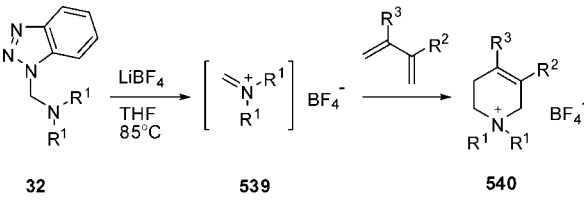
R^1 = $PhCH_2$, $PhCH_2CH_2$ or PhCHMe
R^2 = H or Me

Scheme 151



R = H, *n*-Pr, *i*-Pr, *t*-Bu or Ph
E = MeCHOH, MeC(OH)Et, Et_2COH, PhCHOH or *i*PrNHCO

Scheme 152

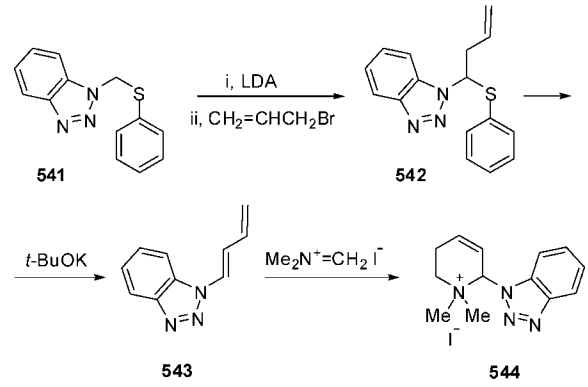


a, 2 R^1 = $CH_2CH_2OCH_2CH_2$, R^2 = Me, R^3 = H
b, 2 R^1 = $CH_2CH_2OCH_2CH_2$, R^2 = R^3 = Me
c, R^1 = R^1 = Me, R^2 = Me, R^3 = H
d, R^1 = R^1 = Me, R^2 = R^3 = Me

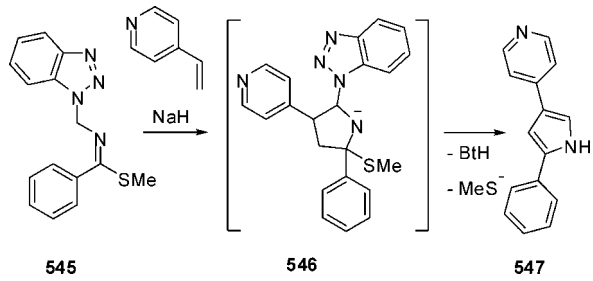
10.2. Tetrahydropyridine

Heating of the THF solutions of *N*-(benzotriazol-1-ylmethyl)amines **32** (also containing benzotriazol-2-yl isomers), lithium tetrafluoroborate, and dienes produces crystalline tetrafluoroborates of 1,2,5,6-tetrahydropyridines **540** that are isolated in 70−90% yields. In reactions with isoprene, 3-substituted tetrahydropyridines **540a** and **540c** are formed regioselectively. To facilitate separation of crystalline products, **540b** and **540d** are converted into the corresponding tetraphenylborates by addition of sodium tetraphenylborate to the reaction mixtures. The reaction mechanism must involve generation of iminium tetrafluoroborates **539** that subsequently undergo hetero-Diels−Alder reactions with dienes to give 1,2,5,6-tetrahydropyridinium salts **540** (Scheme 152).[169]

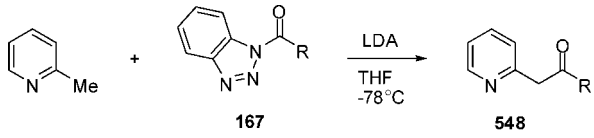
Scheme 153



Scheme 154



Scheme 155



R = Me_2CHCH_2, *n*-C_5H_{11}, PhCH=CH, Ph, 4-ClC_6H_4, 2-furyl, 2-thienyl or 3-pyridyl

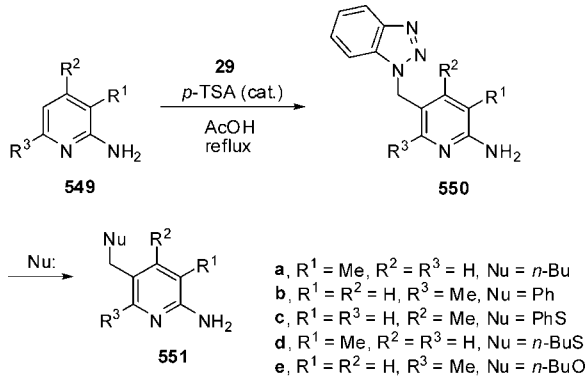
Alkylation of lithiated benzotriazol-1-ylmethyl phenyl sulfide (**541**) with allyl bromide gives derivative **542** in 75% yield, which is subsequently converted into 1-butadien-1-ylbenzotriazole (**543**) by treatment with potassium *tert*-butoxide. Hetero-Diels−Alder reaction of butadiene **543** with Eschenmoser's salt provides *N*,*N*-dimethyl-2-benzotriazol-1-yl-1,2,5,6-tetrahydropyridinium iodide (**544**) in 77% yield (Scheme 153).[170]

10.3. Transformations of Ring Substituents

The rich chemistry of benzotriazole derivatives[171] can be effectively applied to modify functional groups already attached to the pyridine ring. In an example of such reactions shown in Scheme 154, the anion generated from thioimidate **545** upon its treatment with NaH adds to the double bond of 4-vinylpyridine. Obtained pyrrolidine intermediate **546** expels benzotriazole and a thiomethoxide anion to give pyrrole **547**, which is separated in 64% yield. 2-Vinylpyridine reacts similarly.[91]

In another advantageous application of benzotriazole reagents for modification of pyridine substituents (Scheme 155), 2-picoline is lithiated by LDA and treated with 1-acylbenzotriazoles **167** to give pyridin-2-ylmethyl ketones **548** in good yields (60−84%). In comparison with other synthetic methods for such compounds, this approach simplifies the procedure and provides generally higher yields of the products. 4-Picoline gives similar products.[172]

Scheme 156



10.4. Electrophilic and Nucleophilic Substitutions of the Aromatic Ring

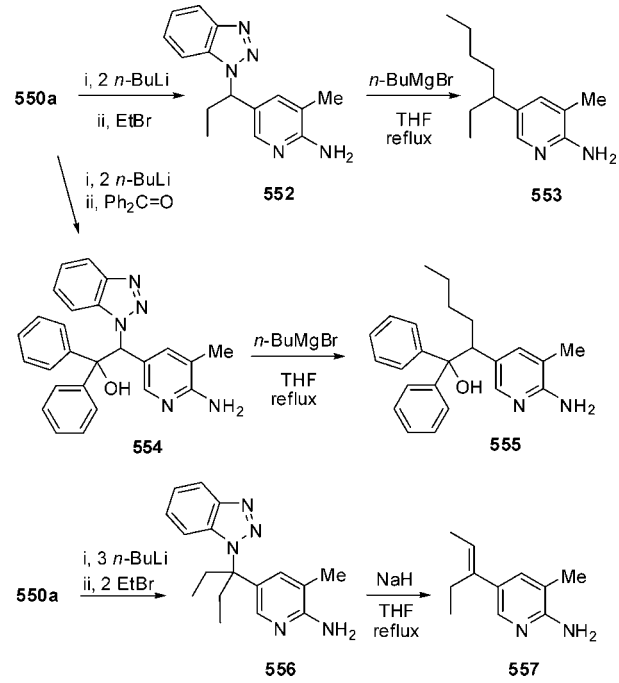
Condensation of **29** with 2-amino-(3, 4, or 6)-methylpyridines **549** in refluxing acetic acid in the presence of catalytic *p*-TSA provides corresponding 2-amino-5-(benzotriazol-1-ylmethyl)pyridines **550** in 60−73% yields. The parent 2-aminopyridine ($R^1 = R^2 = R^3 = H$) and 4,6-dimethyl-2-aminopyridine ($R^1 = H$, $R^2 = R^3 = Me$) give similar products in 53% and 61% yields, respectively. Formation of compounds **550** may involve a direct electrophilic attack of a cation generated from **29** in the presence of an acid on C-5 of the pyridine ring or an attack of such a cation on the amino group followed by Hofmann−Martius rearrangement; possibly this dual pathway mechanism is operating at the same time.

In a reaction with *n*-butylmagnesium bromide carried out in refluxing THF, the benzotriazolyl moiety in **550** is smoothly substituted with an *n*-butyl group to give product **551a** in 77% yield. A similar reaction with phenylmagnesium bromide provides compound **551b** in 49% yield. Thioether derivatives **551c** (94% yield) and **551d** (48% yield) are obtained by refluxing solutions of benzotriazolyl derivatives **550** and sodium salts of the corresponding mercaptans in 2-propanol. Ether **551e** is obtained in 70% yield from a reaction of **550e** with sodium *n*-butoxide in refluxing 1-butanol (Scheme 156).[173]

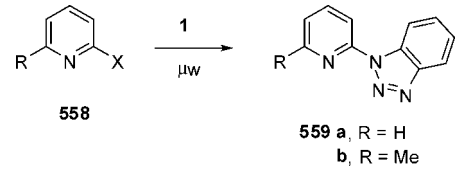
Due to the relative acidity of the CH_2 group attached to the benzotriazol-1-yl ring, the substituent at C-5 in derivatives **550** can be further modified by lithiation followed by reactions with electrophiles. In the examples of such reactions shown in Scheme 157, treatment of **550a** with 2 molar equiv of *n*-BuLi is followed by bromoethane or benzophenone to give derivatives **552** and **554** in 60% and 72% yields, respectively. Substitution of the benzotriazolyl moiety in **552** with a butyl group from *n*-BuMgBr provides 2-amino-3-methyl-5-(1-ethylpentyl)pyridine (**553**) in 65% yield. A similar reaction of **554** with *n*-BuMgBr gives alcohol **555** in 70% yield. Use of 3 equiv of *n*-BuLi followed by 2 equiv of ethyl bromide allows substitution of both methylene protons with ethyl groups, resulting in derivative **556**, which is separated in 85% yield. This process can also be run stepwise using two different electrophiles. Treatment of **556** and similar derivatives with nucleophiles allows substitution of the benzotriazolyl moiety, forming a complex group at C-5. In another approach, **556** is treated with NaH in refluxing THF to eliminate benzotriazole and generate an alkenyl group in product **557** (58% yield).[173]

At 155 °C for 30 min, reaction of benzotriazole with 2-chloro-6-methylpyridine (**558**, R = Me, X = Cl) gives

Scheme 157



Scheme 158



benzotriazolyl derivative **559b** in 70% yield. The reaction is accelerated under microwave irradiation, and the yields are also slightly better: 87% for **559a** and 72% for **559b**. 2-Bromopyridines **558** (X = Br) do not perform as well, giving **559a** and **559b** in 30% and 47% yields, respectively (Scheme 158).[174]

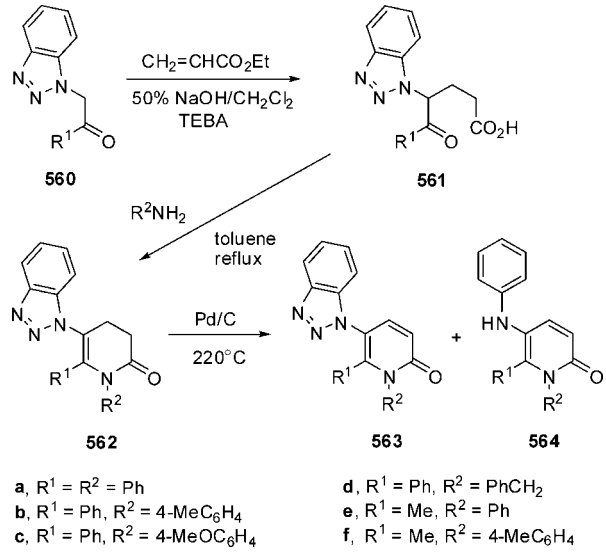
10.5. Aromatic Ring Formation

10.5.1. Pyridones and Thiopyridones

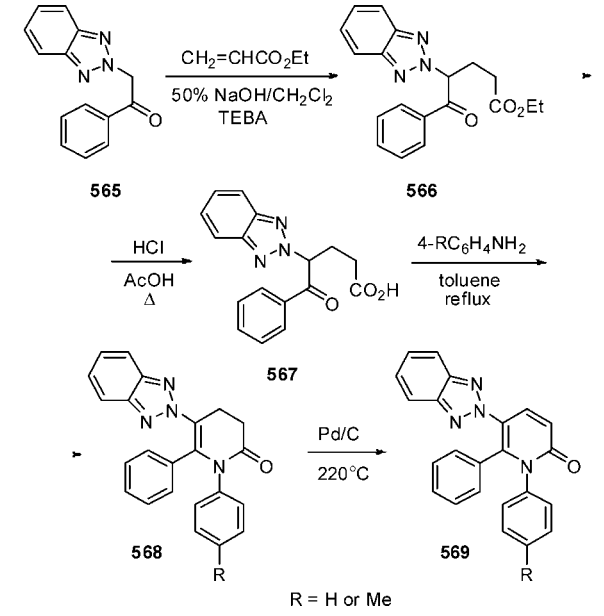
Michael additions of benzotriazol-1-ylmethyl ketones **560** to ethyl acrylate under phase-transfer-catalysis conditions give the corresponding esters that are in situ hydrolyzed to δ-ketoacids **561**, isolated in 70% (R^1 = Ph) and 85% (R^1 = Me) yields. In refluxing toluene under a Dean−Stark trap, anilines and benzylamine convert ketones **561** into 3,4-dihydro-2-pyridones **562** in 56−88% yields. Dehydrogenation of compound **562a** by heating with 10% Pd/C at 220 °C results in partial nitrogen loss from the benzotriazole ring, giving rise to a mixture of 2-pyridones **563a** (70%) and **564a** (20%). For **562b**, the degree of decomposition is even higher with yields of 50% for **563b** and 40% for **564b**, whereas, in the case **562c**, pyridone **564c** is the only product, isolated in 85% yield. Interestingly, 3,4-dihydro-2-pyridone **562e** is cleanly dehydrogenated to pyridone **563e** (85% yield) without indication of nitrogen loss from the benzotriazole ring (Scheme 159).[175]

The benzotriazol-2-yl analogue of ketone **335**, compound **565**, adds readily to ethyl acrylate to give ester **566** in 85% yield. Basic hydrolysis of the ester group in **566** causes elimination of the benzoyl group, but acidic hydrolysis gives

Scheme 159



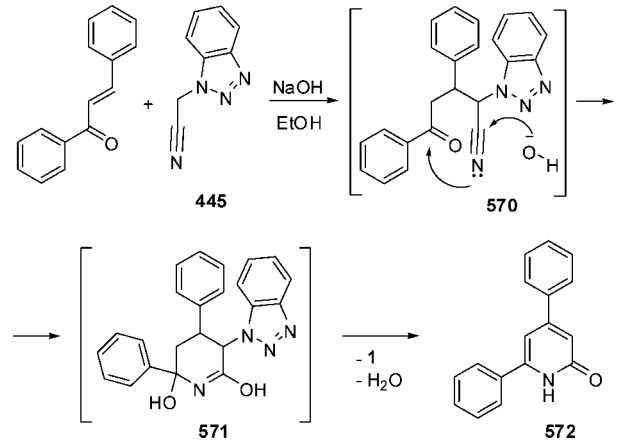
Scheme 160



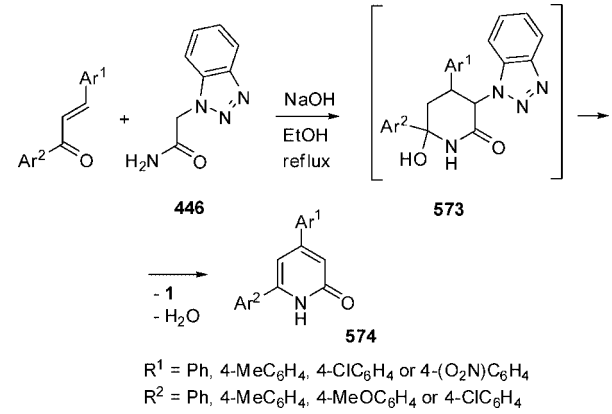
the desired δ-ketocarboxylic acid **567** in 75% yield. Condensations of acid **567** with aniline and *p*-toluidine provide 3,4-dihydro-2-pyridones **568** in 75−78% yields. Contrary to that of their benzotriazol-1-yl analogues, dehydrogenation of **568** proceeds smoothly without nitrogen loss to give 2-pyridones **569** in 82% (R = H) and 75% (R = Me) yields (Scheme 160).[175]

Michael addition of **445** to chalcone, catalyzed by NaOH, gives intermediate **570**. In the following step, nucleophilic attack of the hydroxy anion on the nitrile promotes cyclization to tetrahydropyridine **571**, which spontaneously eliminates benzotriazole and water to furnish 4,6-diphenyl-2-pyridone (**572**) in 47% yield. The side product of this reaction, 2-ethoxy-4,6-diphenylpyridine (15% yield), results from involvement of an ethoxy anion in a nucleophilic attack on intermediate **570**. The method does not seem to be general, as an analogous reaction of nitrile **445** with 4-phenylbut-3-en-2-one fails to give the expected 2-pyridone (Scheme 161).[176]

Scheme 161



Scheme 162

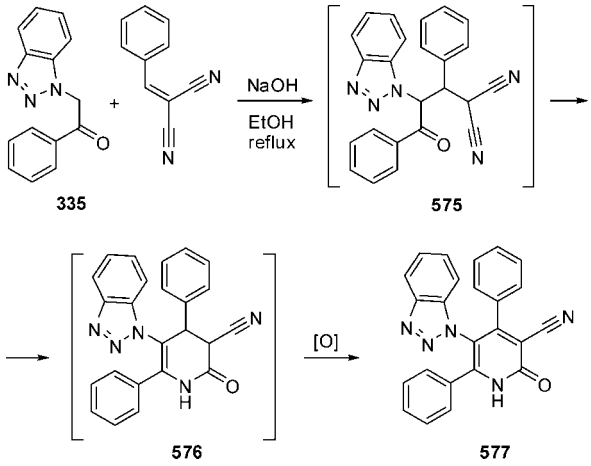


A better synthesis of 4,6-diaryl-2-pyridones involves Michael addition of readily available benzotriazol-1-ylacetamide (**446**) to chalcones. In this case, formation of the pyridone backbone occurs immediately after the addition, which stabilizes the system and prevents side reactions. The just obtained tetrahydropyridines **573** eliminate benzotriazole and water to give pyridones **574** in 53−92% yields. Use of 2-benzotriazol-1-ylpropionamide instead of acetamide **446** introduces a methyl group to C-3 of pyridones **574** (Scheme 162).[176]

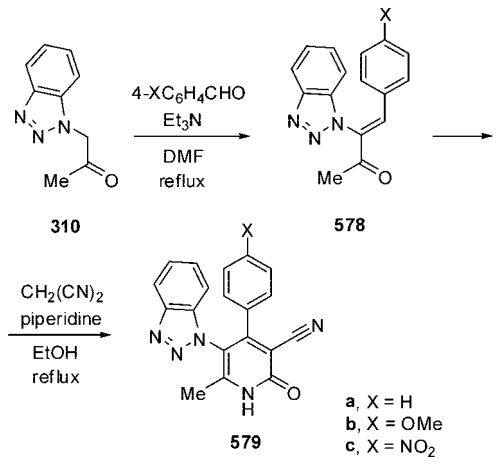
Michael addition of acetophenone **335** to benzylidenemalononitrile gives intermediate **575**, which subsequently undergoes cyclization to 3,4-dihydro-2-pyridone **576**. The mechanism of this cyclization may be similar to that proposed for intermediate **570**, and/or it may involve other modes; formally, it is hydrolysis of one of the cyano groups followed by condensation of the obtained amide with the benzoyl carbonyl. Unlike the similar system **571**, the benzotriazolyl substituent in a molecule of **576** is not located in a position suitable for elimination. However, under the reaction conditions, **576** is rapidly oxidized to furnish tetrasubstituted 2-pyridone **577** in 62% yield (Scheme 163).[177]

Condensation of **310** with aromatic aldehydes gives 4-aryl-3-benzotriazol-1-yl-3-buten-2-ones in 69% (**578a**), 81% (**578b**), and 71% (**578c**) yields. Malononitrile in the presence of catalytic amounts of piperidine converts compounds **578** into 2-pyridones **579** in 75%, 85%, and 92% yields, for **a**, **b** and **c**, respectively. Again, the reaction is expected to proceed through intermediates analogous to structures **575** and **576** and involves an oxidation step (Scheme 164).[117]

Scheme 163



Scheme 164

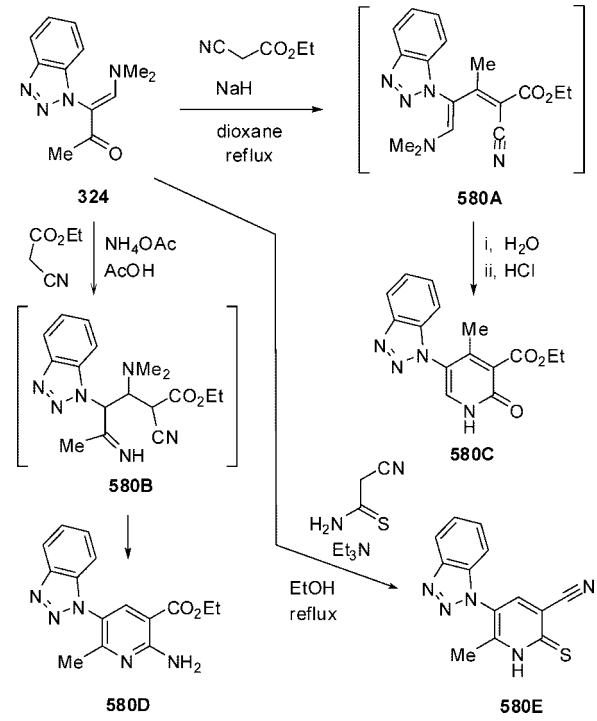


Enaminone **324** is readily prepared by heating **310** with *N*,*N*-dimethylformamide dimethyl acetal under standard[115a] or microwave conditions.[115b] The outcome of the reaction of **324** with ethyl cyanoacetate depends strongly on the reaction conditions. Thus, in the presence of sodium hydride, the carbonyl group reacts first to give intermediate **580A**. During workup, hydrolysis of the cyano group generates an amido group that subsequently undergoes addition to the enamine double bond to form a heterocyclic ring. In the final stage, elimination of dimethylamine leads to 2-pyridone **580C** in 64% yield (Scheme 165).[115b] An analogous cycloaddition/elimination process converts 2-cyano-5-aryl-5-(dimethylamino)-2,4-pentadienamides into the corresponding 6-aryl-3-cyano-2-pyridones in 92−95% yields.[177a]

However, in the presence of acetic acid and ammonium acetate, the process starts from Michael addition of ethyl cyanoacetate to the double bond of **324**. The following condensation of the carbonyl group with ammonia generates imine **580B**. In the final stage, addition of the imine to the cyano group and elimination of dimethylamine results in the corresponding 2-iminopyridine that tautomerizes to the more stable form, 2-aminopyridine **580D**, isolated in 53% yield (Scheme 165).[115b]

The synthesis of 2-thiopyridone **580E** (64% yield) shown in Scheme 165 is similar. Thus, cyclocondensation of **324** with cyanothioacetamide catalyzed by triethylamine consists of three well-known steps: Michael addition, condensation

Scheme 165



between the thioamido and carbonyl groups, and elimination of dimethylamine.[177b]

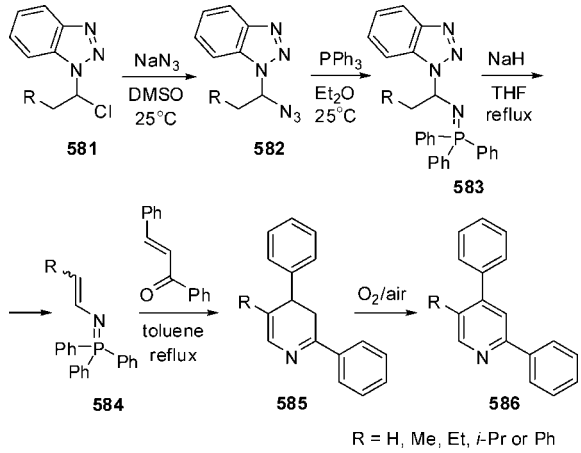
10.5.2. Pyridines

1-(α-Chloroalkyl)benzotriazoles **581** are easily prepared in 80−96% yields by stirring solutions of aldehydes with benzotriazole and $SOCl_2$ in benzene at room temperature. Substitution of the chloride with azide anions in **581** proceeds smoothly in DMSO to provide stable azides **582** in 77−97% yields. Triphenylphosphine converts azides **582** into 1-[α-(phosphoranylideneamino)alkyl]benzotriazoles **583**, which upon treatment with NaH eliminate benzotriazole to give (*N*-vinylimino)phosphoranes **584** as mixtures of *E* and *Z* isomers in 84−94% yields. Prolonged heating of phosphoranes **584** with chalcone in refluxing toluene results in 5-alkyl-2,4-diphenylpyridines **586** that are isolated in 59−84% yields.[178] Two possible routes to intermediate 3,4-dihydropyridines **585** start from (i) Michael-type addition of **584** to the C-3 atom of chalcone and (ii) Wittig reaction of **584** with the carbonyl group of chalcone (Scheme 166).

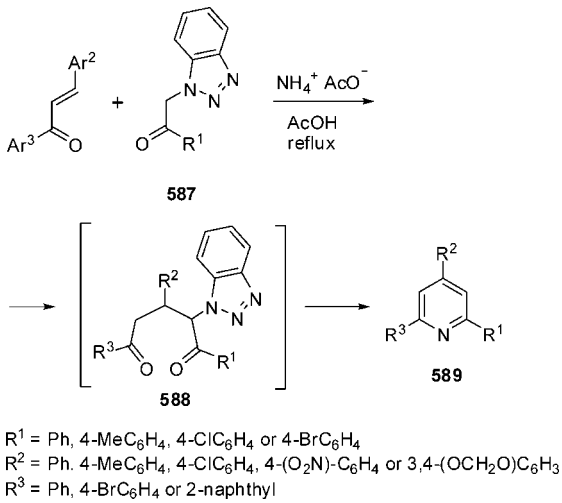
Scheme 167 illustrates application of benzotriazolyl derivatives to the general synthetic method of pyridines based on 1,5-diketones. The procedure involves prolonged heating of chalcones with benzotriazol-1-ylacetophenones **587** and ammonium acetate in acetic acid. The reaction pathway is believed to start from Michael addition of ketone **587** to chalcone, giving diketone **588**, which subsequently undergoes condensation with ammonia and elimination of benzotriazole. The yields of 2,4,6-triarylpyridines **589** obtained by this route vary from 62% (R^1 = Ph, R^2 = 4-$(O_2N)C_6H_4$, R^3 = 2-napthyl) to 87% (R^1 = 4-MeC_6H_4, R^2 = 3,4-$(OCH_2O)C_6H_3$, R^3 = 2-napthyl).[179]

The procedure of Scheme 161 can be adapted to synthesize 2-aminopyridines. Thus, use of secondary amines as bases instead of NaOH provides intermediates **590** that cyclize to tetrahydropyridines **591**. Elimination of water and benzot-

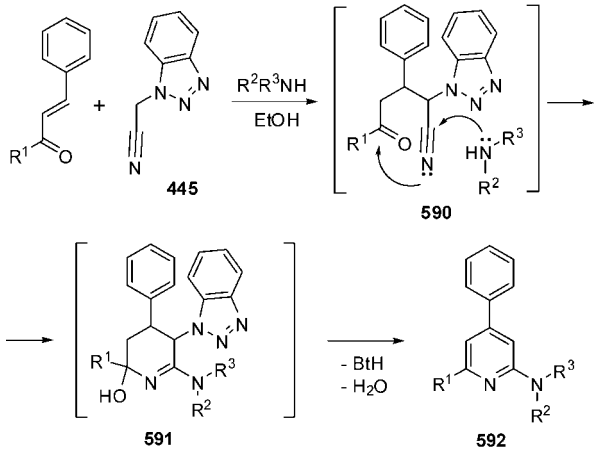
Scheme 166



Scheme 167



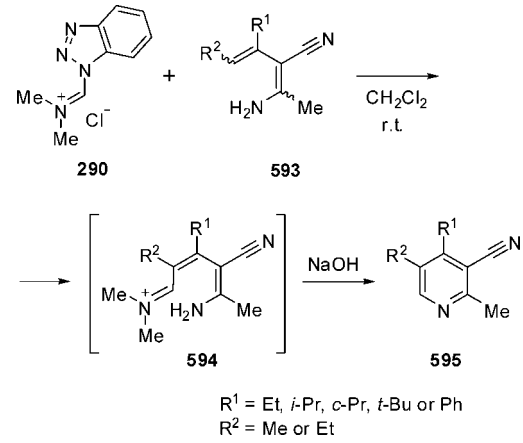
Scheme 168



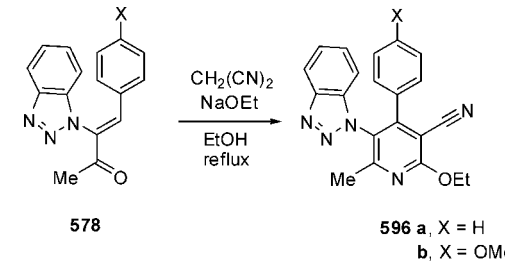
riazole from **591** furnishes 2-aminopyridines **592**. As weaker bases, amines require prolonged heating (48 h), whereas the reaction with sodium hydroxide proceeds well at room temperature. The yields of products **592** vary from 35% (R^1 = Me, R^2R^3N = piperidin-1-yl) to 74% (R^1 = Ph, R^2R^3N = pyrrolidin-1-yl) (Scheme 168).[176]

Nitriles **593**, prepared in 65−78% yields by condensation of β-aminocrotononitrile with ketones in the presence of

Scheme 169



Scheme 170



$TiCl_4$, react with iminium salt **290** to give pyridines **595** in 57% (R^1 = *i*-Pr, R^2 = H) to 75% (R^1 = Et, R^2 = Me) yields. Nitriles **593** derived from cycloalkanones (R^1 and R^2 are parts of a ring) react similarly, giving rise to bicyclic systems **595**. The reaction pathway seems to lead through intermediates **594**, as such structures can be identified in the reaction mixtures before their treatment with a base (Scheme 169).[180]

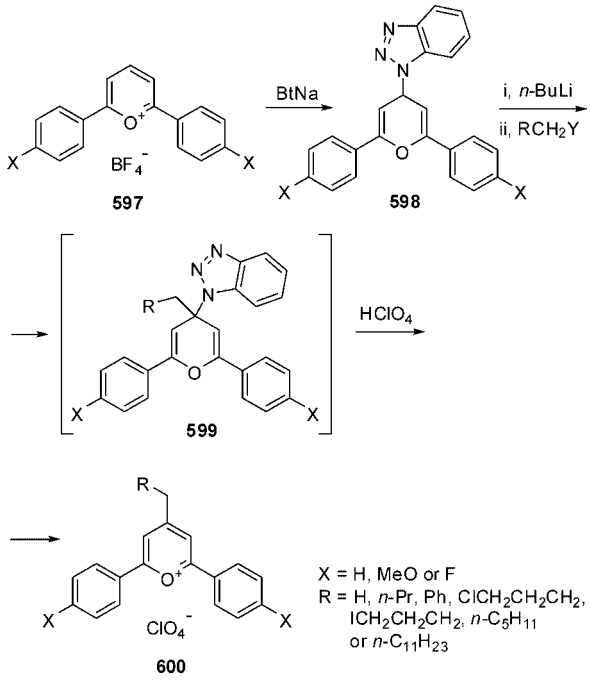
When the reactions shown in Scheme 164 are run in the presence of sodium ethoxide as a base, 2-ethoxypyridines **596** are formed instead of 2-pyridones. The proposed mechanism involves addition of malononitrile to the activated double bond of ketone **578** followed by addition of an ethoxide anion to one of the cyano groups to give an imino ether that undergoes cyclization by a nucleophilic attack of the imine nitrogen atom on the carbonyl group. The yields of products **596a** and **596b** are 76% and 78%, respectively (Scheme 170).[117]

11. Pyran and Thiopyran

11.1. Pyran

The benzotriazolide anion (Bt^-) attacks electron-deficient aromatic rings of pyrylium salts **597** in the position *para* to the oxygen atom to give 4-benzotriazol-1-yl-2,6-diaryl-4*H*-pyrans **598** in 70−95% yields. Crude benzotriazol-1-yl derivatives **598** are contaminated with about 10% of their benzotriazol-2-yl isomers, but the mixtures can be successfully used in further transformations without separation. The *ortho* positions in salts **597** are blocked by aryl groups to avoid reactions there. Derivatives **598** are useful in the synthesis of 4-alkylpyrylium salts **600**. Thus, treatment of **598** with *n*-BuLi at −78 °C followed by alkyl or benzyl halides RCH_2Y and quenching of the reaction mixtures with a solution of ammonium chloride furnishes the corresponding 4-alkyl-2,6-diarylpyrylium salts, which are isolated as perchlorates

Scheme 171



600 in 28−81% yields. The reactions proceed possibly via 4-alkyl-4-benzotriazol-1-yl-2,6-diaryl-4*H*-pyran intermediates **599** that eliminate benzotriazole under acidic conditions to give pyrylium salts **600** (Scheme 171).[181]

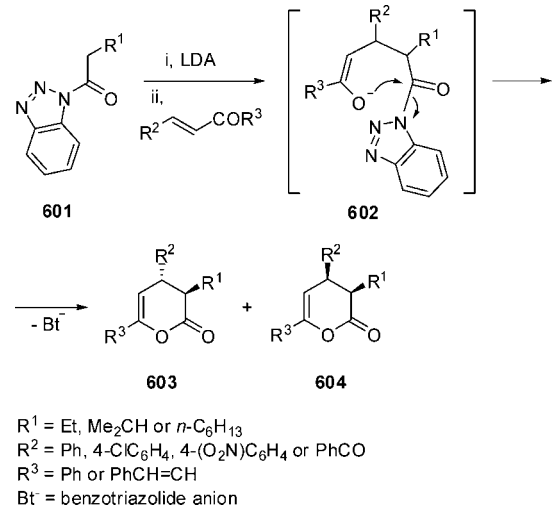
Addition of lithiated 1-acylbenzotriazoles **601** to α,β-unsaturated ketones results in intermediate anions **602** that by a nucleophilic attack of the enolate oxygen on the carbonyl group and consecutive elimination of a benzotriazolide anion provide 3,4-dihydro-2-pyranones **603** and **604**. Due to steric requirements during the initial addition stage, *trans* isomers **603** are strongly predominant, with the *trans*:*cis* ratio varying from 4:1 (R^1 = Et, R^2 = R^3 = Ph) to 100:0 (R^1 = *n*-C_6H_{11}, R^2 = R^3 = Ph). The yields are generally good (53−81%) except in the case of an isopropyl substituent (R^1 = Me_2CH, R^2 = R^3 = Ph), where the yield is only 24%. Introduction of an additional substituent to C-α in starting materials **601** inhibits formation of 2-pyranones **603** and **604**. These and other observations lead to the conclusion that the reaction is kinetically controlled, and the unstable anions derived from compounds **601** add to α,β-unsaturated ketones only under preferable steric conditions; otherwise, they undergo spontaneous disintegration (Scheme 172).[182]

Condensation of **310** with hippuric acid (**605**) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in refluxing acetic anhydride gives 2-pyranone **609** in 90% yield. The proposed reaction mechanism involves cyclization of hippuric acid to oxazoline **606**, which subsequently condenses with DMFDMA to give enamine derivative **607**. The consecutive condensation with **310** gives intermediate **608**, which finally rearranges to 2-pyranone **609** (Scheme 173).[115]

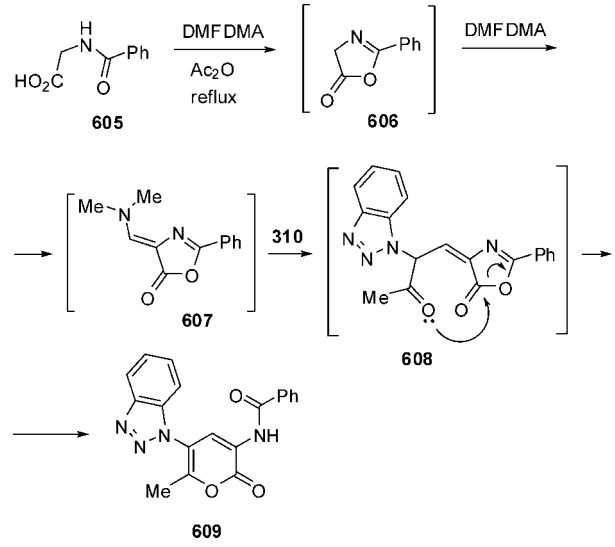
11.2. Thiopyran

Treatment of lithiated monosubstituted α-benzotriazol-1-ylalkyl thioethers with chlorotrimethylsilane produces α-(trimethylsilyl)alkyl thioethers **610**. In reactions with hexamethyldisilathiane and cobalt dichloride hexahydrate, thioethers **610** are converted to thioacylsilanes **611** that can be trapped in a Diels−Alder reaction with 2,3-dimethylbutadiene to

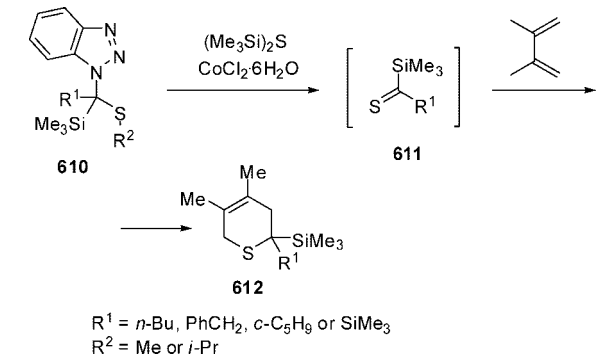
Scheme 172



Scheme 173



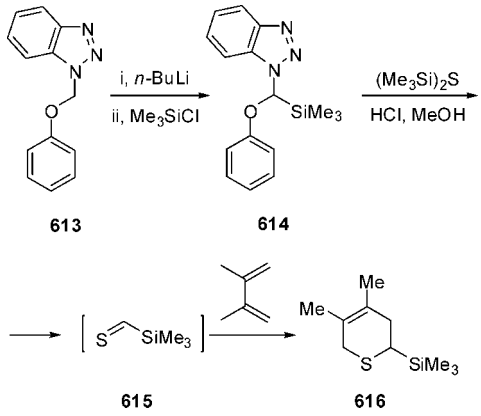
Scheme 174



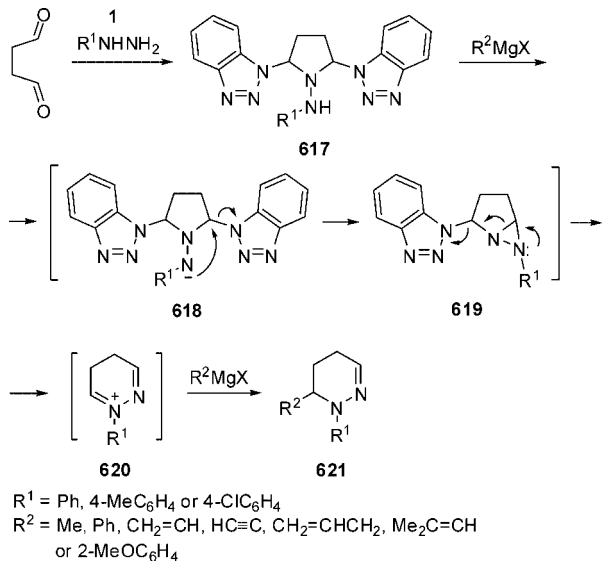
form 2-alkyl-4,5-dimethyl-2-(trimethylsilyl)-3,6-dihydro-2*H*-thiopyrans **612**, isolated in 40−64% yields (Scheme 174).[183]

In another approach, benzotriazol-1-ylmethyl phenyl ether (**613**) is lithiated and treated with chlorotrimethylsilane to give α-trimethylsilyl ether **614**. Reaction of **614** with hexamethyldisilathiane in methanolic HCl generates thioformylsilane **615**, which is trapped by 2,3-dimethylbutadiene to give 4,5-dimethyl-2-(trimethylsilyl)-3,6-dihydro-2*H*-thiopyran (**616**) in 42% yield (Scheme 175).[183]

Scheme 175



Scheme 176



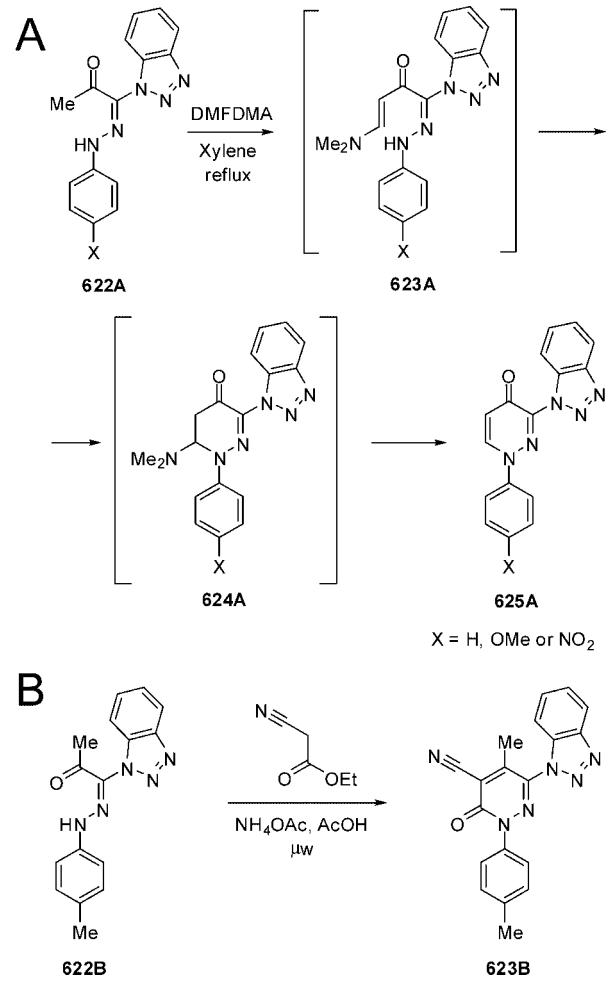
12. Six-Membered Rings with Two or More Heteroatoms

12.1. Pyridazine

Condensation of succinaldehyde with arylhydrazines and benzotriazole gives 1-aminopyrrolidines **617**, isolated in 70−90% yields as complex mixtures of *cis/trans* and benzotriazol-1-yl/2-yl isomers, used in further reactions without separation. Treatment of **617** with Grignard reagents in refluxing THF results in formation of 1,4,5,6-tetrahydropyridazines **621**. For the best results, 5 molar equiv of organomagnesium reagents are used. The reaction is believed to proceed via anion **618**, which by an intramolecular nucleophilic attack on C-2 of the pyrrolidine ring and elimination of a benzotriazolide anion generates aziridine system **619**. Ring enlargement promoted by pulling out electrons by the remaining benzotriazolyl moiety results in iminium cation **620**, which is converted by an organomagnesium reagent into pyridazine **621**. Coordination of the benzotriazolyl N-3 atoms by additional organomagnesium molecules enhances the leaving ability of the benzotriazolyl groups. Yields of products **621** vary from 55% to 89% and are generally higher for phenyl and 4-methylphenyl as R^1 than for their 4-chlorophenyl analogues (Scheme 176).[184]

Hydrazones **622A** are smoothly prepared in 76−78% yields by coupling of benzotriazol-1-ylmethyl methyl ketone (**310**) with appropriate aryldiazonium salts in ethanolic

Scheme 177



NaOH. Prolonged heating of **622A** with *N*,*N*-dimethylformamide dimethyl acetal results in formation of 1-aryl-3-benzotriazol-1-ylpyridazin-4-ones **625A** in 79−83% yields. The reaction pathway involves formation of enaminones **623A** that by intramolecular cycloaddition generate 6-(dimethylamino)-1,4,5,6-tetrahydropyridazin-4-ones **624A**, which eliminate dimethylamine to form final products **625A** (Scheme 177A).[185a]

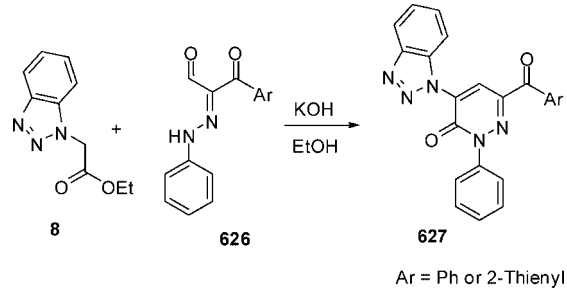
Cyclocondensation of hydrazone **622B** with ethyl cyanoacetate under microwave conditions in the presence of ammonium acetate and acetic acid produces 3-benzotriazol-1-yl-5-cyano-4-methyl-1-(4-methylphenyl)pyridazin-6-one (**623B**) in 91% yield (Scheme 177B).[185b]

Cyclocondensation of **8** with 2-(phenylhydrazono)-3-oxo-3-arylpropanals **626** in ethanolic KOH at room temperature furnishes 3-aroyl-5-benzotriazol-1-yl-1,6-dihydro-1-phenylpyridazin-6-ones **627** in 89−90% yields. 6-Imino analogues of products **627** are obtained in 87−88% yields by condensation of hydrazones **626** with **445** in THF in the presence of sodium hydride (Scheme 178).[185]

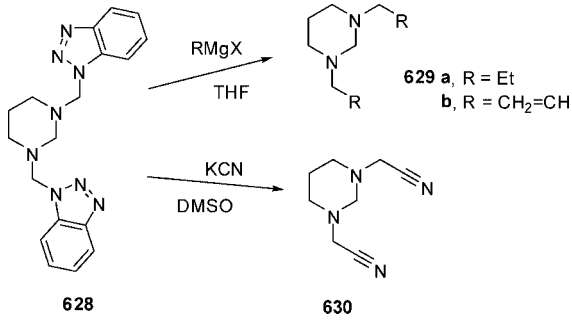
12.2. Pyrimidine

Condensation of 1,3-propanediamine with 3 molar equiv of formaldehyde and 2 molar equiv of benzotriazole provides 1,3-bisbenzotriazol-1-ylhexahydropyrimidine **628** in a mixture with its benzotriazol-2-yl isomer in a ratio of 9:3. Because there is no difference here in reactivity with nucleophiles between both benzotriazolyl isomers, crude

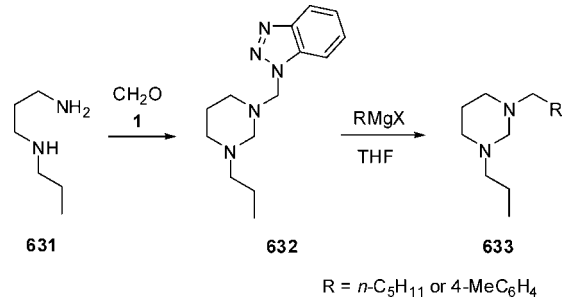
Scheme 178



Scheme 179



Scheme 180



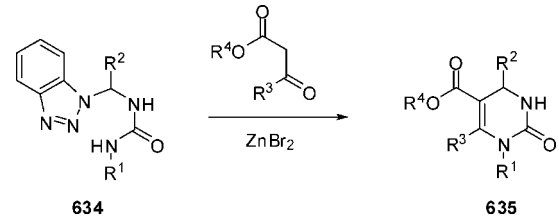
product **628** is treated with organomagnesium reagents to give symmetrically substituted hexahydropyrimidines **629a** (77% yield) and **629b** (87% yield). In a reaction with KCN, both benzotriazolyl groups are replaced to give dinitrile **630** in 87% yield (Scheme 179).[63]

Use of monosubstituted 1,3-propanediamines as the starting materials in this synthesis allows preparation of unsymmetrical hexahydropyrimidines. Thus, as is illustrated by the example in Scheme 180, *N*-propyl-1,3-propanediamine (**631**) reacts with formaldehyde (37% aqueous solution) and benzotriazole in methanol/water to give hexahydropyrimidine **632** in 94% yield, containing about 17% of the corresponding benzotriazol-2-yl isomer. Grignard reagents convert **632** (a mixture of isomers) into hexahydropyrimidines **633** in 90−92% yields.[186]

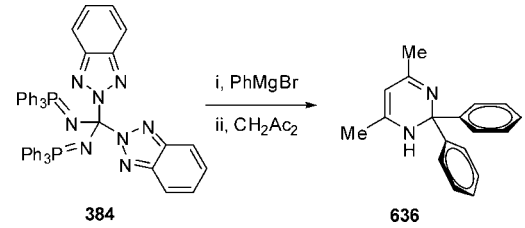
Condensation of benzotriazole with aldehydes and urea or *N*-methylurea provides derivatives **634** in 80−90% yields. Treatment of such derivatized ureas with β-ketoesters in the presence of zinc bromide leads to alkyl 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **635**, isolated in 77−97% yields. Use of thiourea instead of urea in these conversions gives the corresponding 2-thioxo analogues of **635** (Scheme 181).[187]

Reaction of bis(triphenylphosphoranylidene) derivative **384** with phenylmagnesium bromide and acetylacetone provides 4,6-dimethyl-2,2-diphenyl-1,2-dihydropyrimidine (**636**) in 14% yield (Scheme 182).[132]

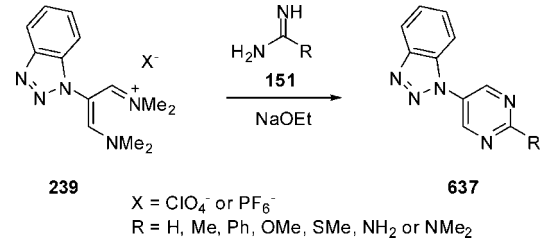
Scheme 181



Scheme 182



Scheme 183



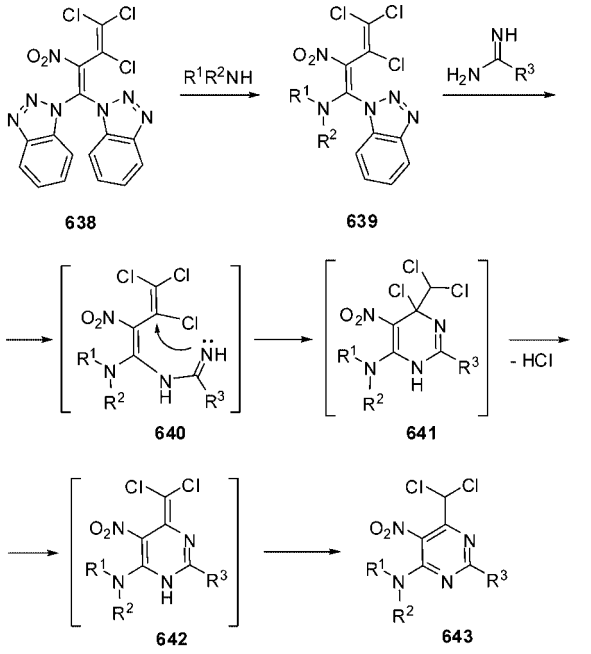
2-Benzotriazol-1-ylvinamidinium salts **239** are convenient for the preparation of pyrimidines with a benzotriazolyl substituent at C-5. In the reactions with amidines and sodium ethoxide carried out in refluxing ethanol, salts **239** are converted into pyrimidines **637** in 60% (R = H) to 95% (R = Ph) yields (Scheme 183).[99]

Condensation of 2-nitro-1,1,3,4,4-tetrachlorobutadiene with benzotriazole allows replacement of two geminal chlorine atoms with benzotriazolyl substituents to give bisbenzotriazol-1-yl derivative **638**. Under mild conditions, 5 °C → room temperature, in MeOH, one of the benzotriazolyl groups in **638** is readily substituted with amines to give enamines **639** in 57−98% yields. Treatment of **639** in DMSO with amidines (as HCl salts) and NaH results in formation of tetrasubstituted pyrimidines **643** that are isolated in 40−85% yields. The reaction pathway is believed to lead through intermediates **640**−**642** (Scheme 184).[188]

12.3. Pyrazine

Condensation of ethyl esters of *N*-monosubstituted glycines **644** with formaldehyde and benzotriazole carried out in water at room temperature provides benzotriazolyl derivatives **645** in 90−98% yields as mixtures with their benzotriazol-2-yl isomers. Upon treatment with sodium hydride in refluxing THF, compounds **645** are converted to esters of *trans*-piperazine-2,3-dicarboxylic acids **646**, isolated in 20% (R = Me) to 80% (R = $PhCH_2$) yields. Molecular structures of **646** are unequivocally assigned on the basis of their NMR spectra and X-ray crystallographic data; however, the mechanism of their formation is not quite clear (Scheme 185).[189]

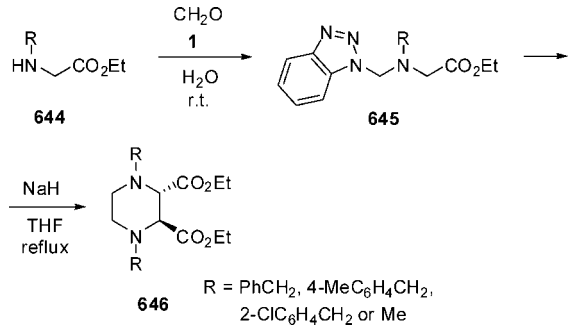
Scheme 184



R^1R^2N = piperidin-1-yl, morpholin-4-yl, 4-(4-fluorophenyl)piperazin-1-yl or 4-ClC_6H_4NH

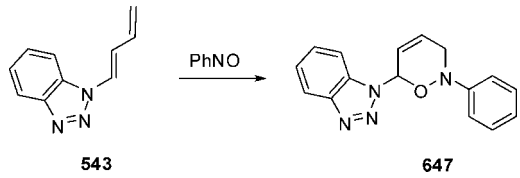
R^3 = Me or Ph

Scheme 185



R = $PhCH_2$, 4-$MeC_6H_4CH_2$, 2-$ClC_6H_4CH_2$ or Me

Scheme 186

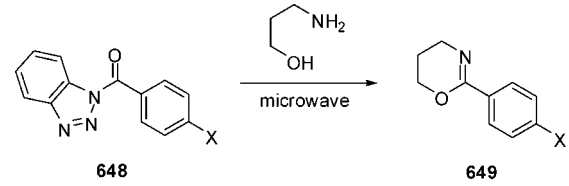


12.4. Oxazines

Hetero-Diels−Alder reaction of **543** with nitrosobenzene provides 6-benzotriazol-1-yl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**647**) in 90% yield. X-ray crystallographic data of the product confirm its molecular structure and exclude an alternative structure with the benzotriazolyl substituent in the 3-position (Scheme 186).[170]

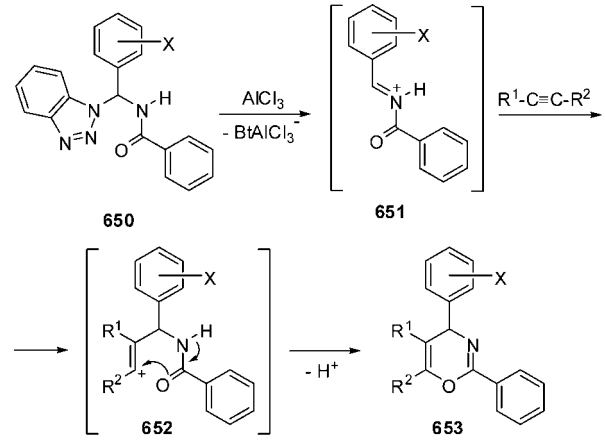
Condensation of 1-benzoylbenzotriazoles **648** with 3-aminopropanol under microwave irradiation provides 2-aryl-5,6-dihydro-4*H*-1,3-oxazines **649** in 96% (X = Cl) and 84% (X = NO_2) yields. The best procedure consists of two steps: (a) a solution of the reagents in chloroform is irradiated at 80 °C for 10 min to give the corresponding *N*-(3-hydroxypropyl)benzamides; (b) thionyl chloride is added, and irradiation is continued for an additional 2 min to close the oxazine ring (Scheme 187).[142]

Scheme 187



X = Cl or NO_2

Scheme 188

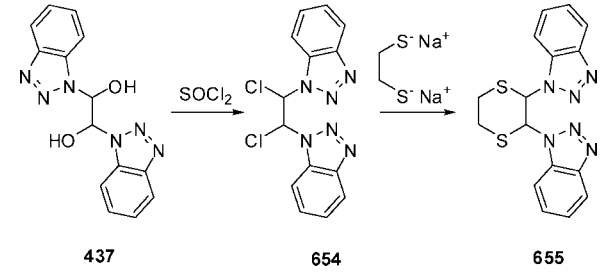


X = H, 4-Cl, 4-OMe or 3-NO_2

R^1 = H or Et

R^2 = Ph or *n*-C_4H_9

Scheme 189

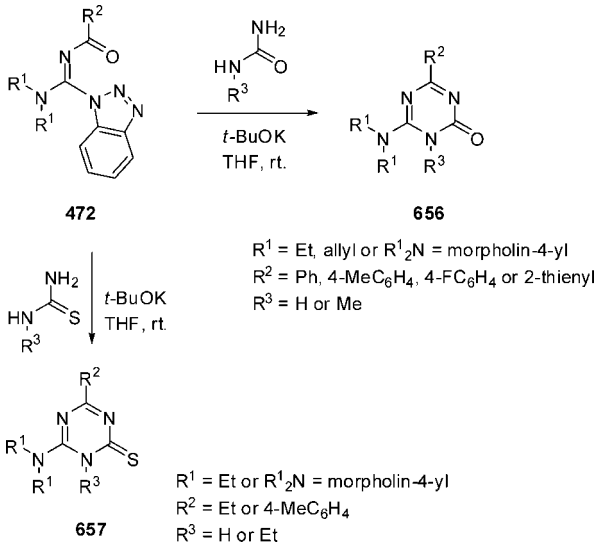


Benzotriazole derivatives **650** are simply prepared by refluxing benzamide, benzotriazole, and aldehyde XC_6H_4CHO in toluene with azeotropic removal of water. In the presence of aluminum chloride as a Lewis acid, compounds **650** undergo cyclocondensation with alkynes to give 4*H*-1,3-oxazines **653** in high yields (76−94%). The proposed reaction mechanism is based on ionization of derivative **650** promoted by aluminum chloride to acyliminium cation **651**, which in an electrophilic attack on the triple bond of alkyne produces intermediate **652**. In the final stage, ring closure occurs by electron shifts and elimination of a proton to furnish oxazine **653** (Scheme 188).[190]

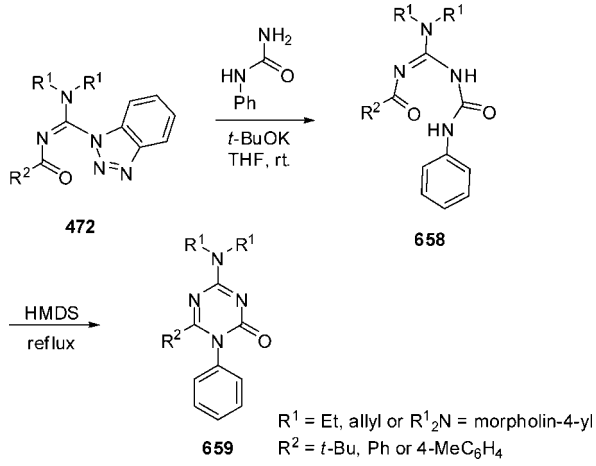
12.5. 1,4-Dithiin

In a reaction with thionyl chloride, the adduct of benzotriazole to glyoxal, **437**, is converted into dichloro derivative **654** in 90% yield. Compound **654** is a convenient building block delivering a two-carbon unit to a heterocyclic ring. In an example of such reactions in Scheme 189, dichloride **654** reacts with 1,2-ethanedithiol disodium salt to provide tetrahydro-2,3-bisbenzotriazol-1-yl-1,4-dithiin (**655**) in 80% yield. The stereochemistry of **655** is not defined.[191]

Scheme 190



Scheme 191



12.6. 1,3,5-Triazine

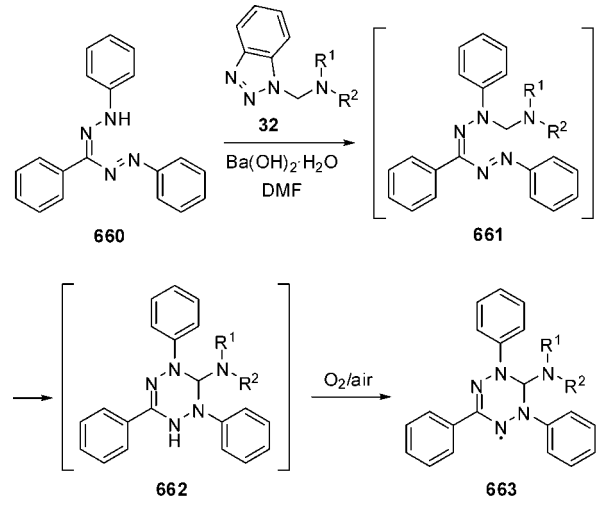
Cyclocondensation of *N*-acyl-benzotriazol-1-ylcarboximidates **472** with urea or *N*-methylurea in the presence of potassium *tert*-butoxide provides 1,3,5-triazin-2-ones **656** in 76−91% yields. A similar reaction of carboximidamides **472** with thioureas leads to 1,3,5-triazine-2-thiones **657** in 44−88% yields (Scheme 190).[192]

In the case of *N*-phenylurea, with the *N*-phenyl nitrogen atom being less reactive, only the first step, substitution of the benzotriazolyl group, occurs under standard conditions, giving derivatives **658** in 61−89% yields. Using HMDS as a dehydrating agent, compounds **658** are easily cyclized into triazinones **659** in 51% (R^2 = *t*-Bu) to 95% (R^2 = Ph) yields (Scheme 191).[192]

12.7. 1,2,4,5-Tetrazine

Aminomethylation of formazan **660** with 1-(dialkylamino)benzotriazoles **32** provides unstable intermediates **661** that under the reaction conditions (barium hydroxide base) undergo cyclization to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines **662**. Rapid oxidation by atmospheric oxygen converts **662** into stable 3-aminoverdazyl radicals **663** that are isolated as dark-colored crystalline substances in 37−69% yields (Scheme 192).[193]

Scheme 192



13. Conclusion

Rapid progress in the chemistry of benzotriazole derivatives in the past two decades has led to a wide range of valuable synthetic methods for all major classes of organic compounds. Application of the benzotriazole methodology to heterocyclic chemistry improves the synthesis of many heterocyclic systems and in some cases allows construction of the molecules with combination of their substituents difficult to achieve by other methods. With heterocycles being the major building blocks in designing biologically active molecules, we hope that this review will provide a useful aid to medicinal, crop protection, and other chemists dealing with heterocyclic systems on a daily basis.

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