Properties and Synthetic Utility of *N*-Substituted Benzotriazoles

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Contents

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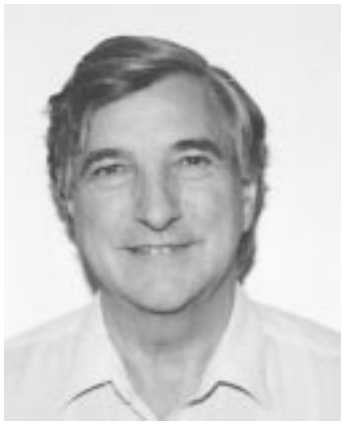


Alan Katritzky is Kenan Professor of Chemistry and Director of the Center of Heterocyclic Compounds at the University of Florida. He was born in 1928 in London, UK, and studied, researched, and taught at the Universities of Oxford, Cambridge, and East Anglia before crossing the Atlantic to take up his present post in 1980. His interests are well-expressed by the title *Heterocycles in Life and Society* of the book he coauthored with Pozharskii and Soldatenkov and which was recently published by Wiley.

Personal note by A. R. Katritzky: Our group has now been heavily engaged in benzotriazole chemistry for more than 10 years; the origins of the project were covered in a *Synthesis Feature Article*.[181] The only previous comprehensive review[2] is now completely out-of-date, and the present work is intended to replace it. The writing of this review has been a frustrating as well as a pleasurable task. Frustrating because I have always wanted to include the latest three months' results and it has been so difficult to finish it, with several deadlines being missed. Finally, successive ultimata, sequentially from all three of my excellent co-authors, has forced a definitive cut off! However, benzotriazole chemistry is as vigorous as ever and this review will be out-of-date before it is published! We hope to keep a continuously updated version on CD-ROM and are formulating a reaction database for distribution to our friends interested in this methodology.

Xiangfu Lan, born in 1965 in China, received his B.En. in chemistry and chemical engineering from Beijing Institute of Technology and his Ph.D. in 1991 from the University of Florida with Professor Alan R. Katritzky. Currently, he is a Senior Research Chemist at Clariant (formerly Sandoz Chemicals) Corporation at Charlotte, NC. His research interests include organic synthesis, color science, organosulfur chemistry, and structure determination.

I. Overview

Benzotriazole is a new synthetic auxiliary which offers many advantages. It is an inexpensive, stable compound. It is soluble in ethanol, benzene, toluene, chloroform, and DMF; sparingly soluble in water but highly soluble in basic solutions because it is an acid of appreciable strength with acid pK_a 8.2.

To be useful as a synthetic auxiliary, a group must display several characteristics. First, it must be easy to remove at the end of the synthetic sequence (it is an added advantage if it can be recovered and used again). Second, it must be able to be introduced readily at the beginning of the sequence. Third, it should be stable during various synthetic operations, and, if possible, exert an activating influence on other parts of the molecule. Benzotriazole displays all of these characteristics to a high degree. This review is accordingly divided, after a brief introduction, into sections describing how benzotriazole residues can be introduced into a molecule, how they activate groups to which they are attached, and how they can

Jason Yang was born on November 25, 1962, in Tangshan, Hebei, China. He received his Ph.D. in Organic Chemistry from the University of Florida in 1994, under the supervision of Professor A. R. Katritzky. After one year postdoctoral research in the same group, he joined Reilly Industries, Inc., Indianapolis, IN, as a Research Chemist. His current research interests have been focused on synthesis and applications of heterocyclic compounds, particularly pyridine and thiazole derivatives.

Olga Denisko was born in December 13, 1967, in Krasnoyarsk, Russia, and educated at Moscow State University, Russia, where she received her Ph.D. degree in organic chemistry under supervision of Professor N. S. Zefirov in 1993. She was a postdoctoral fellow in the Katritzky group from 1994 until 1997 when she returned to Kranoyarsk, Russia.

be removed. It is our intent to draw attention to the versatile applications of benzotriazole in organic chemistry and as much as possible to arouse interest and efforts to explore additional novel and useful aspects of benzotriazole chemistry.

N-Substituted derivatives of benzotriazole have some interesting properties. Benzotriazole possesses both electron-donor and electron-acceptor properties and, because of this, compounds with an α heteroatom (most commonly N, O, and S) attached to a benzotriazole nitrogen can ionize in two ways, either to form the benzotriazole anion and an immonium, oxonium, or thionium cation **2**, or to ionize off the heteroatom substituent to give **4** (see Scheme 1).

A comparison of benzotriazole with other activating groups shows that its leaving ability and its activation of CH toward proton loss are comparable to those of cyano and phenylsulfonyl groups. It is better than both phenyl and vinyl in the activation of an α-CH toward proton loss and in electron donor properties. Few other groups show all three of these properties;

Scheme 1. Benzotriazole and Typical Reactions of *N*-Substituted Benzotriazoles

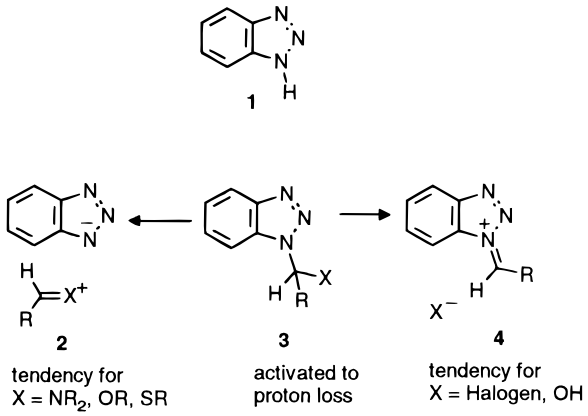
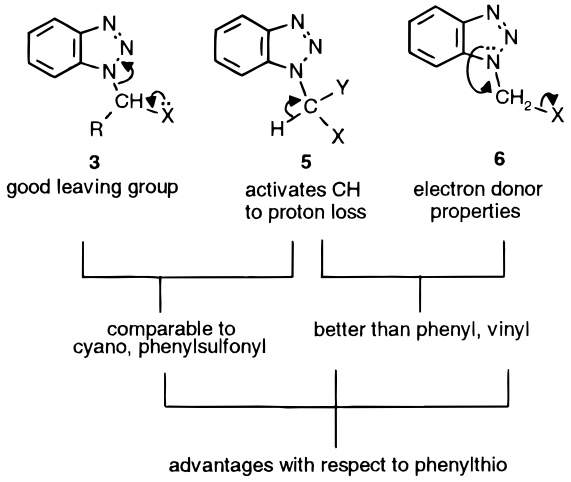


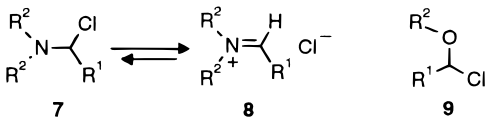
Chart 1. Comparison of Benzotriazole Activation with That of Other Groups



one such is phenylthio and we find that benzotriazolyl has significant advantages with respect to phenylthio, as is made clear in the sequel.

We can compare benzotriazole in many ways to a halogen substituent because of its leaving abilities, but it should be compared to a *tame* halogen substituent. Compounds with a benzotriazolyl group α to an amino or ether functionality **3** (X = NR_2, OR) are stable, nonvolatile, easily prepared, and versatile, while their halogen analogues **7** and **9** (Scheme 2)

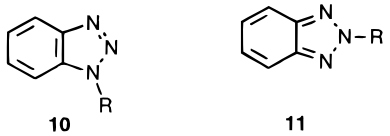
Scheme 2. Benzotriazole Derivatives Can Replace Halogen Analogues



are physiologically dangerous and often too reactive to be conveniently used as reagents.

Since work concerning benzotriazole as a synthetic auxiliary commenced in 1985 in our group, many papers have been published including some reviews.[1–7] Nevertheless, these reviews are either limited to a particular focus, or are now completely outdated. It is the purpose of the present review to systematically describe the chemistry of *N*-substituted benzotri-

Chart 2. 1- and 2-Substituted Benzotriazoles



10 (designated Bt^1-R) 11 (designated Bt^2-R)

azoles with emphasis on the many useful types of reactions employing benzotriazole. It covers research results published from 1985 up into 1996. With major ongoing research efforts concerning benzotriazole, this review also attempts to explore future potential uses of benzotriazole chemistry.

N-Substituted benzotriazoles exist as two isomers: 1- and 2-substituted (Chart 2). Frequently they exist in equilibrium, with **11** perhaps surprisingly being of the same order of stability as **10** (see section III.D.1) and often the isomers **10** and **11** show the same reactions. Throughout this review, we employ the following notations: Bt^1 = benzotriazol-1-yl; Bt^2 = benzotriazol-2-yl; Bt = benzotriazol-1-yl and benzotriazol-2-yl.

II. The Introduction of Benzotriazolyl Groups

Important methods for the introduction of benzotriazolyl groups comprise both substitutions and additions as are summarized in Scheme 3. Generally, a benzotriazole derivative can be obtained by

Scheme 3. Important Methods for Introduction of Benzotriazole Groups

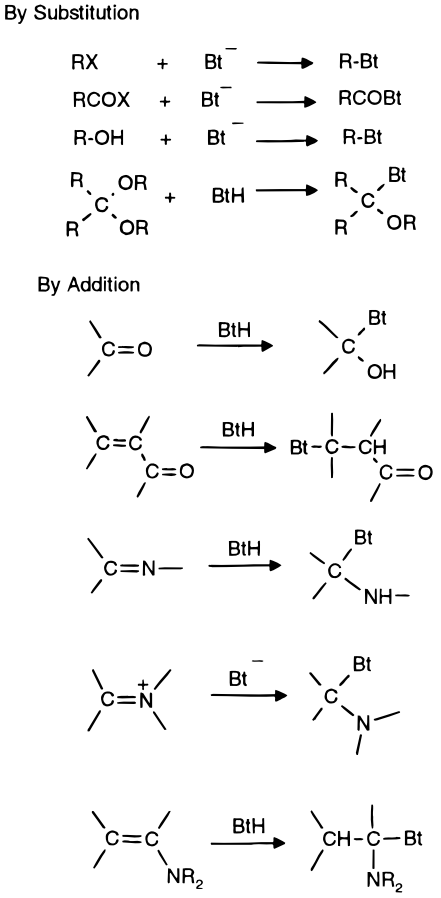


Table 1. Preparation of *N*-Alkylbenzotriazoles 13[15]

RX	R	yield %
MeI	Me	95
i-PrI	*i*-Pr	80
n-BuBr	*n*-Bu	86
Et(Me)CHBr	Et(Me)CH	65
$PhCH_2Br$	$PhCH_2$	99
Ph_3CCl	Ph_3C	100
$EtOOCCH_2Cl$	$EtOOCCH_2$	95
$PhCOCH_2Br$	$PhCOCH_2$	98

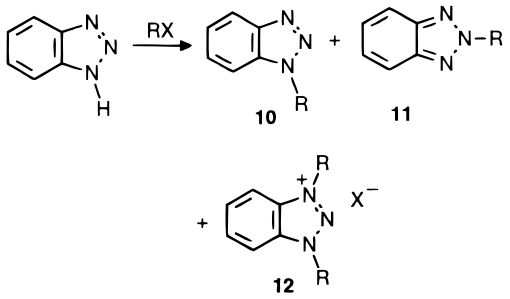
displacement of a halogen in alkyl or acyl halides, of a hydroxy group in alcohols, and of an alkoxy group in acetals or ketals. Other important routes involve additions of benzotriazole to aldehydes (and their conjugate analogues), to imines, to iminium salts, and to enamines.

A. Formation of Bt–C Bond by Substitution

1. Displacements from Alkyl Halides, etc.

In early work, the simple alkyl halide 2-chloroethanol and sodium benzotriazolate gave a mixture of benzotriazol-1-yl (Bt^1) and -2-yl (Bt^2) isomers.[8] Traditional methods have employed sodium alkoxides[9,10] or sodium hydride[11] as base, or phase-transfer catalysis (PTC) with quaternary ammonium salts,[12] with 18-crown-6,[13] or with polyethylene glycols (PEG) or their dialkyl ethers (PEG ethers).[14] An improved method for the reaction of benzotriazole with alkyl halides employs DMF as the solvent and NaOH as the base:[15] yields are higher than those reported in literature before (see Table 1). Alkylation of benzotriazole with alkyl halides can also be achieved without a solvent either in basic media in the presence of a phase-transfer catalyst or in the absence of base by conventional and microwave heating[16] (Scheme 4). In general, a mixture of *N*-1

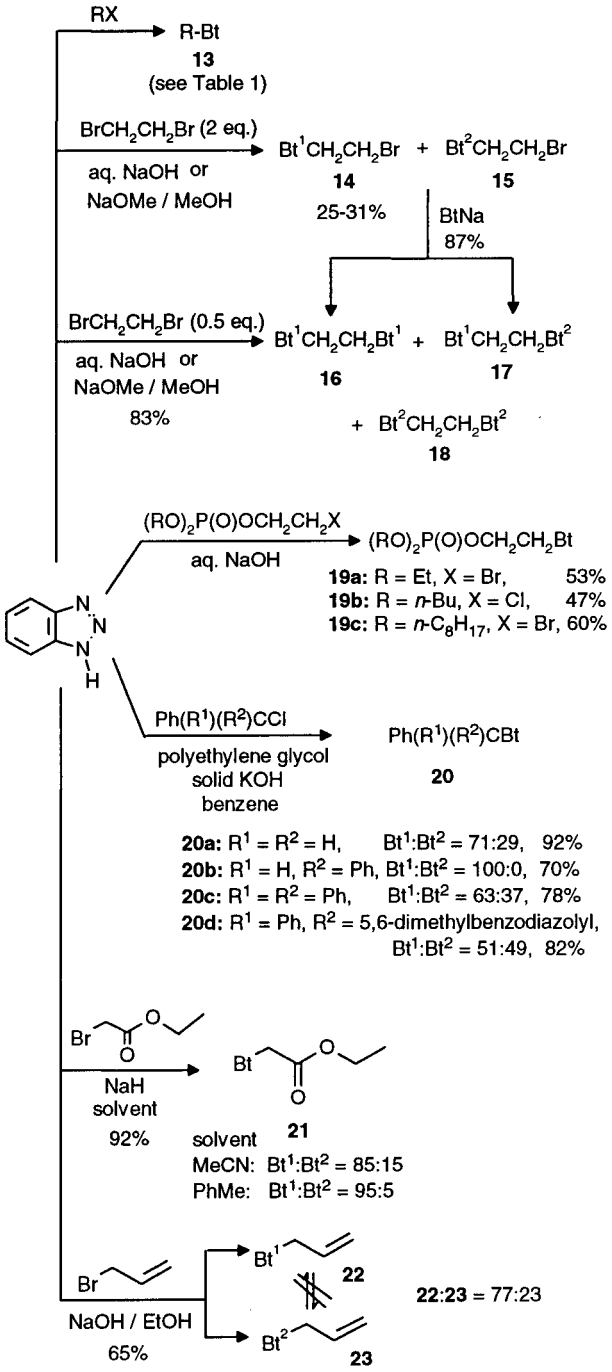
Scheme 4. Reaction of Benzotriazole with Primary Alkyl Halides



and *N*-2 isomers is obtained with the *N*-1 isomer predominant in all cases. Quaternization product **12** is also observed in some cases.

When a dibromide (1,2-dibromoethane) was used, depending on the molar ratio of the bromide to sodium benzotriazolate, mono- (**14** and **15**) or disubstituted derivatives (**16**−**18**), as a mixture of three possible isomers, were obtained.[17] The monosubstituted product **14**, when treated further with BtNa, gave a mixture of two isomers **16** and **17** (Scheme 5). This method can also be used for the formation of benzotriazolylethyl phosphates **19a**−**c**. In all cases, mixtures of Bt^1 and Bt^2 isomers were obtained.

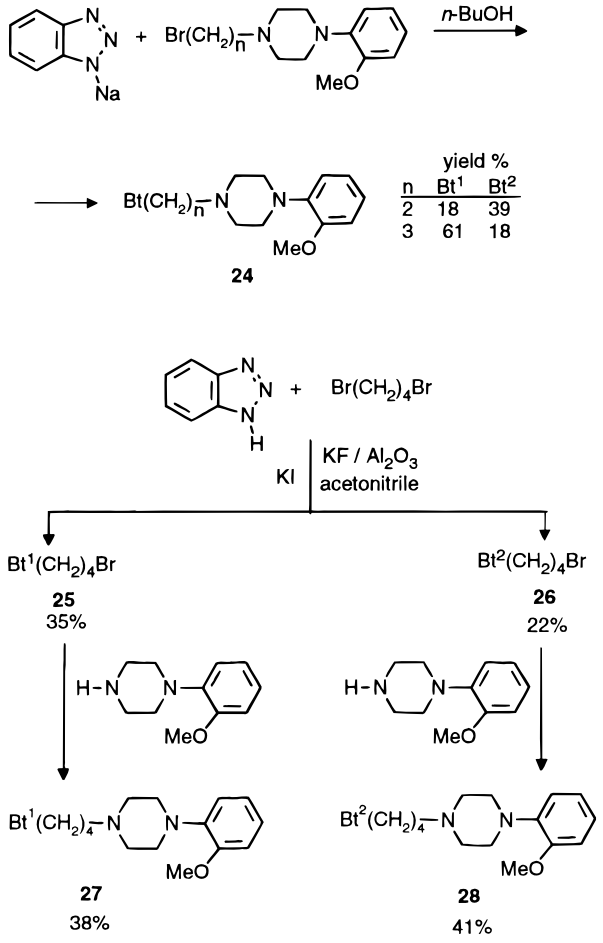
Scheme 5. Reaction of Benzotriazole with Alkyl Halides



The reaction of sodium benzotriazolate in 1-butanol with 1-(*ω*-bromoalkyl)-4-arylpiperazine gives a mixture of benzotriazol-1-yl and benzotriazol-2-yl isomers[10] (Scheme 6). In an alternative route to these compounds, benzotriazole was treated with 1,4-dibromobutane to yield a mixture of 1-(4-bromobutyl)- and 2-(4-bromobutyl)benzotriazoles, which reacted with 1-(*o*-methoxyphenyl)piperazine to give 4-(4-benzotriazol-1-ylbutyl)-1-(2-methoxyphenyl)piperazine (**27**) and 4-(4-benzotriazol-2-ylbutyl)-1-(2-methoxyphenyl)piperazine (**28**), respectively.

Substitution at the α carbon of an alkyl halide may influence the reaction conditions. Reactions of benzotriazole with arylmethyl chlorides were first achieved employing phase-transfer catalysis.[12] Such

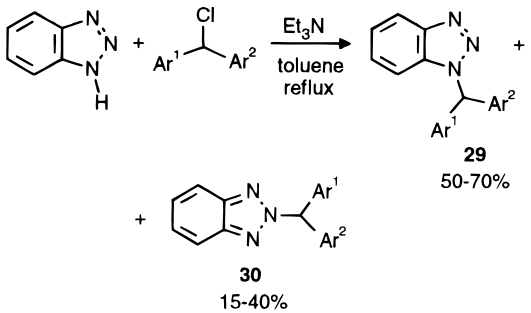
Scheme 6. Reactions of Benzotriazole or Its Sodium Salt with Bromo- and α,ω-Dibromoalkanes



reactions can also be accomplished in benzene in the presence of solid potassium hydroxide and polyethylene glycol[18] to give **20** (Scheme 5). Except for diphenylmethyl chloride where only the Bt^1 isomer is formed, mixtures of Bt^1 and Bt^2 isomers are obtained.

Reactions of benzotriazole with diarylmethyl chlorides are also effected by triethylamine in toluene, affording a mixture of Bt^1 and Bt^2 isomers (Scheme 7).[19]

Scheme 7. Reaction of Benzotriazole with 1,1-Diarylalkyl Chlorides



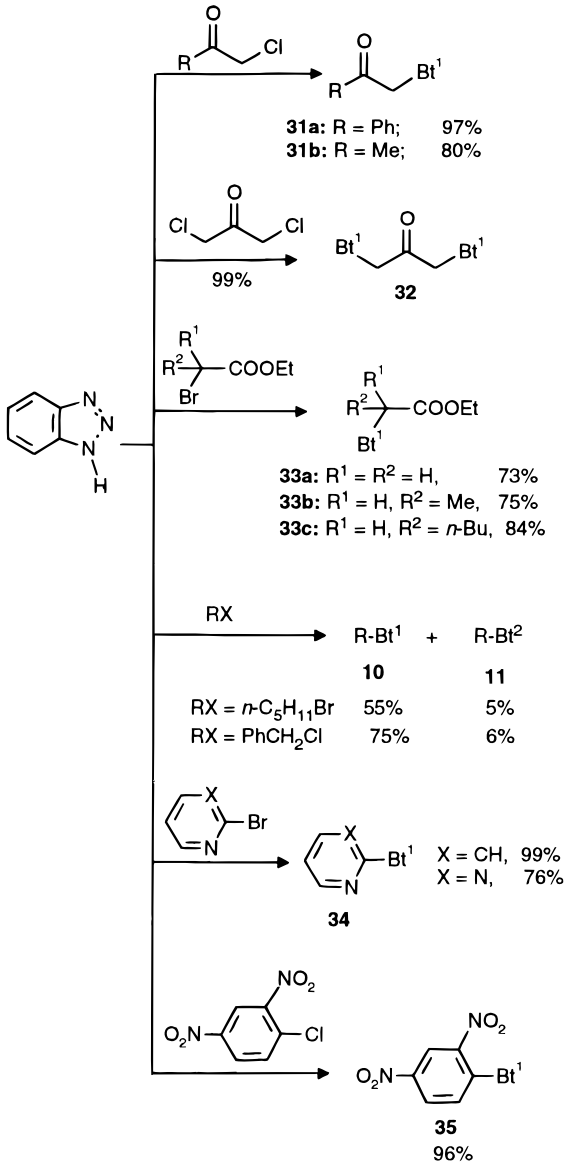
Ar^1	Ar^2	yield of **29** (%)
Ph	Ph	70
4-ClC_6H_4	Ph	70
4-FC_6H_4	4-FC_6H_4	50
dibenzosuberandiyl		53

Sodium benzotriazolate reacts with ethyl bromoacetate to give a mixture of the Bt^1 and Bt^2 iso-

mers[20,21,22] (Scheme 5). When different solvents are used, different ratios of the isomers are obtained. Allylation of benzotriazole with allyl bromide yields a mixture of Bt^1 (**22**) and Bt^2 isomers (**23**) in 77:23 ratio (Scheme 5). These two isomers are not easily interconverted.[23,24]

The reaction of benzotriazole with alkyl halides in general, and with α-halogenated ketones or esters in particular, can also be carried out in the absence of a base, in high yield and with regioselective formation of 1-alkylbenzotriazoles[25,26] (Scheme 8). Activated

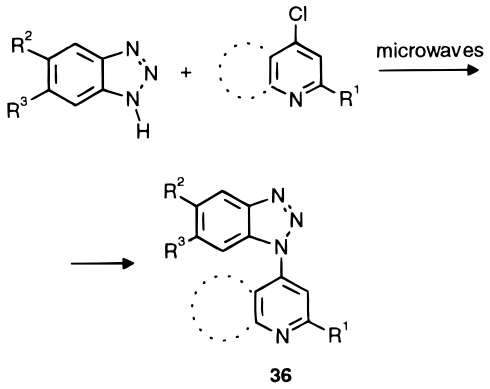
Scheme 8. Reactions of Benzotriazole with Activated Halides in the Absence of a Base



aryl halides and heteroaryl halides also undergo this type of reactions.[25,27] The existence of benzotriazole as its hydrogen-bonded dimer or in higher agglomerates, as well as intermolecular hydrogen bonding explains the regioselectivity.

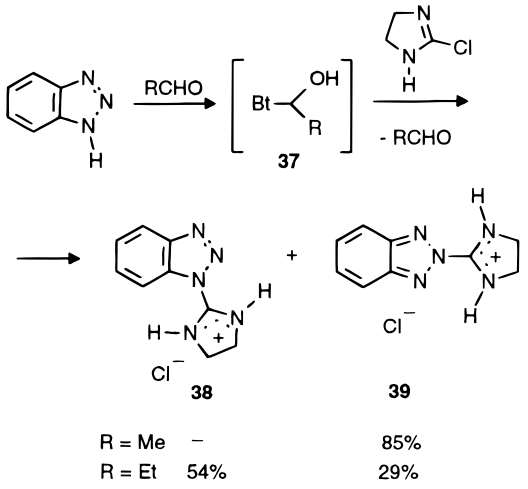
Under microwave irradiation,[28] *C*-substituted benzotriazoles react with 4-chloropyridine derivatives to afford 4-benzotriazolyl-substituted pyridines **36** in fairly good yields (Scheme 9).

Scheme 9. Microwave-Promoted Heteroaromatic Substitution with Benzotriazole



Reaction of benzotriazole with 2-chloro-4,5-dihydroimidazole in the presence of an equimolar amount of an aliphatic aldehyde gives *N*-imidazolylbenzotriazoles as their hydrochloride salts **38** and **39** in good yields (Scheme 10).[29] The mechanism involves the

Scheme 10. Aldehyde-Assisted Preparation of *N*-(4,5-Dihydro-1*H* -imidazol-2-yl)benzotriazole Hydrochlorides

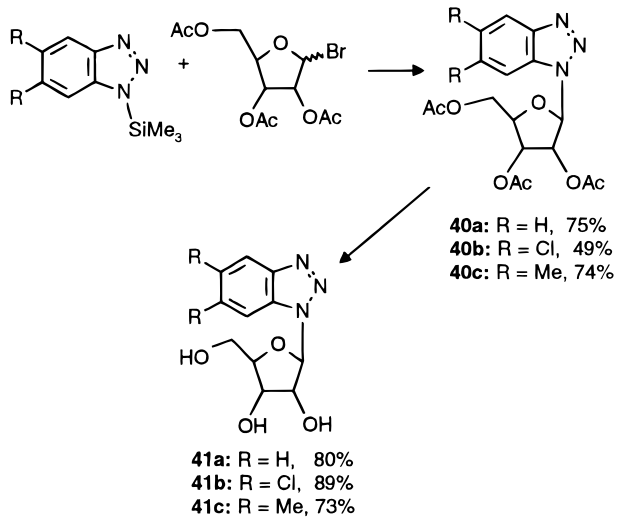


initial formation of unstable hemiaminals **37** (see also section II.B.1.a) from benzotriazole and an aldehyde. Nucleophilic substitution of chlorine in 2-chloro-4,5-dihydroimidazole by a hydroxy group of **37** is followed by intra- or intermolecular rearrangement of the intermediate obtained with the simultaneous extrusion of the aldehyde. The ratio of the isomers **38** and **39** depends strongly on the concentration and ratio of the reagents and the nature of the aldehyde used.

Benzotriazole, or its silver or mercury salt, or 1-(trimethylsilyl)benzotriazole, reacts with acetylated sugar halides such as tetra-*O*-acetyl-β-D-glucopyranosyl halides,[30−34] per-*O*-acetyl monosaccharide halides,[35,36] acetylated glycosyl halides,[37−39] and 1-bromo-1-methoxy-aldehydo-D-galactose pentaacetate[40] to give the corresponding benzotriazole derivatives. The silver and mercury ions function as halide acceptors. The protecting acetyl groups can then be cleaved by methanolic ammonia leading to benzotriazolyl glucose or ribose which show biological activity.[41−43] Mixtures of the benzotriazol-1-yl and benzotriazol-2-yl isomers were obtained and it was claimed that

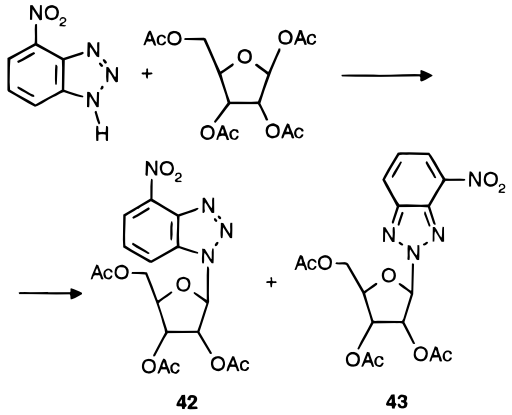
use of the silver salt gave predominantly the benzotriazol-1-yl isomer while the mercury salt gave mainly the 2-yl isomer. Thus, 1-(trimethylsilyl)-benzotriazole reacts with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, yielding the acetylated ribose benzotriazole derivative **40** which is hydrolyzed in methanolic ammonia to give benzotriazolyl ribose **41**[32] (Scheme 11).

Scheme 11. Preparation of Benzotriazolyl Glycosides (Part 1)



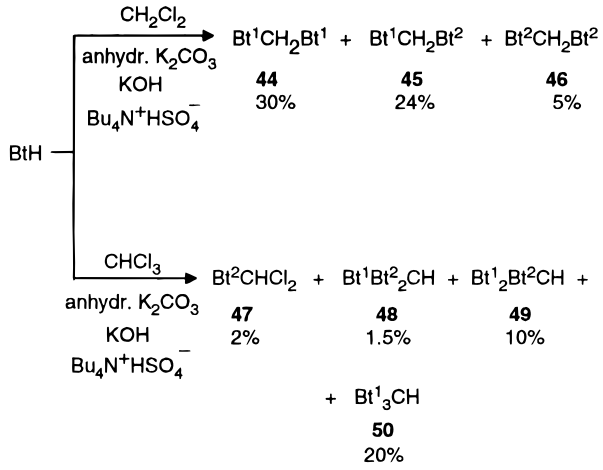
Benzotriazoles can also displace an acetyl group in per-*O*-acetyl ribose.[34,44] Thus, 4-nitrobenzotriazole was treated with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose at 135−145 °C under reduced pressure to give a mixture of the benzotriazol-1-yl **42** and 2-yl **43** isomers[34] (Scheme 12).

Scheme 12. Preparation of Benzotriazolyl Glycosides (Part 2)



Reactions of benzotriazole with methylene chloride and chloroform in the presence of a phase-transfer catalyst were found to give mixtures of all possible benzotriazol-1-yl and benzotriazol-2-yl isomers.[45] With chloroform, the isomers shown in Scheme 13 were identified[46] and isolated. The ^{13}C NMR chemical shifts of the central sp^3 carbon in such di- or trisubstituted methanes have been studied and the effects of the specific *N*-substituents on the ^{13}C chemical shifts of the heterocyclic nuclei are reported.[47]

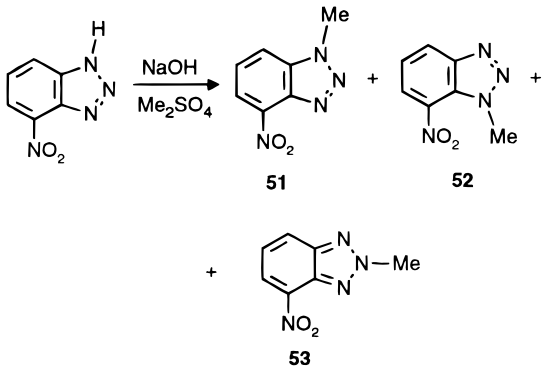
Scheme 13. Reactions of Benzotriazole with Polychloromethanes



In summary, the displacement of a halogen by benzotriazole usually affords a mixture of Bt^1 and Bt^2 isomers; the ratio depends largely on the solvents used.

N-Methylation of 4-nitrobenzotriazole was achieved by treatment with dimethyl sulfate in aqueous alkali (Scheme 14). The formation of a mixture of all three

Scheme 14. Alkylation of Benzotriazole with Dimethyl Sulfate

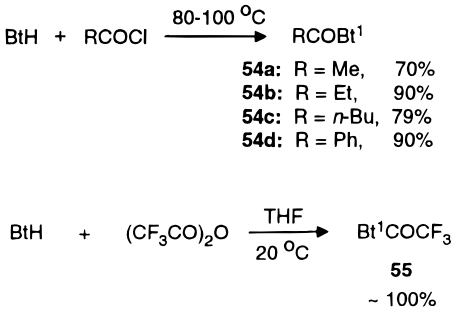


possible isomers was shown by ^1H NMR spectroscopy and the least basic of them, 2-methyl-4-nitrobenzotriazole (**53**), could be easily separated by treatment with hydrochloric acid.[48]

2. Displacements from Acyl Halides, etc.

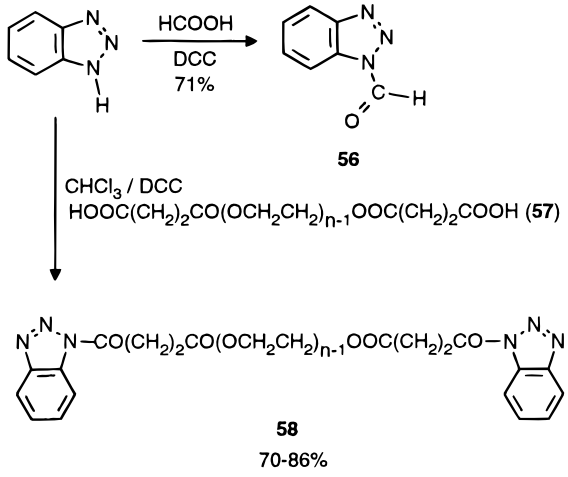
N-Acylbenzotriazoles have been prepared from reactions of acid chlorides (i) with 1-(trimethylsilyl)-benzotriazole,[49] (ii) with 1-(tributylstannyl)benzotriazole,[50] or (iii) with 1-(hydroxymethyl)benzotriazole which loses formaldehyde.[51,52] A direct method from benzotriazole and an acid chloride at 80−100 °C without solvent allows the preparation of 1-acylbenzotriazoles **54a**−**d** in good yields (Scheme 15):[53] in all cases only the Bt^1 isomers were isolated. The analogous *N*-thioacylbenzotriazoles can be prepared similarly. As reported in ref 54, the direct reaction of thiobenzoyl chloride with benzotriazole affords higher yield than the similar reaction with 1-(trimethylsilyl)benzotriazole. 1-(Trifluoroacetyl)benzotriazole (**55**) is easily synthesized in almost quantitative yield by reaction of benzotriazole with

Scheme 15. Reactions of Benzotriazole with Acyl Chlorides and Anhydrides in the Absence of Base



trifluoroacetic anhydride in the absence of base (Scheme 15).[55] 1-Formylbenzotriazole (**56**) is obtained from formic acid and benzotriazole in the presence of DCC.[56] Application of the same procedure to succinic half-esters of polyethylene glycols **57** leads to macromolecular *N*-acylbenzotriazoles **58** (Scheme 16), from which both benzotriazolyl moieties

Scheme 16. Reactions of Benzotriazole with Acids in the Presence of DCC



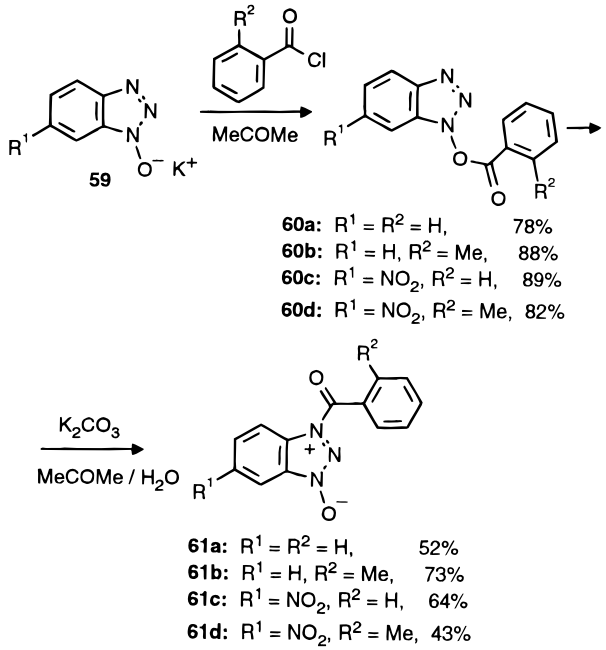
could be displaced in reactions with amines or alcohols (see section IV.B.10.a).[57]

1-(Aroyloxy)benzotriazoles **60**, prepared in high yields by treatment of potassium salts 1-hydroxybenzotriazoles **59** with aroyl chlorides, undergo intermolecular rearrangement under mild basic conditions to give the corresponding 3-acylbenzotriazole 1-oxides **61** (Scheme 17).[58]

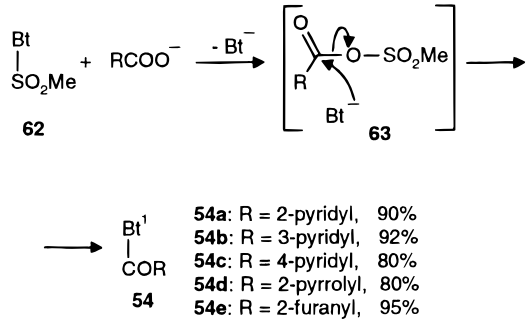
Acylation of 1-(hydroxymethyl)benzotriazole with benzoyl chloride yields different products depending on the reaction conditions used.[59] In the presence of pyridine and in dioxane solution at 60 °C, the loss of formaldehyde occurs and 1-benzoylbenzotriazole is obtained in 66% yield[51] while in 10% sodium hydroxide solution 1-(benzoyloxy)methylbenzotriazole is obtained in 40% yield at 20 °C, and in 26.5% yield at 45−65 °C.[52]

Reaction of 1-(methylsulfonyl)benzotriazole (**62**) with carboxylic acid anions leads to the formation of 1-acylbenzotriazoles, an activated form of an acid.[53] Such 1-acylbenzotriazoles are more stable than the corresponding acid chlorides. The reaction is believed to involve attack of the acid anion on the sulfonyl group to give a mixed anhydride **63**. The benzotriazole anion then attacks the carbonyl group of the anhydride to form the acylbenzotriazole **54** (Scheme 18).

Scheme 17. Preparation of 3-Benzoylbenzotriazole 1-Oxides



Scheme 18. Conversion of Carboxylate Anions into *N*-Acylbenzotriazoles Mediated by *N*-Sulfonylbenzotriazole



Benzotriazole reacts with excess of phosgene to give the 1-benzotriazolecarboxylic acid chloride (**64**) in almost quantitative yield[60] (Scheme 19, Table 2). Sub-

Scheme 19. Preparation of *N*-Carbamoylbenzotriazoles

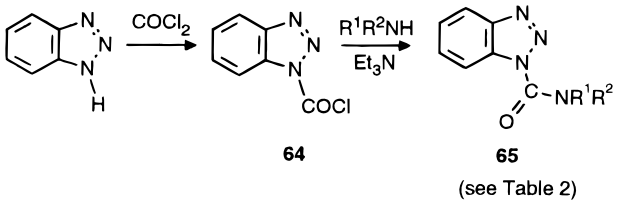


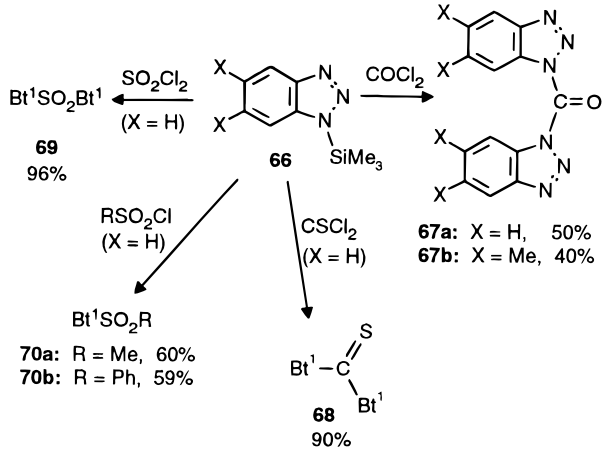
Table 2. Preparation of *N*-Carbamoylbenzotriazoles 65

R^1	R^2	yield %	R^1	R^2	yield %
Me	H	75	Et	Et	88
n-Bu	H	78	C_6H_5	H	82
n-$C_{18}H_{37}$	H	66	NHPh	H	40
i-Pr	H	95	NH-1-azepinyl	H	88
c-C_6H_{11}	H	70			

sequent aminolysis of **64** provides a simple and convenient approach to substituted carbamoylbenzotriazoles **65** which are important intermediates in the preparation of pharmacologically active substances.

Reactions of 1-(trimethylsilyl)benzotriazole (**66**) with phosgene[61] and thiophosgene[62] gives 1,1′-carbonyldibenzotriazole (**67a**) and 1,1′-thiocarbonyldibenzotriazole (**68**), respectively. Compound **68** can also be prepared from sodium benzotriazolate and thiophosgene.[63] Interestingly use of free benzotriazole results in the formation of 1-(2-benzothiazolyl)benzotriazole as a result of ring cleavase and rearrangement (see section V.D). Using the 1-(trimethylsilyl)-benzotriazole method, **67a** and 1,1′-carbonyldi(5,6-dimethylbenzotriazole) (**67b**) were later obtained in 50% and 40% yield, respectively.[64] Similarly, 1-(trimethylsilyl)benzotriazole reacts with sulfuryl chloride affording 1,1′-sulfonyldibenzotriazole (**69**),[65] and with alkane- or arenesulfonyl chlorides giving *N*-(alkylsulfonyl)- or *N*-(arylsulfonyl)benzotriazoles **70a**,**b**.[53,66,67] Again, only the Bt^1 isomers were isolated (Scheme 20).

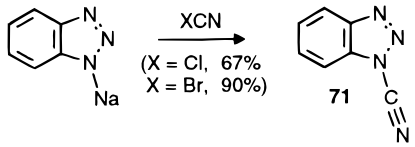
Scheme 20. Acyl- and Sulfonylbenzotriazoles Prepared from 1-(Trimethylsilyl)benzotriazoles



Although too unstable to be isolated, sulfinylbisbenzotriazole **72** (see Scheme 22) can be prepared *in situ* from 1-(trimethylsilyl)benzotriazole and thionyl chloride in THF at 0 °C.[68]

Sodium benzotriazolate reacts with cyanogen chloride to give 1-cyanobenzotriazole (**71**, Scheme 21).[69,70]

Scheme 21. Preparations of 1-Cyanobenzotriazole



A similar reaction with cyanogen bromide under carefully controlled conditions affords **71** in 90% yield.[71]

3. Formation of Imidoylbenzotriazoles

Reactions of secondary amides with dibenzotriazolyl sulfoxide (**72**) give 1-imidoylbenzotriazoles **73**[68,72] (Scheme 22, Table 3). The reaction involves the initial addition of the amide oxygen to the sulfoxide and elimination of benzotriazolate anion. The anion

Scheme 22. Conversion of Amides into Imidoylbenzotriazoles Mediated by Sulfinylbisbenzotriazole

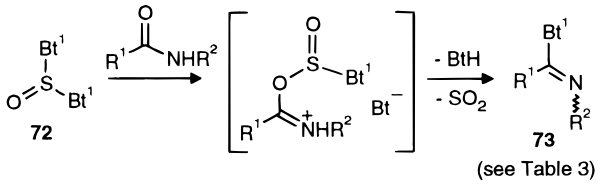


Table 3. Preparation of 1-Imidoylbenzotriazoles 73

R^1	R^2	yield %	R^1	R^2	yield %
Ph	Ph	41	Me	Ph	49
Ph	$PhCH_2$	15	Me	4-BrC_6H_4	57
Ph	Bu	61	Me	4-$EtOC_6H_4$	25
Ph	*i*-Bu	75	Me	2-$MeCOC_6H_4$	45
Ph	Me	15	Me	4-MeC_6H_4	31
Ph	4-ClC_6H_4	43	4-MeC_6H_4	Ph	62
Ph	4-(*i*-Pr)C_6H_4	39	4-BrC_6H_4	*i*-Bu	58

adds back to the iminium cation and with the departure of another molecule of benzotriazole and sulfur dioxide forms the imidoylbenzotriazoles. Sulfinyl bisbenzotriazolyl (**72**) thus acts as both a dehydrating agent and an activated source of benzotriazole.

A similar addition of benzotriazole to imidoyl phosphoric esters is achieved by the reaction of an amide, triethylamine, benzotriazole, and phosphoryl chloride.[73] The intermediates **76** then eliminate

Scheme 23. Addition of Benzotriazole to Imidoyl Phosphoric Esters

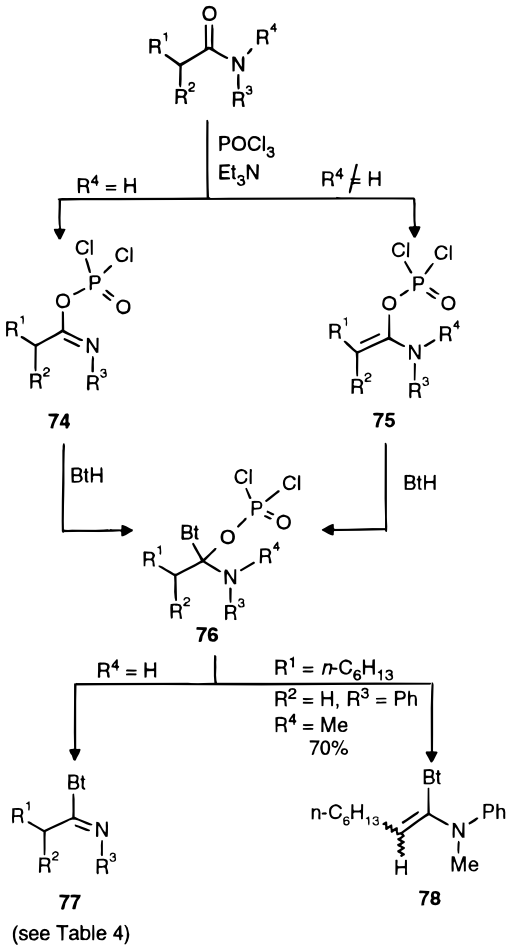


Table 4. Preparation of 1-Imidoylbenzotriazoles 77

R^1	R^2	R^3	yield %	R^1	R^2	R^3	yield %
H	H	Ph	96	Et	H	Ph	60
H	H	4-BrC_6H_4	89	*n*-C_6H_{13}	H	Ph	87
H	H	4-MeC_6H_4	88	Ph	H	Ph	38
Me	H	Ph	57	Me	Me	4-MeC_6H_4	62

dichlorophosphoric acid to give 1-imidoylbenzotriazoles **77** or enamines **78** (Scheme 23, Table 4).

4. Displacement of OH in Alcohols, etc.

Benzotriazole reacts with activated benzylic type alcohols in the presence of a catalytic amount of *p*-toluenesulfonic acid. Thus, in benzene or toluene with azeotropic removal of water, the reactions of benzotriazole and 5,6-dimethylbenzotriazole with diarylmethanols (Scheme 24, Table 5) gave mixtures

Scheme 24. Reactions of Benzylic Alcohols with Benzotriazole

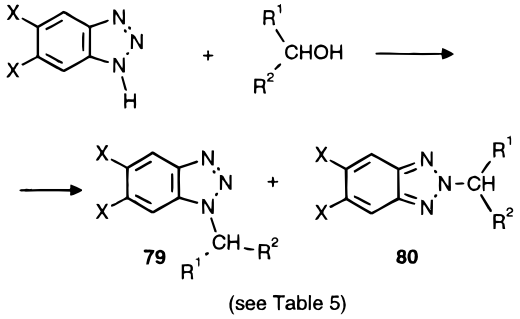


Table 5. Preparation of *N*-(Diarylmethyl)benzotriazoles 79 and 80

R^1	R^2	X	total yield %	ratio **79**:**80**
4-$Me_2NC_6H_4$	4-$Me_2NC_6H_4$	H	85	68:32
4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	90	67:33
4-ClC_6H_4	4-ClC_6H_4	H	75	43:57
4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	84	71:29
4-MeC_6H_4	Ph	H	76[a]	*b*
4-$Me_2NC_6H_4$	Ph	H	67[a]	*b*
4-MeC_6H_4	4-MeC_6H_4	H	66[a]	*b*

[a] Isolated yield for Bt^1 isomer. [b] Exact ratio not available.

of the corresponding Bt^1 (**79**) and Bt^2 (**80**) isomers.[18,19] These reactions of diarylmethanols under acidic conditions can be viewed as S_N1 reactions.

Unactivated alcohols, such as methanol and primary alcohols, can be transformed into their benzotriazole derivatives in one pot using 1,1′-sulfonyldibenzotriazole. Thus, sodium alkoxides react with 1,1′-sulfonyldibenzotriazole to give *N*-alkylbenzotriazoles as mixtures of Bt^1 and Bt^2 isomers. The initial attack of the alkoxide anion on the sulfonyl group forms the unstable intermediate **81** which is attacked by benzotriazolate anion to give Bt^1 **10** and Bt^2 isomers **11**. The benzotriazole-1-sulfonic acid sodium salt (**82**) is hydrolyzed to benzotriazole and sodium sulfate[74] (Scheme 25). This method is particularly valuable for the preparation of those *N*-alkylbenzotriazoles which cannot conveniently be synthesized from the corresponding alkyl halides either because these are not readily available or are unstable, or if the

Scheme 25. Conversion of Sodium Alkoxides into Alkylbenzotriazoles

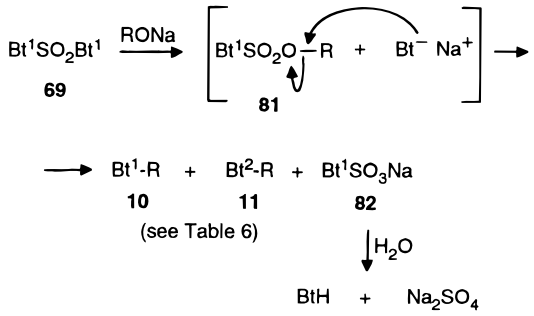


Table 6. Preparation of *N*-Alkylbenzotriazoles 10 and 11 Using 1,1′-Sulfonyldibenzotriazole

R	yield %	R	yield %
Me	71	2-$FuCH_2$	73
n-Bu	69	*sec*-Bu	46
$Me_2NCH_2CH_2$	74	*t*-Bu	45
2-$PyCH_2CH_2$	45	4-$PyCH_2$	10

corresponding alcohols are more easily available and/or more stable than the halides; thus Table 6 includes the preparation of pyridyl, furfuryl, and dimethylamino derivatives.

In an alternative preparation of *N*-alkylbenzotriazoles, 1,1′-carbonylbisbenzotriazoles react with alcohols at room temperature to yield 1-(alkoxycarbonyl)benzotriazoles **83**.[64] On thermolysis, these 1-(alkoxycarbonyl)benzotriazoles undergo clean decarboxylation to form a mixture of 1- and 2-alkylbenzotriazoles (**84** and **85**, respectively), with the N-1 isomer predominating in all cases (Scheme 26, Table 7).

Scheme 26. Preparation of *N*-Alkylbenzotriazoles from 1,1′-Carbonylbisbenzotriazoles

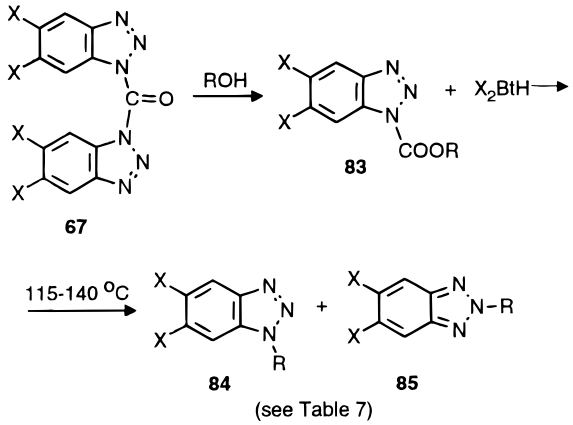


Table 7. Preparation of *N*-Alkylbenzotriazoles 84 and 85 by Pyrolysis of 1-(Alkoxycarbonyl)benzotriazoles

R	X	product ratio[a] % **84**	**85**	R	X	product ratio[a] % **84**	**85**
Me	H	71	29	CH_2=$CHCH_2$	H	71	29
Et	H	73	27	$PhCH_2$	Me	76	24
n-Bu	H	78	22	4-$MeC_6H_4CH_2$	Me	74	26
$PhCH_2$	H	82	18	$MeCH$=$CHCH_2$	Me	73	27
4-$MeC_6H_4CH_2$	H	74	26				

[a] Ratios were determined from the relative intensities of integrated ^1H NMR signals.

Table 8. Preparation of 1-(α-Alkoxyalkyl)benzotriazoles 86 and 87

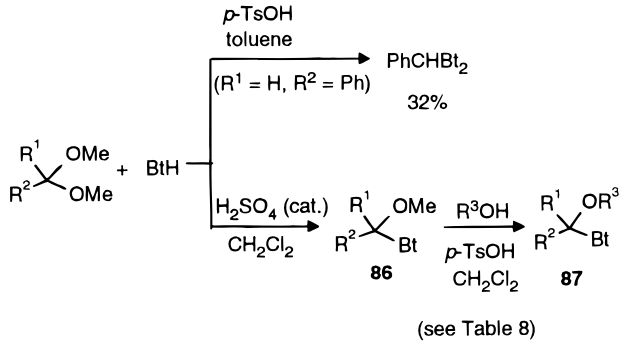
compound	R^1	R^2	R^3	yield, %
86	Me	Me		88[76]
	Et	Et		78[76]
	$-(CH_2)_5-$			70[76]
	Me	Ph		65[76]
87	Ac	H	Me	92[75]
	Me	Me	Me	90[75]
	Me	Me	n-C_6H_{13}	88[75]
	Me	Me	c-C_5H_9	70[76]
	Et	Et	n-C_6H_{13}	94[76]
	Et	Et	$PhCH_2$	63[76]
	Et	Et	i-Pr	62[76]
	$-(CH_2)_5-$		$PhCH_2$	90[76]
	$-(CH_2)_5-$		i-Pr	69[76]

Cross-over experiments clearly indicate that the decarboxylation proceeds via an intermolecular process.

5. Displacement of Alkoxy Group in Acetals, Ketals, etc.

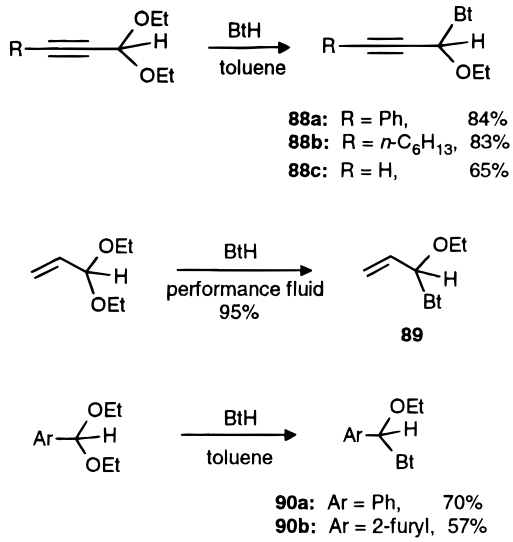
Benzotriazole can displace one of the alkoxy groups in acetals or ketals to give 1-(α-alkoxyalkyl)benzotriazoles (**86**)[75,76] (Scheme 27, Table 8). If a dimethyl

Scheme 27. Introduction of Benzotriazole Group by Dispacement of Methoxy Group in Ketals or Acetals



acetal is used, then one of the methoxy groups can be replaced by benzotriazole and the second by another alcohol by distilling off the methanol formed. A similar transformation is realized with diethyl acetals[77−80] (Scheme 28). In the reaction of acrolein

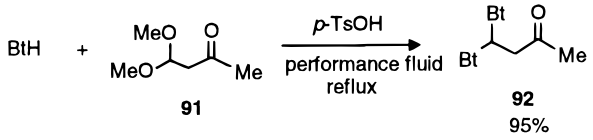
Scheme 28. Conversion of Diethyl Acetals to Benzotriazole Derivatives



diethyl acetal with benzotriazole in performance fluid,[77,78] no rearrangement product is detected.

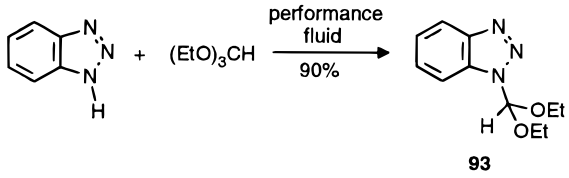
Generally, only one alkoxy group of acetals and ketals can be substituted by the benzotriazole group, even when an excess of benzotriazole is used. However, the presence of a β carbonyl group promotes this reaction. For example, with 4,4-dimethoxy-2-butanone (**91**), *gem*-dibenzotriazolyl derivative **92** was obtained in 95% yield (Scheme 29).[81b]

Scheme 29. Displacement of Both Alkoxy Groups in Acetals by Benzotriazole



Ethyl orthoformate also reacts with benzotriazole to give (benzotriazol-1-yl)diethoxymethane **93** in 90% yield (Scheme 30).[27]

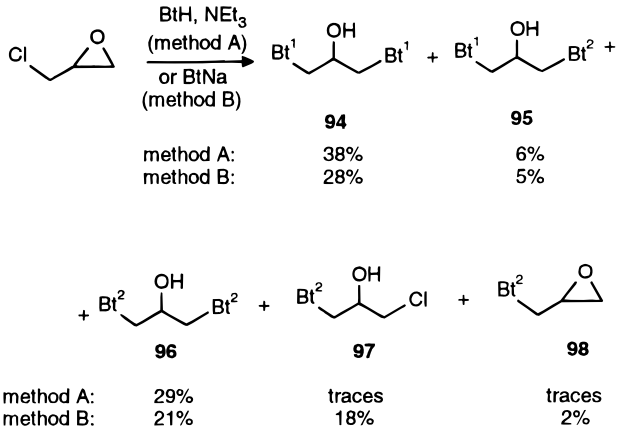
Scheme 30. Reaction of Benzotriazole with Triethyl Orthoformate



Similarly, when aldehyde diacyloxy derivatives are used, (acyloxyalkyl)benzotriazoles are obtained.[81a,82]

In the presence of triethylamine, benzotriazole reacts with epichlorohydrin with oxirane ring opening and simultaneous substitution of chlorine by benzotriazolyl group to produce a mixture of mono- and dibenzotriazolyl-substituted compounds **94**−**98** (Scheme 31). Replacement of benzotriazole with

Scheme 31. Reaction of Benzotriazole or Sodium Benzotriazolate with Epichlorohydrin

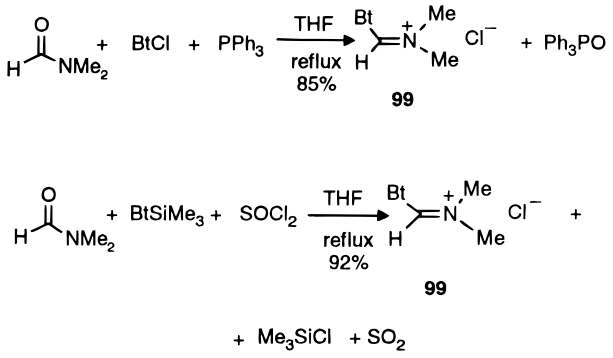


sodium benzotriazolate leads to increased yields of monosubstituted products **97** and **98**.[83]

6. Displacement of Oxygen in Amides

Addition of 1-chlorobenzotriazole to *N*,*N*-dimethylformamide in the presence of triphenylphosphine results in benzotriazolylmethyleniminium chloride **99** in high yield (Scheme 32). This compound can also

Scheme 32. Preparation of *N*,*N*-Dimethylbenzotriazolylmethyleniminium Chloride

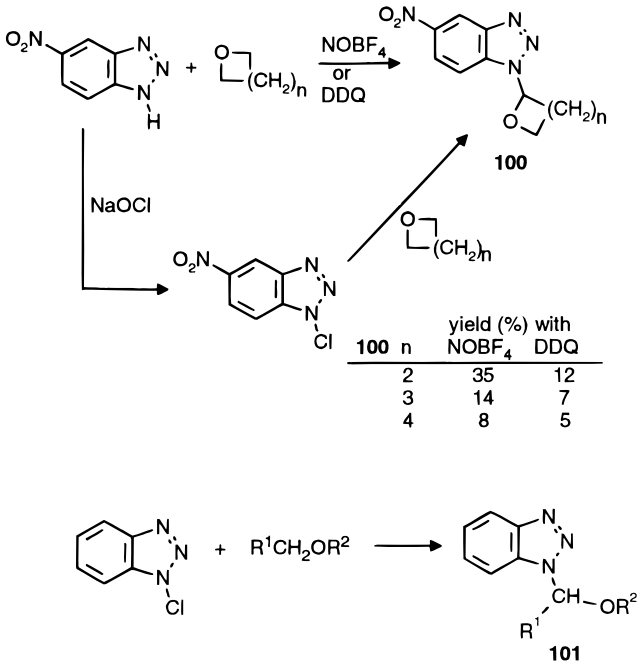


be prepared by treatment of *N*,*N*-dimethylformamide with *N*-(trimethylsilyl)benzotriazole and thionyl chloride under mild conditions.[83]

7. Miscellaneous Substitution Reactions

5-Nitrobenzotriazole reacts with cyclic aliphatic ethers in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or $NOBF_4$ to give the corresponding C−N coupling products **100** (Scheme 33). Instead of

Scheme 33. Reaction of Benzotriazoles with Alkyl Ethers

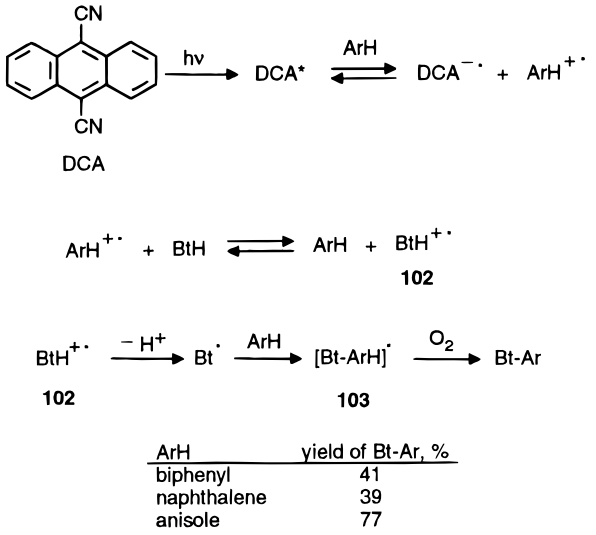


100	n	yield (%) with $NOBF_4$	DDQ
	2	35	12
	3	14	7
	4	8	5

free benzotriazole, 1-chloro-5-nitrobenzotriazole can be used in this reaction which in this case occurs without an additional oxidizing agent and under mild conditions.[84] These reactions probably involve initial conversion of the cyclic ether to an oxonium cation. Analogous reactions of 1-chlorobenzotriazole with cyclic and noncyclic aliphatic and benzylic ethers gives the corresponding α-alkoxybenzotriazoles **101**, however, in yields consistently below 50%.[85,86]

Irradiation of benzotriazole, an aromatic hydrocarbon and a photosensitizer, such as 9,10-dicyanoanthracene (DCA), in acetonitrile under an oxygen atmosphere leads to the formation of 1-arylbenzotriazoles in moderate yields[87] (Scheme 34). A SET mechanism with formation of benzotriazolyl cation radical **102**, which loses a proton easily to give the benzotriazolyl radical Bt•, was proposed for this reaction. The Bt• radical adds to a neutral aromatic hydrocarbon to give the radical **103**, which is oxidized with oxygen to the final aryl-substituted benzotriazole.

Scheme 34. Preparation of *N*-Arylbenzotriazoles



ArH	yield of Bt-Ar, %
biphenyl	41
naphthalene	39
anisole	77

B. Formation of Bt–C Bond by Addition Reactions

1. Addition to C=O and C=O+

a. Addition to Aldehydes and Ketones. Benzotriazole reacts with aliphatic aldehydes to give isolable adducts.[81] That from formaldehyde has long been known but this property is found to be general for aliphatic aldehydes (Scheme 35). The products **104** from benzotriazole and aliphatic aldehydes are crystalline compounds. The mechanism presumably involves the nucleophilic attack of benzotriazole to

Scheme 35. Formation of Addition Products from Benzotriazole and Aldehydes

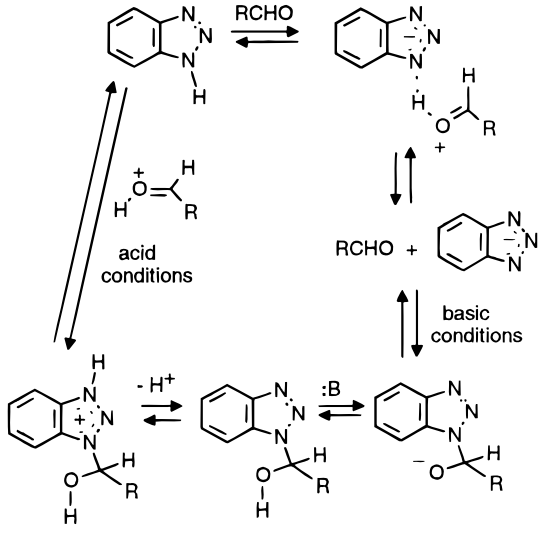


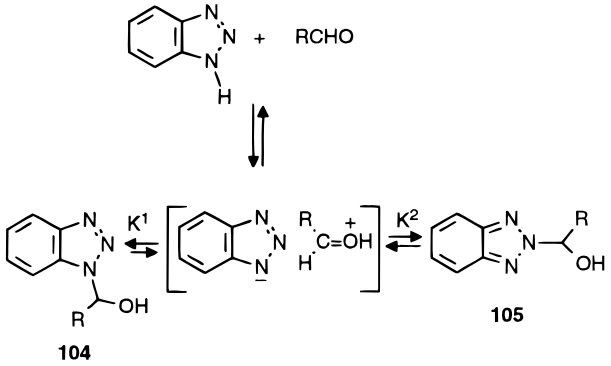
Table 9. Equilibrium Constants for the Isomerization of 1-Benzotriazolyl and 2-Benzotriazolyl Alcohols

carbonyl compound	K^1, M^{-1}	K^2, M^{-1}	$\Delta G_1°$, kcal/mol	$\Delta G_2°$, kcal/mol
MeCHO	22.3	1.87	−1.83	−0.368
EtCHO	18.6	1.40	−1.72	−0.198
i-PrCHO	14.7	1.16	−1.58	−0.087
t-BuCHO	1.28	0.114	−0.145	1.28
2-PyCHO	2.62	0.200	−0.567	0.947
4-MeC_6H_4CHO	<0.001	<0.001		
cyclohexanone	0.100	0.034	1.35	1.99
MeCOCOOEt	0.110	0.018	1.30	2.36
MeCOMe	<0.001	<0.001		

the protonated form of an aldehyde under acidic conditions; or of benzotriazole anion to an aldehyde under basic conditions.

In solution these benzotriazole aldehyde adducts **104** dissociate into their components and also equilibrate between the 1 and the 2 positions of the benzotriazole ring (Scheme 36). The equilibrium

Scheme 36. Aldehyde−Benzotriazole Equilibria in Solution

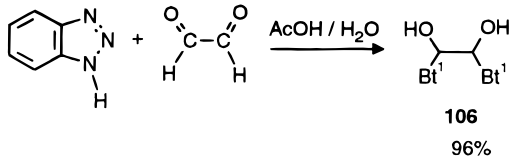


constants shown in Table 9 for these reactions in hexadeuteriobenzene at 23 °C[88] are obtained by ^1H and ^{13}C NMR study of the equilibrium mixture of benzotriazole with an appropriate carbonyl compound and their adducts: in general, the N-1 isomer predominates over the N-2 isomer.

An attempt to carry out a similar reaction with an aromatic aldehyde, such as benzaldehyde, was unsuccessful. The corresponding condensation product could be obtained when benzaldehyde is replaced with its dimethyl acetal (see Scheme 27) or with benzal chloride.[89]

When a dialdehyde such as glyoxal is used, the expected adduct **106** is formed in almost quantitative yield in aqueous acetic acid[90] (Scheme 37). Diol **106**

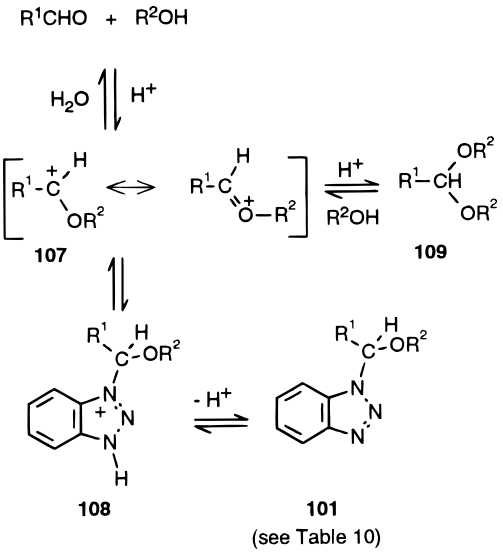
Scheme 37. Addition of Benzotriazole to Glyoxal



is stable in water and in organic solvents, but is hydrolyzed to the starting benzotriazole and glyoxal on treatment with aqueous hydrochloric or hydrobromic acid.

b. Addition to C=O⁺R. 1-(1-Alkoxyalkyl)benzotriazoles are formed quite generally from benzotriazole, an alcohol, and an aliphatic or aromatic aldehyde, and two examples were reported early on.[91] The reaction occurs readily and gives products **101** in high yields[80,81,92,93] (Scheme 38, Table 10). The reaction

Scheme 38. Condensation of Alcohol, Aldehyde, and Benzotriazole



is believed to involve electrophilic attack of the cation **107** (formed by addition of alcohol to the aldehyde) on N-3 of the benzotriazole system to give the more stable **108** which on deprotonation gives the final

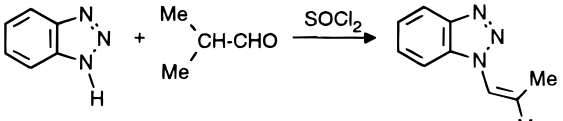
Table 10. Preparation of Adducts 101 from Alcohol, an Aldehyde, and Benzotriazole

R^1	R^2	yield %	R^1	R^2	yield %
H	Me	20[81]	Ph	CH_2=CHCH(*n*-C_5H_{11})	71[93]
Me	Me	75[81]	2-ClC_6H_4	Et	76[80]
i-Pr	Me	99[81]	4-MeC_6H_4	Me	64[81]
i-Pr	*i*-Pr	96[81]	4-MeC_6H_4	Et	77[80]
i-Pr	*i*-Pr	97[75]	4-MeC_6H_4	*i*-Pr	80[92]
i-Pr	*t*-Bu	98[81]	4-MeC_6H_4	Me_2C=$CHCH_2$	67[93]
i-Pr	c-C_6H_{11}	96[75]	4-MeC_6H_4	CH_2=CHCH(Et)	60[93]
i-Pr	c-C_6H_{11}	98[81]	2-$MeOC_6H_4$	Et	75[80]
t-Bu	Me	54[81]	3-$MeOC_6H_4$	Et	79[80]
t-Bu	*i*-Pr	82[81]	1-naphthyl	Et	71[80]
t-Bu	*t*-$BuCH_2$	90[81]	1-naphthyl	*i*-Pr	56[92]
Ph	Me	91[81]	2-furyl	Et	57[80]
Ph	Et	70[80]	3-furyl	Et	71[80]
Ph	*i*-Pr	65[75]	2-thiophenyl	Et	58[80]
Ph	Me_2C=$CHCH_2$	61[93]	3-thiophenyl	Et	82[80]
Ph	PhCH=$CHCH_2$	53[93]	2-pyridyl	Et	51[80]

product **101**. An alternate route involving addition of BtH to aldehyde to give 1-benzotriazolyl-1-alkanol is less likely. A similar mechanism also applies for acetals **109** where the initial step under acidic conditions is the cleavage of an alcohol group to form the cation **107** as already discussed in section II.A.5.

When benzotriazole was heated with thionyl chloride and an aldehyde containing an α-hydrogen, the corresponding 1-alkenylbenzotriazole was produced, as exemplified by the formation of 1-benzotriazol-1-yl-2-methylpropene (**110**) from isobutyraldehyde (Scheme 39).[27]

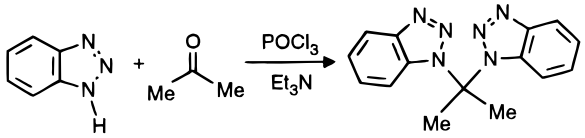
Scheme 39. Preparation of 1-Alkenylbenzotriazole from Benzotriazole and Isobutyraldehyde



110
29%

Addition of benzotriazole to ketones is energetically unfavorable: the lower reactivity of ketones compared with aldehydes is caused by steric hindrance in ketone adducts. As a result, 1-(α-hydroxyalkyl)-benzotriazoles of type $BtC(OH)R^1R^2$ (R^1, $R^2 \neq H$) are unknown. However, benzotriazole does react with ketones in the presence of phosphorus oxychloride to give *gem*-dibenzotriazol-1-ylalkanes, as exemplified by the preparation of 2,2-dibenzotriazol-1-ylpropane (**111**) from acetone (Scheme 40).[27]

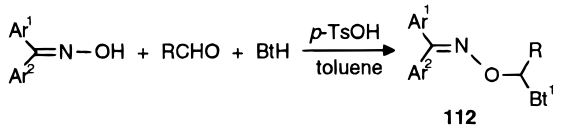
Scheme 40. Condensation of Benzotriazole with Acetone in the Presence of Phosphorus Oxychloride



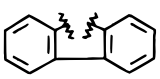
111
50%

Mannich-type condensation reactions of benzotriazole with an aldehyde and an diaryl oxime under acid catalysis affords the corresponding *O*-(1-benzotriazolylalkyl)oximes (**112**) in moderate yields (Scheme 41).

Scheme 41. Mannich Condensation of an Oxime, an Aldehyde, and Benzotriazole



112

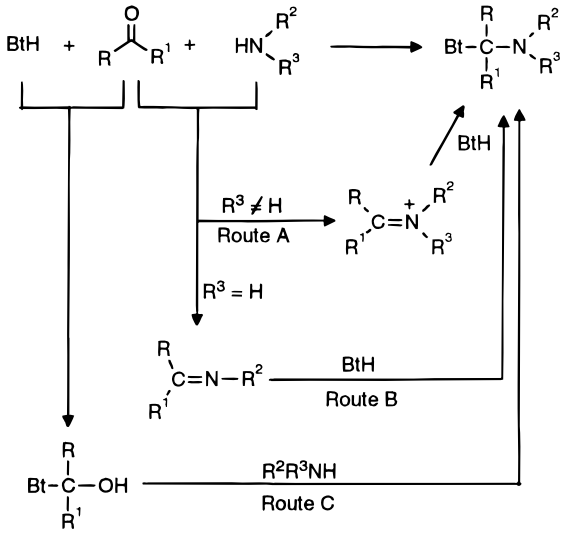
Ar^1	Ar^2	R	yield %
Ph	Ph	*c*-C_6H_{11}	65
Ph	Ph	*i*-Pr	52
Ph	Ph	BuCH(Et)	60
Ph	Ph	*t*-Bu	45
		*c*-C_6H_{11}	45

However, the application of this procedure is limited to branched aliphatic aldehydes.[94]

2. Addition to C=NR and C=N⁺R₂

One of the most important methods of introducing a Bt group into a molecule is condensation of benzotriazole with a carbonyl compound and an NH derivative (Scheme 42). Mechanistically, most of

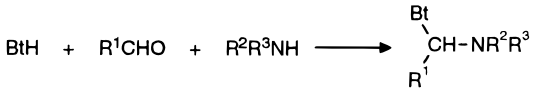
Scheme 42. Condensation Products of Benzotriazole with an Aldehyde or Ketone and an Amine



these reactions involve addition of BtH to an intermediate imine or immonium cation (routes A and B). We treat all such condensations in this manner, although some may take the alternative route in which the NH compound reacts with the BtH carbonyl condensation product (route C of Scheme 42).

a. Secondary Amines as Starting Materials. A secondary aliphatic amine reacts with an aldehyde and benzotriazole and the condensation products **113** are obtained in high yields (Scheme 43).[95−100] For

Scheme 43. Condensation of Benzotriazole, Aldehyde, and Secondary Amines



113

(see Table 11)

the condensation products derived from formaldehyde, the reaction of the amine and 1-(hydroxymethyl)benzotriazole is a significant alternative.[101] This approach has been successfully applied in the synthesis of *N*-benzotriazolylmethyl-substituted azacrown ethers,[102] valuable intermediates for the preparation of *N*-pivot lariat crown ethers with a propylene linkage in the side arm. Secondary aromatic amines[98,103,104] or secondary heteroaromatic amines[105] react similarly. Alkyl glyoxylates[106] and *N*-alkylglycine ethyl esters[107] are also employed for this type of condensations in the course of preparation of tertiary α-amino esters. Polyfluoroaldehydes, although different somewhat in their reactivity from their hydro-

Table 11. Preparation of 1-[1-(Dialkylamino)alkyl]benzotriazoles 113 (All Reactions at 20 °C)

R^1	R^2	R^3	solvent	yield %
H	Me	Me	$MeOH/H_2O$	97[97]
H	Me	Me	$MeOH/H_2O$	92[339]
H	Me	c-C_6H_{11}	$MeOH/H_2O$	76[339]
H	Me	CH_2COOEt	H_2O	98[107]
H	Me	4-Py	C_6H_6	63[105]
H	Et	Et	$MeOH/H_2O$	96[98]
H	Et	Et	$MeOH/H_2O$	91[339]
H	*i*-Bu	*i*-Bu	$MeOH/H_2O$	88[339]
H	*n*-Bu	3-$O_2NC_6H_4$	C_6H_6	68[104]
H	c-C_6H_{11}	CH_2CN	C_6H_6	100[a,109]
H	*n*-C_8H_{17}	CH_2CN	C_6H_6	100[a,109]
H	*n*-C_8H_{17}	*n*-C_8H_{17}	$MeOH/H_2O$	100[a,98]
H	Ph	Me	$MeOH/H_2O$	64[98]
H	Ph	Me	H_2O	91[99]
H	$PhCH_2$	$PhCH_2$	$MeOH/H_2O$	95[98]
H	$PhCH_2$	$PhCH_2$	$MeOH/H_2O$	72[339]
H	$PhCH_2$	CH_2COOEt	H_2O	90[107]
H	2-$ClC_6H_4CH_2$	CH_2COOEt	H_2O	100[a,107]
H	4-$MeC_6H_4CH_2$	CH_2COOEt	H_2O	100[a,107]
H	Me_3SiCH_2	*i*-Bu	H_2O	95[382]
H	Me_3SiCH_2	allyl	H_2O	93[382]
H	Me_3SiCH_2	c-C_6H_{11}	H_2O	90[382]
H	Me_3SiCH_2	*n*-C_6H_{13}	H_2O	94[382]
H	$Me_3SiOCH_2CH_2$	$Me_3SiOCH_2CH_2$	C_6H_6	100[a,102]
H	$-(CH_2)_4-$		$MeOH/H_2O$	98[97]
H	$-(CH_2)_4-$		H_2O	92[99]
H	$-(CH_2)_4-$		$MeOH/H_2O$	84[339]
H	$-(CH_2)_5-$		$MeOH/H_2O$	78[339]
H	$-(CH_2)_2O(CH_2)_2-$		$MeOH/H_2O$	91[99]
H	$-(CH_2)_2O(CH_2)_2-$		$MeOH/H_2O$	96[339]
H	$-CH_2(CH_2OCH_2)_4CH_2-$		EtOH	97[102]
Me	*n*-C_8H_{17}	CH_2CN	C_6H_6	100[a,109]
i-Pr	*n*-C_8H_{17}	CH_2CN	C_6H_6	100[a,109]
i-Pr	$-(CH_2)_2O(CH_2)_2-$		$MeOH/H_2O$	74[339]
i-Pr	$PhCH_2$	$PhCH_2$	C_6H_6	78[98]
i-Pr	$PhCH_2$	$PhCH_2$	C_6H_6	81[339]
i-Pr	$-(CH_2)_4-$		C_6H_6	76[98]
n-Pr	*n*-C_8H_{17}	CH_2CN	C_6H_6	100[a,109]
n-Pr	$-(CH_2)_2O(CH_2)_2-$		C_6H_6	79[98]
n-Pr	$-(CH_2)_2O(CH_2)_2-$		C_6H_6	84[339]
Ph	*n*-C_8H_{17}	CH_2CN	C_6H_6	100[a,109]
Ph	$-(CH_2)_5-$		C_6H_6	59[98]
Ph	$-(CH_2)_2O(CH_2)_2-$		C_6H_6	87[98]
$CHF_2(CF_2)_3$	$-(CH_2)_5-$		C_6H_6	85[108]
$CHF_2(CF_2)_3$	$-(CH_2)_2O(CH_2)_2-$		C_6H_6	71[108]
$CClF_2(CF_2)_5$	$-(CH_2)_5-$		C_6H_6	85[108]
$CF_3(CF_2)_2OCFCF_3$	$-(CH_2)_5-$		C_6H_6	69[108]
C_6F_5	$PhCH_2$	$PhCH_2$	C_6H_6	100[a,108]
EtOOC	Et	Et	C_6H_6	80[106]
EtOOC	$-(CH_2)_4-$		C_6H_6	100[a,106]
EtOOC	$-(CH_2)_5-$		C_6H_6	78[106]
EtOOC	$-(CH_2)_2O(CH_2)_2-$		C_6H_6	100[a,106]
EtOOC	$-(CH_2CH_2)_2NCH(Bt)COOEt$		C_6H_6	76[106]
MenthylO$_2$C	$-(CH_2)_5-$		C_6H_6	92[106]
MenthylO$_2$C	$-(CH_2)_2O(CH_2)_2-$		C_6H_6	95[106]
$CH(OEt)_2$	$-(CH_2)_5-$		Et_2O or EtOH	76[100]
$CH(OEt)_2$	$-(CH_2)_2O(CH_2)_2-$		Et_2O or EtOH	77[100]
$CH(OEt)_2$	$PhCH_2$	$PhCH_2$	Et_2O or EtOH	72[100]
$CH(OEt)_2$	Ph	Me	Et_2O or EtOH	75[100]

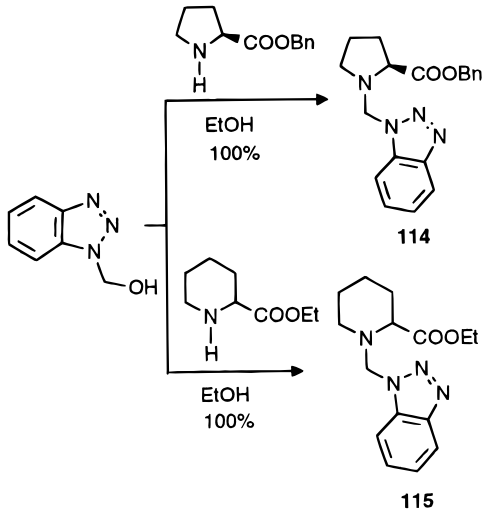
[a] Crude product was obtained in nearly quantitative yield and was used for following transformations without additional purification.

carbon analogues, also condense with benzotriazole and a secondary amine at room temperature to give the expected products.[108]

N-Alkylaminoacetonitriles react readily with a variety of aldehydes and benzotriazole at room temperature providing selectively unsymmetrical (*N*,*N*-dialkylamino)acetonitriles[109] in quantitative yields (see Table 11). Both aliphatic and aromatic aldehydes can be used successfully in these reactions.

L-Proline benzyl ester and racemic pipecolinic acid ethyl ester react readily as secondary amines with 1-(hydroxymethyl)benzotriazole to give the corresponding adducts **114** and **115** in quantitative yields (Scheme 44).[110]

Scheme 44. Reaction of 1-Hydroxybenzotriazole with Proline and Pipecoline Esters



Some ketones, in particular, cyclic ketones, can be employed in this type of condensation,[111] although the yields are not as high as those with aldehydes (Scheme 45, Table 12).

Scheme 45. Condensation of Benzotriazole with Ketone and an Amine

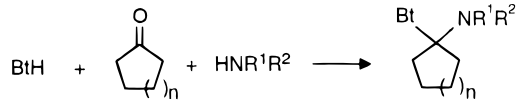


Table 12. Preparation of 1-[1-(Dialkylamino)alkyl]-benzotriazoles 116 from Ketones

n	R^1	R^2	yield %
1	$-(CH_2)_2O(CH_2)_2-$		66
2	$-(CH_2)_2O(CH_2)_2-$		85
2	$-(CH_2)_4-$		88
2	$-(CH_2)_5-$		50
2	H	$PhCH_2$	85
3	$-(CH_2)_2O(CH_2)_2-$		35

b. Ammonia as Starting Material. In the condensation reactions of ammonia and benzotriazole with hindered aliphatic aldehydes, bis(1-benzotriazol-1-ylalkyl)amines (**117**) are obtained, while aromatic aldehydes yield (1-benzotriazol-1-ylalkyl)*N*-alkylideneamines **118**[112] (Scheme 46). Ammonia reacts with 1-(hydroxymethyl)benzotriazole at room temperature to give the bis condensation product **119**. Further treatment with 1-(hydroxymethyl)benzotriazole in refluxing toluene yields the tris product **120**.[98,113] These compounds are valuable reagents for preparation of secondary and tertiary amines (see section IV.B.1).

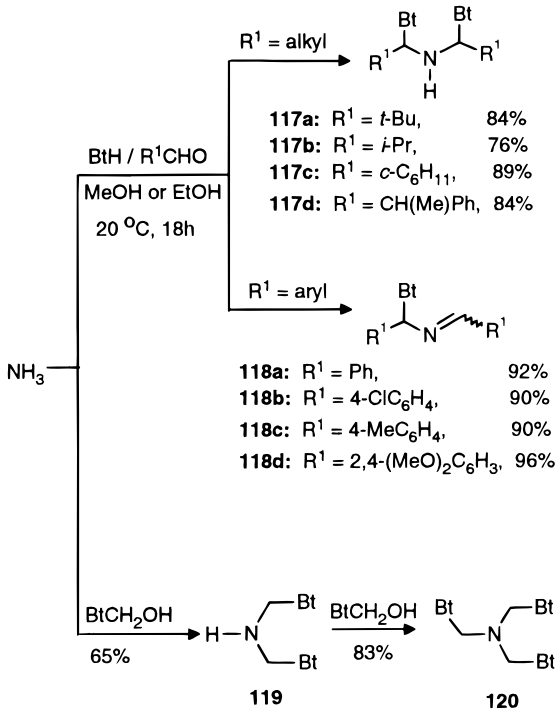
c. Primary Aliphatic Amines as Starting Materials. Reaction of 1 mol of a primary amine with 2 mol of formaldehyde and 2 mol of benzotriazole or 2 mol of 1-(hydroxymethyl)benzotriazole gives the condensation products **121** in high yield (Scheme 47, Table 13).[98,113]

The preparation of a mono(benzotriazolylalkyl) product from a primary aliphatic amine is somewhat more tricky as products **122** tend to undergo further condensation to bis adducts **121**. However, reasonable yields of the products **122** can be obtained if hindered primary amines are used (Scheme 47, Table 13).[114,115]

If 1 mol of a primary amine is condensed with 1 mol of BtH and excess of CH_2O, the bis product **123** is produced,[115] presumably through the formation of a methylene-linked bisamine.

d. Primary Aromatic and Heteroaromatic Amines as Starting Materials. At room temperature, aromatic and heteroaromatic primary amines react just once with an aldehyde and benzotriazole to give monosubstituted products **124** (Scheme 48, Table 14).[100,104,105,113,116,117] For example, the direct conden-

Scheme 46. Reaction of Benzotriazole with Ammonia and an Aldehyde



Scheme 47. Reactions of Benzotriazole with Aldehydes and Primary Amines

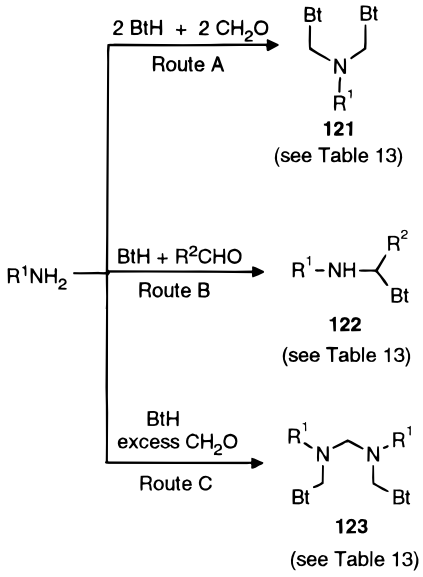
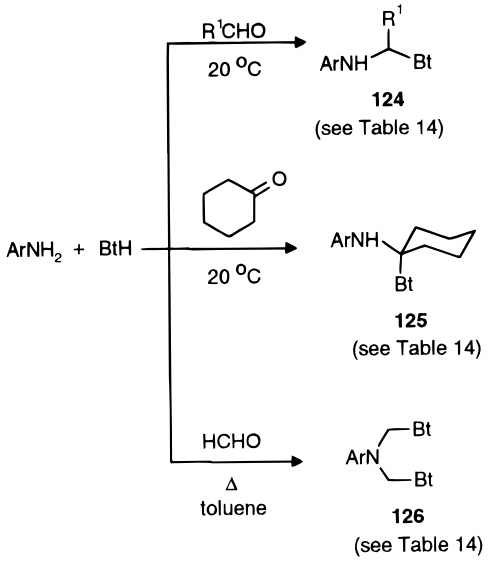


Table 13. Adducts 121−123 from Primary Aliphatic Amines, Aldehydes, and Benzotriazole

compound	R^1	R^2	yield %
121	Me		76[113]
	Et		84[113]
	n-Pr		62[113]
	i-Pr		80[113]
	n-Bu		85[115]
	neopentyl		50[115]
	c-C_6H_{11}		89[113]
	c-C_6H_{11}		89[115]
	n-C_8H_{17}		90[113]
	n-C_8H_{17}		91[98]
	n-C_8H_{17}		90[115]
	$PhCH_2$		98[113]
	$PhCH_2$		87[115]
	$PhCH_2CH_2$		87[113]
	$Me_2N(CH_2)_2$		92[115]
122	*i*-Pr	H	96[115]
	sec-Bu	H	86[114]
	sec-Bu	H	86[115]
	t-Bu	H	89[114]
	t-Bu	H	89[115]
	neopentyl	H	98[115]
	c-C_5H_9	H	89[114]
	c-C_6H_{11}	H	85[114]
	c-C_6H_{11}	H	100[115]
	n-C_8H_{17}	H	85[114]
	PhCH(Me)	H	90[114]
	$PhCH_2$	$CHF_2(CF_2)_3$	76[108]
123	*n*-Bu		87[115]
	i-Bu		99[115]
	n-C_8H_{17}		91[115]
	$PhCH_2$		65[115]

Scheme 48. Reactions of Primary Aromatic Amines with Benzotriazole and an Aldehyde



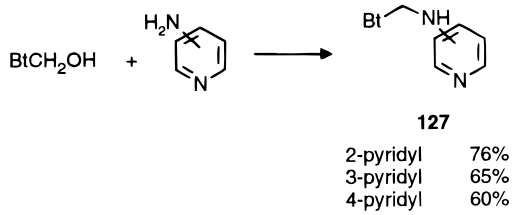
sation of 1-(hydroxymethyl)benzotriazole and aminopyridines gives the expected products **127**[118] (Scheme 49). This difference to the behavior of aliphatic primary amines is due to the lower nucleophilicity of aromatic amines and to the electron-withdrawing ability of the benzotriazol-1-ylmethyl groups further decreasing the nucleophilicity of the substituted aromatic amine. A ketone can also be used as the carbonyl component to yield **125**.[113]

In the presence of excess formaldehyde, the aromatic diamine **128** undergoes condensation with

Table 14. Adducts 124−126 from Primary Aromatic Amine, Aldehyde (or Ketone), and Benzotriazole

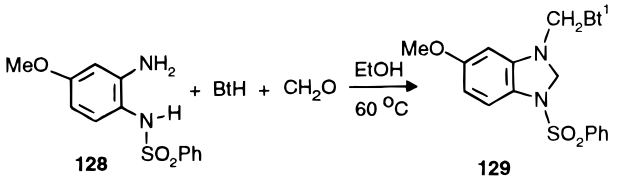
compound	R^1	Ar	solvent	yield %
124	H	4-ClC_6H_4	EtOH	91[113]
	H	4-ClC_6H_4	H_2O	80[99]
	H	4-$O_2NC_6H_4$	EtOH:H_2O:AcOH = 1:1:1	99[113]
	H	3-$O_2NC_6H_4$	H_2O	97[99]
	H	2-$PhCOC_6H_4$	EtOH	96[113]
	H	2-$HOOCC_6H_4$	EtOH	99[113]
	H	4-$HOOCC_6H_4$	EtOH:H_2O:AcOH = 1:1:1	98[113]
	H	2-MeC_6H_4	EtOH/H_2O	93[116]
	H	2-MeC_6H_4	EtOH/H_2O	93[117]
	H	4-BuC_6H_4	EtOH/H_2O	94[117]
	H	4-BuC_6H_4	H_2O	97[99]
	H	Ph	EtOH/H_2O	82[117]
	H	Ph	H_2O	90[99]
	H	4-$MeOC_6H_4$	EtOH/H_2O	87[117]
	H	3-ClC_6H_4	EtOH/H_2O	92[117]
	H	2-EtC_6H_4	EtOH/H_2O	92[117]
	H	2,4-(*i*-Pr)$_2C_6H_3$	H_2O	87[99]
	H	2-pyridyl	EtOH	98[113]
	H	2-pyridyl	H_2O	84[99]
	H	4-methyl-2-pyridyl	EtOH	96[113]
	H	6-methyl-2-pyridyl	EtOH	95[113]
	H	4,6-dimethyl-2-pyridyl	EtOH	97[113]
	H	5-chloro-2-pyridyl	EtOH	94[113]
	H	5-bromo-2-pyridyl	EtOH	99[113]
	H	5-nitro-2-pyridyl	EtOH:H_2O:AcOH = 1:1:1	94[113]
	H	4-pyridyl	EtOH	85[113]
	H	2-pyrimidyl	EtOH	91[113]
	H	pyrazinyl	EtOH	88[113]
	H	6-purinyl	H_2O	86[99]
	H	6-purinyl	EtOH:H_2O:AcOH = 1:1:1	95[113]
	H	2-thiazolyl	EtOH	95[113]
	H	5,7-dimethyl-1,8-naphthyridin-2-yl	EtOH	86[113]
	Me	Ph	H_2O	87[99]
	Me	4-BuC_6H_4	H_2O	99[99]
	Me	3-$O_2NC_6H_4$	EtOH	98[104]
	Me	2-pyridyl	H_2O	89[99]
	Me	2-pyridyl	EtOH	98[113]
	Me	4-pyridyl	neat	85[113]
	Et	2-pyridyl	neat	87[113]
	n-Pr	3-$O_2NC_6H_4$	EtOH	65[104]
	n-Pr	3,5-$Cl_2C_6H_3$	EtOH	82[113]
	n-Pr	4-$HOOCC_6H_4$	EtOH	90[113]
	n-Pr	2-pyridyl	EtOH	82[113]
	n-Pr	pyrimidin-2-yl	EtOH	86[113]
	i-Pr	4-MeC_6H_4	performance fluid	95[144]
	i-Pr	2-pyridyl	EtOH	98[113]
	i-Pr	5-bromo-2-pyridyl	EtOH	83[113]
	t-Bu	2-pyridyl	EtOH	85[113]
	$PhCH_2$	3-$O_2NC_6H_4$	Et_2O	79[104]
	Ph	2-pyridyl	performance fluid	98[144]
	4-ClC_6H_4	2-pyridyl	EtOH	85[113]
	4-MeC_6H_4	pyrimidin-2-yl	EtOH	76[113]
	$CH(OEt)_2$	Ph	EtOH or Et_2O	78[100]
	$CH(OEt)_2$	3-MeC_6H_4	EtOH or Et_2O	75[100]
	$CHF_2(CF_2)_3$	4-MeC_6H_4	C_6H_6	87[108]
	COOEt	Ph	H_2O:EtOH = 4:1	77[99]
	COOEt	4-$MeOC_6H_4$	H_2O:EtOH = 4:1	93[99]
125		4-ClC_6H_4	neat	81[113]
		2-pyridyl	neat	90[113]
126		Ph	toluene	40[117]
		4-MeC_6H_4	toluene	25[117]
		4-BuC_6H_4	toluene	100[117]
		4-$MeOC_6H_4$	toluene	55[117]
		4-$Me_2NC_6H_4$	toluene	62[117]
		4-ClC_6H_4	toluene	73[117]
		3-ClC_6H_4	toluene	32[117]
		3-$O_2NC_6H_4$	toluene	25[117]
		2-MeC_6H_4	toluene	58[117]
		2-EtC_6H_4	toluene	100[117]
		2,6-$Me_2C_6H_3$	toluene	68[117]

Scheme 49. Reaction of 1-(Hydroxymethyl)benzotriazole with Aminopyridines



benzotriazole and 2 equiv of formaldehyde to give cyclization product, an *N*-(benzotriazolylmethyl)-dihydrobenzimidazole **129** in high yield (Scheme 50).[119]

Scheme 50. Preparation of 1-(Phenylsulfonyl)-3-(Benzotriazol-1-ylmethyl)-5-methoxy-2,3-dihydrobenzimidazole



The bis(benzotriazolylmethylation) of aromatic amines can be achieved by reacting a primary aromatic amine with 2 mol of formaldehyde and 2 mol of benzotriazole (Scheme 48), but this requires refluxing in toluene with removal of the water using a Dean−Stark apparatus.[117] Mixtures of all three isomers, the benzotriazole-1,1′, -1,2′, and -2,2′ derivatives, are obtained. Electron-donating groups in the aniline ring tend to favor the formation of the *N*,*N*-bis(benzotriazolylmethylated) products and speed up the equilibration between isomers, whereas electron-withdrawing *para* or *meta* substituents favor the monoalkylated products and make the individual isomer more stable toward isomerization. For *o*-alkylanilines, steric interactions play an important role.[117]

e. Reactions Using Dialdehydes. Condensation occurs as expected between 1 mol of glyoxal, 2 mol of benzotriazole, and 2 mol of a secondary amine (Scheme 51, Table 15).[120] Aliphatic primary amines under the same conditions give oligomers or polymers.

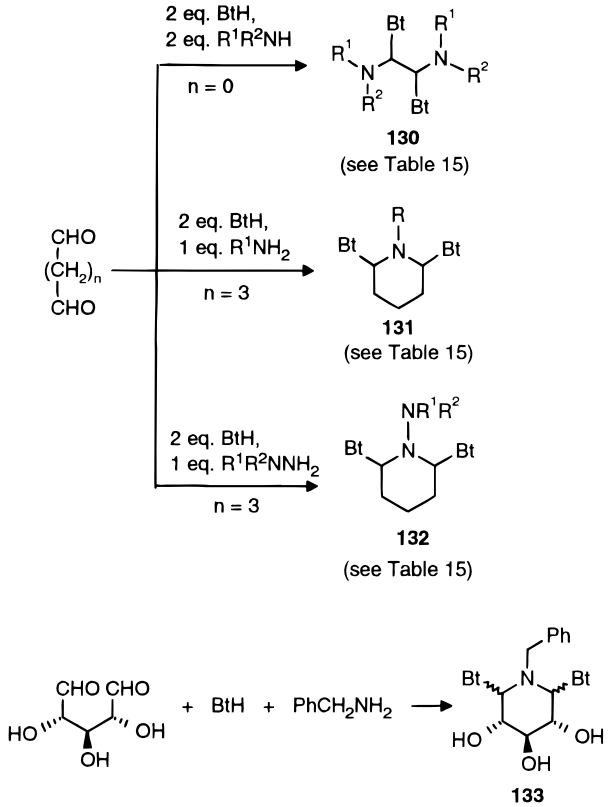
Reactions of 1 mol of a primary amine and 2 mol of benzotriazole with 1 mol of glutaraldehyde give the *N*-substituted piperidines **131** in high yields.[121] Extension of this method allows synthesis of 2,6-disubstituted 3,4,5-trihydroxypiperidines **133** starting from a polyhydroxylated carbohydrate derived dialdehyde[122] (Scheme 51). These reactions can be conveniently carried out in water.[99] With monosubstituted and unsymmetrically disubstituted hydrazines, *N*-(alkylamino)piperidine derivatives **132** are obtained. This procedure also applies easily to acyl hydrazines (see examples in Table 15).

The double Mannich condensation of *o*-phthalaldehyde with primary aromatic amines in the presence of excess (3 or 4 equiv) of benzotriazole in acetonitrile[123] or at 120 °C without solvent[113] gives exclusively Bt-substituted isoindoline derivatives **134**

Table 15. Preparation of Adducts 130−132 from Amines, Benzotriazole, and Dialdehydes

compound	R^1	R^2	yield %
130	$-(CH_2)_5-$		92[120]
	$-(CH_2)_2O(CH_2)_2-$		94[120]
	n-Bu	*n*-Bu	85[120]
	$PhCH_2$	$PhCH_2$	88[120]
	Ph	H	90[120]
	4-MeC_6H_4	H	84[120]
	3-$CH_3C_6H_4$	H	82[120]
131	*i*-Pr	H	82[121]
	n-Bu	H	75[121]
	$PhCH_2$	H	91[121]
	Ph	H	85[121]
	3-MeC_6H_4	H	80[121]
	2-pyridyl	H	79[121]
132	H	Ph	86[121]
	Me	Me	73[121]
	PhCO	H	95[121]
	MeCO	H	86[121]
	EtOOC	H	94[121]
	t-BuOOC	H	97[121]
	$PhCH_2OOC$	H	93[121]

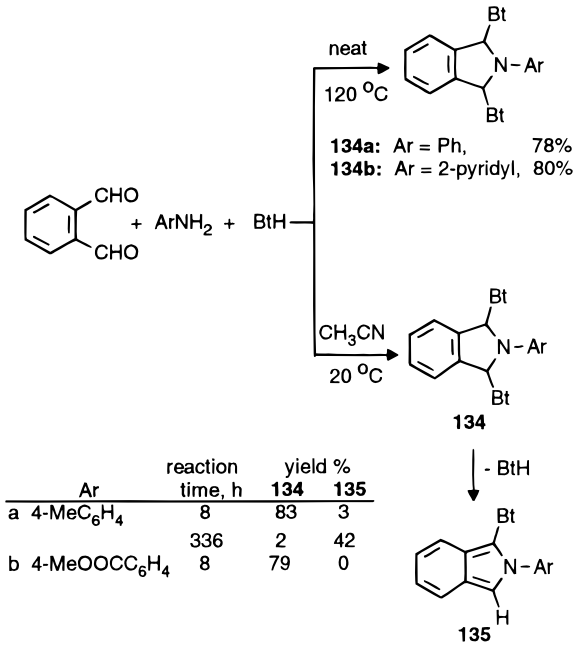
Scheme 51. Reactions of Dialdehydes with Benzotriazole and an Amine



(Scheme 52). Use of 2 equiv of benzotriazole or an extended reaction time in acetonitrile at 20 °C facilitates the elimination of benzotriazole from **134** to produce 2*H*-isoindole derivatives **135**. The nature of the *para* substituent in the arylamine used significantly affects on the product outcome, as evidenced by the fact that no formation of 2*H*-isoindole **135b** from **134b** was detected under these conditions.

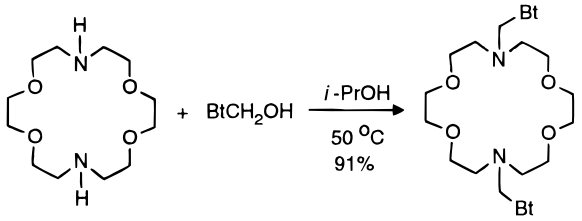
f. Reactions Using Diamines. Secondary aliphatic diamines behave similarly to the corresponding monoamines (see section II.B.2.a), giving *N*,*N*′-bis-(benzotriazolylmethyl) adducts in condensations with 2 equiv each of benzotriazole and an aldehyde. *N*,*N*′-

Scheme 52. Reactions of *o*-Phthalaldehyde with Benzotriazole and Primary Aromatic Amines



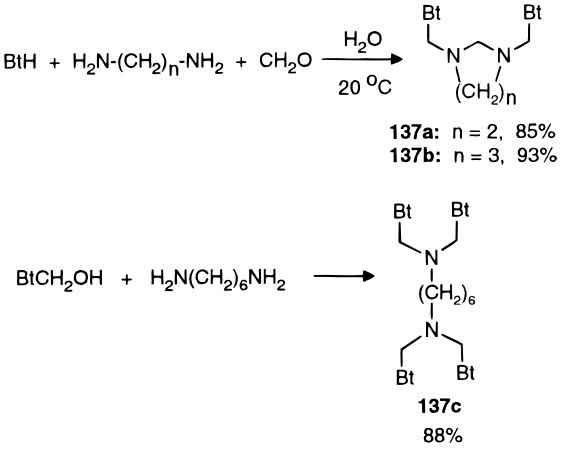
Bis(benzotriazolylmethyl)-substituted 4,13-diaza-18-crown-6 **136** is prepared by this procedure[124] (Scheme 53).

Scheme 53. Condensation of 4,13-Diaza-18-crown-6 with 1-(Hydroxymethyl)benzotriazole



Reactions of benzotriazole with formaldehyde and primary diamines yield cyclic products if a five- or six-membered ring can be formed. Thus, ethylenediamine and 1,3-propylenediamine give derivatives **137a**,**b** of imidazoline and hexahydropyrimidine, respectively (Scheme 54).[115]

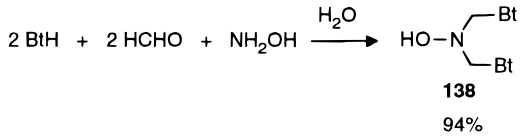
Scheme 54. Reactions Of Aliphatic Bis-Primary Amines with Benzotriazole and Formaldehyde



Aliphatic diamines containing a longer chain linking the amino groups tend not to undergo cyclocondensation with formaldehyde and benzotriazole, as exemplified by the formation of tetrabenzotriazolyl derivative **137c** from 1-(hydroxymethyl)benzotriazole and 1,6-hexadiamine[125] (Scheme 54).

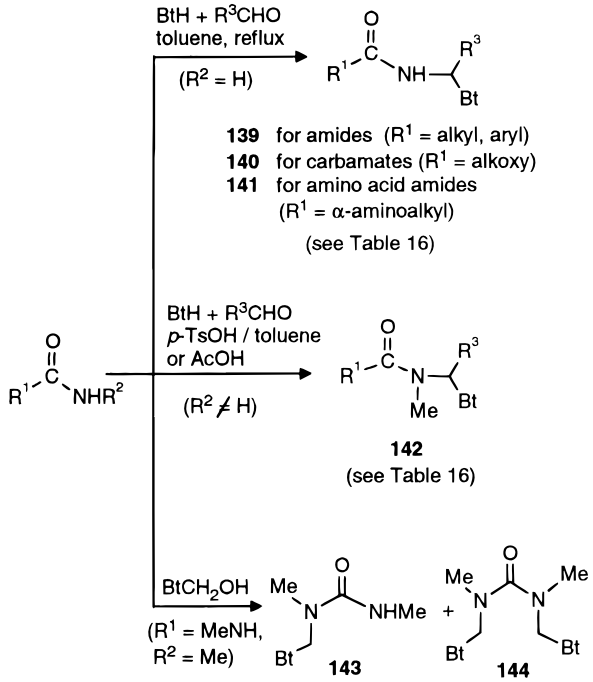
g. Hydroxylamine as Starting Material. Similar to ammonia, 1 mol of hydroxylamine, 2 mol of formaldehyde, and 2 mol of benzotriazole, in aqueous solution at room temperature give the bis condensation product **138** (Scheme 55).[98,113,115]

Scheme 55. Reactions of Hydroxylamine with Benzotriazole and Formaldehyde



h. Amides as Starting Materials. The preparation of amide condensation products with an aldehyde and benzotriazole is shown in Scheme 56 and Table 16.

Scheme 56. Condensation Products from Amides, Benzotriazole, and Aldehydes



1 eq. $BtCH_2OH$	60%	0%
2 eq. $BtCH_2OH$	52%	14%
4 eq. $BtCH_2OH$	0%	80%

The preparation of such condensation products directly from an amide, aldehyde, and benzotriazole was first thought to be limited to primary amides, to give **139** but was later applied also to secondary amides to give **142**. The reaction conditions required are more vigorous than for amines probably due to the lower nucleophilicity of amides compared to amines.[126−132] Primary amides react on refluxing in dry toluene with azeotropic removal of water, but secondary amides require the use of catalytic amounts of *p*-toluenesulfonic acid, or carrying out the reaction in acetic

Table 16. Preparation of Adducts 139−142 from Amide, Aldehyde, and Benzotriazole

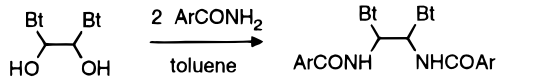
compound	R^1	R^2	R^3	solvent	yield %
139	H	H	H	toluene	79[127]
	H	H	Ph	toluene	35[130]
	Me	H	*i*-Pr	toluene	51[126]
	Me	H	Ph	toluene	45[126]
	Me	H	Ph	toluene	48[128]
	Me	H	Ph	toluene	61[130]
	Me	H	4-MeC_6H_4	toluene	42[126]
	Me	H	4-$MeOC_6H_4$	toluene	54[128]
	Me	H	COOEt	toluene	72[136]
	Me	H	COOH	benzene	91[136]
	Et	H	H	AcOH	63[132]
	Et	H	Ph	toluene	54[130]
	i-Pr	H	H	AcOH	79[132]
	i-Pr	H	Ph	toluene	72[130]
	t-Bu	H	Ph	toluene	71[130]
	n-C_8H_{17}	H	H	AcOH	57[132]
	Ph	H	H	toluene	78[126]
	Ph	H	*i*-Pr	toluene	52[126]
	Ph	H	*n*-Pr	toluene	59[126]
	Ph	H	*n*-C_5H_{11}	toluene	48[126]
	Ph	H	*n*-C_8H_{17}	toluene	74[126]
	Ph	H	Ph	toluene	60[126]
	Ph	H	Ph	toluene	60[128]
	Ph	H	Ph	toluene	74[130]
	Ph	H	4-$MeOC_6H_4$	toluene	63[128]
	Ph	H	PhCHMe	toluene	51[128]
	Ph	H	$PhCH_2$	toluene	65[128]
	Ph	H	1-naphthyl	toluene	49[128]
	Ph	H	4-$O_2NC_6H_4$	toluene	81[128]
	Ph	H	COOEt	toluene	74[136]
	Ph	H	COOH	benzene	90[136]
	3-pyridyl	H	H	AcOH	69[132]
	$PhCH_2$	H	Ph	toluene	61[131]
	$PhCH_2$	H	2-MeC_6H_4	toluene	65[131]
	$PhCH_2$	H	4-ClC_6H_4	toluene	60[131]
	4-$MeOC_6H_4CH_2$	H	Ph	benzene	63[131]
	4-$MeOC_6H_4CH_2$	H	4-ClC_6H_4	benzene	63[131]
	1-naphthyl-CH_2	H	H	AcOH	77[132]
	1-naphthyl-CH_2	H	Ph	benzene	53[131]
	$MeOCOCH_2C[N(H)OCOCH_2Ph]H$	H	$PhCH_2$	benzene	60[129]
140	MeO	H	Ph	toluene	43[130]
	t-BuO	H	COOH	benzene	40[136]
	$PhCH_2O$	H	H	toluene	80[136]
	$PhCH_2O$	H	$PhCH_2$	toluene	52[135]
	$PhCH_2O$	H	*n*-Pr	toluene	90[136]
	$PhCH_2O$	H	*i*-Pr	toluene	75[136]
	$PhCH_2O$	H	*i*-Bu	toluene	85[136]
	$PhCH_2O$	H	*t*-Bu	toluene	67[135]
	$PhCH_2O$	H	Ph	toluene	87[136]
	$PhCH_2O$	H	Ph	toluene	87[135]
	$PhCH_2O$	H	COOEt	toluene	70[136]
	$PhCH_2O$	H	COOH	benzene	78[136]
141	Bz-Gly	H	*i*-Pr	toluene	74[136]
	Z-l-Val	H	*i*-Bu	toluene	80[136]
	Z-iLeu	H	*i*-Pr	toluene	50[136]
	Z-Phg	H	*i*-Bu	toluene	88[136]
	Z-Phe	H	*i*-Pr	toluene	73[136]
	Bz-Gly	H	COOEt	toluene	70[136]
	Z-Gly	H	COOEt	toluene	70[136]
142	H	Me	H	toluene	62[133]
	H	Me	*i*-Pr	toluene	73[133]
	H	Me	Ph	toluene	33[133]
	H	Et	H	toluene	60[133]
	H	$PhCH_2$	H	toluene	73[133]
	Me	Me	H	AcOH	77[133]
	Me	Me	*i*-Pr	toluene	67[133]
	Me	Me	Ph	toluene	34[133]
	Me	Ph	H	AcOH	80[133]
	Me	Ph	H	toluene	77[133]
	Me	Ph	*n*-C_8H_{17}	toluene	29[133]
	Ph	H	4-$O_2NC_6H_4$	performance fluid	97[144]
	Ph	Me	H	AcOH	80[133]
	Ph	Me	H	performance fluid	80[144]
	4-MeC_6H_4	H	H	performance fluid	95[144]
	$-(CH_2)_2-$		H	toluene	43[133]
	$-(CH_2)_3-$		H	AcOH	96[133]
	$-(CH_2)_3-$		H	performance fluid	95[144]

Table 16 (Continued)

compound	R^1	R^2	R^3	solvent	yield %
142	$-(CH_2)_5-$		H	AcOH	62[133]
	$-(CH_2)_3-$		n-C_8H_{17}	toluene	67[133]
	$-(CH_2)_3-$		Ph	performance fluid	95[144]
	$-(CH_2)_3-$		i-Pr	performance fluid	92[144]
	$-(CH_2)_4-$		Ph	performance fluid	52[144]
	$-(CH_2)_4-$		i-Pr	performance fluid	77[144]
	$-(CH_2)_5-$		i-Pr	performance fluid	44[144]
	$-CH_2C_6H_4(o)-$		H	AcOH	95[133]
	$-CH_2NHC(O)-$		H	AcOH	76[133]
	$-CH_2NHC(S)-$		H	AcOH	61[133]
	NH_2	H	H	performance fluid	97[144]

acid[133] to give the benzotriazole adducts **142** (Scheme 56). Formaldehyde and other aldehydes ($R^3 \neq H$) can be used. Aromatic primary amides react with 1,2-dibenzotriazol-1-ylethane-1,2-diol (**106**) (obtained from condensation of benzotriazole with glyoxal) to give 1,2-(diacylamino)-1,2-dibenzotriazol-1-ylethanes (**145**) in nearly quantitative yields (Scheme 57).[134]

Scheme 57. Preparation of Benzotriazole-Substituted Aromatic Bis-Amides



106 **145**

Ar = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 2-MeC_6H_4

Reaction of carbamates with an aldehyde and benzotriazole requires *p*-toluenesulfonic acid as catalyst in toluene with azeotropic removal of water. Good yields of the expected products **140** (Scheme 56, Table 16) were obtained.[135,136] When glyoxylic acid is used as the aldehyde component, no acid catalyst is required and the reaction can be carried out in benzene. Protected amino acid amides also react with aldehydes and benzotriazole to give **141**.[136]

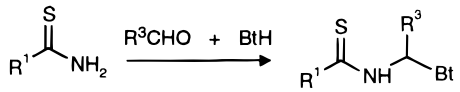
Extension of this methodology to phthalimide and succinimide failed, probably due to their lower nucleophilicity.[133] Thus, for hydantoin, only the 3-monoalkylated hydantoin was obtained. *N*,*N*′-Substituted ureas react with 1-(hydroxymethyl)benzotriazole to give products depending on the molar ratio of the latter. With 1 equiv of 1-(hydroxymethyl)-benzotriazole, only the monoalkylated product **143** was obtained while with 4 equiv of 1-(hydroxymethyl)benzotriazole, only the disubstituted product **144** was yielded. When 2 equiv of 1-(hydroxymethyl)-benzotriazole were used, compounds **143** and **144** were formed in 52% and 14% yields, respectively.[133]

i. Thioamides as Starting Materials. Similar transformations occur for thioamides. The benzotriazole adducts **146** shown in Scheme 58 are formed in moderate to good yields (Table 17).[137,138] Thioureas behave as thioamides in their reactions with benzotriazole and aldehydes. Depending on the molar equivalents of aldehyde and benzotriazole used, either the mono[138] or the bis condensation products[139] can be prepared. However, with thiourea and benzaldehyde, even if 2 equiv of benzaldehyde, 2 equiv of benzotriazole, and 1 equiv of thiourea are used, only the monoalkylated product is obtained.[139] This is probably due to the relatively low reactivity of benzaldehyde. Phenylthiourea reacts similarly with isobutyraldehyde and benzotriazole to afford the monoalkylated product.[139] With secondary thioamides, reactions occur in refluxing toluene in the presence of *p*-toluenesulfonic acid or in refluxing acetic acid to give **148**.[133]

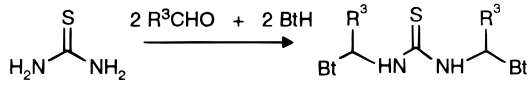
Table 17. Preparation of Adducts 146−148 from Thioamide, an Aldehyde, and Benzotriazole

compound	R^1	R^2	R^3	yield %
146	Ph		H	53[138]
	Ph		i-Pr	48[138]
	Ph		n-Pr	71[138]
	Ph		n-C_5H_{11}	44[138]
	Ph		n-C_7H_{15}	62[138]
	Ph		n-C_8H_{17}	67[138]
	Ph		n-$C_{11}H_{23}$	45[138]
	4-ClC_6H_4		H	72[233]
	4-pyridyl		n-C_5H_{11}	48[138]
	4-pyridyl		n-C_7H_{15}	85[138]
	4-pyridyl		n-C_9H_{19}	75[138]
	NH_2		i-Pr	46[138]
	NH_2		n-C_7H_{15}	35[138]
	NH_2		Ph	85[139]
	PhNH		i-Pr	40[139]
147			H	98[139]
			Me	25[139]
			i-Pr	82[139]
			n-Pr	42[139]
148	Me	Ph	H	42[133]
	$-NHC(O)CH_2-$		H	61[133]

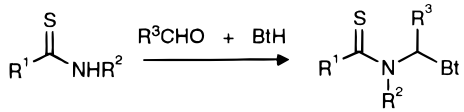
Scheme 58. Condensation Products from Thioamides, Benzotriazole, and Aldehydes



146
(see Table 17)



147
(see Table 17)



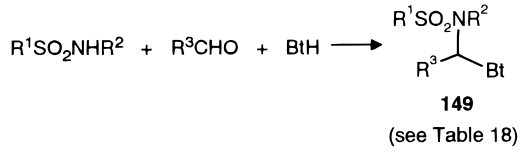
148
(see Table 17)

Table 18. Preparation of Adducts 149 from Sulfonamide, an Aldehyde, and Benzotriazole

R^1	R^2	R^3	yield %
Me	H	H	64[140]
Me	H	H	98[141]
Ph	H	H	94[140]
Ph	H	*i*-Pr	84[140]
Ph	H	Ph	52[140]
Ph	H	*n*-C_7H_{15}	60[140]
Ph	H	2-pyridyl	80[140]
Ph	Me	H	94[133]
4-MeC_6H_4	H	*n*-Pr	84[140]
4-MeC_6H_4	H	Ph	61[140]
4-MeC_6H_4	H	Ph	90[141]
4-MeC_6H_4	H	H	95[141]
4-MeC_6H_4	H	Me	91[141]
4-MeC_6H_4	H	Et	95[141]
4-MeC_6H_4	H	4-MeC_6H_4	94[141]
4-MeC_6H_4	H	1-naphthyl	55[141]

j. Sulfonamides as Starting Materials. Reactions of this type can be extended to both primary[140,141] and secondary[133] sulfonamides as shown in Scheme 59 and Table 18.

Scheme 59. Condensation Products from Sulfonamides, Benzotriazole, and Aldehydes

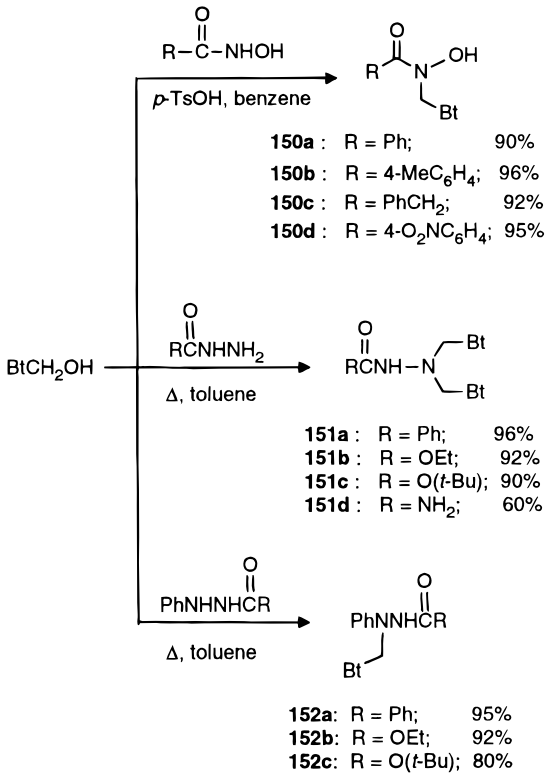


149

(see Table 18)

k. Hydroxamic Acids and Acylhydrazines as Starting Materials. Hydroxamic acids react as expected at the NH group to give **150a**−**d** (Scheme 60).[142] With 2 mol of 1-(hydroxymethyl)benzotriazole, an acylhydrazine is disubstituted at the primary amino group to give **151a**−**d**,[143] whereas compounds of type PhNHNHCOR undergo a single condensation at the PhNH group forming **152**, the NHCOR is unreactive.[143]

Scheme 60. Reactions of Hydroxamic Acids and Acylhydrazines with Benzotriazole and Formaldehyde

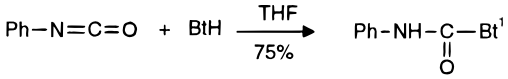


l. Reactions in Aqueous Solutions. Reactions of a secondary aliphatic amine or a primary or secondary aromatic amine can be carried out at room temperature in aqueous solution, again in very high yield (see examples in Tables 11 and 14).[99] The appropriate aldehyde is added to an aqueous mixture of benzotriazole and an amine. This order of addition seems to be important as experiments using different addition orders give lower yields or less pure products. Isolation of the products is simply done by filtration. This procedure is suitable for use in a scale-up process.

m. Use of Performance Fluid as Reaction Medium. Condensations of benzotriazole with an aldehyde and an amine or amide are generally carried out in a solvent such as benzene or toluene with azeotropic removal of water. This method sometimes gives low yields and requires long reaction times. We found later that performance fluid (a fluorocarbon inert from 3M company) can be used as an inert medium to achieve the condensation with higher yields and much shorter reaction times.[144] Two phases are present throughout the reaction and a reverse Dean−Stark trap is used due to the high density of performance fluid. Examples and yields are given in Tables 14 and 16.

n. Isocyanates as Starting Materials. Benzotriazole adds to the C=N bond of phenyl isocyanate affording the corresponding benzotriazolecarboxanilide **153** in 75% yield (Scheme 61).[61]

Scheme 61. Addition of Benzotriazole to Phenyl Isocyanate



153

o. Miscellaneous Additions to C=N−R. 1-Chlorobenzotriazole and *N-tert*-butyl-α-phenylnitrone (**154**)

Scheme 62. Addition of 1-Chlorobenzotriazole to *tert*-Butyl-α-phenylnitrone

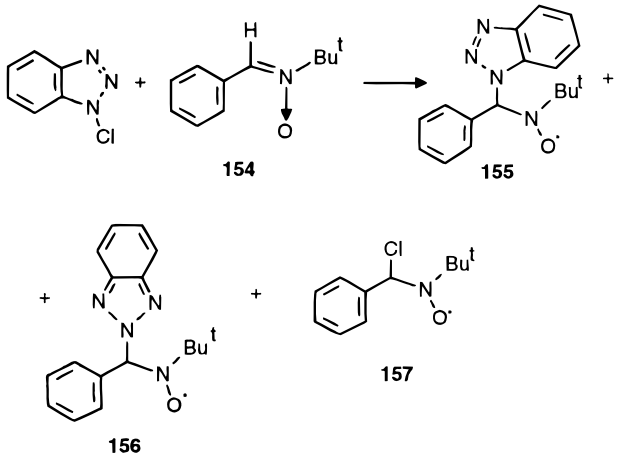


Table 19. Preparation of *N*-[1-(Alkylthio)alkyl]-benzotriazoles 158

R^1	R^2	R^3	yield %	Bt^1:Bt^2 ratio
Ph	*n*-Pr	H	80	70:30[146]
Ph	*i*-Pr	H	75	67:33[146]
Ph	Et	H	78	70:30[146]
Ph	Ph	H	47	100:0[147]
Ph	Ph	H	47	100:0[140]
Ph	4-MeC_6H_4	H	64	100:0[140]
Ph	Me	Me	11[a]	66:34[146]
Ph	$-(CH_2)_4-$		34	78:22[146]
Ph	$-(CH_2)_5-$		47	50:50[146]
Ph	$-(CH_2)_6-$		41	75:25[146]
3-MeC_6H_4	*i*-Pr	H	73	71:29[146]
$PhCH_2$	$-(CH_2)_5-$		62	43:57[146]
n-C_8H_{17}	$-(CH_2)_4-$		56	70:30[146]
n-C_8H_{17}	$-(CH_2)_5-$		53	60:40[146]

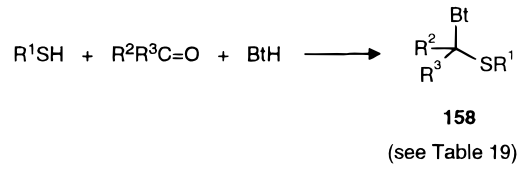
[a] Yield is 72% if 2,2-dimethoxypropane is the starting material; see text.

react thermally or photochemically with the formation of two isomeric benzotriazolyl spin adducts **155** and **156** together with the chloro spin adduct **157**, as monitored by EPR spectroscopy (Scheme 62). The nature of the solvent does not substantially influence the spin adduct distribution, but the reaction rate increases in more polar solvents.[145]

3. Addition to C═S and/or C═S⁺R

Similar to the reaction with NH compounds, the condensation of benzotriazole with an aromatic thiol and an aliphatic aldehyde occurs in the presence of an acid catalyst to give Bt^1 and Bt^2 isomers which can be separated by column chromatography[146] (Scheme 63, Table 19). The reaction can be viewed

Scheme 63. Reactions of Aldehydes and Ketones with Benzotriazole and Thiols



158

(see Table 19)

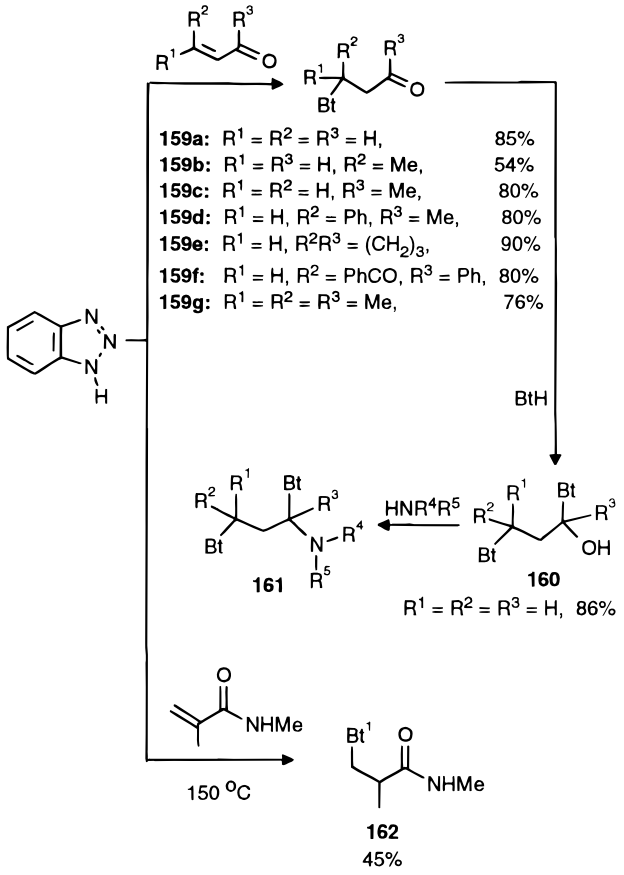
as an initial addition of thiol to the aldehyde followed by loss of water to give $C{=}S^+R$. Addition of benzotriazole to $C{=}S^+R$ then yields the condensation product. Alternatively, a benzotriazole-stabilized cation intermediate may be involved (see route C, Scheme 42). With aromatic aldehydes the Bt^1 isomer predominates and traces of the Bt^2 isomer can be readily removed via recrystallization.[147,148]

This acid-catalyzed condensation also succeeded with acetone and several cyclic ketones and gave mixtures of Bt^1 and Bt^2 isomers[146] while with 2-methylcyclohexanone it failed due to steric interactions, producing only 1-methyl-2-(phenylthio)cyclohexene. The ketal, 2,2-dimethoxypropane, gave the same reaction product as acetone, but in much better yield (72% vs 11%).[146]

4. Addition to C═C and C≡C

a. Addition to Electron-Deficient Olefins: Michael Addition. Benzotriazole undergoes 1,4-addition to α,β-unsaturated aldehydes and ketones to form the corresponding β-benzotriazolyl aldehydes and ketones **159** in high yields.[149,150] No products from 1,2-addition were observed. A second mole of benzotriazole adds to the aldehyde group to form reversibly the adduct **160** or, in the presence of an amine, the product **161** containing two benzotriazole groups and one amino group. Product **161** is generally a mixture of all possible Bt^1 and Bt^2 isomers at the 1 and 3 positions (see Scheme 64).

Scheme 64. Addition of Benzotriazole to α,β-Unsaturated Aldehydes, Ketones, and Amides



The addition of benzotriazole to α,β-unsaturated amides such as *N*-methylmethacylamide gives as expected the simple Michael addition product **162**.[151]

1-(Trimethylsilyl)benzotriazole[49] behaves as a pseudo-benzotriazolate anion and undergoes 1,4-addition to 2-cyclopentenone and 2-cyclohexenone to form the corresponding silyl ether derivatives **163**[152] (Scheme 65). These compounds, although extremely sensitive

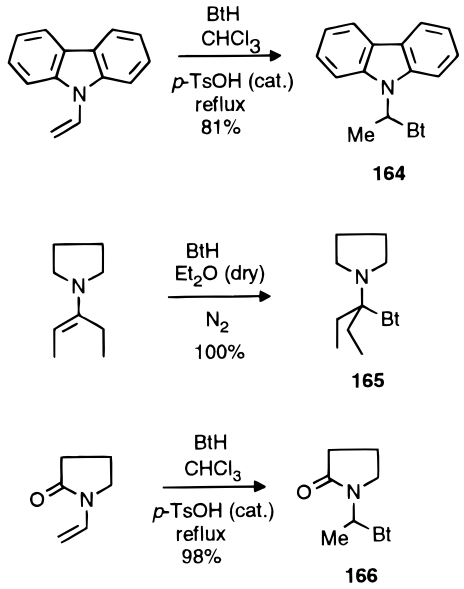
Scheme 65. Addition of 1-(Trimethylsilyl)benzotriazole to 2-Cyclopentenone and 2-Cyclohexenone

163a: n = 1
163b: n = 2

to acid and moisture, are sufficiently stable to strong basic conditions for further transformations[152] (see section III.A.2.c).

b. Addition to Electron-Rich Olefins. The addition of benzotriazole to enamines allows access to products that cannot be directly prepared from amines and carbonyl compounds (Scheme 66).[153] Thus, the enamine route succeeds for products such as **164** derived from very weakly basic amines such as carbazole and also allows the preparation of the adducts such as **165** from the pyrrolidine enamines derived from ketones. This method complements the condensation process previously described in Scheme 42 which, although general for aldehydes, fails for many ketones. Benzotriazole adds to the enamide 1-vinylpyrrolidin-2-one in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford adduct **166** in an almost quantitative yield.

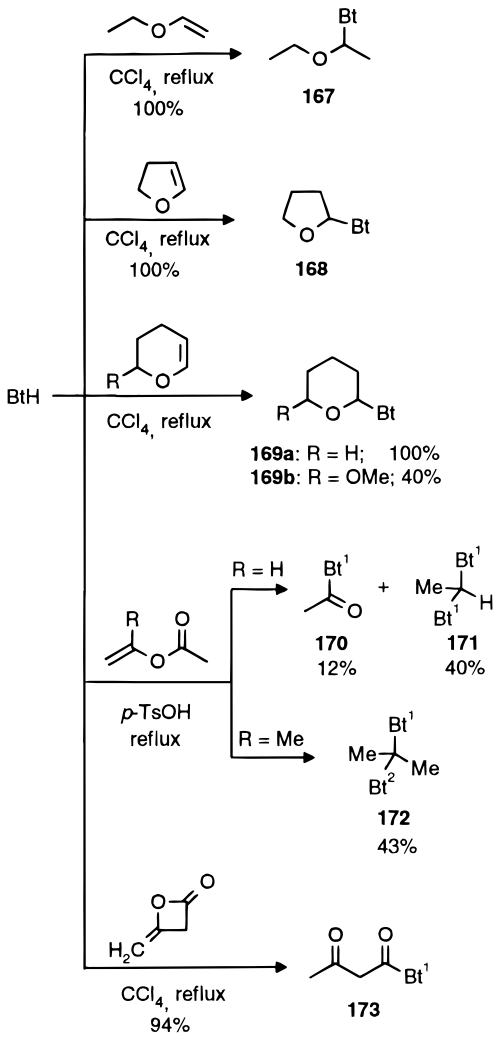
Scheme 66. Additions of Benzotriazole to Enamines and Enamides



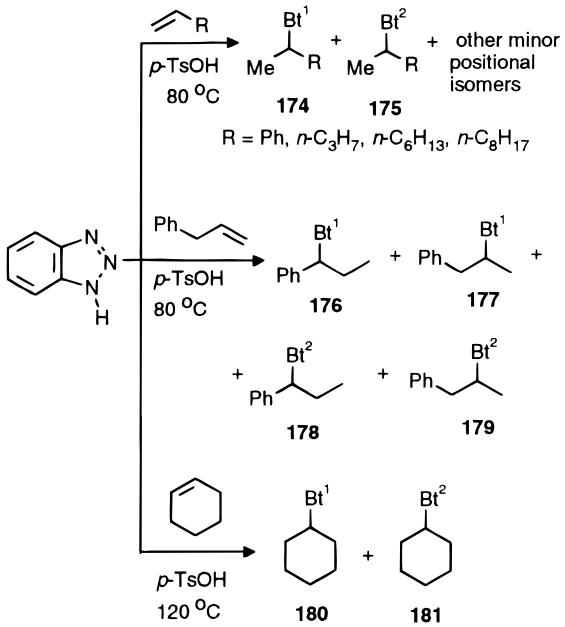
Benzotriazole also adds easily to vinyl ethers such as ethyl vinyl ether, 2,3-dihydrofuran, and 3,4-dihydro-2*H*-pyran to give the corresponding α-benzotriazolylalkyl ethers **167**−**169** with the Bt^1 isomers predominant[154] (Scheme 67). Addition of benzotriazole to vinyl acetates gives more complicated results. Reaction of benzotriazole with vinyl acetate yields a mixture of **170** and **171**, while with propenyl acetate, product **172** is formed in 43% yield. Addition of benzotriazole to diketene results in the ring-opened product **173** in 94% yield.

c. Addition to Unactivated Olefins and Acetylenes. Michael additions of aromatic heterocyclic NH compounds to electron-deficient olefins are well-documented. In contrast, analogous additions to unactivated olefins and alkynes have remained until recently virtually unexplored although similar reactions are reported with ammonia and amines under rather harsh conditions, generally high temperatures and high pressure. We found that benzotriazole adds to unactivated olefins under acid catalysis to give the corresponding addition products in moderate yields.[155] Typical conditions involve treatment of an olefin with benzotriazole and catalytic amounts of *p*-toluenesulfonic acid at 80 °C in a sealed tube, and the products are uniformly mixtures of Bt^1 and Bt^2 isomers (Scheme 68). Normal terminal olefins give exclusively or predominantly the adducts in which

Scheme 67. Additions of Benzotriazole to Vinyl Ethers



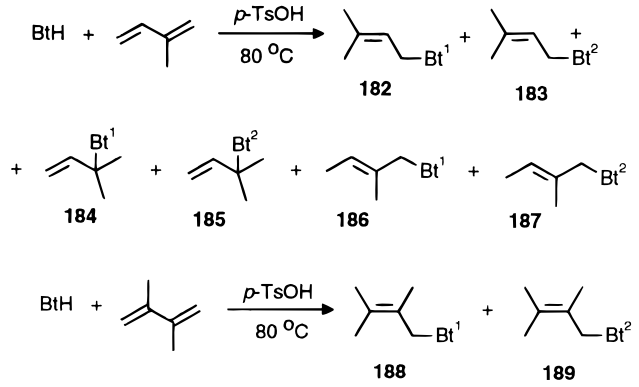
Scheme 68. Addition of Benzotriazole to Unactivated Olefins



the benzotriazolyl group is located at the position 2 of the alkyl chain, while highly branched and phenyl-substituted olefins afford all positional isomers due to the nonspecificity of the initial carbocation formation and/or the rearrangement of the carbocation formed. The Bt^1 and Bt^2 isomers are readily distinguishable by NMR spectroscopy and mass spectra. A detailed study of the fragmentation patterns of 1- and 2-alkylbenzotriazoles indicates that Bt^1 isomers lose nitrogen much more easily than their Bt^2 counterparts resulting in generally weak parent ions.[156]

Under similar conditions, benzotriazole also adds to some 1,3-butadienes. With 2-methyl-1,3-butadiene, six adducts are formed[157] (Scheme 69), while

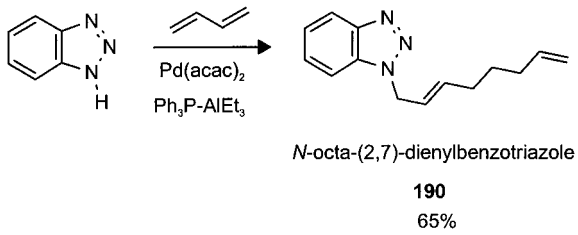
Scheme 69. Addition of Benzotriazole to 1,3-Dienes



with 2,3-dimethyl-1,3-butadiene only two products (Bt^1 and Bt^2) are obtained, probably due to their thermal stability and/or the steric hindrance of the initially formed tertiary carbocation which is resistant to react with benzotriazole and rather rearranges to a primary carbocation.

The telomerization of benzotriazole with 1,3-butadiene was investigated in the presence of palladium-containing complex catalysts activated by electron-donating and electron-withdrawing ligands.[158] The telomerization occurs at the N-1 atom to give *N*-octadi-2,7-enylbenzotriazole (**190**) in 65% yield (Scheme 70).

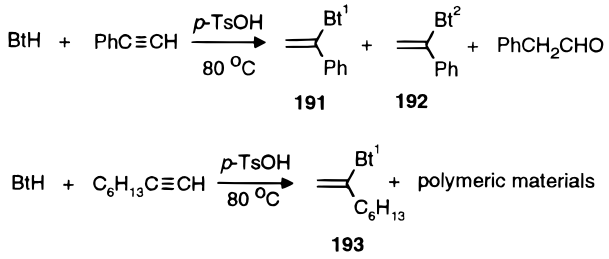
Scheme 70. Telomerization of Benzotriazole with 1,3-Butadiene



Addition of benzotriazole to alkynes is less facile. Heating benzotriazole with phenylacetylene and *p*-toluenesulfonic acid at 80 °C gives 1-benzotriazol-1-ylethylene (**191**) in 10% yield along with a small amount of Bt^2 isomer **192** and traces of phenylacetaldehyde[157] (Scheme 71). Similarly, *n*-octyne affords 2-benzotriazol-1-yloctene (**193**) in only 5% yield together with large amounts of polymeric materials.

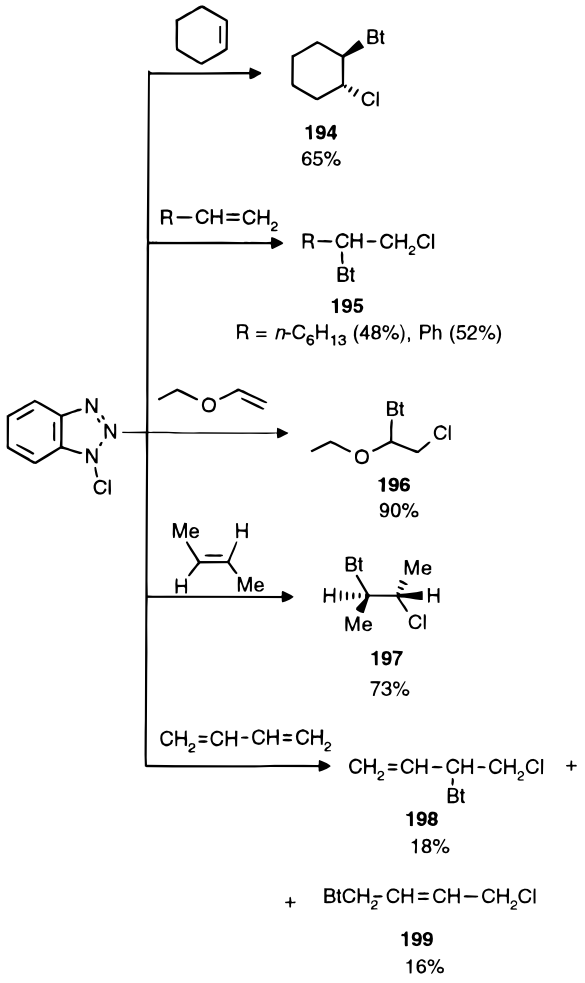
d. Addition of 1-Chlorobenzotriazole. 1-Chlorobenzotriazole adds rapidly to unactivated olefins and to

Scheme 71. Addition of Benzotriazole to Alkynes



vinyl ethers (see also Scheme 171, section III.C.5) to give a mixture of Bt^1- and Bt^2-substituted products in good yield, with the Bt^2 isomer predominating.[23] Reaction with unsymmetrical olefins, such as octene-1 (Scheme 72) or styrene, occurs according to Mark-

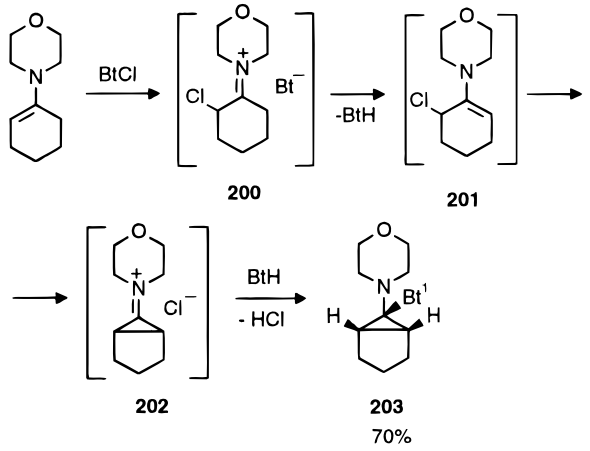
Scheme 72. Addition of 1-Chlorobenzotriazole to Olefins



ovnikov's rule of orientation with formation of 1-chloro-2-benzotriazolylalkanes **195**. The stereochemistry of addition in the reactions with *cis*- and *trans*-but-2-ene and cyclohexene was shown to be stereospecifically *trans*. With buta-1,3-diene both 1,2- and 1,4-addition occur to about equal extents.

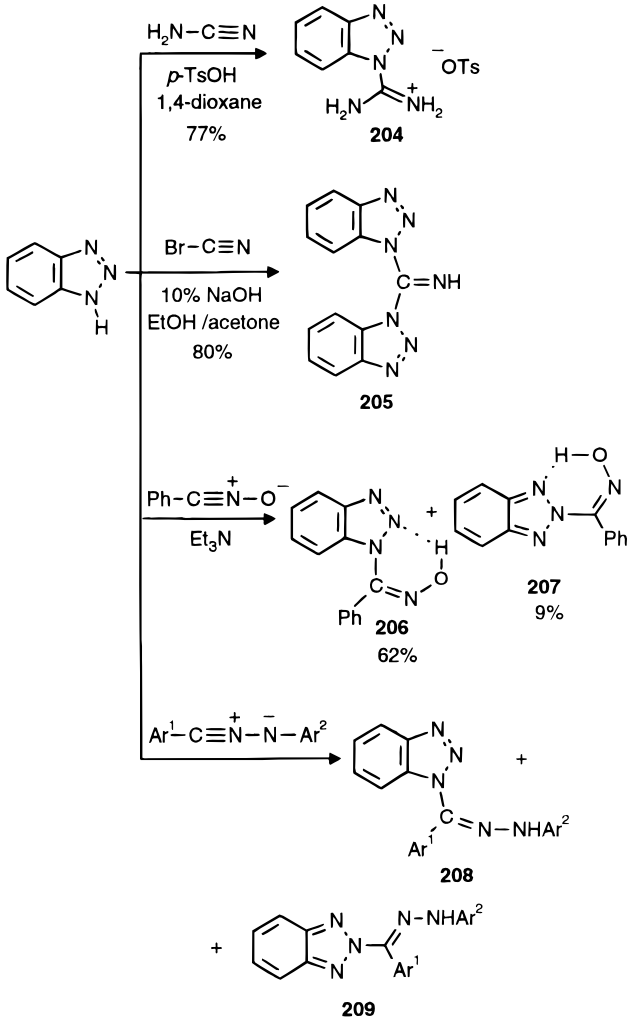
1-Chlorobenzotriazole adds to the enamine, 1-morpholin-4-ylcyclohexene, forming the novel benzotriazole bicyclo[3.1.0]hexane derivative **203**[159] in 70% yield (Scheme 73). The structure and its stereochemistry are supported by high-resolution NMR and

Scheme 73. Additions of 1-Chlorobenzotriazole to Enamines



2D proton−carbon correlations (HETCOR), and further by X-ray crystallographic data. The mechanism is believed to involve an initial electrophilic attack of the chloro atom followed by deprotonation to give enamine **201**. Elimination of chloro atom leads to the formation of bicyclo[3.1.0]hexane cation **202**. Finally, addition of benzotriazole from the less hindered side gives the stated derivative **203**.

Scheme 74. Addition of Benzotriazole to C≡N Bond



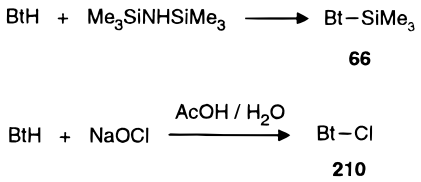
5. Addition to C≡N

Benzotriazole reacts readily with cyanamide and *p*-toluenesulfonic acid to afford benzotriazole-1-carboxamidinium tosylate (**204**) in 77% yield (Scheme 74).[160] Reaction of an excess of benzotriazole with cyanogen bromide under basic conditions as a result of both bromine substitution by the benzotriazole moiety and addition to C≡N bond gives dibenzotriazol-1-ylmethylimine (**205**) in 80% yield.[161] Addition of benzotriazole to the C≡N of benzonitrile oxide[162] or diarylnitrile imines[163] affords oximes **206** and **207** and arylhydrazones **208** and **209**, respectively. Oximes **206** and **207** are obtained stereoselectively as *Z* isomers due to hydrogen bond formation (Scheme 74).

C. Formation of Bt–X Bonds

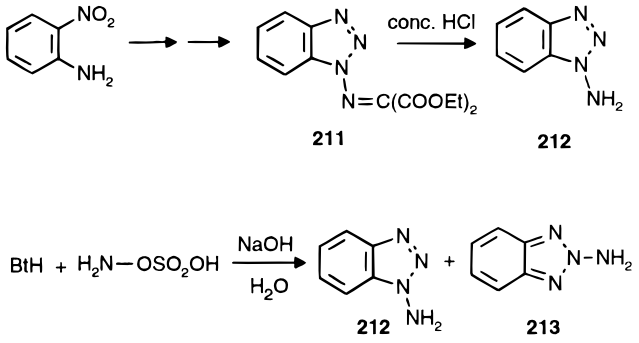
Heating a mixture of benzotriazole and hexamethyldisilazane gives 1-(trimethylsilyl)benzotriazole (**66**)[49] (Scheme 75). Benzotriazole is rapidly and quantitatively converted by treatment with sodium hypochlorite into stable, crystalline 1-chlorobenzotriazole (**210**), which can be used as a mild oxidant for oxidation of alcohols to carbonyl compounds, hydrazo to azo compounds, etc.[85]

Scheme 75. Preparation of 1-(Trimethylsilyl)-benzotriazole and 1-Chlorobenzotriazole



1-Aminobenzotriazole (**212**, Scheme 76) was first prepared by a multistep synthesis starting from *o*-nitroaniline in 54% overall yield.[164a] In this procedure, *N*-iminobenzotriazole (**211**), obtained by a benzotriazole ring-closure reaction, undergoes mild hydrolysis upon treatment with cold concentrated hydrochloric acid to give **212** in high yield. 1-Amino-5-methylbenzotriazole was prepared similarly in 41% overall yield from 4-methyl-2-nitroaniline. Recently the preparation of 1-amino-7-methylbenzotriazole was improved.[341a] Treatment of *N*-Boc-1-amino-7-methybenzotriazole with 2 equiv of *n*-butyllithium followed by electrophiles allowed the synthesis of a variety of 7-substituted 1-aminobenzotriazole derivatives.[341a,b]

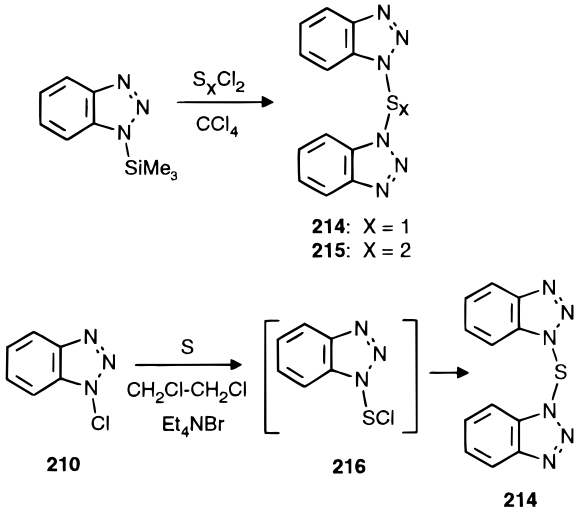
Scheme 76. Preparation of *N*-Aminobenzotriazoles



Although *N*-aminotriazoles can be prepared by reaction of the triazole sodium salt with chloramine solution, no analogous *N*-aminobenzotriazoles could not be obtained this way. Attempts to prepare **212** by treatment of 1-chlorobenzotriazole, 1-(tosyloxy)-benzotriazole, or 1-(phenylacetoxy)benzotriazole with sodamide also failed. However, it was subsequently found that *N*-aminobenzotriazole could be obtained in a single-stage synthesis by treatment of benzotriazole with hydroxylamine-*O*-sulfonic acid in aqueous potassium hydroxide solution[164a] (Scheme 76). A mixture of the Bt[1] (**212**) and Bt[2] (**213**) isomers was obtained with **212**:**213** a ratio of ~4:1.

1,1′-Thio- and 1,1′-dithiobisbenzotriazoles (**214** and **215**, respectively) are synthesized in nearly quantitative yields by reactions of 2 equiv of 1-(trimethylsilyl)-benzotriazole (**66**) with the corresponding sulfur chlorides (Scheme 77).[165] Although rather unstable

Scheme 77. Preparation of 1,1′-Thio- and 1,1′-Dithiobisbenzotriazoles



and highly hygroscopic, compounds **214** and **215** can be used as sulfur-transfer reagents (see section IV.B.11). An attempt to prepare **214** and **215** by the reaction of sulfur chlorides with the sodium salt of benzotriazole failed.[165]

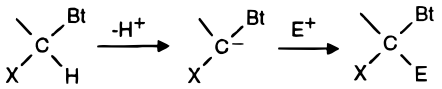
Although *N*-chlorosuccinimide and *N*-chlorohydantoin react with sulfur to produce the corresponding *N*-(chlorothio)imides, *N*-(chlorothio)benzotriazole **216** could not be isolated by this procedure. It may be formed as an intermediate and react immediately with a second molecule of *N*-chlorobenzotriazole with chlorine elimination or decomposition under the reaction conditions to give 1,1′-thiobisbenzotriazole **214** in 76% yield (Scheme 77).[166]

III. Transformations in Which the Benzotriazole Group Is Retained

The benzotriazolyl derivatives as described in section II can undergo two main classes of further transformations: (1) transformations in which the Bt group is retained; (2) transformations where the Bt group has been displaced or ring opened. The most important subclasses of transformations of the first type are summarized in Scheme 78, i.e. (i) deprotonation, (ii) substitution, (iii) addition, (iv) isomerization among the Bt-ring nitrogen atoms, (v) isomerization of Bt group within the molecule, and (vi) proton loss followed by rearrangement. These subclasses of transformations are now considered individually in that order.

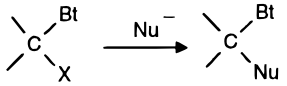
Scheme 78. Major Types of Transformations in Which the Benzotriazole Group Is Retained

1. Proton loss followed by reaction with electrophile



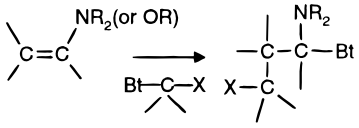
Classes: a. unactivated
b. X = C=C or (hetero)aromatic
c. X = heteroatom

2. Substitution either alpha to Bt-group or otherwise

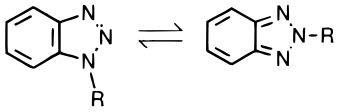


for X = halogen or OR

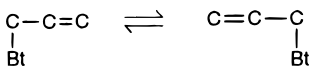
3. Addition of Bt-C-X to C=C-Y



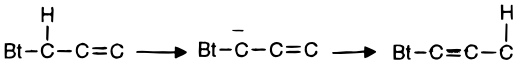
4. Isomerization to different position in Bt-ring



5. Isomerism of Bt group to a different position in molecule



6. Proton loss followed by rearrangement



A. Deprotonation of Benzotriazole α-CH and Subsequent Reaction with Electrophiles

Heteroatom-assisted deprotonation of an α-hydrogen is well-known.[167] For example, the *N*-alkyl protons α to a nitrogen incorporated in a five-membered heteroaromatic ring such as *N*-alkylpyrazole are activated.[168] A benzotriazolyl moiety also provides sufficient activation so deprotonation of benzotriazole α-CH is facilitated.

1. Bt–CH Unactivated: Alkylbenzotriazoles

Metalations of *N*-alkylheterocycles often involve replacement of a ring proton[169,170] and, where the

Table 20. Products 218 Formed from Lithiated 1-Methylbenzotriazole

E^+	E	yield %
MeI	Me	80
n-BuI	*n*-Bu	53
$PhCH_2Br$	$PhCH_2$	30
PhCHO	PhCH(OH)	95
CH_2=CHCHO	CH_2=CHCH(OH)	57
Ph_2C=O	Ph_2C(OH)	70
PhCOOEt	PhCO	54
CO_2	COOH	54

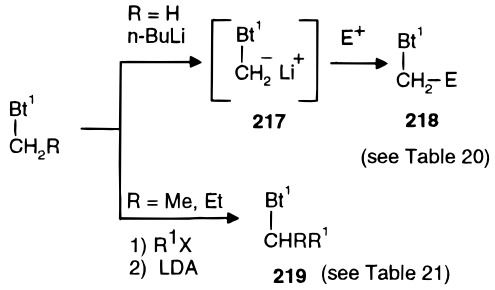
Table 21. Products 219 Formed from Lithiated 1-Ethyl- and 1-Propylbenzotriazoles

R	R^1X	R^1	yield %
Me	MeI	Me	15
Me	EtBr	Et	72
Me	*n*-PrI	*n*-Pr	44
Et	EtBr	Et	40
Et	*n*-$C_{10}H_{21}Br$	*n*-$C_{10}H_{21}$	65

alternative *N*-alkyl deprotonation is desired, carbanion-stabilizing substituents are frequently used to provide better regioselectivity at the α-C. Such substituents include an aryl group as in *N*-benzylpyrazole[169] and *N*-benzylimidazole;[171] a second nitrogen-linked heterocyclic ring as in bis(pyrazolyl)methanes;[168] a sulfur moiety as in 1-[(phenylthio)methyl]benzimidazole[170] and 9-[(phenylthio)methyl]carbazole.[172] Reactions involving such substituents in the case of *N*-(α-substituted alkyl)benzotriazoles are considered in later subsections.

However, even without such a second activating group, 1-alkylbenzotriazoles can undergo lithiation at the α-CH[173] (Scheme 79, Tables 20 and 21). Thus,

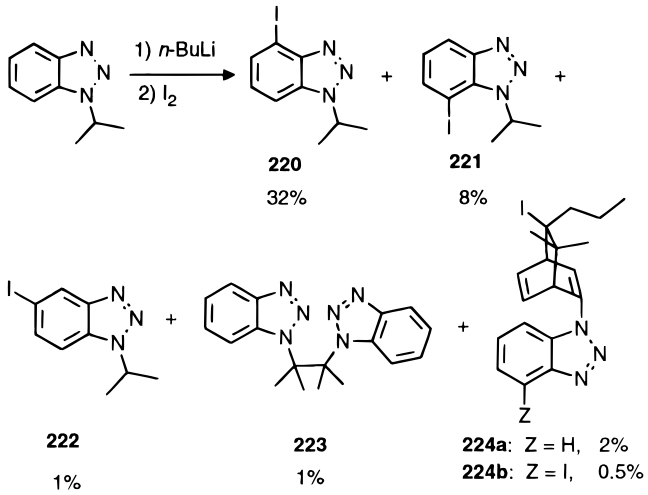
Scheme 79. Lithiation of 1-Alkylbenzotriazoles and Subsequent Reactions with Electrophiles



1-methylbenzotriazole is lithiated with *n*-BuLi and the anion quenched with electrophiles such as alkyl halides, aldehydes, ketones, esters, and carbon dioxide to yield the desired products **218** (for reaction with azobenzenes, see section IV.B.1.g). However, these reaction conditions are not suitable for 1-ethyl- and 1-propylbenzotriazole, which require simultaneous treatment of the *N*-alkylbenzotriazole with LDA and the appropriate alkyl halide internal quenching. Such a difference is rationalized as due to the fact that 1-ethyl- and 1-propylbenzotriazole are less acidic and the corresponding carbanions are more reactive and less stable than the anion generated from 1-methylbenzotriazole. The low yield with methyl iodide as electrophile seems to reflect the higher reactivity of methyl iodide toward LDA in comparison with that of ethyl bromide. Aldehydes and ketones as electrophiles under similar conditions gave back starting materials.[173]

Lithiation of 1-ethylbenzotriazole with *n*-BuLi gave recovered starting material together with products, indicating both ring and α-CH substitution. The lithiation of 1-isopropylbenzotriazole, followed by treatment with iodine affords a complex mixture of products (Scheme 80) with substitution occurring at

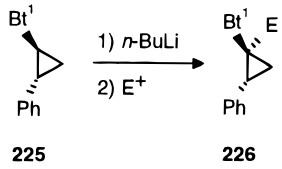
Scheme 80. Lithiation of 1-Isopropylbenzotriazole and Subsequent Reactions with Electrophiles



three of the benzotriazole benzene ring positions as well as 40% of unreacted 1-isopropylbenzotriazole.[174] A complex mixture is also obtained when methyl iodide is used as the electrophile.

1-Cyclopropylbenzotriazole (**225**) undergoes lithiation at the methine group adjacent to the Bt group, indicating stronger activating ability of benzotriazole compared to phenyl. The resulting anion reacts with alkyl halides, iodine, aldehydes, and diaryl disulfides allowing introduction of alkyl, iodide, alcohol, and arylthio groups at the cyclopropyl carbon to give **226a**−**d** (Scheme 81).[175]

Scheme 81. Lithiation of 1-Cyclopropylbenzotriazole and Subsequent Reactions with Electrophiles



	E^+	E	yield, %
226a:	*n*-BuI	*n*-Bu	76
226b:	I_2	I	83
226c:	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	54
226d:	PhSSPh	PhS	43

Treatment of β-benzotriazolyl propionamide **162** with 2 equiv of *n*-BuLi gives a dianion **227a**. In contrast to carbanions derived from 1-ethyl- and 1-propylbenzotriazole, this carbanion **227** is stabilized by the amide group as shown in Scheme 82. Quenching **227** with 1 equiv of electrophile affords

Scheme 82. Reactions of Dilithiated *β*-Benzotriazolylpropionamides

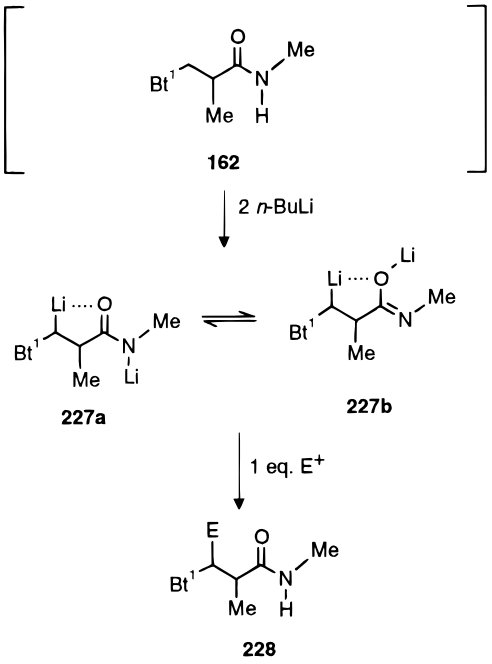


Table 22. Products 228 from Reactions of Lithiated Amide 162

E^+	E	yield %
MeI	Me	58
n-BuI	*n*-Bu	56
n-$C_6H_{13}I$	*n*-C_6H_{13}	64
n-$C_8H_{17}I$	*n*-C_8H_{17}	62
$PhCH_2Br$	$PhCH_2$	73
4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	46
Ph_2CO	$Ph_2C(OH)$	56

the *C*-substituted compounds **228** in good yields (Table 22).[151]

Lithiations of 2-alkylbenzotriazoles exhibit some unusual features compared to their Bt^1 counterparts.[176] Reactions of 2-methylbenzotriazole with LDA and an alkyl halide gives products **229** of alkylation and coupling (Scheme 83). Treatment with LDA alone produces coupling products **230**. The composition of **230** depends on both the size of the R^1 group and the reaction time: in general, smaller R^1 groups and longer reaction times favor the formation of racemic isomers (Table 23).[177] 2-Benzylbenzotriazole does not dimerize under these reaction conditions. Leaving solutions of lithiated 2-alkylbenzotriazoles for a prolonged time leads to reductive elimination of both the benzotriazolyl moieties from **230** and formation of the mixtures of *cis*- and *trans*-olefins of type $R^1CH{=}CHR^1$ (see section IV.F). 2-Isopropylbenzotriazole is also lithiated only at the α-CH position and subsequent reaction of the anion with iodine affords the dimer in 74% yield. 2-Methylbenzotriazole undergoes lithiation in the presence of benzophenone to give the expected alcohol **231**, while under similar conditions, benzaldehyde does not react as an electrophile. 2-Propyl- and 2-pentylbenzotriazole react with LDA in the presence of an electrophile giving the expected alkyl products **232a**,**b**. A radical mechanism is proposed for the unusual behavior of lithiated 2-alkylbenzotriazoles and confirmed by ESR spectra[176,178] and by reactions of lithiated 2-alkylbenzotriazoles with benzophenone.[177]

Scheme 83. Products from Lithiation of 2-Alkylbenzotriazoles

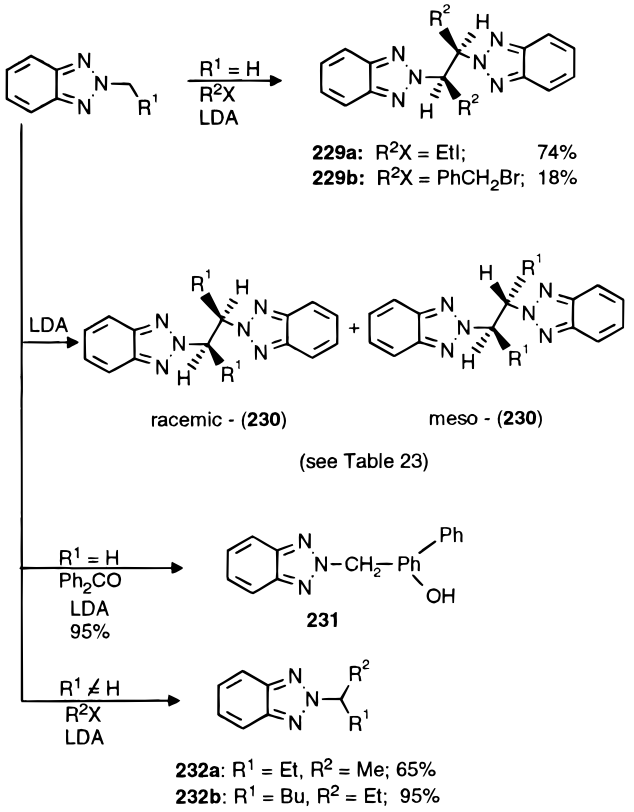


Table 23. Dehydrodimerization of 2-Alkylbenzotriazoles

		yields of dimers **230**, %		
R^1	reaction time, min	meso	racemic	total
Me	5	25	48	73
Me	60	0	46	46
Me	3 days	0	24	24
Et	5	25	38	63
Et	120	9	36	45
n-Pr	5	38	27	65
n-Pr	120	37	21	58
n-Pr	7 days	14	0	24
n-C_6H_{13}	5	39	20	59
n-C_6H_{13}	3 days	<5	<2	<7
n-C_7H_{15}	5	41	32	73
n-C_7H_{15}	120	38	17	55
n-C_7H_{15}	7 days	<3	<1	<4
CH_2Ph	5	10	0	10
Ph	120	0	0	0

2. Bt—CH—C═C and Bt—CH—C≡C

a. Allylbenzotriazoles. Unlike simple alkylbenzotriazoles, the methylene groups in 1- and 2-allylbenzotriazoles are additionally activated by the double bond. 1-Allylbenzotriazole is lithiated by *n*-BuLi and subsequently treated with electrophiles to give the expected products **233** (R = H) in excellent yields. Similar reaction occurs for the benzotriazol-2-yl isomer and quenching with methyl iodide results in the desired product **234** in 85% yield[24] (Scheme 84 and Table 24). Deprotonation of *trans*-1,3-dibenzotriazol-1-ylpropene with *n*-BuLi or LDA and subsequent treatment with electrophiles affords the cor-

Scheme 84. Lithiation of *N*-Allylbenzotriazoles and Subsequent Reactions with Electrophiles

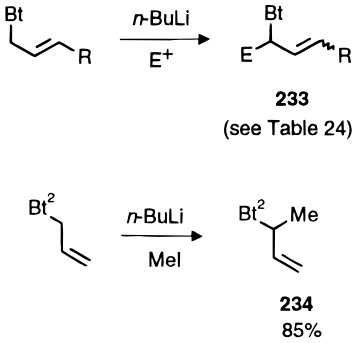


Table 24. Products 233 from the Lithiation of *N*-Allylbenzotriazoles

R	E^+	E	yield %
H	MeI	Me	52
H	Ph_2CO	$Ph_2C(OH)$	70
H	*n*-BuBr	*n*-Bu	91
H	$PhCH_2Br$	$PhCH_2$	95
H	c-$C_6H_{11}I$	c-C_6H_{11}	88
H	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	95
H	*n*-$C_6H_{13}I$	*n*-C_6H_{13}	97
Bt^1	MeI	Me	48[a]
Bt^1	EtI	Et	81
Bt^1	$PhCH_2Cl$	$PhCH_2$	55
Bt^1	Ph_2CO	$Ph_2C(OH)$	35[a]

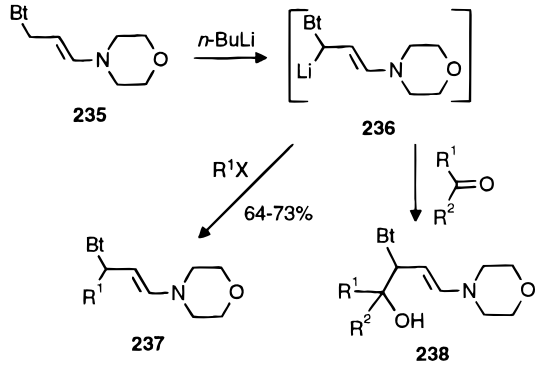
[a] Mixtures of *trans* and *cis* isomers are obtained.

responding α-substituted derivatives **233** (R = Bt^1).[83] While the alkylation with ethyl iodide or benzyl chloride occurs with retention of double-bond stereochemistry, treatment with methyl iodide or benzophenone gives mixtures of *trans* and *cis* isomers with *trans* isomer predominating.

Lithiation of 1-(α-ethoxyallyl)benzotriazole occurs at the α-methine position and the resulting anion reacts readily with halides, ketones, or electron-deficient olefins, but these transformations are considered later as reactions of Bt−CH−O derivatives (see section III.A.7).

b. Bt−CH−C=C−N. Lithiation of 1-(3-morpholinoprop-2-enyl)benzotriazole (**235**) occurs at the methylene position α to the benzotriazole moiety.[179,180] The resulting anion **236** is quenched with alkyl halides or carbonyl compounds to afford the corresponding adducts **237** and **238** (Scheme 85). Compounds **238** are not isolated but converted *in situ* into 2,5-tetrahydrofurans by treatment with water (see Scheme 281, section IV.B.9.a) or into substituted 1-amino-4-hydroxybut-1-enes by treatment with Grignard reagents (see Scheme 280, section IV.B.9.a).

Scheme 85. Lithiation and Subsequent Reactions of 1-(3-Morpholinoprop-2-enyl)benzotriazole



237: R = Me, *n*-Bu, *n*-C_8H_{17}

238: $R^1 = R^2$ = Ph; R^1 = Ph, R^2 = 2-ClC_6H_4; R^1 = Ph, R^2 = 2,4-$Cl_2C_6H_3$; R^1 and R^2 = fluoren-9-yl; R^1 = Ph, R^2 = Me; R^1 and R^2 = -$(CH_2)_5$-

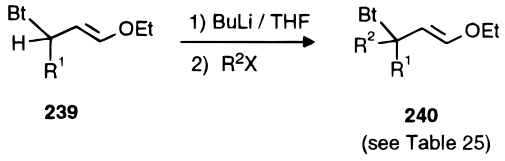
Table 25. Preparation of Substituted 1-(Ethoxyallyl)benzotriazoles 240

R^1	R^2	yield %
H	Me	95
H	$PhCH_2CH_2$	*a*
H	PhS	*a*
H	$PhCH_2$	*a*
Et	Et	94
Et	*n*-Bu	*a*
Et	*n*-C_5H_{11}	*a*
n-Bu	*n*-Bu	*a*
$PhCH_2CH_2$	Me	*a*
Me	Ph	*a*
$PhCH_2$	Et	*a*

[a] Not isolated but used directly for further transformations.

c. Bt−CH−C=C−O. Similar to 1-allylbenzotriazole, 1-(3-ethoxyallyl)benzotriazoles (**239**) undergo lithiation with *n*-butyllithium and the resulting anions react with alkyl halides to give more highly substituted derivatives **240**[181] (Scheme 86, Table 25).

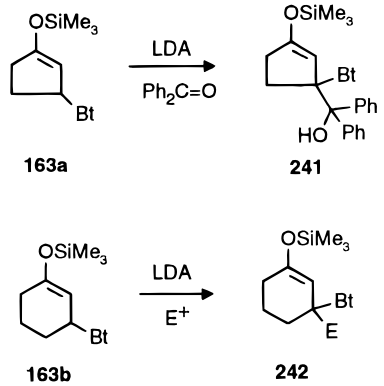
Scheme 86. Lithiation of 1-(3-Ethoxyallyl)benzotriazoles and Subsequent Reaction with Electrophiles



The adducts from aldehydes and aromatic imines are not isolated, but directly subjected to $ZnBr_2$-promoted cyclization (see section IV.B.9.b).

3-Benzotriazol-1-yl-1-[(trimethylsilyl)oxy]cyclopentene (**163a**) and -cyclohexene (**163b**) undergo deprotonation with LDA to give the corresponding α-ben-

Scheme 87. Lithiation of Silyl Ethers and Subsequent Reactions with Electrophiles



E^+ = *n*-$C_{10}H_{21}Br$; $PhCH_2Cl$; 4-$ClC_6H_4CH_2Cl$; 3,5-$Me_2C_6H_3CH_2Cl$; PhCOOEt; PhCHO; Ph_2CO; PhNCS; 4-ClC_6H_4NCS

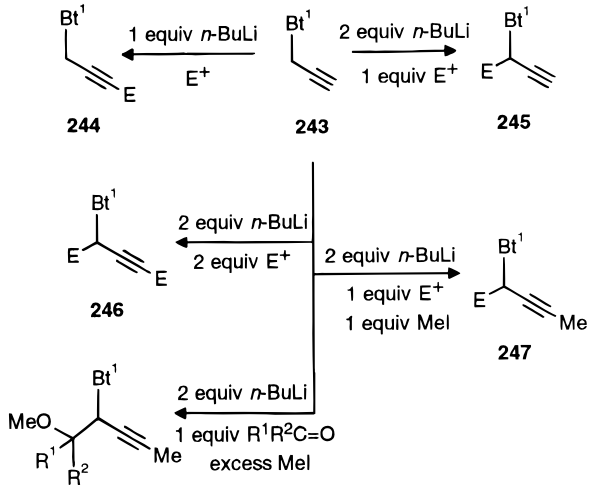
Table 26. Products 244−247 from Reactions of Lithiated 1-Propargylbenzotriazole

compound	E^+	E	yield %
244	Ph_2CO	$Ph_2C(OH)$	64
	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	70
	PhCHO	PhCH(OH)	68
	2-furyl-CHO	2-furyl-CH(OH)	63
245	Ph_2CO	$Ph_2C(OH)$	67
	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	81
	$PhCH_2Br$	$PhCH_2$	67
	n-$C_6H_{13}I$	*n*-C_6H_{13}	78
246	Ph_2CO	$Ph_2C(OH)$	79
	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	54
247	$PhCH_2Br$	$PhCH_2$	51

zotriazolyl anions which react with a range of electrophiles[152] (Scheme 87). Unlike those generated from simple alkyl benzotriazoles, these carbanions are not very stable, and therefore an internal trapping electrophile is required (i.e., added prior to LDA). The resulting adducts are not isolated but subjected to direct hydrolysis (see section IV.C.5.c).

d. N-Propargylbenzotriazoles. Treatment of 1-propargylbenzotriazole with *n*-BuLi first lithiates the strongly acidic acetylenic proton. The products finally obtained depend on the amount of *n*-BuLi and of the electrophiles used.[24] As shown in Scheme 88

Scheme 88. Products from Treatment of 1-Propargylbenzotriazole with 1 or 2 Equiv of BuLi Followed by 1 or 2 Equiv of Electrophile

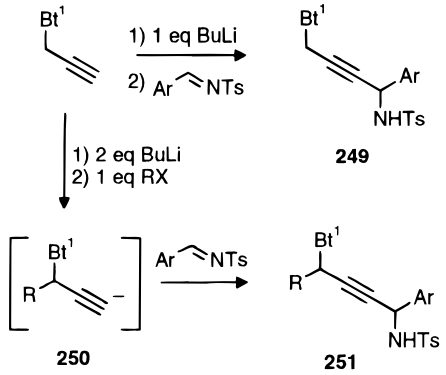


248a: $R^1 = R^2 = Ph$; 69%
248b: R^1, $R^2 = -(CH_2)_5-$; 49%

(and Table 26): (i) when 1 equiv of *n*-BuLi and 1 equiv of electrophile are used, the alkylation occurs solely at the more acidic acetylenic carbon to give **244**, (ii) with 2 equiv of *n*-BuLi and 1 equiv of electrophile, the alkylation occurs at the carbon α to the benzotriazolyl group to give **245**; (iii) with 2 equiv of *n*-BuLi and 2 equiv of electrophile, dialkylated products **246** are obtained; (iv) quenching the dianion successively with 1 equiv of one electrophile (alkylation at the benzotriazolyl α-carbon) followed by a different one (alkylation at the acetylenic carbon) results in the formation of unsymmetrically disubstituted products **247**. When a ketone is used as the first electrophile and methyl iodide (excess) as the second, products **248a**,**b** are obtained.

Similarly, mono- and dilithiated 1-propargylbenzotriazoles react regioselectively with *N*-tosylarylimines to give in high yields the corresponding adducts **249** and **251**, respectively[182] (Scheme 89). No

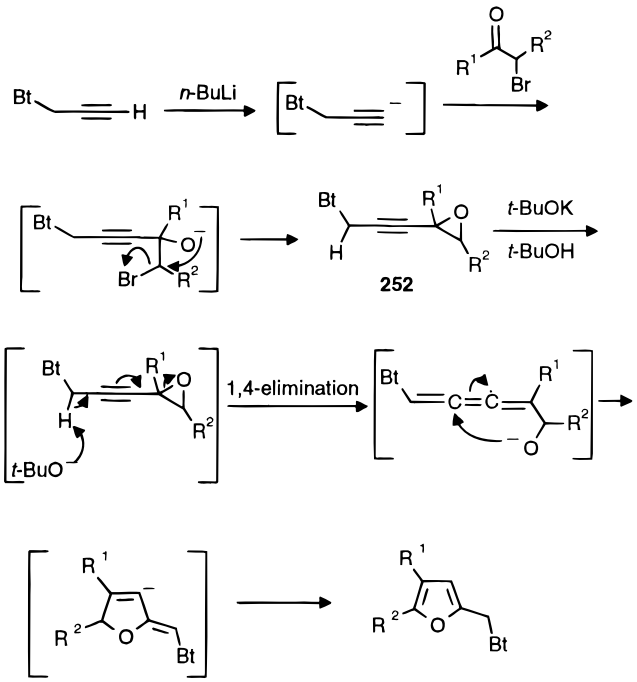
Scheme 89. Reaction of Lithiated 1-Propargylbenzotriazoles with *N*-Tosylarylimines



isomeric allene derivatives are detected in the reaction mixtures. Compounds **249** and **251** are subsequently used for the preparation of 2-substituted pyrroles (see section IV.C.3.b).

The diverse reactivity of 1-propargylbenzotriazole has been successfully employed in synthesis of some five-membered heterocycles. Treatment of 1-propargylbenzotriazole with butyllithium followed by with α-bromo ketones gives initially the corresponding 1-hydroxy-4-benzotriazolyl-1-alkynes which undergo immediate intramolecular displacement of bromine to give the isolable epoxides **252.** Upon treatment with *t*-BuOK, these give 2-(benzotriazolylmethyl)-furans **253a**−**d** in moderate yields[183] (Scheme 90).

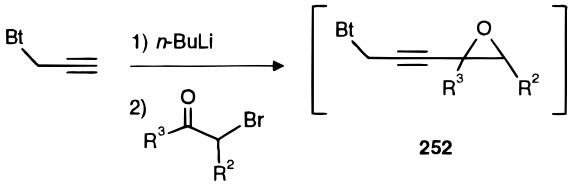
Scheme 90. Preparation of 2-(Benzotriazolylmethyl)furans from 1-Propargylbenzotriazole



253a: R^1 = Ph, R^2 = H, 61%
253b: R^1 = 2-naphthyl, R^2 = H, 51%
253c: R^1 = Ph, R^2 = Me, 53%
253d: $R^1 = R^2$ = Me, 55%

When the epoxide **252** is treated with primary aliphatic or benzylic amines, the corresponding *N*-substituted 2-(benzotriazolylmethyl)pyrroles **254** are obtained in moderate yields (Scheme 91).[184,185]

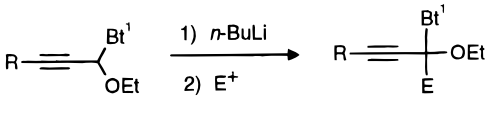
Scheme 91. Preparation of 2-(Benzotriazolylmethyl)pyrroles from 1-Propargylbenzotriazole



R^1	R^2	R^3	Yield %
$PhCH_2$	Me	Ph	48
t-Bu	H	Ph	32
$MeO(CH_2)_2$	Me	Me	58
4-$MeOC_6H_4CH_2$	Me	Me	59
n-Bu	Me	Me	62
$PhCH_2$	H	Ph	82
n-Bu	H	*t*-Bu	63

The presence of an ethoxy group at the benzotriazolyl α carbon is tolerated as demonstrated by the successful lithiation of 1-(α-ethoxypropargyl)benzotriazoles **255** (R = H, Ph, *n*-C_6H_{13})[79,186,187] (Scheme 92, Table 27). With terminally protected propargyl

Scheme 92. Lithiation of 1-(α-Ethoxypropargyl)-benzotriazoles and Subsequent Reactions with Electrophiles



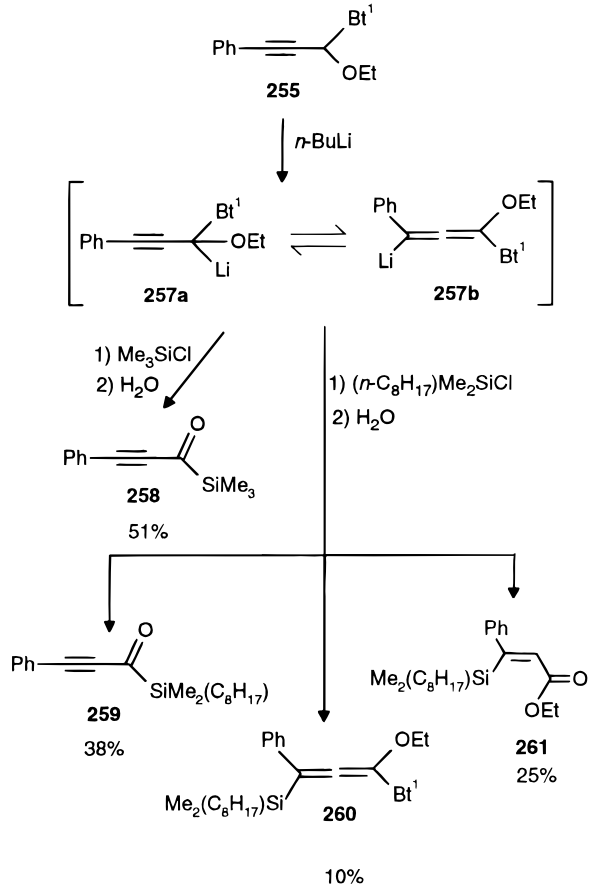
255 **256**

(see Table 27)

aldehydes as electrophiles this reaction provides valuable intermediates for the synthesis of unsymmetrical dialkyne-1,2-diones.[186]

Deprotonation of α-benzotriazolylpropargyl ethyl ether **255** (R = Ph) generates organolithium species of two possible types (**257a** and **257b**), which may exist in equilibrium with each other and with a common mesomeric anion. The bulkiness of electrophile used determines the composition of products formed. Thus, when trimethylchlorosilane is used as an electrophile, intermediate **256** (R = Ph, E = $SiMe_3$) is obtained *in situ* which, after hydrolysis, gives exclusively the acetylenic acylsilane **258** in 51% yield (Scheme 93). However, the steric effects in

Scheme 93. Lithiation of α-Benzotriazolylpropargyl Ethers and Subsequent Reactions with Trialkylchlorosilanes



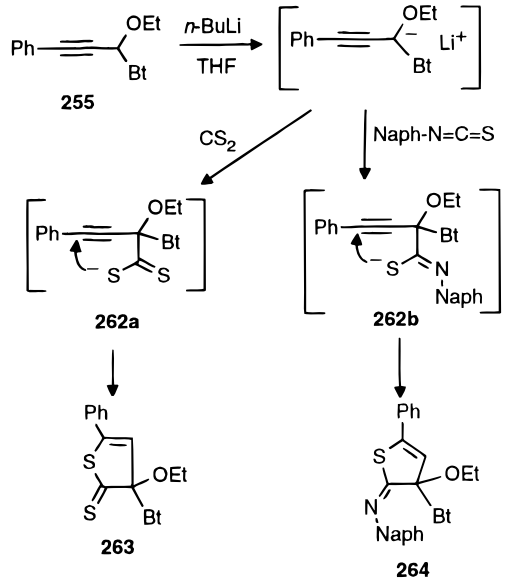
n-octyldimethylchlorosilane apparently cause the formation of some of the γ-silylated allene derivative **260** along with expected product **259**. Partial hydrolysis of **260** in site leads to the β-silylated α,β-unsaturated ester **261**.[188]

Treatment of 3-phenyl-1-benzotriazolylpropargyl ethyl ether **255** (R = Ph) with 1 equiv of *n*-BuLi followed by carbon disulfide produces directly 2,3-dihydro-2-thiophenethione (**263**) via formation and intramolecular cyclization of dithiocarboxylate anion

Table 27. Products 256 from Reactions of Lithiated 1-(α-Ethoxypropargyl)benzotriazoles with Electrophiles

R	E^+	E	yield %	R	E^+	E	yield %
H	*n*-$C_7H_{15}Br$	*n*-C_7H_{15}	90	Ph	PhCHO	PhCHOH	73
H	*n*-$C_8H_{17}Br$	*n*-C_8H_{17}	95	Ph	4-MeC_6H_4CHO	4-MeC_6H_4CHOH	75
n-C_6H_{13}	EtBr	Et	90	Ph	*t*-BuC≡CCHO	*t*-BuC≡CCH(OH)	55
n-C_6H_{13}	*n*-BuC≡CCH_2Br	*n*-BuC≡CCH_2	60	Ph	PhC≡CCHO	PhC≡CCH(OH)	50
Ph	EtBr	Et	98	Ph	Me_3SiC≡CCHO	Me_3SiC≡CCH(OH)	17
Ph	*n*-BuBr	*n*-Bu	90	Ph	$(i\text{-}Pr)_3SiC$≡CCHO	$(i\text{-}Pr)_3SiC$≡CCH(OH)	40
Ph	3-MeBuBr	3-MeBu	96	Ph	MeCOMe	$Me_2C(OH)$	66
Ph	*n*-$C_8H_{17}Br$	*n*-C_8H_{17}	60	Ph	PhCOPh	$Ph_2C(OH)$	77
Ph	*n*-$C_{16}H_{33}Br$	*n*-$C_{16}H_{33}$	94	Ph	MeCOOEt	MeCO	65
Ph	$PhCH_2Br$	$PhCH_2$	95	Ph	EtOC(O)OEt	EtOC(O)	35
Ph	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	90	Ph	4-MeC_6H_4CH=N-(4′-MeC_6H_4)	4-MeC_6H_4CHNH(4′-MeC_6H_4)	85
Ph	HC≡CCH_2Br	HC≡CCH_2	70	Ph	*t*-BuNCO	*t*-BuNHC(O)	54
Ph	*n*-BuC≡CCH_2Br	*n*-BuC≡CCH_2	90	Ph	Me_3SiCl	Me_3Si	78

Scheme 94. Preparation of 2,3-Dihydrothiophene Derivatives



262a[79] (Scheme 94). An analogous reaction with 1-naphthyl isothiocyanate gives the corresponding cyclized product **264**.

3. Bt–CH–Aryl

a. Benzylbenzotriazoles. In benzylbenzotriazoles, the methylene group is activated by both the benzotriazole ring and the phenyl ring. Thus, 1-(arylmethyl)benzotriazoles undergo lithiation easily with *n*-BuLi[189−192] (Scheme 95, Table 28); even weaker bases, such as potassium *tert*-butoxide, can be used successfully.[193,194] Alkyl,[190] halogen,[195] and alkoxy[196] substituents in the benzyl ring do not affect lithiation at the methylene group. (Dialkylamino)benzyl derivatives also afford the expected products,[192,197,198] but unsubstituted amino- and (monoalkylamino)benzyl derivatives require at least 2 equiv of *n*-BuLi.[199] 1,1-Diarylethylenes can also be employed as electrophiles[195] to give new anions **268** which can either be quenched with proton donors to give products **269**, or undergo elimination of benzotriazole to form cyclopropane products **270** (see also section IV.B.9.e).

The lithiated (arylmethyl)benzotriazoles **265** also add to arylideneamines to give the addition products **272**.[191] Interestingly, when (arylmethyl)benzotriazoles are treated with *t*-BuOK and arylideneamines (R^1 = Ph, R^2 = Ar) in DMF at elevated temperature (75 °C), immediate elimination of aniline and benzotriazole occurs to produce the corresponding sym-

Table 28. Lithiation of 1-(Arylmethyl)benzotriazole and Subsequent Reactions with Electrophiles To Give Products 266

Ar	E^+	E	yield %
Ph	Me_3SiCl	Me_3Si	91[189]
Ph	*n*-BuI	*n*-Bu	82[190]
Ph	*i*-PrI	*i*-Pr	80[190]
4-$MeOC_6H_4$	MeI	Me	80[196]
4-$MeOC_6H_4$	EtBr	Et	66[192]
4-$MeOC_6H_4$	$PhCH_2Br$	$PhCH_2$	85[196]
4-$MeOC_6H_4$	Ph_2CO	$Ph_2C(OH)$	80[196]
4-$MeOC_6H_4$	CO_2	CO_2H	78[196]
3-Me-2-$MeOC_6H_3$	MeI	Me	90[196]
3-Me-2-$MeOC_6H_3$	$PhCH_2Br$	$PhCH_2$	70[196]
3-Me-2-$MeOC_6H_3$	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	87[196]
3-Me-2-$MeOC_6H_3$	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	80[196]
3-Me-2-$MeOC_6H_3$	Ph_2CO	$Ph_2C(OH)$	75[196]
3-Me-2-$MeOC_6H_3$	PhCOOEt	PhCO	76[196]
2-MeO-naphth-1-yl	MeI	Me	98[196]
2-MeO-naphth-1-yl	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	60[196]
2-MeO-naphth-1-yl	$PhCH_2Br$	$PhCH_2$	16[196]
3,4-$(MeO)_2C_6H_3$	EtBr	Et	54[192]
2,4,6-$(MeO)_3C_6H_2$	D_2O	D	95[196]
2,4,6-$(MeO)_3C_6H_2$	MeI	Me	85[196]
2,4,6-$(MeO)_3C_6H_2$	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	72[196]
2,4,6-$(MeO)_3C_6H_2$	$PhCH_2Br$	$PhCH_2$	64[196]
4-$Me_2NC_6H_4$	MeI	Me	99[196]
4-$Me_2NC_6H_4$	EtBr	Et	66[192]
4-$Me_2NC_6H_4$	D_2O	D	90[196]
4-$Me_2NC_6H_4$	$PhCH_2Br$	$PhCH_2$	68[196]
4-$Me_2NC_6H_4$	PhCHO	PhCH(OH)	61[199]
4-$Me_2NC_6H_4$	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	79[196]
4-$Me_2NC_6H_4$	Ph_2CO	$Ph_2C(OH)$	85[196]
4-$Me_2NC_6H_4$	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	77[196]
4-$Me_2NC_6H_4$	4-MeC_6H_4COOEt	4-MeC_6H_4CO	62[196]
4-$Me_2NC_6H_4$	4-Py-CHO	4-Py-CH(OH)	65[196]
4-$Me_2NC_6H_4$	Me_2(*n*-Bu)SiCl	Me_2(*n*-Bu)Si	51[198]
4-$Me_2NC_6H_4$	Me_3SiCl	Me_3Si	67[198]
4-$Et_2NC_6H_4$	MeI	Me	72[196]
4-$Et_2NC_6H_4$	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	69[196]
4-$MeHNC_6H_4$	*n*-BuI	*n*-Bu	53[199]
4-$MeHNC_6H_4$	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	85[199]
4-$H_2NC_6H_4$	$PhCH_2Br$	$PhCH_2$	88[199]

Scheme 95. Lithiation and Subsequent Reactions of Benzylbenzotriazoles

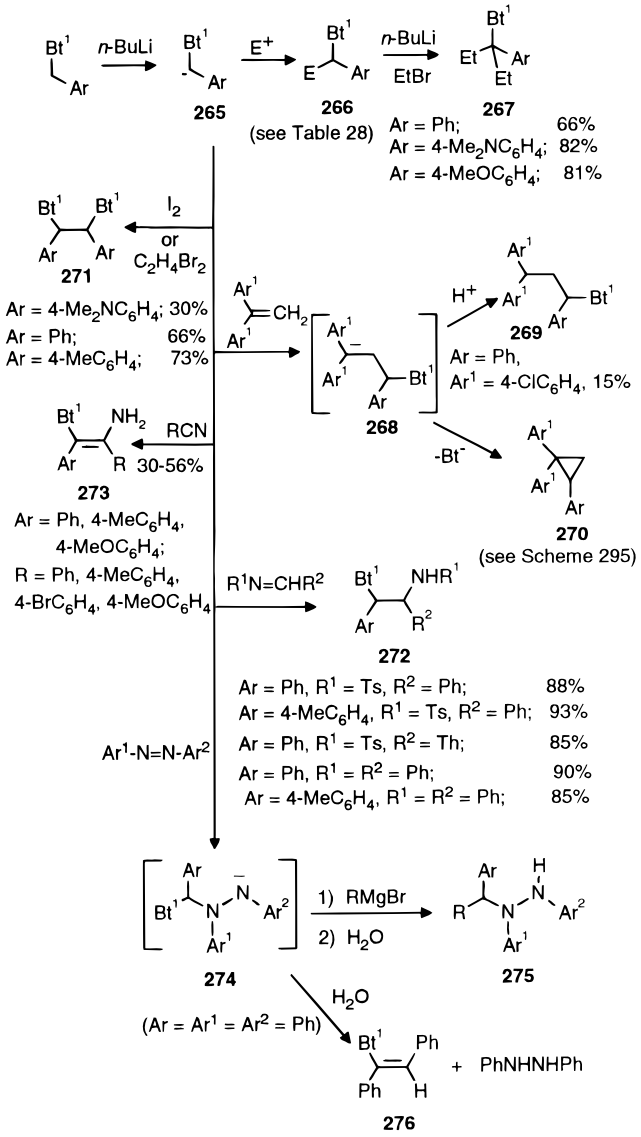
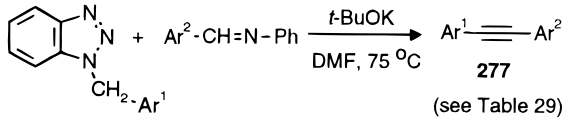


Table 29. Preparation of Diarylacetylenes 277

Ar^1	Ar^2	yield %	Ar^1	Ar^2	yield %
Ph	Ph	75	4-FC_6H_4	4-FC_6H_4	50
Ph	4-$MeOC_6H_4$	67	3-FC_6H_4	3-FC_6H_4	30
Ph	1-naphthyl	88	Ph	3-pyridyl	80
1-naphthyl	1-naphthyl	67	Ph	2-furanyl	90
2-naphthyl	2-naphthyl	76			

metrical or unsymmetrical diarylacetylenes [193,194] (Scheme 96, Table 29). The anion **265** is oxidized in

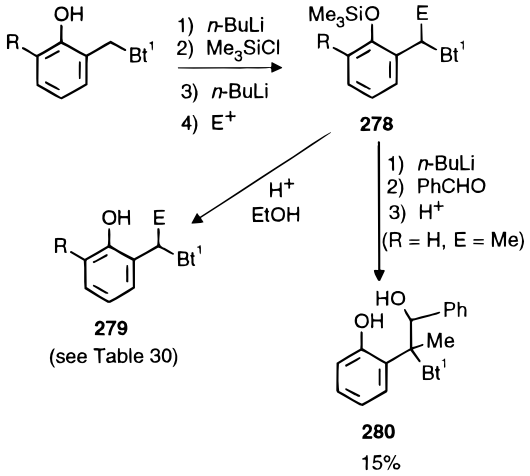
Scheme 96. Reaction of 1-(Arylmethyl)benzotriazoles with *N*-Phenylarylmethylenimines



the presence of I_2 or $BrCH_2CH_2Br$ to the coupling products **271**.[190,197] When a 2-fold excess of both *n*-butyllithium and ethyl bromide is used, the diethylated products **267** are obtained.[192] When a nitrile is used as the electrophile, addition to the nitrile is followed by tautomerization to form 1-(2-amino-1-aryl-1-alkenyl)benzotriazoles **273**.[200] Addition of the anion **265** to azobenzenes produces the unstable intermediates **274**, which upon trapping with Grignard reagent and subsequent hydrolysis give unsymmetrical trisubstituted hydrazines **275** (see also section IV.B.1.g).[201]

Hydroxybenzyl groups, as in (benzotriazolylmethyl)phenols, prevent the formation of the desired carbanion due to deactivation of the methylene hydrogens and formation of the low-solubility phenoxide ion. However, the lithiation succeeds in good overall yields using a one-pot reaction, employing the easily removable trimethylsilyl protecting group[131,202,203,257] (Scheme 97, Table 30). A second electrophile can also

Scheme 97. Lithiation of 2-(Benzotriazolylmethyl)-phenols and Subsequent Reactions with Electrophiles



be introduced as exemplified by presentation of compound **280**.[131]

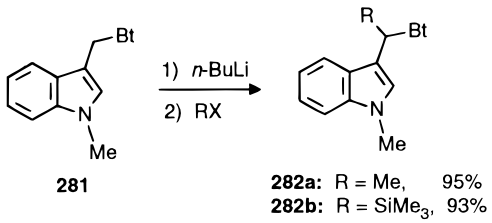
b. C-(Benzotriazolylmethyl)heterocycles. Like an aryl group, heteroaryl also activates the benzotriazolyl α-methylene CH_2 and deprotonation is facile. Thus, 3-(benzotriazol-1-ylmethyl)-1-methylindole (**281**)

Table 30. Lithiation of 2-(Benzotriazol-1-ylmethyl)-phenols and Subsequent Reactions with Electrophiles To Give Compounds 279

R	E^+	E	yield %
H	MeI	Me	35[203]
H	PhCHO	PhCH(OH)	68[257]
H	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	60[202]
H	*n*-BuI	*n*-Bu	36[202]
H	*i*-PrCHO	*i*-PrCH(OH)	74[131]
H	*n*-$C_8H_{17}CHO$	*n*-$C_8H_{17}CH(OH)$	35[131]
H	$Ph_2C{=}O$	$Ph_2C(OH)$	85[131]
Me	MeI	Me	71[257]
Me	*n*-BuI	*n*-Bu	50[257]
Me	CO_2	CO_2H	71[257]
Me	Ph_2CO	$Ph_2C(OH)$	62[257]

is lithiated and the anion quenched with alkyl halides to afford products **282a**,**b** (Scheme 98).[204] Reaction

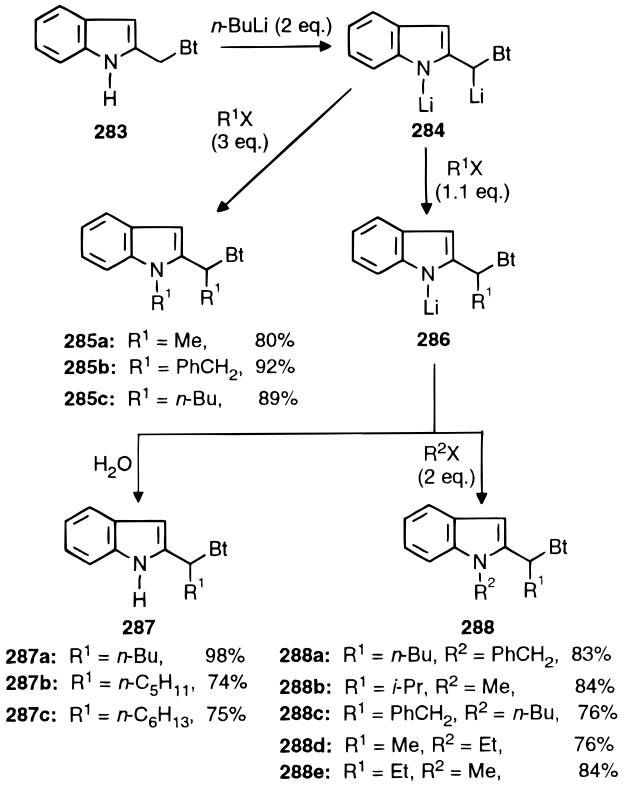
Scheme 98. Lithiation of 3-(Benzotriazol-1-ylmethyl)-1-methylindole



with α,β-unsaturated ketones leads to γ-benzotriazolyl-substituted ketones which are used for further transformations without isolation (see section IV.C.3.b).[205]

N-Unsubstituted 2-(benzotriazol-1-ylmethyl)indole **283**, unavailable by the conventional condensation

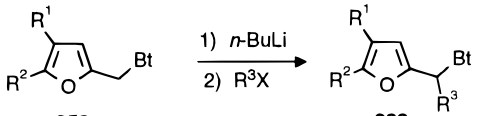
Scheme 99. Lithiation of 2-(Benzotriazolylmethyl)-indole and Subsequent Reactions with Electrophiles



method used for the preparation of its 3-substituted analogue but prepared by ring synthesis, also undergoes deprotonation at the methylene group.[206] Treatment of **283** with 2 equiv of *n*-butyllithium affords dianion **284** which gives dialkylated products **285** when quenched with excess of alkyl halides, or monoalkylated products **287** with 1 equiv of alkylating agents. Further treatment of intermediate **286** with different alkyl halides provides adducts **288** with different alkyl groups attached to the nitrogen atom and to the methylene carbon (Scheme 99).

Successful elaboration of this type is also achieved with 2-(benzotriazol-1-ylmethyl)furans **253** to give products **289** (Scheme 100).[183]

Scheme 100. Lithiation of 2-(Benzotriazol-1-ylmethyl)furans and Subsequent Reactions with Electrophiles

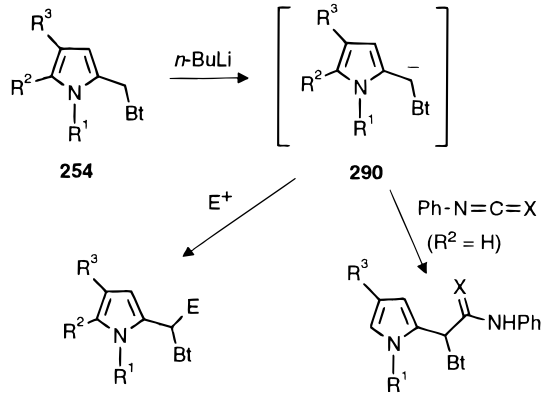


253 289

289a: R^1 = Ph, R^2 = H, R^3 = $PhCH_2$, 87%
289b: R^1 = 2-naphthyl, R^2 = H, R^3 = *i*-Pr, 78%
289c: R^1 = Ph, R^2 = Me, R^3 = *n*-Bu, 65%
289d: R^1 = R^2 = R^3 = Me, 82%

Although it is well-known that *N*-substituted pyrroles smoothly undergo lithiation at the 2 position of the heteroaromatic ring, deprotonation of pyrroles **254** (R^2 = H) occurs regiospecifically at the carbon attached to the benzotriazolyl group due to the electron-withdrawing ability of the benzotriazolyl moiety. Subsequent quenching with the appropriate electrophile, such as methyl iodide, phenyl isocyanate, or phenyl isothiocyanate, yields the corresponding products **291** and **292** in high yields (Scheme 101).[184]

Scheme 101. Lithiation of 2-(Benzotriazolylmethyl)pyrroles and Subsequent Reactions with Electrophiles



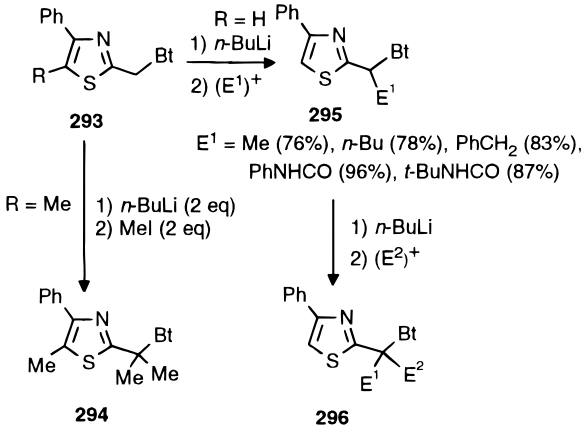
254 290 291 292

291a: R^1 = $PhCH_2$, R^2 = H, R^3 = Ph, E = Me, 98%
291b: R^1 = $(CH_2)_2OMe$, R^2 = Me, R^3 = Ph, E = *n*-Bu, 77%
292a: X = O, R^1 = $PhCH_2$, R^3 = Ph, 87%
292b: X = S, R^1 = *n*-Bu, R^3 = *t*-Bu, 94%

1,4-Nucleophilic addition of lithiated 2-(benzotriazolylmethyl)-substituted pyrroles **254** to α,β-unsaturated ketones and aldehydes affords isolable 2-(4-oxo-1-benzotriazolylalkyl)pyrroles **1086** (see Scheme 336), which generally are used directly for further transformations (see section IV.C.3.b).[185]

Lithiation of 2-(benzotriazol-1-ylmethyl)thiazoles **293** occurs exclusively at the methylene group, an indication of strong activating ability of a benzotriazole group (Scheme 102).[207] Use of 2 equiv of both

Scheme 102. Lithiation of 2-(Benzotriazol-1-ylmethyl)thiazoles and Subsequent Reactions with Electrophiles



293 295

E^1 = Me (76%), *n*-Bu (78%), $PhCH_2$ (83%), PhNHCO (96%), *t*-BuNHCO (87%)

294 (56%) 296

296a: E^1 = Me, E^2 = Me, 89%
296b: E^1 = Me, E^2 = *n*-Bu, 86%
296c: E^1 = Me, E^2 = $PhCH_2$, 93%

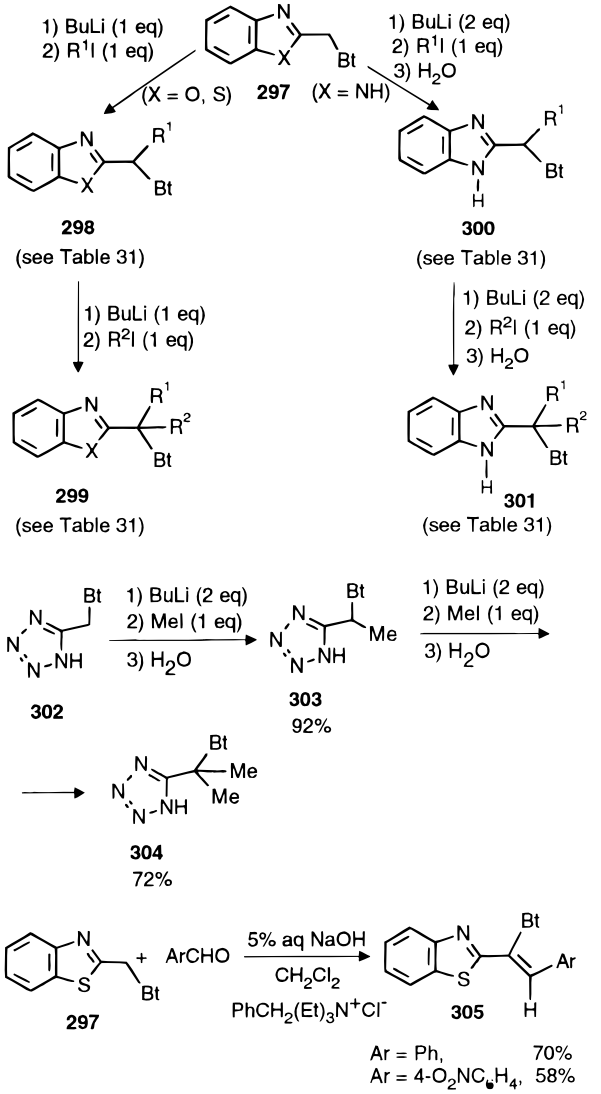
n-butyllithium and an electrophile gives the disubstituted product **294** in one pot, while 1 equiv of *n*-butyllithium and of an electrophile affords the monosubstituted product **295**, which can be further treated with *n*-butyllithium and a different electrophile to thus allow the introduction of two different groups in a controllable manner.

Bis(azolo)methanes **297** (X = O, S) (for preparation see section III.E.4) readily react with 1 equiv of butyllithium at −100 °C to form the corresponding *C*-anions. Subsequent addition of 1 equiv of alkyl iodide then gives the monoalkyl-substituted derivatives **298** in good yields[208] (Scheme 103, Table 31). Raising the reaction temperature to −78 °C causes the formation of the mixtures of mono- and dialkylated products **298** and **299** (R^1 = R^2) in ratio ∼3:1. The introduction of a second alkyl group into a molecule can be achieved by the repetition of lithia-

Table 31. Preparation of Substituted Benzazolyl(benzotriazol-1-yl)methanes 298−301

compound	X	R^1	R^2	yield %
298	O	Me		92
	O	*n*-C_5H_{11}		80
	O	*n*-C_8H_{17}		85
	S	*n*-Bu		43
	S	*n*-C_8H_{17}		72
299	O	Me	Me	32
	O	*n*-C_5H_{11}	*n*-C_5H_{11}	40
	O	*n*-C_8H_{17}	*n*-C_8H_{17}	38
	S	Me	Me	35
	S	*n*-Bu	*n*-Bu	35
	S	Me	*n*-C_7H_{15}	40
300	NH	Me		68
	NH	*n*-Bu		57
	NH	*n*-C_8H_{17}		62
301	NH	*n*-Bu	*n*-Bu	40

Scheme 103. Deprotonation of (1,3-Benzazol-2-yl)- and (1,2,3,4-Tetrazol-5-yl)(benzotriazol-1-yl)methanes and Subsequent Reactions with Electrophiles



tion−alkyl iodide quenching procedure. Benzimidazole (**297**, X = NH) or tetrazole (**302**) derivatives can be alkylated in a similar manner, with exception that 2 equiv of organolithium reagent are required. Due to the high acidity of methylene protons in **297**, deprotonation of these compounds can be carried out even with aqueous alkali under phase-transfer conditions (Scheme 103).[208]

Scheme 104. Lithiation of 2-Amino-5-(benzotriazol-1-ylmethyl)pyridine and Subsequent Reactions with Electrophiles

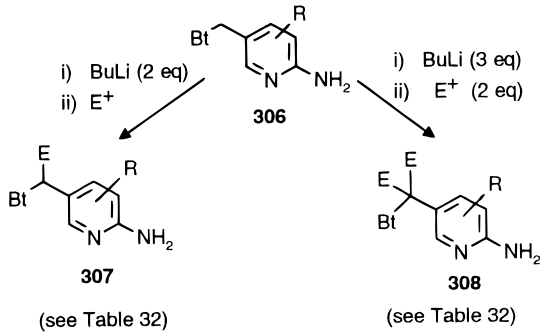


Table 32. Preparation of 5-Substituted 2-Aminopyridines 307 and 308

compound	R	E	yield %
307	3-Me	Et	60
	3-Me	*i*-Pr	78
	3-Me	3-methylbutyl	61
	3-Me	*n*-C_8H_{17}	65
	4,6-di-Me	Et	59
	3-Me	PhCH(OH)	53
	3-Me	$Ph_2C(OH)$	72
	3-Me	$Me_2C(OH)$	69
	4-Me	$Me_2C(OH)$	66
308	3-Me	Et	85
	4-Me	3-methylbutyl	78
	3-Me	*n*-C_8H_{17}	81
	3-Me	(1) Et, (2) *n*-Pr	60

Treatment of 2-amino-5-(benzotriazol-1-ylmethyl)-pyridines **306** with 2 equiv of *n*-butyllithium in THF at −78 °C followed by 1 equiv of an electrophile results in monosubstitution of the methylene hydrogen, while with 3 equiv of *n*-butyllithium and 2 equiv of an electrophile both of the methylene hydrogens can be displaced[209] (Scheme 104, Table 32).

4. Bt−CH=C and Bt−CH=C=C

a. Vinylbenzotriazoles. 1-Vinylbenzotriazoles **309** undergo lithiation at the α carbon and the anion can be quenched with various electrophiles to give **310**.[24] When an alkyl substituent is attached to the β carbon (R^1 or $R^2 \neq H$), the lithiation does not occur at the allylic position, but still at the α carbon (Scheme 105, Table 33).[24,189] Lithiation of 1,1-propylidenebenzo-

Scheme 105. Lithiations of 1- and 2-Vinylbenzotriazoles and Subsequent Reactions with Electrophiles

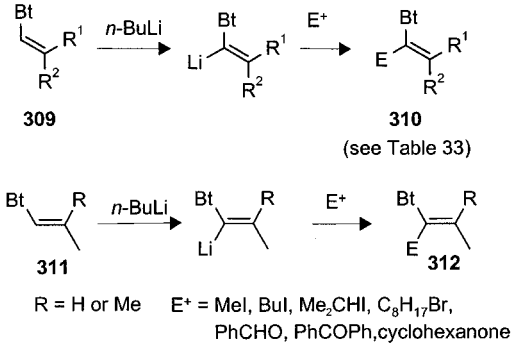


Table 33. Products 310 from the Lithiation of 1- and 2-Vinylbenzotriazoles and Subsequent Reaction with Electrophiles

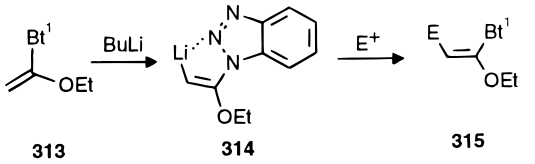
Bt	R^1	R^2	E^+	E	yield %
Bt^1	H	H	MeI	Me	44[24]
Bt^1	H	H	Ph_2CO	$Ph_2C(OH)$	32[24]
Bt^1	H	H	*n*-BuI	*n*-Bu	48[24]
Bt^1	H	H	*n*-$C_6H_{13}I$	*n*-C_6H_{13}	40[24]
Bt^1	H	Me	MeI	Me	78[24]
Bt^1	Me[a]	H[a]	MeI	Me	68[24]
Bt^1	Me[a]	H[a]	Ph_2CO	$Ph_2C(OH)$	76[24]
Bt^2	H	Me	MeI	Me	82[24]
Bt^2	Me[a]	H[a]	MeI	Me	84[24]
Bt^1	$-(CH_2)_5-$		D_2O	D	94[189]
Bt^1	$-(CH_2)_5-$		MeI	Me	90[189]
Bt^1	$-(CH_2)_5-$		*n*-$C_6H_{13}I$	*n*-C_6H_{13}	76[189]
Bt^1	$-(CH_2)_5-$		4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	74[189]

[a] Mixtures of *trans* and *cis* isomers are used.

triazole **311** occurs at the methine group, and quenching the anion with various electrophiles gives the corresponding substitution products **312** in good to moderate yields (Scheme 105).[210]

1-(α-Ethoxyvinyl)benzotriazole (**313**) is deprotonated at the β position and subsequent reaction with electrophiles gives exclusively the *E* isomers **315** probably due to chelation of the lithium atom with the benzotriazole nitrogen[211] (Scheme 106).

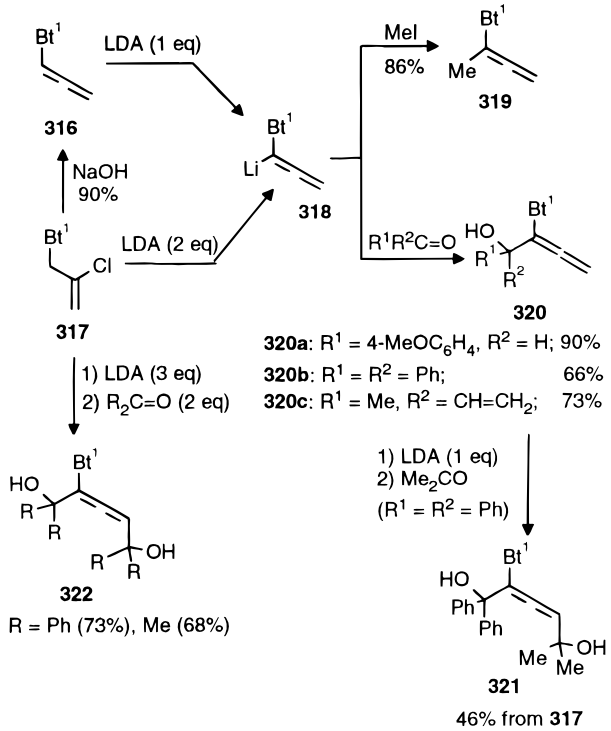
Scheme 106. Lithiation of 1-(α-Ethoxyvinyl)-benzotriazole and Subsequent Reactions with Electrophiles



315a: E = Me; 58%
315b: E = $PhCH_2$; 64%
315c: E = Me_3Si; 77%
315d: E = $(CH_2)_5C(OH)$; 35%
315e: E = 3-$MeC_6H_4CH(OH)$; 43%

b. Allenylbenzotriazoles. 1-Allenylbenzotriazole (**316**), available from 3-(benzotriazol-1-yl)-2-chloropropene (**317**),[212] is lithiated at the α position. Alternatively, **317** is treated directly with 2 equiv of LDA to form the same anion **318**, which reacts with methyl iodide to give **319**. The anion is also quenched with an aldehyde or ketone followed by addition of 1 equiv of LDA and of ketone to allow introduction of two different alcohols at the α and γ positions giving **321**. When the chloro derivative **317** is treated with 3 equiv of LDA followed by 2 equiv of a ketone, the same alcohol functionality is introduced at both the α and γ position to form **322** (Scheme 107).

Scheme 107. Lithiation of 1-Allenylbenzotriazole and Subsequent Reactions with Electrophiles

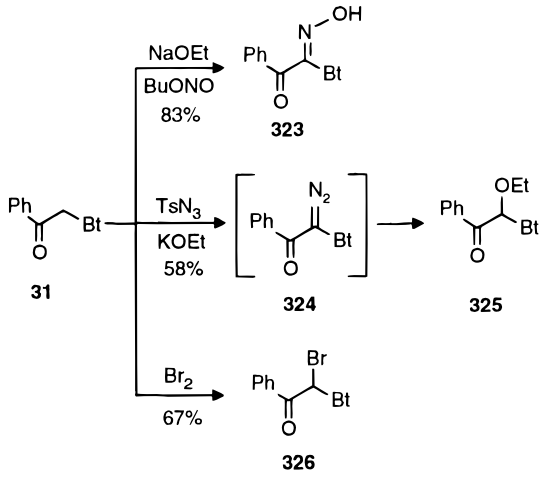


320a: R^1 = 4-$MeOC_6H_4$, R^2 = H; 90%
320b: $R^1 = R^2$ = Ph; 66%
320c: R^1 = Me, R^2 = $CH{=}CH_2$; 73%

5. *Bt—CH—C═X*

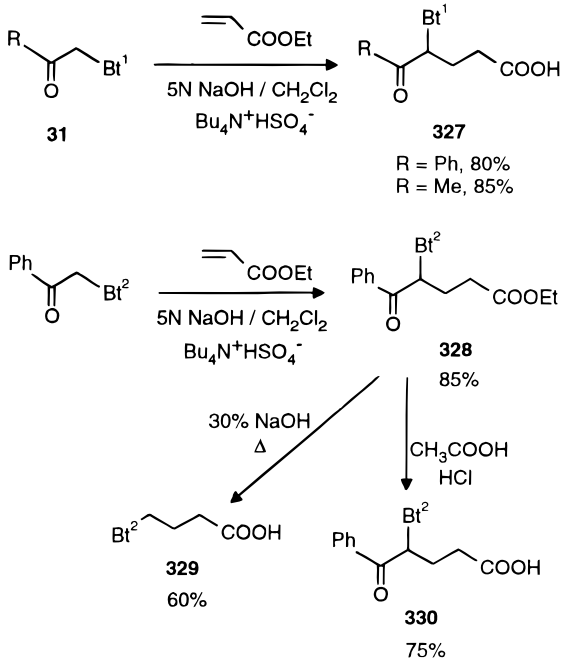
a. $BtCH_2COR$. The anion-stabilizing ability of a carbonyl group renders the methylene protons in $BtCH_2COPh$ highly acidic, which allows for reactions with NaOEt and butyl nitrite to give **323**, with *p*-toluenesulfonyl azide in the presence of alkoxides to give **325**, or with bromine in the absence of a base to form **326**[213] (Scheme 108). The formation of compound **325** probably occurs via displacement of N_2^- in **324** by an ethanol.

Scheme 108. Reactions of 1-Phenacylbenzotriazole



Alkylation of 1-(acylmethyl)benzotriazoles **31** with ethyl acrylate under phase-transfer catalysis affords the corresponding δ-oxo carboxylic acids **327** (Scheme 109) in high yields.[26] A similar reaction with Bt^2 isomer (R = Ph) leads to ester **328**, which upon basic hydrolysis eliminates benzoyl group together with

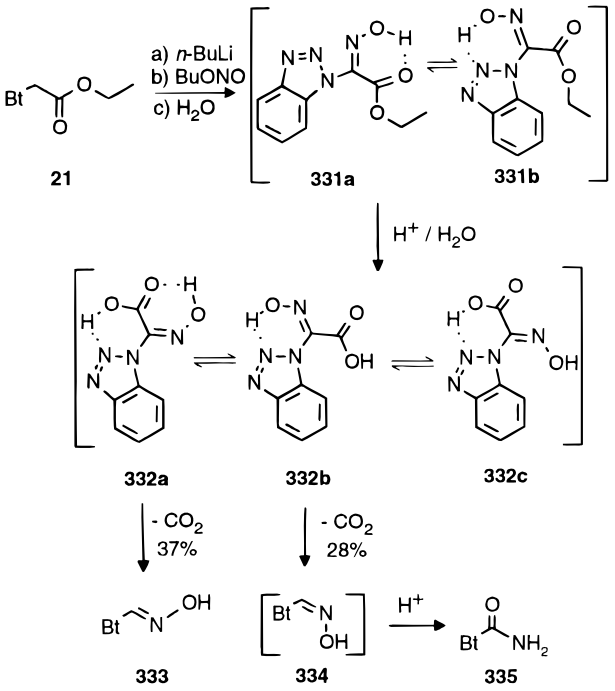
Scheme 109. Addition of 1-(Acylmethyl)benzotriazoles to Electron-Deficient Olefins



ethoxy group to give acid **329**. Elimination of benzoyl moiety can be prevented by using acidic conditions. Thus, acid-catalyzed hydrolysis of **328** gives the expected acid **330**.

Treatment of ethyl (benzotriazol-1-yl)acetate (**21**) with *n*-BuLi followed by butyl nitrite gives oxime **333** or amide **335**[213] (Scheme 110). The initial reaction

Scheme 110. Reactions of Ethyl 2-(Benzotriazol-1-yl)acetate



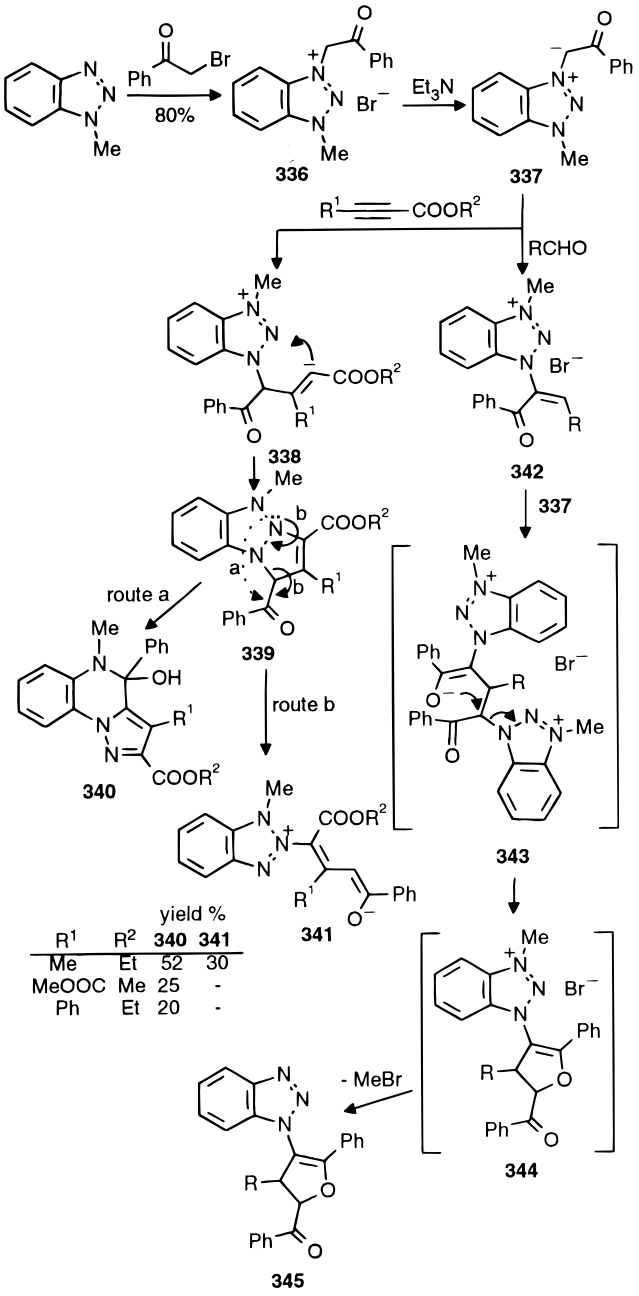
involves the formation of oximes **331a** and **331b** which are stabilized through intramolecular hydrogen bonding with either the benzotriazole nitrogen or the ester carbonyl group. Hydrolysis of the ester group under acidic conditions followed by decarboxylation gives either the (*E*)-oxime **333** or the (*Z*)-oxime **334** which undergoes Beckmann rearrangement to form amide **335** in 28% yield.

Similar deprotonation occurs with 3-methyl-1-phenacylbenzotriazolium bromide (**336**)[214] (Scheme 111). Ylide **337**, readily formed by treatment with triethylamine, adds to acetylenic esters to form hetero pyrazoloquinoxalines **340** and to aldehydes to form 4,5-dihydrofurans **345**.

b. Bt−CH−C≡N. Activated by both a benzotriazole moiety and a cyano group, the methylene carbon undergoes lithiation easily.[215] Quenching the anion with alkyl halides leads to products with monoalkylation (**347**) as the major and dialkylation (**348**) as the minor component. When an aldehyde or a ketone is used as the electrophile, the alcohol formed eliminates a molecule of water forming alkenes **346** (Scheme 112).

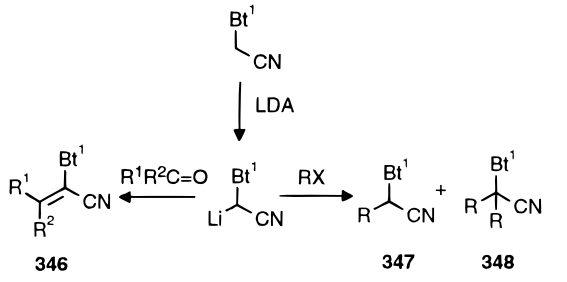
c. Bt−CH$_2$COOH. Although the preparation of 2-substituted vinamidinium salts from the corresponding substituted acetic acids under Vilsmeier−Haack conditions is a well-known process, benzotriazole-containing vinamidinium salts were synthesized only in 1993[21] by treatment of 2-benzotriazol-1-ylacetic acid with phosphorus oxychloride

Scheme 111. Reactions of 3-Methyl-1-Phenacylbenzotriazonium Bromide



R1	R2	yield % 340	341
Me	Et	52	30
MeOOC	Me	25	-
Ph	Et	20	-

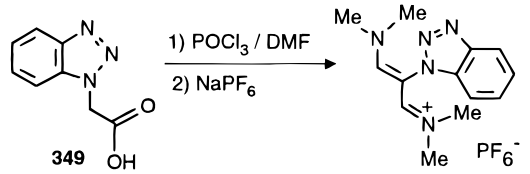
Scheme 112. Lithiation of 1-(Cyanomethyl)benzotriazole and Subsequent Reactions with Electrophiles



346a: R^1 = H, R^2 = Ph; 34%
346b: R^1 = H, R^2 = 4-MeC_6H_4; 55%
346c: R^1 = H, R^2 = *c*-C_6H_{11}; 64%
346d: R^1 = R^2 = Ph; 81%

R	yield % 347	348
Me	59	16
$PhCH_2$	40	23
n-Bu	57	33

Scheme 113. Preparation of 2-Benzotriazol-1-yl)-vinamidinium Salt



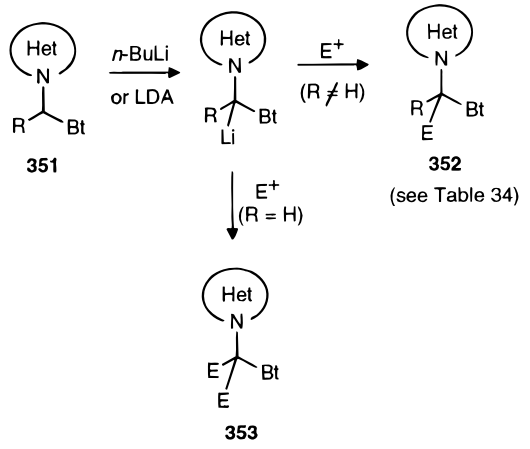
350
89%

in DMF (Scheme 113). The salt **350** obtained by this procedure is stable and can be used successfully for a number of cyclization reactions (see section III.E.2).

6. Bt–CH–N

a. N-(Benzotriazolylmethyl)heterocycles. Additional activation of the C-α hydrogens is provided by an *N*-linked heterocycle such as pyrrole[216] indole[198,216,217] carbazole[198,216,218−221] and a second benzotriazole.[222,223] These substrates can be easily prepared by reaction of the appropriate N−H heterocycle with 1-(chloromethyl)benzotriazole under basic conditions (see Scheme 143, section III.B.2). Lithiation of *N*-(benzotriazolylmethyl)heterocycles occurs readily at the C-α position and the anions formed are trapped with various electrophiles to give **352** (Scheme 114

Scheme 114. Lithiation of *N*-(Benzotriazol-1-yl-methyl)heterocycles and Subsequent Reactions with Electrophiles

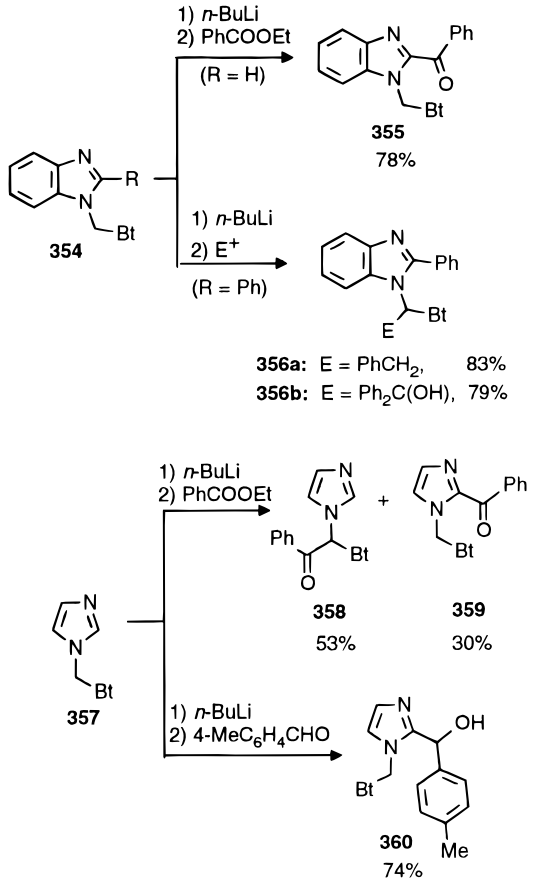


353a: Het = Pyrrol-1-yl, E = Me_3Si; 36%
353b: Het = Pyrrol-1-yl, E = PhS; 67%
353c: Het = Bt[1], E = N_3; 22%

and Table 34). For α-substituted (benzotriazol-1-ylmethyl)heterocycles, when aldehydes are used as electrophiles, trimethylsilyl chloride needs to be added and the products isolated are the trimethylsilyl ethers from the initially formed alcohols. With some of the (benzotriazol-1-ylmethyl)heterocycles, disubstituted products **353** are obtained when trimethylsilyl chloride, phenyl disulfide, and *p*-tosyl azide are used as electrophiles.[216,224]

When the second heterocycle is imidazole, benzimidazole, or 1,2,4-triazole the ring deprotonation of these heterocycles competes with the lithiation at the C-α position, sometimes leading to complex mixtures as in the lithiation of 1-(1,2,4-triazol-1-ylmethyl)-benzotriazole.[216] For example, 1-(benzotriazol-1-ylmethyl)benzimidazole, when lithiated and quenched with ethyl benzoate, gives the ring-substituted product, 1-(benzotriazol-1-ylmethyl)-2-benzoylbenzimidazole **355** in 78% yield (Scheme 115). When the

Scheme 115. Lithiation of *N*-(Benzotriazol-1-yl-methyl)benzimidazole and -imidazole and Subsequent Reactions with Electrophiles



benzimidazole 2 position is blocked by a phenyl group, lithiation occurs at the C-α position to give **356**. 1-(Imidazol-1-ylmethyl)benzotriazole (**357**), upon successive treatment with *n*-BuLi and ethyl benzoate, gives a mixture of products with substitution at the C-α **358** and at the 2 position of the imidazole ring **359**. However, *p*-tolualdehyde as electrophile yields only the 2-substituted product **360**.[216]

The steric hindrance of a third heterocyclic ring does not prevent the lithiation but does have influence on the subsequent quenching with certain types of electrophiles. Trisbenzotriazol-1-ylmethane undergoes a normal lithiation at the methine carbon, and the anion can be quenched with primary halides, acyl chlorides, aldehydes, and isothiocyanates to give the expected products **361**[225] (Scheme 116, Table 35). Again, as for the lithiation of substituted *N*-(benzotriazolylmethyl)heterocycles, the reaction with aldehydes requires protection (or stabilization) of the hydroxy group of the product by reaction with trimethylsilyl chloride. Reactions do not occur with secondary halides or with ketones, probably due to steric hindrance.

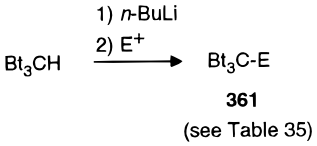
Table 34. Products 352 from Reactions of Lithiated *N*-(Benzotriazolalkyl)heterocycles with Electrophiles

heterocycle	R	E^+	E	yield %
pyrrol-1-yl	H	$PhCH_2Br$	$PhCH_2$	47[216]
pyrrol-1-yl	H	Me_3SiCl	Me_3Si	13[216]
pyrrol-1-yl	H	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	35[216]
pyrrol-1-yl	H	Ph_2CO	$Ph_2C(OH)$	72[216]
pyrrol-1-yl	H	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	76[216]
indol-1-yl	H	*n*-BuI	*n*-Bu	64[217]
indol-1-yl	H	$PhCH_2Br$	$PhCH_2$	86[216]
indol-1-yl	H	*i*-PrCOOEt	*i*-PrCO	95[216]
indol-1-yl	H	Me_2(*t*-Bu)SiCl	Me_2(*t*-Bu)Si	66[198]
indol-1-yl	H	PhCHO	PhCH(OH)	63[216]
indol-1-yl	H	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	71[216]
indol-1-yl	H	MeCHO	MeCH(OH)	45[216]
indol-1-yl	H	*i*-PrCHO	*i*-PrCH(OH)	98[216]
indol-1-yl	H	PhCOOEt	PhCO	88[216]
indol-1-yl	H	*n*-PrCOOEt	*n*-PrCO	84[216]
indol-1-yl	H	EtCOOMe	EtCO	68[216]
indol-1-yl	H	4-$BrC_6H_4CH_2Br$	4-$BrC_6H_4CH_2$	78[218]
carbazol-9-yl	H	*n*-$C_8H_{17}Br$	*n*-C_8H_{17}	71[218]
carbazol-9-yl	H	*n*-Bu	*n*-Bu	84[218]
carbazol-9-yl	H	*t*-BuCHO	*t*-BuCH(OH)	96[218]
carbazol-9-yl	H	Et_2CO	$Et_2C(OH)$	86[218]
carbazol-9-yl	H	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	91[218]
carbazol-9-yl	H	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	84[218]
carbazol-9-yl	H	PhNCS	PhNHCS	78[218]
carbazol-9-yl	H	PhNCO	PhNHCO	93[218]
carbazol-9-yl	H	Ph_2CO	$Ph_2C(OH)$	94[218]
carbazol-9-yl	H	$(i\text{-Pr})_3SiCl$	$(i\text{-Pr})_3Si$	92[198]
carbazol-9-yl	H	Me_3SiCl	Me_3Si	91[198]
carbazol-9-yl	H	Ph_3SiCl	Ph_3Si	95[198]
carbazol-9-yl	H	Me_2(*t*-Bu)SiCl	Me_2(*t*-Bu)Si	89[198]
carbazol-9-yl	H	$(i\text{-Bu})_3SiCl$	$(i\text{-Bu})_3Si$	90[198]
carbazol-9-yl	H	(*t*-Bu)Ph_2SiCl	(*t*-Bu)Ph_2Si	78[221]
carbazol-9-yl	$PhCH_2$	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	87[219]
carbazol-9-yl	$PhCH_2$	PhSSPh	PhS	95[219]
carbazol-9-yl	$PhCH_2$	PhCHO/Me_3SiCl	PhCH($OSiMe_3$)	67[219]
carbazol-9-yl	$PhCH_2$	*t*-BuCHO/Me_3SiCl	*t*-BuCH($OSiMe_3$)	85[219]
carbazol-9-yl	$PhCH_2$	$PhCH_2Br$	$PhCH_2$	86[219]
carbazol-9-yl	$PhCH_2$	MeI	Me	88[219]
carbazol-9-yl	$PhCH_2$	*n*-BuI	*n*-Bu	78[219]
carbazol-9-yl	$PhCH_2$	ClCOOEt	COOEt	87[219]
carbazol-9-yl	$PhCH_2$	PhNCO	PhNHCO	88[219]
carbazol-9-yl	$PhCH_2$	*t*-BuNCO	*t*-BuNHCO	84[219]
carbazol-9-yl	$PhCH_2$	2-cyclopentenone	cyclopentan-1-on-3-yl	76[219]
carbazol-9-yl	$PhCH_2$	2-cyclohexenone	cyclohexan-1-on-3-yl	81[219]
carbazol-9-yl	*n*-Bu	MeI	Me	91[219]
carbazol-9-yl	*n*-Bu	*n*-BuI	*n*-Bu	94[219]
carbazol-9-yl	*n*-Bu	PhNCO	PhNHCO	86[219]
carbazol-9-yl	*n*-Bu	PhSSPh	PhS	94[219]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	$PhCH_2Br$	$PhCH_2$	78[220]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	4-$BrC_6H_4CH_2Br$	4-$BrC_6H_4CH_2$	74[220]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	*n*-$C_6H_{13}I$	*n*-C_6H_{13}	86[220]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	*n*-$C_8H_{17}I$	*n*-C_8H_{17}	82[220]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	PhCHO/TMSCl	PhCH(OTMS)	61[220]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	4-MeC_6H_4CHO/TMSCl	4-MeC_6H_4CH(OTMS)	68[220]
carbazol-9-yl	$O(CH_2)_2NCH_2CH_2$	c-$C_6H_{11}CHO$/TMSCl	c-$C_6H_{11}CH$(OTMS)	57[220]
carbazol-9-yl	$(CH_2)_5NCH_2CH_2$	$PhCH_2Br$	$PhCH_2$	69[220]
carbazol-9-yl	$(CH_2)_5NCH_2CH_2$	*n*-$C_8H_{17}I$	*n*-C_8H_{17}	71[220]
benzotriazol-1-yl	H	$PhCH_2Br$	$PhCH_2$	46[218]
benzotriazol-1-yl	H	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	70[218]
benzotriazol-1-yl	H	4-MeC_6H_4COOEt	4-MeC_6H_4CO	76[218]
benzotriazol-1-yl	4-MeC_6H_4	MeI	Me	92[223]
benzotriazol-1-yl	4-MeC_6H_4	*i*-PrI	*i*-Pr	52[223]
benzotriazol-1-yl	4-MeC_6H_4	*n*-BuBr	*n*-Bu	78[223]
benzotriazol-1-yl	4-MeC_6H_4	*sec*-BuBr	*sec*-Bu	8[223]
benzotriazol-1-yl	4-MeC_6H_4	*n*-$C_6H_{13}I$	*n*-C_6H_{13}	52[223]
benzotriazol-1-yl	4-MeC_6H_4	*n*-$C_6H_{13}Br$	*n*-C_6H_{13}	83[223]
benzotriazol-1-yl	4-MeC_6H_4	$PhCH_2Br$	$PhCH_2$	95[223]
benzotriazol-1-yl	4-MeC_6H_4	allylbr	allyl	84[223]
benzotriazol-1-yl	4-MeC_6H_4	MeCOCl	MeCO	45[223]
benzotriazol-1-yl	4-MeC_6H_4	PhCOCl	PhCO	61[223]
benzotriazol-1-yl	4-MeC_6H_4	2-cyclohexenone	cyclohexan-1-on-3-yl	78[223]
benzotriazol-1-yl	4-MeC_6H_4	PhCHO/Me_3SiCl	PhCH($OSiMe_3$)	60[223]
benzotriazol-1-yl	4-MeC_6H_4	4-MeC_6H_4CHO/Me_3SiCl	4-MeC_6H_4CH($OSiMe_3$)	76[223]
benzotriazol-1-yl	4-MeC_6H_4	*n*-PrCHO/Me_3SiCl	*n*-PrCH($OSiMe_3$)	6[223]

Table 35. Products 361 from Lithiation of Tris(benzoltriazol-1-yl)methane and Subsequent Reactions with Electrophiles

E^+	E	yield %
$PhCH_2Br$	$PhCH_2$	92
$PhCH{=}CHCH_2Br$	$PhCH{=}CHCH_2$	84
PhCOCl	PhCO	98
$4\text{-}MeC_6H_4COCl$	$4\text{-}MeC_6H_4CO$	98
PhCHO/TMSCl	PhCH(OTMS)	91
$4\text{-}MeC_6H_4CHO$/TMSCl	$4\text{-}MeC_6H_4CH(OTMS)$	94
n-BuI	*n*-Bu	86
PhNCS	PhNHC(S)	90
1-naphthylNCS	1-naphthylNHC(S)	89
$PhCH_2NCS$	$PhCH_2NHC(S)$	80
$CS_2/PhCH_2Br$	$PhCH_2SC(S)$	58
ClCOOEt	COOEt	95

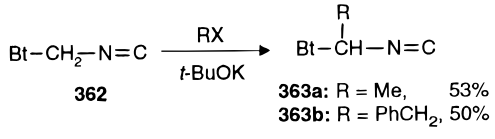
Scheme 116. Lithiation of Tris(benzotriazol-1-yl)-methane and Subsequent Reactions with Electrophiles



b. Bt−CH−NC. Benzotriazol-1-ylmethyl isocyanide (Betmic) (**362**), readily available from 1-[(formylamino)methyl]benzotriazole (for preparation see section II.B.2.c), reacts with aldehydes and ketones in the presence of potassium *tert*-butoxide to afford oxazoles **1170** and α-hydroxy aldehydes **1172**, respectively (see Scheme 365, section IV.E). Presumably, this reaction involves the initial abstraction of one of the acidic methylene protons in Betmic followed by reaction of the resulting anion with an aldehyde or a ketone and cyclization of the intermediate formed with simultaneous elimination of benzotriazole. Similar cycloadditions of Betmic or its α-substituted derivatives with aldimines and with electron-deficient olefins afford imidazoles **1173** and pyrroles **1174**, respectively (see Scheme 366, section IV.E).

α-Alkylated derivatives of Betmic **363** can be prepared in moderate yields by treatment of Betmic with alkyl or benzyl halides in the presence of potassium *tert*-butoxide (Scheme 117).[226]

Scheme 117. α-Alkylation of Benzotriazolylmethyl Isocyanide

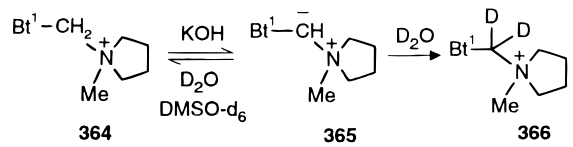


c. $BtCH_2N^+$. The methylene group adjacent to benzotriazole as in **364** (Scheme 118) can be deprotonated to form the *N*-ylide species **365** which react with D_2O to give **366**.[105] However, **365** does not undergo H−D exchange with KOH/D_2O/DMSO-d_6.

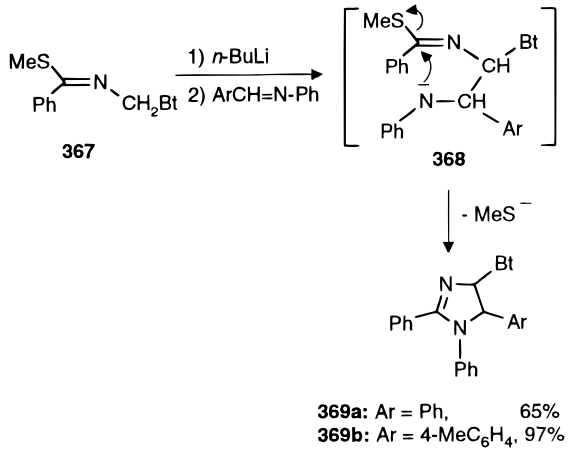
d. $Bt{-}CH_2{-}N{=}CR_2$. *N*-Arylmethylene[(benzotriazol-1-yl)arylmethyl]amines (**1175**) (see Scheme 367) are deprotonated with *n*-butyllithium to yield *N*-lithiated azomethine ylides **1176** which undergo 1,3-dipolar cycloaddition with a wide variety of dipolarophiles (see section IV.E).

Addition of deprotonated *N*-(benzotriazolylmethyl)-benzothioimidate (**367**) to the C=N bond of *N*-phenylarylimines generates the intermediate **368**, which undergoes intramolecular cyclization with simultaneous elimination of methylthio group to give the corresponding 4,5-dihydroimidazoles **369** in good yields (Scheme 119).[227]

Scheme 118. Hydrogen Exchange in (Benzotriazol-1-ylmethyl)ammonium Cations



Scheme 119. Lithiation of *N*-(Benzotriazolylmethyl)benzothioimidate and Subsequent Cyclization with Imines



e. Bt−CH−NH−C=O and Bt−CH−NR−C=O. By using 2 equiv of alkyllithium, *N*-(benzotriazol-1-ylmethyl) amides **370** undergo deprotonation initially at the amide nitrogen followed by deprotonation at the active α-methylene groups.[228a] Such amide-assisted lithiation has been reported previously for *N*-substituted amides and *N*,*N*-disubstituted amides [228b,229−232] The resulting dianion is then quenched with various electrophiles including alkyl halides, ketones, and esters (Scheme 120, Table 36). Some

Scheme 120. Lithiation of *N*-(Benzotriazol-1-ylmethyl) Amides and Subsequent Reactions with Electrophiles

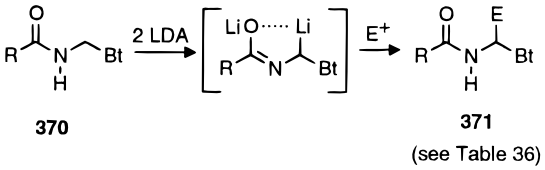


Table 36. Products 371 from Lithiation of *N*-(Benzotriazol-1-ylmethyl) Amides and Subsequent Reactions with Electrophiles

R	E	yield %	R	E	yield %
Ph	Me	78	Ph	$(CH_2)_5C(OH)$	74
Ph	Et	81	Ph	$4\text{-}MeC_6H_4CO$	82
Ph	*n*-Pr	80	*t*-Bu	Me	30
Ph	$PhCH_2$	76	*t*-Bu	$PhCH_2$	33
Ph	$CH_2{=}CHCH_2$	73			

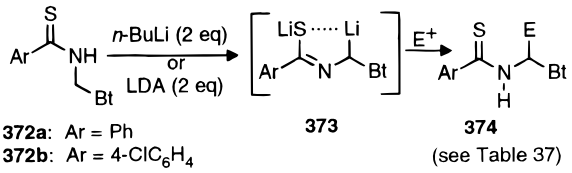
Table 37. Preparation of *N*-(Alkylbenzotriazolylmethyl)arenethioamides 374

Ar	E^+	E	yield %
Ph	EtBr	Et	95
Ph	*n*-BuBr	*n*-Bu	83
Ph	*n*-$C_7H_{15}Br$	*n*-C_7H_{15}	82
Ph	*n*-$C_8H_{17}Br$	*n*-C_8H_{17}	95
Ph	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	83
Ph	PhCHO	PhCH(OH)	62
Ph	*n*-$C_6H_{13}CHO$	*n*-$C_6H_{13}CH(OH)$	53
Ph	Me_2CO	$Me_2C(OH)$	40
4-ClC_6H_4	*n*-BuBr	*n*-Bu	65
4-ClC_6H_4	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	65

of the products obtained, e.g. by quenching with allyl bromide, cyclohexanone, and ethyl 4-methylbenzoate, are not readily available by the direct condensation of an amide, benzotriazole, and an aldehyde.[126]

f. Bt—CH—NH—C═S. Similarly to *N*-(benzotriazol-1-ylmethyl) amides, *N*-(benzotriazol-1-ylmethyl) thioamides **372** can undergo deprotonation with *n*-butyllithium or LDA to give the corresponding dianions which, upon quenching with electrophiles, afford a variety of highly functionalized derivatives **374** (Scheme 121, Table 37).[233] Considering the fact

Scheme 121. Lithiation of *N*-(Benzotriazolylmethyl)arenethioamides and Subsequent Reactions with Electrophiles

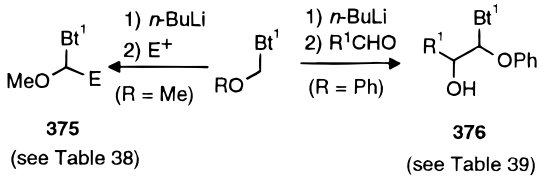


that sulfur is substantially less electronegative than oxygen, the formation of the cyclic dilithium intermediate **373** probably accounts for the easy deprotonation of the methylene group and for the preference of deprotonation over substitution when highly nucleophilic *n*-butyllithium is used as the base.

7. Bt–CH–O

1-(Methoxymethyl)benzotriazole undergoes deprotonation with *n*-butyllithium exclusively at the methylene proton[234,235] allowing a substitution at the methylene group. Among the electrophiles used are alkyl halides, aldehydes, ketones, and esters (Scheme 122, Tables 38 and 39). 1-(Phenoxymethyl)benzotriazole behaves rather similarly.[236]

Scheme 122. Lithiation of 1-(Methoxymethyl)- and 1-(Phenoxymethyl)benzotriazole



Application of this methodology to α-alkyl-substituted 1-(phenoxymethyl)benzotriazoles provides a convenient approach to the synthesis of α-(benzotriazolyl)phenoxyalkanes **377**, β-hydroxy-α-benzotriazolyl-α-phenoxyalkanes **378** and β-amino-α-benzotriazolyl-α-phenoxyalkanes **379** in high yields (Scheme

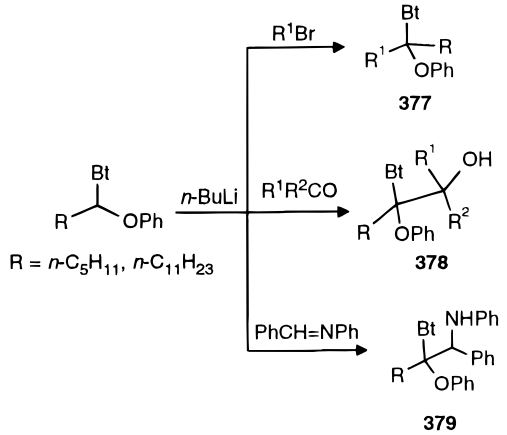
Table 38. Products 375 from Lithiation of 1-(Methoxymethyl)benzotriazole and Subsequent Reactions with Electrophiles

E^+	E	yield %
MeI	Me	85[234]
n-BuBr	*n*-Bu	80[234]
n-$C_{10}H_{21}Br$	*n*-$C_{10}H_{21}$	71[234]
$PhCH_2Br$	$PhCH_2$	81[234]
n-$C_8H_{17}Br$	*n*-C_8H_{17}	67[234]
Me_3SiCl	Me_3Si	75[234]
2-cyclohexenone	1-hydroxycyclohex-2-en-1-yl	45[234]
PhCHO	PhCH(OH)	53[234]
MeCHO	MeCH(OH)	80[234]
PhCOOEt	PhCO	91[235]
4-MeC_6H_4COOEt	4-MeC_6H_4CO	92[235]
$Ph(CH_2)_3Br$	$Ph(CH_2)_3$	91[235]
4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	82[235]
Ph_2CO	$Ph_2CH(OH)$	84[235]
t-BuCHO	*t*-BuCH(OH)	74[235]

Table 39. Products 376 from Lithiation of 1-(Phenoxymethyl)benzotriazole and Subsequent Reactions with Aldehydes

R	yield %	R	yield %
Ph	88	*n*-C_7H_{15}	61
4-MeC_6H_4	95	(*n*-Bu)EtCH	79
2-ClC_6H_4	77	c-C_6H_{11}	87
4-PhC_6H_4	82		

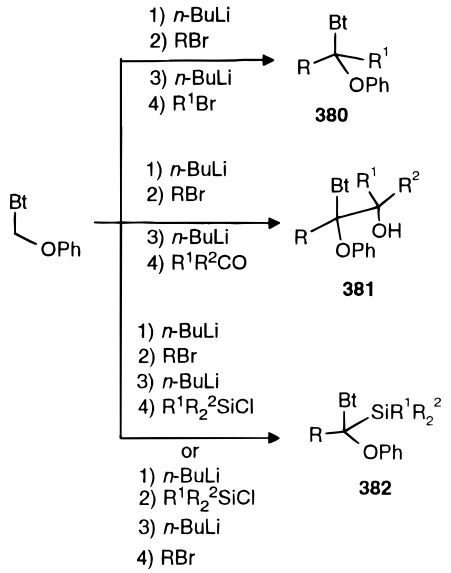
Scheme 123. Lithiation of 1-(α-Phenoxyalkyl)-benzotriazoles and Subsequent Reactions with Electrophiles



123).[237] Due to steric hindrance in the anion generated from 1-(1-phenoxyalkyl)benzotriazole, the size of an electrophile can significantly affect the composition of the products formed. For example, the anion prepared by deprotonation of 1-benzotriazolyl-1-phenoxyhexane (R = *n*-C_5H_{11}) undergoes regioselective 1,4-addition to 2-cyclohexenone, while the reaction with *trans*-chalcone affords the products of both 1,4- and 1,2-addition.[237] Generally, compounds **377**—**379**, although stable enough to be isolated, are subjected to acidic hydrolysis to prepare a wide variety of substituted ketones (see section IV.D.3).

Having two highly acidic α-methylene protons, 1-(phenoxymethyl)benzotriazole can be successfully used as a substrate in the double-lithiation technique with considerable flexibility. Successive treatment of 1-(phenoxymethyl)benzotriazole with 1 equiv of *n*-BuLi, 1 equiv of electrophile, another equivalent of *n*-BuLi and different electrophile allows preparation of highly substituted functionalized ethers **380**—

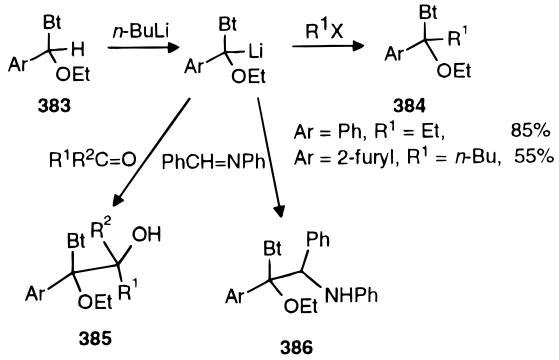
Scheme 124. Double-Lithiation Reactions of 1-(Phenoxymethyl)benzotriazole



382 (Scheme 124).[237] Among the electrophiles used are alkyl halides, aldehydes, ketones, and trialkylsilyl chlorides. Compounds **380**−**382** are usually hydrolyzed directly to the corresponding carbonyl compounds (see section IV.D.3).

Treatment of α-(benzotriazol-1-yl)arylmethyl ethyl ethers **383** with *n*-butyllithium followed by electrophiles gives the corresponding adducts **384**, **385**, and **386**[80,188] which can be isolated (see Scheme 125 for

Scheme 125. Lithiation of α-(Benzotriazol-1-yl)arylmethyl Ethyl Ethers



two examples) but usually are directly subjected to acid hydrolysis without isolation (see section IV.D.3).

1-(α-Ethoxyallyl)benzotriazole (**89**) has been shown to be a highly versatile synthon equivalent for a variety of organic transformations.[77,78,181,238] With additional activation from the allyl group, **89** readily undergoes lithiation at the α carbon and the resulting anion **387** is trapped with a wide spectrum of electrophiles. The outcome of these reactions depends significantly on the reaction conditions and on the electrophile used. Alkyl halides and esters give the normal α-alkylated or acylated products[77,238] (Scheme 126). Aldehydes and less sterically hindered aliphatic ketones form the intermediates **389** which can be (i) quenched with water to give the corresponding alcohols **390**, (ii) quenched with trimethylsilyl chloride to give the siloxy derivatives **391**,[77,78] or (iii)

Scheme 126. Lithiation of 1-(α-Ethoxyallyl)benzotriazole and Subsequent Reactions with Electrophiles

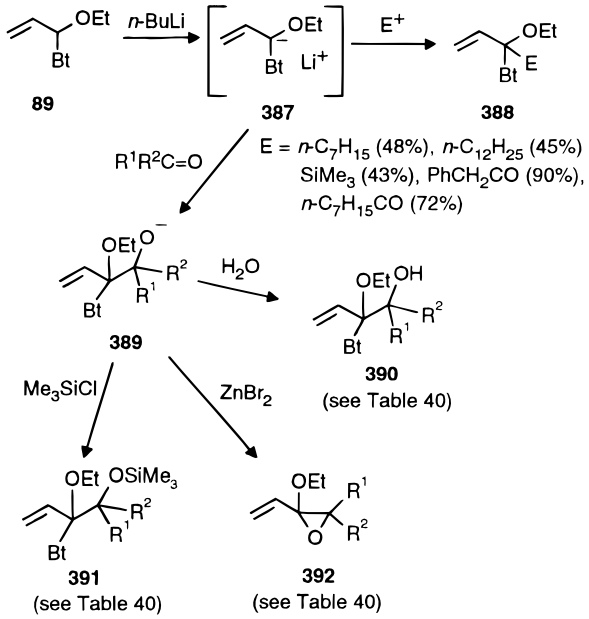


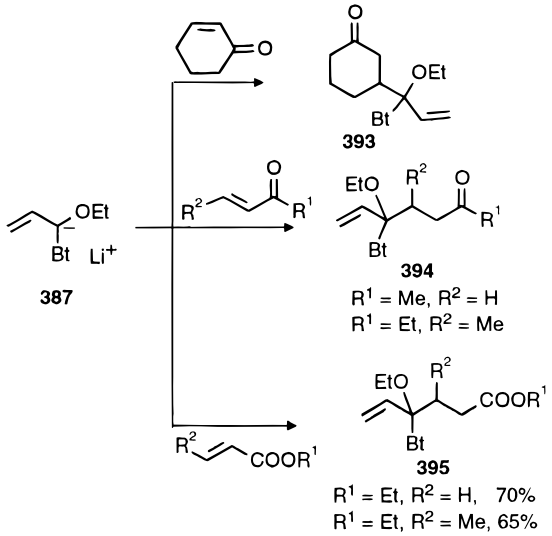
Table 40. Preparation of Adducts 390−392 from 1-(α-Ethoxyallyl)benzotriazole

compound	R^1	R^2	yield %	compound	R^1	R^2	yield %
390	4-MeC_6H_4	H	46[77]	**391**	4-MeC_6H_4	Ph	*a*[238]
	4-ClC_6H_4	H	48[77]		4-MeC_6H_4	Me	*a*[238]
	$PhCH_2$	H	48[77]		Ph	Me	*a*[238]
	$-(CH_2)_5-$		75[78]	**392**	$-(CH_2)_5-$		72[78]
	Ph	Me	55[78]		*n*-Bu	Me	65[78]

[a] Products not isolated but used directly for further transformations.

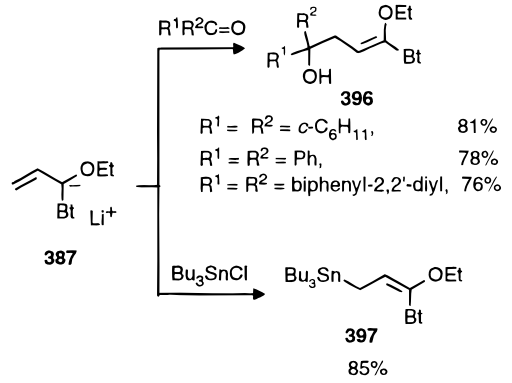
caused to undergo intramolecular cyclization via zinc bromide-promoted displacement of benzotriazole to form the corresponding epoxides **392** (see also section IV.B.6.a)[78] (Scheme 126, Table 40). Anion **387** adds regiospecifically to α,*β*-unsaturated ketones and esters to yield the corresponding 1,4-addition products[77,78,238] (Scheme 127).

Scheme 127. Lithiation of 1-(α-Ethoxyallyl)benzotriazole and Subsequent Reactions with α,*β*-Unsaturated Ketones and Esters



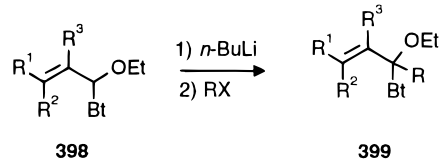
On the other hand, highly sterically hindered electrophiles, such as tributyltin chloride and bulky aliphatic and aromatic ketones tend to give the γ-alkylated products by reaction at the less sterically hindered terminal carbon atom[77,78] (Scheme 128).

Scheme 128. Lithiation of 1-(α-Ethoxyallyl)benzotriazole and Subsequent Reactions with Electrophiles (Part 2)



3-Mono- and 3,3-disubstituted *N*-(α-ethoxyallyl)-benzotriazoles **398** also undergo lithiation and subsequent reactions with electrophiles to give the corresponding adducts **399** (Scheme 129).[181,188]

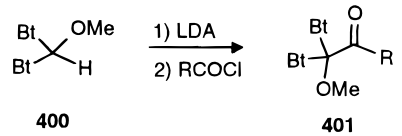
Scheme 129. Lithiation of 3-Mono- and 3,3-Disubstituted 1-(α-Ethoxyallyl)benzotriazoles and Subsequent Reactions with Electrophiles



399a: $R^1 = R^2 = n$-Bu, R^3 = H, R = n-C_5H_{11}, 50%
399b: $R^1 = R^2$ = Me, R^3 = H, R = $Me_2(n\text{-}C_8H_{17})Si$, 80%
399c: $R^1 = R^2 = n$-Bu, R^3 = H, R = $Me_2(n\text{-}C_8H_{17})Si$, 66%
399d: R^1 = H, R^2 = Ph, R^3 = Me, R = Me_3Si, 71%

Dibenzotriazol-1-ylmethoxymethane (**400**), with additional activation from the second benzotriazole group, affords a stable carbanion upon treatment with LDA. This anion, although less reactive compared with those generated from 1-(methoxymethyl)- and 1-(phenoxymethyl)benzotriazoles, does react with non-α-hydrogen-containing acid chlorides to give in good yields the corresponding carbonyl products **401**[239] (Scheme 130).

Scheme 130. Lithiation of Dibenzotriazolylmethoxymethane and Subsequent Reactions with Acyl Chlorides

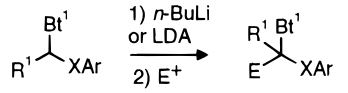


R = *t*-Bu (83%), Ph (76%), 2-MeC_6H_4 (54%), 4-$MeOC_6H_4$ (82%), 4-ClC_6H_4 (77%), 2-naphthyl (61%)

8. Bt–CH_2–S

1-Benzotriazol-1-ylalkyl thioethers **402a** react similarly as their oxygen analogues.[146,147,240−242] The sulfoxide **402b** and sulfone **402c** derivatives also undergo similar transformations[240] (Scheme 131). A

Scheme 131. Lithiation of 1-Benzotriazol-1-ylalkyl Thioethers, Sulfoxides, and Sulfones and Subsequent Reactions with Electrophiles



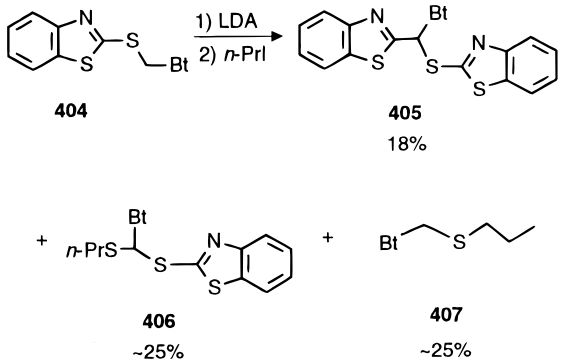
402a: X = S
402b: X = SO
402c: X = SO_2

403
(see Table 41)

substantial difference in yields is observed between using *n*-BuLi and LDA when 1-[(phenylsulfinyl)-methyl]benzotriazole is lithiated and quenched with benzyl chloride[240,243] (Table 41). When 2-(methylthio)benzothiazole is used as electrophile the substitution of methylthio group takes place.[244]

However, lithiation of 2-[(benzotriazolylmethyl)-thio]benzothiazole (**404**) with following treatment with alkyl halides does not give the expected alkyl-substituted products. Instead, in the reaction with *n*-propyl iodide, three products **405**, **406**, and **407** are isolated in nearly equal amounts (Scheme 132). The

Scheme 132. Lithiation of 2-[(Benzotriazolylmethyl)thio]benzothiazole and Subsequent Reaction with *n*-Propyl Iodide



formation of these compounds may be explained by preferable S−benzothiazole bond cleavage under lithiation conditions to provide $BtCH_2S^-$ anion, which then reacts with *n*-propyl iodide or with **404**.[244]

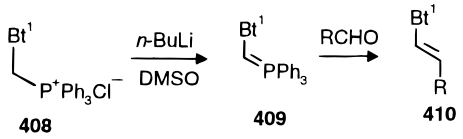
9. Bt–CH–P

The phosphonium compound **408**, easily prepared from 1-(chloromethyl)benzotriazole and triphenylphosphine, reacts with dimsyl anion (formed from BuLi and DMSO) in DMSO to give the phosphonium ylide **409**, which undergoes *in situ* Wittig-type reactions with aliphatic, aromatic, heteroaromatic, and α,β-unsaturated aldehydes to yield 1-(*trans*-1-alkenyl)-benzotriazoles **410** as the only products (Scheme 133).[245] The methylene carbon in (benzotriazol-1-ylmethyl)diphenylphosphine oxide **411** is easily deprotonated[175] and quenching the resulting anion with alkyl halides introduces alkyl groups at the α posi-

Table 41. Products 403 from Lithiation of 1-[α-(Arylthio)alkyl]benzotriazoles or Corresponding Sulfoxides or Sulfones, and Subsequent Reaction with Electrophiles

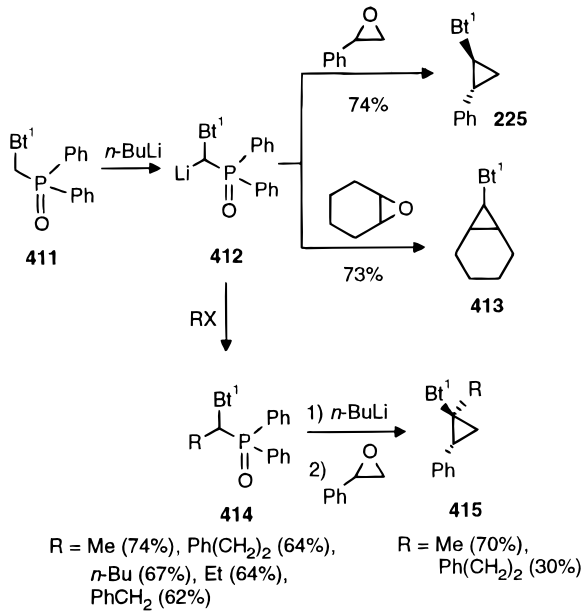
Ar	X	R^1	E^+	E	yield %
Ph	S	H	MeI	Me	49[240]
Ph	S	H	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	46[240]
Ph	S	H	$PhCH_2Br$	$PhCH_2$	79[147]
Ph	S	H	$PhCH_2Cl$	$PhCH_2$	68[240]
Ph	S	H	4-$MeC_6H_4CH_2Cl$	4-$MeC_6H_4CH_2$	74[147]
Ph	S	H	2-$PhC_6H_4CH_2Br$	2-$PhC_6H_4CH_2$	91[242]
Ph	S	H	PhCH=$CHCH_2Br$	PhCH=$CHCH_2$	89[242]
Ph	S	H	$Ph(CH_2)_2Br$	$Ph(CH_2)_2$	68[242]
Ph	S	H	$PhO(CH_2)_2Br$	$PhO(CH_2)_2$	84[242]
Ph	S	H	naphthyl-1-$(CH_2)_2Br$	naphthyl-1-$(CH_2)_2$	79[242]
Ph	S	H	$Ph(CH_2)_3Br$	$Ph(CH_2)_3$	89[242]
Ph	S	H	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	44[240]
Ph	S	H	Ph_2CO	$Ph_2C(OH)$	76[240]
Ph	S	H	2-(methylthio)benzothiazole	2-benzothiazolyl	92[244]
Ph	S	*n*-Pr	MeI	Me	99[146]
Ph	S	*n*-Pr	$PhCH_2Br$	$PhCH_2$	83[146]
Ph	S	*n*-Pr	PhCHO	PhCH(OH)	78[146]
Ph	S	*i*-Pr	$PhCH_2Br$	$PhCH_2$	92[146]
Ph	S	*i*-Pr	*n*-BuI	*n*-Bu	95[146]
Ph	S	*i*-Pr	MeI	Me	98[146]
Ph	S	Ph	EtI	Et	75[147]
Ph	S	Ph	*n*-BuI	*n*-Bu	80[147]
Ph	S	Ph	$PhCH_2Br$	$PhCH_2$	95[147]
Ph	S	Ph	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	65[241]
Ph	S	$PhCH_2$	MeI	Me	88[147]
Ph	S	$PhCH_2$	EtI	Et	70[147]
Ph	S	$PhCH_2$	*n*-BuI	*n*-Bu	86[147]
Ph	S	$PhCH_2$	*n*-$C_7H_{15}Br$	*n*-C_7H_{15}	86[147]
Ph	S	$PhCH_2$	$PhCH_2Br$	$PhCH_2$	83[147]
Ph	S	$PhCH_2$	4-$MeC_6H_4CH_2Cl$	4-$MeC_6H_4CH_2$	90[147]
Ph	S	4-$MeC_6H_4CH_2$	4-$MeC_6H_4CH_2Cl$	4-$MeC_6H_4CH_2$	80[147]
4-MeC_6H_4	S	H	$PhCH_2Br$	$PhCH_2$	81[147]
4-MeC_6H_4	S	$PhCH_2$	MeI	Me	81[147]
4-MeC_6H_4	S	$PhCH_2$	EtI	Et	70[241]
4-MeC_6H_4	S	4-$MeC_6H_4CH_2$	*n*-BuCl	*n*-Bu	81[241]
4-MeC_6H_4	S	$PhCH_2$	$PhCH_2Br$	$PhCH_2$	90[147]
4-MeC_6H_4	S	4-$MeC_6H_4CH_2$	4-$MeC_6H_4CH_2Cl$	4-$MeC_6H_4CH_2$	82[147]
Ph	SO	H	$PhCH_2Br$	$PhCH_2$	63[240]
Ph	SO_2	H	$PhCH_2Cl$	$PhCH_2$	44[240]
Ph	SO_2	H	$PhCH_2Br$	$PhCH_2$	73[240]

Scheme 133. Wittig Reactions of (Benzotriazol-1-ylmethyl)phosphonium Salts



R = *n*-Pr (30%), Ph (50%), 4-$O_2NC_6H_4$ (40%), 4-$Me_2NC_6H_4$ (98%), pyridin-4-yl (30%), Ph-CH=CH (56%)

Scheme 134. Reactions of (Benzotriazol-1-ylmethyl)diphenylphosphine Oxide Anions



R = Me (74%), $Ph(CH_2)_2$ (64%), *n*-Bu (67%), Et (64%), $PhCH_2$ (62%)

R = Me (70%), $Ph(CH_2)_2$ (30%)

tion. Similarly, the anions generated from **411** or from alkylated derivatives **414** react with epoxides leading exclusively to *trans*-1,2-disubstituted cyclopropanes **225**, **413**, and **415** (Scheme 134).

10. Bt–CH–Si: Deprotonation and Desilylation Reactions

The lithiation of 1-[(trimethylsilyl)methyl]benzotriazoles **416** with *n*-butyllithium occur exclusively at the α-methylene carbon.[189,245,246a] The anion is quenched with alkyl and silyl halides to yield products **417**. With aldehydes and ketones[189,246b] the Peterson olefination[246b] products **418** are obtained. The anion also undergoes 1,4-addition with cyclohexanone to yield a ketone derivative **419**. A methyl, phenyl, methoxy, or trimethylsilyl substituent at the methylene carbon does not affect the reactivity (Scheme 135, Table 42).

Scheme 135. Reactions of Anions Formed from 1-[(Trimethylsilyl)methyl]benzotriazole

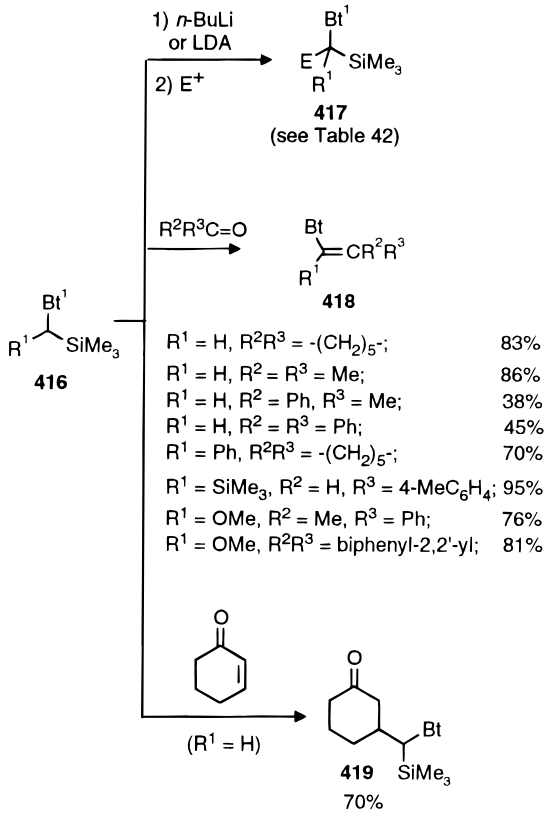
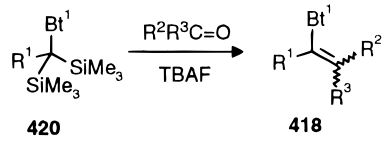


Table 42. Products 417 from Lithiation of 1-[α-(Trimethylsilyl)alkyl]benzotriazoles and Subsequent Reactions with Electrophiles

R^1	E^+	E	yield %
H	Me_3SiCl	Me_3Si	90[245]
H	MeI	Me	86[189]
H	n-$C_6H_{13}I$	n-C_6H_{13}	82[189]
H	$PhCH_2Br$	$PhCH_2$	81[189]
H	Me_3SiCH_2Cl	Me_3SiCH_2	83[189]
H	2-cyclohexenone	3-oxocyclohexan-1-yl	70[189]
Me	n-$C_6H_{13}I$	n-C_6H_{13}	80[189]
Me	$PhCH_2Br$	$PhCH_2$	71[189]
Me_3Si	MeI	Me	90[245]
Me_3Si	$PhCH_2Br$	$PhCH_2$	95[245]

Scheme 136. Desilylative Olefinations



R^1 = Me, R^2 = 4-MeC_6H_4, R^3 = H; 40%
R^1 = Me, R^2 = R^3 = Ph; 60%
R^1 = $PhCH_2$, R^2 = 4-MeC_6H_4, R^3 = H; 42%
R^1 = $PhCH_2$, R^2 = MeCH=CH, R^3 = H; 23%

Similar to the corresponding 1,2,4-triazole derivatives,[247,248] 1-[1-[α,α-bis(trimethylsilyl)alkyl]]benzotriazoles **420**, undergo fluoride-catalyzed alkylative desilylation (Peterson olefination) with tetrabutylammonium fluoride (TBAF).[245] The alkenes **418** are thus obtained as mixtures of *E* and *Z* isomers (Scheme 136).

Similar desilylation occurs with 1-[1-[α-(trimethylsilyl)alkyl]]benzotriazoles **421** (Scheme 137, Table 43).[189] With a slight excess of TBAF and no other reagents present, the trimethylsilyl group is replaced by hydrogen to yield 1-alkylbenzotriazoles **422**. With aldehydes or ketones present, addition of the anion to carbonyl group gives alcohols **423**. The desilylation can also be achieved in the absence of fluoride with the more reactive acyl chlorides to give **424**.

Scheme 137. Desilylations of 1-[1-[α-(Trimethylsilyl)alkyl]]benzotriazoles

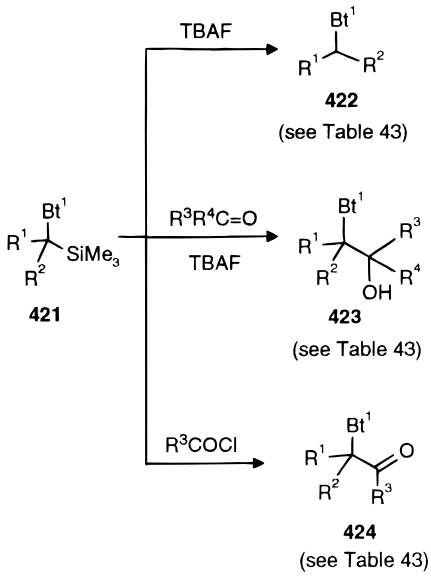


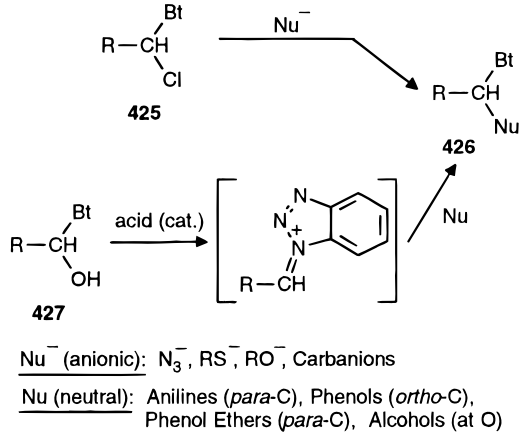
Table 43. Products 422−424 from Desilylation Reactions of 1-[α-(Trimethylsilyl)alkyl]benzotriazoles

compound	R^1	R^2	R^3	R^4	yield %
422	n-C_6H_{13}	H			73
	$PhCH_2$	H			79
	Me	n-C_6H_{13}			84
	Me	$PhCH_2$			82
423	H	H	$-(CH_2)_5-$		39
	H	H	4-MeC_6H_4	H	76
	Me	H	4-MeC_6H_4	H	72
	$PhCH_2$	H	n-Pr	H	73
	$PhCH_2$	H	4-MeC_6H_4	H	57
	Me	n-C_6H_{13}	4-MeC_6H_4	H	65
	Me	$PhCH_2$	$-(CH_2)_5-$		44
424	H	H	4-MeC_6H_4		72
	H	H	Me		73
	H	H	Ph		72
	H	H	$BtCH_2CO(CH_2)_4$		63
	H	H	$PhCH_2$		70
	Me	H	4-MeC_6H_4		77
	$PhCH_2$	H	4-MeC_6H_4		55

B. Substitutive Benzotriazolylalkylations

There are two main categories of such reactions as shown in Scheme 138. Thus, *N*-(α-haloalkyl)benzotriazoles **425** (and analogues) undergo the normal nucleophilic displacements with a variety of usual anionic nucleophiles such as RO^-, RS^-, N_3^-, and carbanions. On the other hand, the corresponding hydroxy derivatives **427** (and certain analogues) react with nucleophiles in the presence of an proton or Lewis acid catalyst which is used to promote the formation of a benzotriazole-stabilized cationic intermediate (Scheme 138).

Scheme 138. Substitution Reactions of 1-(α-Chloroalkyl)- and 1-(α-Hydroxyalkyl)benzotriazoles with Nucleophiles



1. Conversion of OH to Halogen

The conversion of OH in 1-(hydroxymethyl)benzotriazole to Cl by thionyl chloride has long been known.[222] This conversion has been extended to the general type of compounds **427** where $R^1 \neq H$.[90,249] The chlorides **425** can also be obtained in a one-pot process from the aliphatic aldehydes and benzotriazole (route B). Although chlorides **425** tend to eliminate a molecule of HCl to give **428** when there is an α-H available, they are generally stable when isolated (Scheme 139 and Table 44). The corresponding bromo and iodo analogues of 1-(chloromethyl)benzotriazole are easily obtained in 76% and 87%, respectively, by treatment of the latter with sodium bromide or iodide in acetone.[213] The fluoro derivatives **430** are obtained through one-pot reactions of benzotriazole, an aldehyde, and DAST [(diethylamido)sulfur trifluoride] (route D), but the yields are low.[250] Alternatively, the chloro derivatives **425** are treated with potassium fluoride in the presence of 18-crown-6, giving the corresponding fluoro derivatives **430** in much higher yields (Table 44).

Scheme 139. Conversions of 1-(α-Hydroxyalkyl)-benzotriazoles into 1-(α-Halogenoalkyl)-benzotriazoles

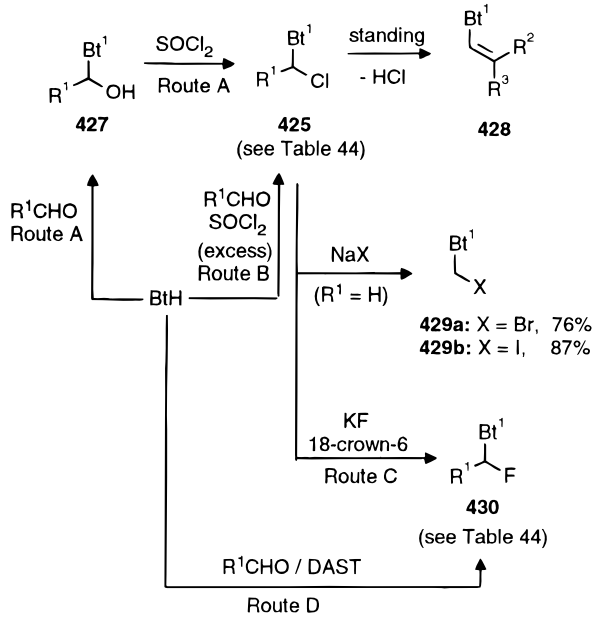


Table 44. Preparation of 1-(α-Haloalkyl)benzotriazoles 425 and 430

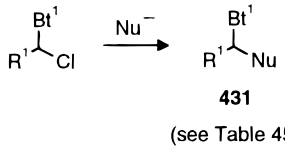
compound	R^1	yield %
425	Me	55[249]
	Et	52[249]
	n-Pr	100[249]
	i-Pr	51[249]
	t-Bu	82[249]
	n-C_8H_{17}	98[249]
	Bt^1-CH(Cl)	90[90]
430[a]	H	90[250]
	Me	73[250]
	Me	21 (route D)[250]
	Et	72[250]
	Pr	70[250]
	i-Pr	65[250]
	i-Pr	30 (route D)[250]
	t-Bu	86[250]

[a] Route C (Scheme 139) unless otherwise noted.

2. Halogen Displacement by H, O, S, Se, Te, N, P, or C Nucleophiles

The chloro atom in 1-(chloromethyl)benzotriazole is readily replaced (Scheme 140) by a wide range of nucleophiles[240] such as oxygen, sulfur, nitrogen (including pyridine derivatives),[105] phosphorus, and carbon nucleophiles. Further extention of this general type is shown by reactions of 1-(chloroalkyl)benzotriazoles with sodium or potassium alkoxides,[75,93] sodium phenoxide,[237] carboxylates,[82] sodium thiophenoxide,[90,146,147] sodium 2-mercaptobenzothiazolate,[244] sodium azide,[251,252] and oxime anions[94] (Table 45).

Scheme 140. Displacements of Chlorine in 1-(α-Chloroalkyl)benzotriazoles



Scheme 141. Preparation of 1-(Mercaptomethyl)-benzotriazole

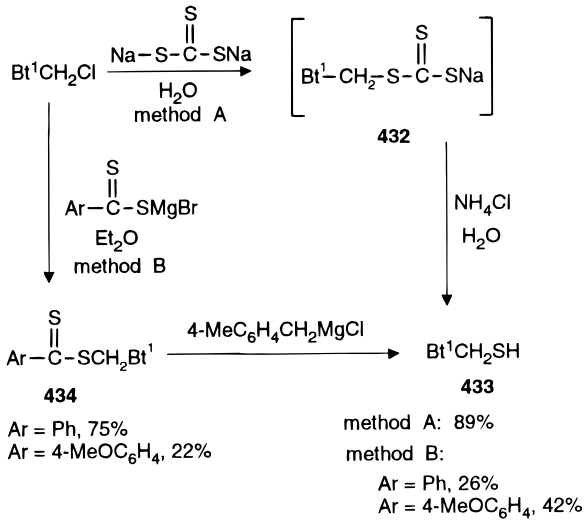


Table 45. Products 431 from Displacements of Chlorine in 1-(α-Chloroalkyl)benzotriazoles by Nucleophiles

R^1	Nu^-	Nu	yield %
H	EtONa	EtO	81[240]
H	PhONa	PhO	45[240]
H	MeONa	MeO	40[75]
H	*t*-BuOK	*t*-BuO	83[75]
H	$Me_2C{=}CHCH_2OK$	$Me_2C{=}CHCH_2O$	79[93]
H	$PhCH{=}CHCH_2OK$	$PhCH{=}CHCH_2O$	63[93]
H	$CH_2{=}CHCH(n\text{-}C_5H_{11})OK$	$CH_2{=}CHCH(n\text{-}C_5H_{11})O$	78[93]
H	$CH_2{=}CHCH(Et)OK$	$CH_2{=}CHCH(Et)O$	83[93]
H	$PhCH_2CH_2OH/NaH$	$PhCH_2CH_2O$	57[75]
H	$4\text{-}MeOC_6H_4ONa$	$4\text{-}MeOC_6H_4O$	86[75]
H	PhCOONa	PhCOO	88[82]
H	$Ph_2C{=}NOK$	$Ph_2C{=}NO$	83[94]
H	PhSNa	PhS	64[240]
H	$PhCH_2SNa$	$PhCH_2S$	68[240]
H	$4\text{-}MeC_6H_4SNa$	$4\text{-}MeC_6H_4S$	80[147]
H	2-benzothiazolyl-SNa	2-benzothiazolylthio	92[244]
H	$PhSO_2Na$	$PhSO_2$	44[240]
H	pyrrolidine	1-pyrrolidyl	27[240]
H	Py	Pyr^+Cl^-	59[240]
H	NaN_3	N_3	82[240]
H	DMAP	$DMAP^+Cl^-$	76[240]
H	PPh_3	$PPh_3{+}Cl^-$	23[240]
H	$Ph_2P(O)Li$	$Ph_2P{=}O$	69[175]
H	NaCN	CN	49[240]
Me	NaN_3	N_3	82[252]
i-Pr	PhONa	PhO	60[75]
i-Pr	2-naphthyl-ONa	2-naphthyl-O	20[75]
n-Pr	PhCOONa	PhCOO	91[249]
n-Pr	MeCOONa	MeCOO	71[82]
n-Pr	$n\text{-}C_5H_{11}COONa$	$n\text{-}C_5H_{11}COO$	85[82]
n-Pr	PhSNa	PhS	80[146]
n-Pr	PhSNa	PhS	88[249]
n-Pr	NaN_3	N_3	77[252]
t-Bu	NaN_3	N_3	80[252]
t-Bu	NaCN	CN	74[249]
t-Bu	NaCN	CN	83[94]
$PhCH_2$	NaN_3	N_3	97[252]
$Bt^1(PhS)CH-$	PhSNa	PhS	86[90]
$Bt^1(i\text{-}PrS)CH-$	*i*-PrSNa	*i*-PrS	82[90]
$Bt^1(PhCH_2S)CH$	$PhCH_2SNa$	$PhCH_2S$	87[90]
$Bt^1(n\text{-}C_8H_{17}S)CH$	$n\text{-}C_8H_{17}SNa$	$n\text{-}C_8H_{17}S$	72[90]

Treatment of 1-(chloromethyl)benzotriazole with aqueous solution of sodium trithiocarbonate followed by hydrolysis of the resultant intermediate **432** gives 1-(mercaptomethyl)benzotriazole (**433**, Scheme 141) in high yield.[253] Partial oxidation of thiol **433** under reaction conditions leads to formation of the corresponding disulfide in 11% yield. Transformation of 1-(chloromethyl)benzotriazole into **433** can also be performed via benzotriazolylmethyl dithiocarboxylates **434** (method B, Scheme 141); however, yield of the final product in this reaction is lower.

Reaction of 1-(chloromethyl)benzotriazole with diorganyl diselenides or diorganyl ditellurides in the presence of SmI_2 results in the formation of α-benzotriazol-1-yl-substituted unsymmetrical selenides **435** and tellurides **436**, respectively (Scheme 142, Table 46), which can be subjected to further transformations to various α-functionalized selenides and tellurides.[254]

Scheme 142. Benzotriazolylmethylation of Diselenides and Ditellurides

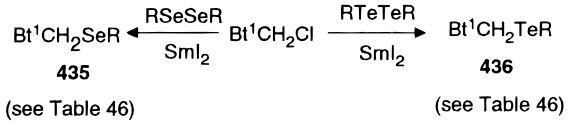
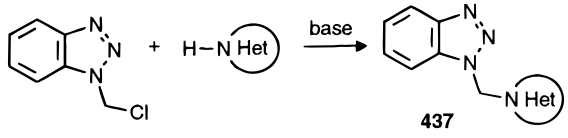


Table 46. Preparation of Unsymmetrical Selenides 435 and Tellurides 436

compound	R	yield, %	compound	R	yield, %
435	Et	80	**435**	Ph	75
	Me_2CHCH_2	78		$4\text{-}ClC_6H_4$	72
	n-Bu	82		$c\text{-}C_6H_{11}$	76
	$n\text{-}C_5H_{11}$	81	**436**	Ph	80
	$n\text{-}C_6H_{13}$	80		$4\text{-}MeC_6H_4$	83

N-(Benzotriazol-1-ylmethyl)heterocycles **437** are readily prepared in good yields by heating the corresponding N−H heterocycles with 1-(chloromethyl)-benzotriazole under basic conditions (Scheme 143).

Scheme 143. Benzotriazolylmethylation of *N*-Unsubstituted Heterocycles



(see Table 47)

Depending on the nature of N−H heterocycles, sodium hydroxide in DMSO, sodium ethoxide in ethanol, or sodamide in toluene are used as bases (Table 47).[216,218,222]

Table 47. Preparation of *N*-Benzotriazolylmethyl-Substituted Heterocycles 437

heterocyclic group	base	yield %
pyrrol-1-yl	NaOH/DMSO	61[216]
indol-1-yl	NaOH/DMSO	84[216]
carbazol-9-yl	NaOH/DMSO	87[216]
carbazol-9-yl	NaOH/DMSO	80[218]
imidazol-1-yl	NaOH/DMSO	62[216]
benzimidazol-1-yl	EtONa/EtOH	80[216]
2-methylbenzimidazol-1-yl	NaOH/DMSO	78[216]
2-phenylbenzimidazol-1-yl	EtONa/EtOH	89[216]
1,2,4-triazol-1-yl	EtONa/EtOH	82[216]
benzotriazol-1-yl	$NaNH_2$/toluene	88[222]

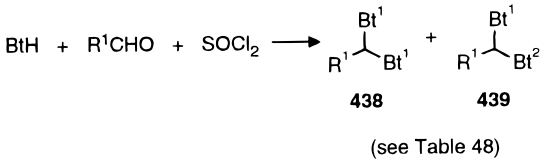
Table 48. Preparation of 1,1-Bis(benzotriazolyl)-alkanes 438 and 439

	yield %[a]			yield %	
R^1	**438**	**439**	R^1	**438**	**439**
Me	32	5	*t*-Bu	52	9
Et	60	13	*n*-C_8H_{17}	52	24
n-Pr	29	14	Ph	25 (75)	12 (0)
i-Pr	41	18	4-MeC_6H_4	65 (85)	4 (0)

[a] The data in parentheses are the corresponding yields obtained by the general method for the preparation of bis-(benzotriazolyl)methylarenes,[249] when the excess of thionyl chloride was removed by distillation instead of washing with aqueous $NaHCO_3$ solution.

A special case of the benzotriazolylalkylation is shown in the preparation of 1,1-dibenzotriazolylalkanes where 2 equiv of benzotriazole are reacted with 1 equiv of an aldehyde in excess of thionyl chloride.[249] Normally, mixtures of the Bt^1Bt^1 and Bt^1Bt^2 isomers are obtained but the Bt^1Bt^1 isomer is always predominant (Scheme 144, Table 48).

Scheme 144. Preparation of 1,1-Dibenzotriazolylalkanes

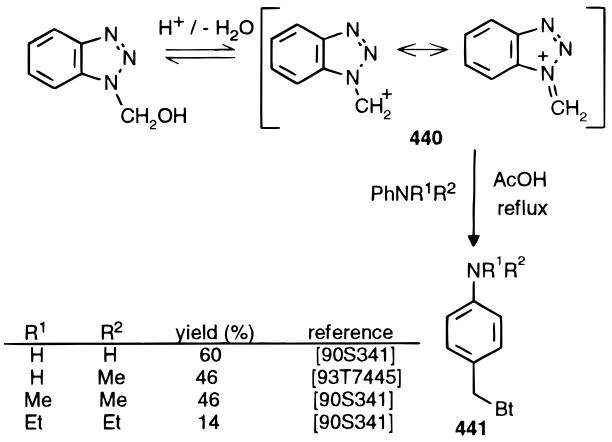


1-(Chloromethyl)benzotriazole is reduced with lithium aluminum hydride in refluxing tetrahydrofuran to give 1-methylbenzotriazole in 86% yield[57] while all attempts to reduce 1-(hydroxymethyl)-benzotriazole by treatment with sodium borohydride or lithium aluminum hydride[255] or by catalytic hydrogenation in the presence of Raney nickel[51] failed.

3. Benzotriazolylmethylation of Anilines

On treatment with 1-(hydroxymethyl)benzotriazole, aniline, *N*-alkylanilines, and *N*,*N*-dialkylanilines all undergo *para* substitution to give the *p*-benzotriazolylmethylated derivatives **441**.[199,256] Unlike the substitution of chloro by nucleophiles, this type of reaction requires an acid catalysis. Our explanation is that the protonated hydroxy compound loses a molecule of water to give the benzotriazolyl-stabilizer cation **440**, which then attacks the electron-rich aniline ring in the more sterically favorable *para* position (Scheme 145).

Scheme 145. Benzotriazolylalkylation of Anilines

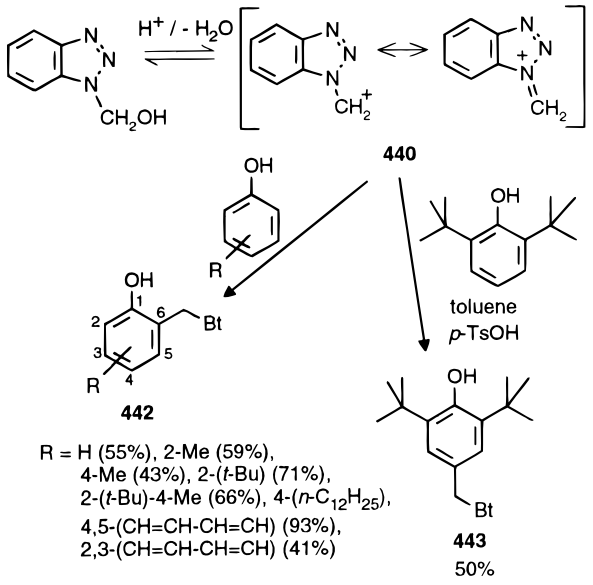


R^1	R^2	yield (%)	reference
H	H	60	[90S341]
H	Me	46	[93T7445]
Me	Me	46	[90S341]
Et	Et	14	[90S341]

4. Benzotriazolylalkylation of Phenols and Naphthols

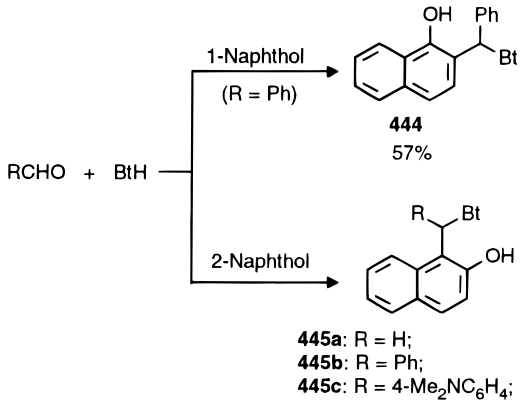
Under similar conditions, phenols react with 1-(hydroxymethyl)benzotriazole to give exclusively *ortho*-substituted products **442**.[257] Here again an acid is needed for the generation of the reactive cation **440**, but instead of *para* substitution, *ortho* substitution occurs exclusively. When both *ortho* positions are occupied, the reaction does occur at the *para* position but this requires more rigorous conditions[257] as shown by the formation of compound **443** (Scheme 146).

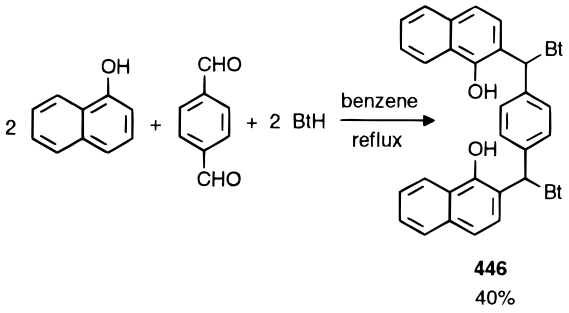
Scheme 146. Benzotriazolylalkylation of Phenols



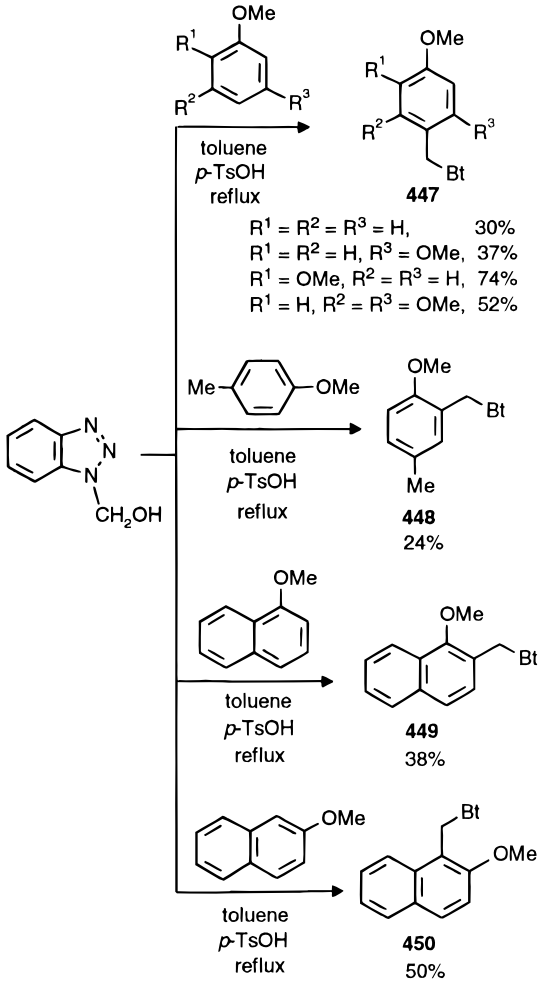
1- and 2-naphthols react not only with 1-(hydroxymethyl)benzotriazole but also condense directly with benzotriazole and other aldehydes to give hydroxyalkyl-substituted products **444**−**446** in refluxing toluene or benzene in the presence of a catalytic amount of piperidine.[257,258] Again the alkylation occurs at the *ortho* position; for 2-naphthol the 1 substitution at the more reactive 1 position is observed while 2 substitution is found for 1-naphthol (Scheme 147). Mixtures of the Bt^1 and Bt^2 isomeric products are obtained with the Bt^1 isomer predominant in all cases.

Scheme 147. Benzotriazolylalkylation of Naphthols





Scheme 148. Benzotriazolylmethylation of Phenol and Naphthol Ethers

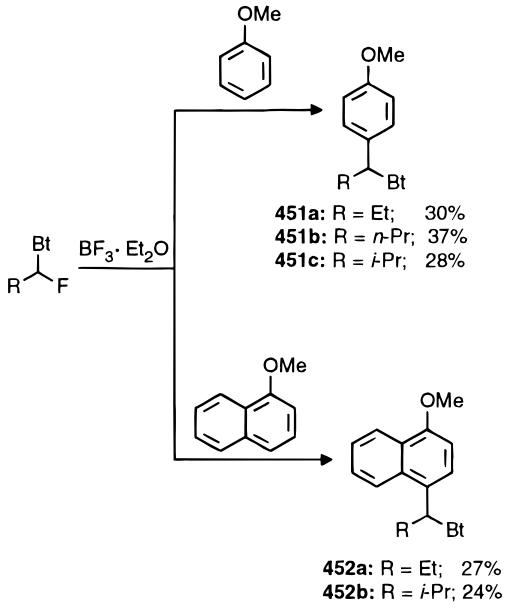


5. Benzotriazolylmethylation of Phenol and Naphthol Ethers

Interestingly, the benzotriazolylmethylation of phenol ethers occurs predominantly in the *para* rather than the *ortho* position but, although originally considered to be regiospecific[257] (Scheme 148), we now know that mixtures of the *para* with some *ortho* isomer are formed. 1-Methoxynaphthalene reacts similarly to give **449** in 38% yield. When the *para* position is not available, regiospecific *ortho* substitution is observed as shown for the formation of compounds **448** and **450**. For 2-naphthyl methyl ether, the alkylation occurs at the more reactive *ortho* position to give **450**.

More generally, the benzotriazolylalkylation of phenol and naphthol alkyl ethers has been achieved, albeit in modest yields, through reactions of *N*-(α-fluoroalkyl)benzotriazoles with methoxybenzenes and -naphthalenes in the presence of boron trifluoride etherate (Scheme 149).[250]

Scheme 149. Benzotriazolylalkylation of Phenol and Naphthol Ethers with 1-(α-Fluoroalkyl)-benzotriazoles

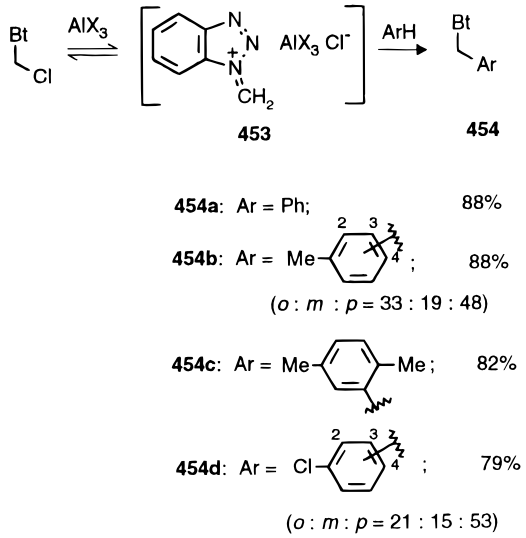


6. Benzotriazolylmethylation of Arenes

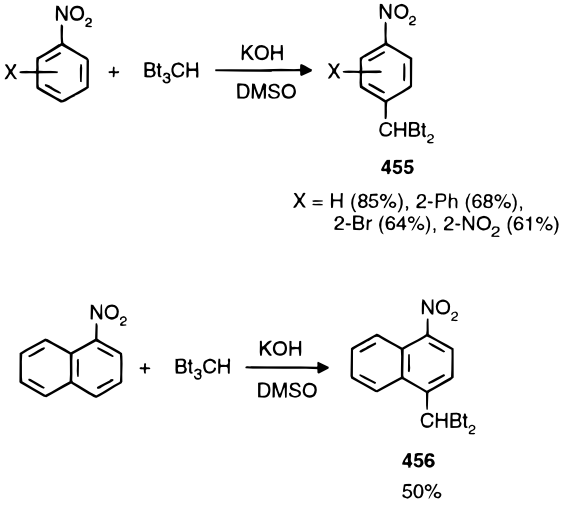
The methylenebenzotriazolium salt **453**, generated *in situ* from 1-(chloromethyl)benzotriazole and aluminum trihalide as a Lewis acid, reacts with unactivated aromatic substrates to allow benzotriazolylmethylation of arenes to yield **454** as mixtures of all the possible *ortho*, *meta*, and *para* isomers (Scheme 150).[190] The mild reaction conditions and the relatively low selectivity of the process indicates the high reactivity of the complex **453**.

Nucleophilic benzotriazolylalkylation of electron-deficient substrates, such as nitroarenes, with the anion of tribenzotriazol-1-ylmethane (see section II.A.1) occurs exclusively in *para* position to the nitro group due to the bulkiness of tribenzotriazol-1-ylmethyl carbanion[259] (Scheme 151). This reaction proceeds satisfactorily with nitrobenzene, its *ortho*-substituted derivatives and 1-nitronaphthalene. How-

Scheme 150. Benzotriazolylmethylation of Arenes



Scheme 151. Benzotriazolylmethylation of Nitroarenes with Trisbenzotriazolylmethane Anion



ever, *meta*-substituted nitrobenzenes could not be alkylated probably because of the steric demands of the Bt_3C^- anion. Attempts to *ortho*-alkylate *para*-substituted nitrobenzenes also failed.

Scheme 152. Benzotriazolylmethylation of Nitroarenes with 1-[(Phenylsulfonyl)methyl]-benzotriazole

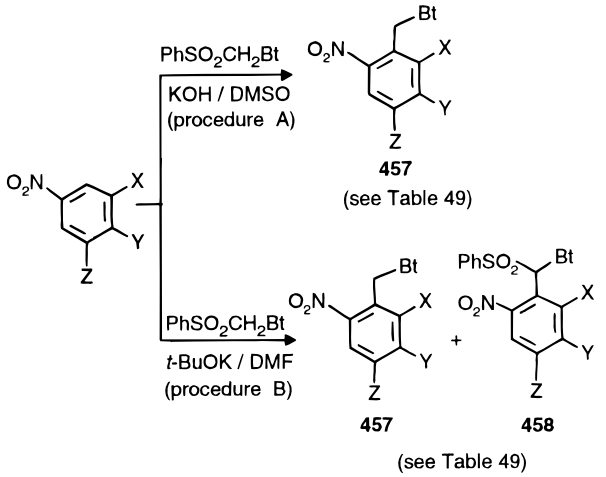


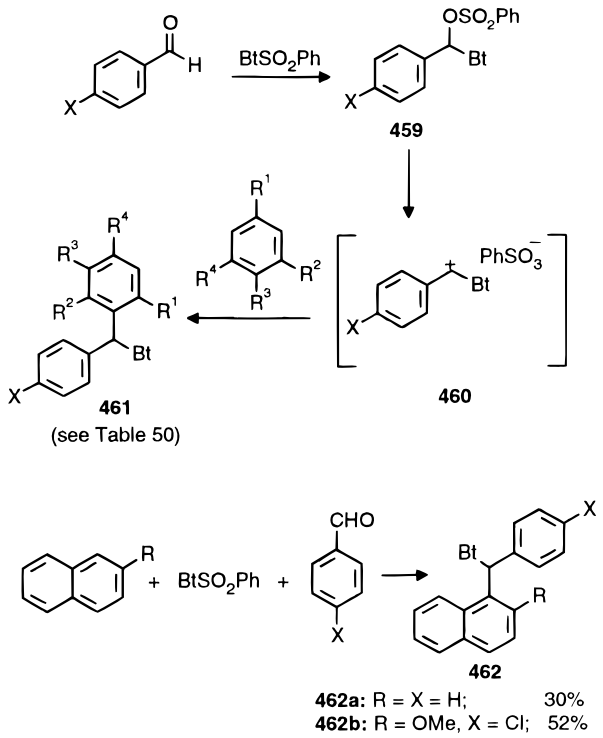
Table 49. Preparation of Benzotriazolylmethyl Nitroarenes 457 and 458

X	Y	Z	procedure (see Scheme 152)	yield % **457**	**458**
H	Cl	H	A	49	traces
H	H	NO_2	A	71	traces
H	Cl	NO_2	A	49	2
		H	A	72	0
		H	A	48	2
H	Cl	H	B	11	41
H	H	NO_2	B	4	45
H	Cl	NO_2	B	4	37
		H	B	6	15
		H	B	20	9

Nevertheless, *para*-substituted nitroarenes can be successfully benzotriazolylalkylated in the *ortho* position by treatment with less bulky 1-[(phenylsulfonyl)-methyl]benzotriazole in the KOH/DMSO system.[260] Here the phenylsulfonyl group serves as a leaving group, and the corresponding (benzotriazolylmethyl)-arenes **457** are prepared in moderate yields (Scheme 152, Table 49). When *t*-BuOK in DMF is used as a base, mixtures of **457** and the oxidation products **458** are obtained, with the latter being usually predominant.

1-(Phenylsulfonyl)benzotriazole adds to an aromatic aldehyde to form 1-(benzotriazolyl)benzyl benzenesulfonate (**459**) which can dissociate into a benzylic cation and undergoes (Scheme 153) Friedel–

Scheme 153. α-Benzotriazolylbenzylation of Arenes Mediated by 1-(Phenylsulfonyl)benzotriazole



Crafts-type reactions with mesitylene, naphthalene, and aryl methyl ethers to give (diarylmethyl)-benzotriazoles **461** (Table 50) and **462**.[261] 1-(Phenylsulfonyl)benzotriazole served both as a Lewis acid and as a dehydration reagent during these reactions.

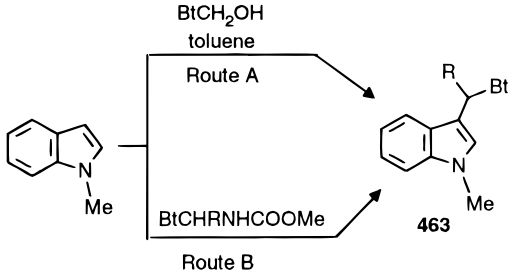
Table 50. Products 461 from Reaction of 1-(Phenylsulfonyl)benzotriazole, Aldehydes, and Arenes

X	R^1	R^2	R^3	R^4	yield %
H	Me	Me	H	Me	48
Cl	Me	Me	H	Me	56
MeO	Me	Me	H	Me	60
HO	Me	Me	H	Me	32
Cl	MeO	MeO	H	MeO	55
Cl	Me	H	Me	H	25

7. Benzotriazolylalkylation of Heteroaromatic Compounds

1-(Hydroxymethyl)benzotriazole reacts with electron-rich 1-methylindole in refluxing toluene to give 3-(benzotriazol-1-ylmethyl)-1-methylindole (**463a**, Scheme 154, route A).[204,262a] Alternatively, for the preparation of the analogues with an alkyl substituent at the methylene group, the corresponding methyl *N*-(benzotriazol-1-ylalkyl)carbamate is used as the reagent (Scheme 154, route B);[204,263] here, the methoxycarbamoyl moiety acts as the leaving group.

Scheme 154. Benzotriazolylalkylation of 1-Methylindoles

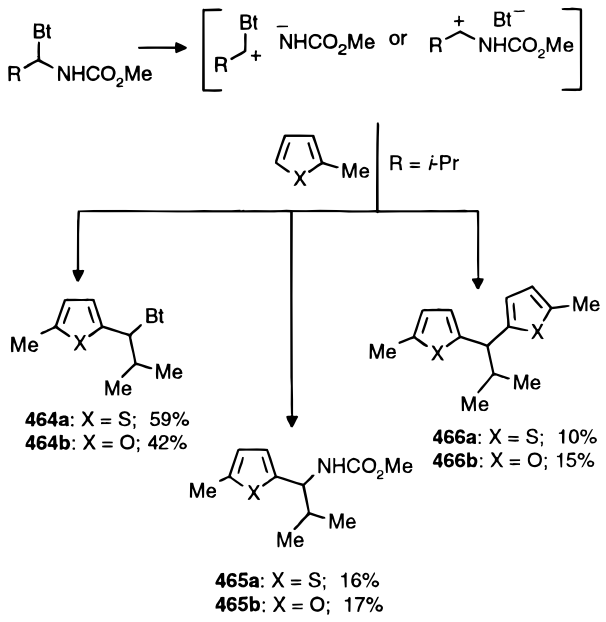


463a: Route A, R = H; 40%
463b: Route B, R = *i*-Pr; 70%
463c: Route B, R = Et; 58%

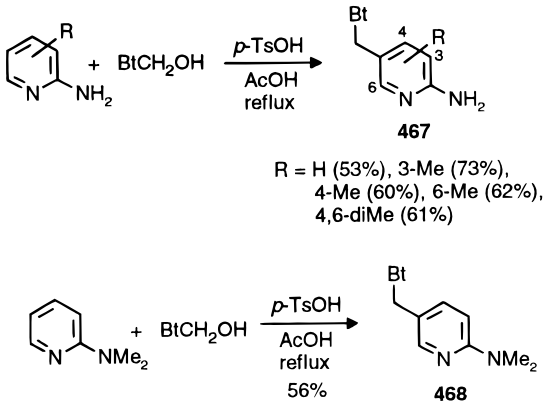
2-Methylthiophene and 2-methylfuran react similarly with methyl *N*-(benzotriazol-1-ylalkyl)carbamates[263] to give mixtures of three products: **465** resulting from attack on the thiophene or furan ring of a cation by loss of benzotriazole, **464** by loss of a methoxycarbamoyl anion; and **466** from further nucleophilic displacement in **464** and/or **465** (Scheme 155).

Heating 2-aminopyridines with 1-(hydroxymethyl)-benzotriazole at reflux in acetic acid results regiospecifically in the formation of the corresponding 5-(benzotriazol-1-ylmethyl)-2-aminopyridines **467** in good yields (Scheme 156).[209] This is attributed to the electron-rich nature of the 5 position of 2-aminopyridines. It is well-known that direct alkylation of a pyridine ring which contains no strong electron-donating groups is extremely difficult (if not impossible). The fact that the amino group can be readily removed by diazotation, coupled with the reactivity of both the methylene group and the benzotriazolyl group in compounds **467**, should thus allow a variety of 3-substituted pyridines to be readily accessible (see section IV.B.9.c).

Scheme 155. Benzotriazolylalkylation of 1-Methylthiophene and 1-Methylfuran



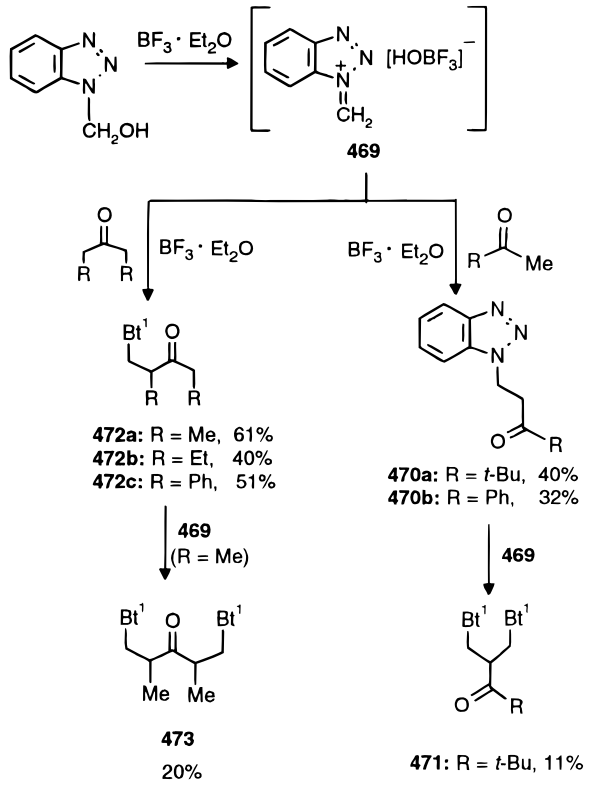
Scheme 156. Benzotriazolylalkylation of 2-Aminopyridines



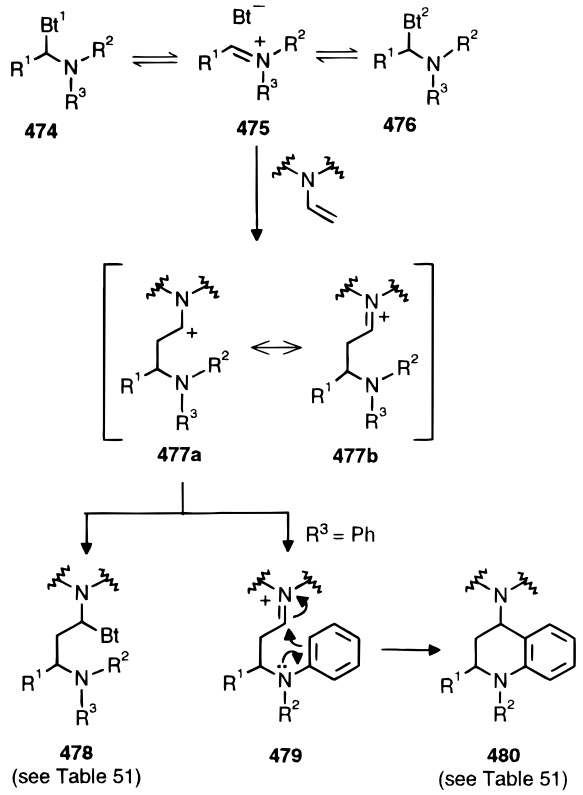
8. Benzotriazolylmethylation of Ketones

In the presence of Lewis acid, such as boron trifluoride etherate, 1-(hydroxymethyl)benzotriazole reacts with methyl ketones to give predominantly monosubstituted products **470**, although for R = *t*-Bu, disubstituted product **471** was also isolated (Scheme 157). For symmetrical dialkyl ketones, reaction occurs at both the α carbon atoms affording mixtures of mono- (**472**) and disubstituted derivatives (**473**). Use of equimolar amounts of reagents allows preparation of monosubstituted derivatives in moderate yields.[264]

Scheme 157. Benzotriazolylmethylation of Ketones



Scheme 158. Additions of 1-(α-Aminoalkyl)benzotriazoles to Enamines and Enamides



C. Additive Benzotriazolylalkylation

1. Addition of Immonium Benzotriazolides

1-(α-Aminoalkyl)benzotriazoles exist in solution in equilibrium with ion pairs **475** which are the intermediates for the isomeric interconversion of the benzotriazol-1-yl (**474**) and benzotriazol-2-yl (**476**) derivatives. The ion pairs **475** add to enamines and enamides, as exemplified by reactions with 9-vinylcarbazole and 1-vinyl-2-pyrrolidinone (Scheme 158). The immonium cation adds at the β position of the enamine or enamide to form a cation **477** which is resonance stabilized by the electron pair on the nitrogen. The benzotriazolyl anion then adds at the α position to give a new α-benzotriazolyl-substituted amine or amide **478** retaining a reactive group[125,205,220,265] (Table 51). An interesting extension of this type of reaction is the addition of the derivatives containing multiple benzotriazolylmethyl groups to enamines or enamides (Scheme 159).[125] The resulting adducts react with $LiAlH_4$ to give complex 1,3-diamines (see Scheme 250, section IV.B.4.a).

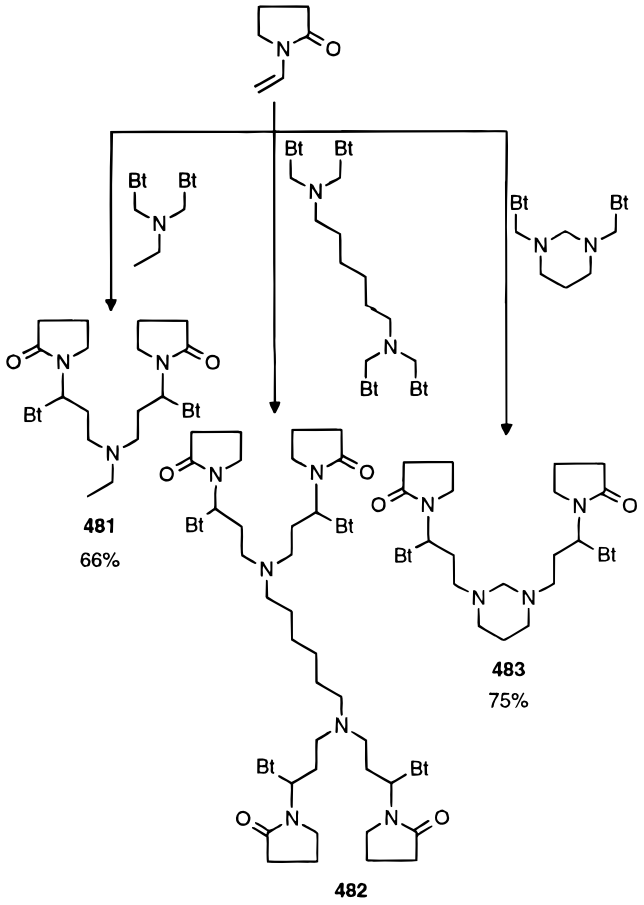
Application of this method to *N*-benzotriazolylmethyl-substituted monoaza-[205] and diaza[124] crown ethers leads to the preparation of novel *N*-(aminopropyl)-substituted lariats **484** and **485**, bearing a benzotriazolyl group in the side arm (Scheme 160).

Table 51. Products 478 and 480 from Addition of 1-(α-Aminoalkyl)benzotriazoles to Enamines and Enamides

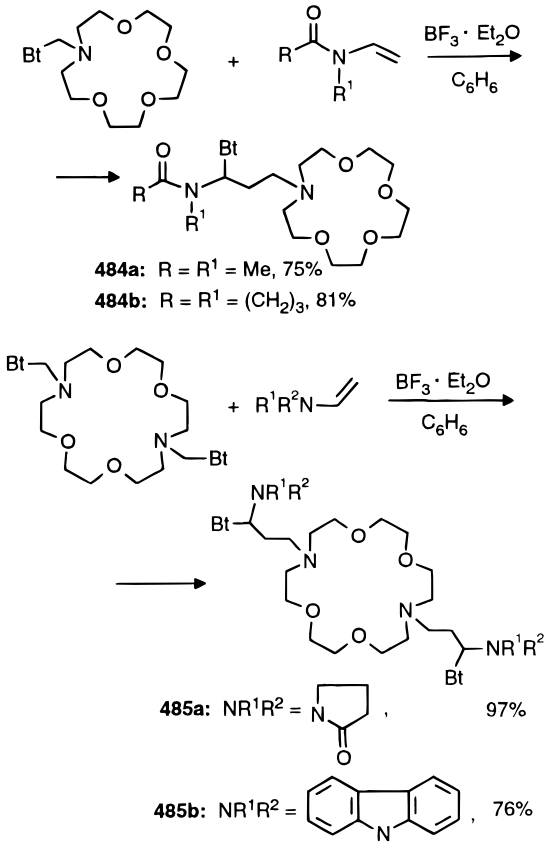
compound	∿N∿	R^1	R^2	R^3	yield %[a]
478	carbazol-9-yl	H	Me	Me	75[265]
	carbazol-9-yl	H	Me	Me	93[125]
	carbazol-9-yl	H	$-(CH_2)_2O(CH_2)_2-$		43[265]
	carbazol-9-yl	H	$-(CH_2)_4-$		84[125]
	carbazol-9-yl	H	$-(CH_2)_4-$		26[220]
	carbazol-9-yl	Ph	$-(CH_2)_2O(CH_2)_2-$		88[125]
	pyrrolidin-2-one-1-yl	H	Me	Me	64[265]
	pyrrolidin-2-one-1-yl	H	Et	Et	85[265]
	pyrrolidin-2-one-1-yl	H	$-(CH_2)_4-$		89[265]
	pyrrolidin-2-one-1-yl	H	$PhCH_2$	$PhCH_2$	48[125]
	pyrrolidin-2-one-1-yl	Ph	$PhCH_2$	$PhCH_2$	46[125]
	MeC(O)N(Me)−	H	Et	Et	91[125]
	MeC(O)N(Me)−	H	$-(CH_2)_2O(CH_2)_2-$		95[125]
	MeC(O)N(Me)−	Ph	$-(CH_2)_2O(CH_2)_2-$		
480	carbazol-9-yl	H	Me		53[265]
	pyrrolidin-2-one-1-yl	H	Me		90[265]
	pyrrolidin-2-one-1-yl	H	$PhCH_2$		92[265]
	pyrrolidin-2-one-1-yl	H	H		65[265]

[a] Of all isomers.

Scheme 159. Multiple Additions of Polybenzotriazolylamino Derivatives to 1-Vinylpyrrolidone



Scheme 160. Preparation of *N*-Aminopropyl-Substituted Lariat Crown Ethers



If **474** is an aniline derivative (one of R^2 or R^3 is a phenyl group), the reaction yields directly 4-substituted tetrahydroquinolines **480** (Scheme 158).[266] The initially formed cation **479** evidently attacks intramolecularly the electron-rich *ortho* carbon atom of the aniline ring. This method has opened a conceptionally novel and convergent route to functionalized tetrahydroquinolines **486**−**490** (Scheme 161, Table 52).

Scheme 161. Preparation of 4-Amino- or 4-Amido-Substituted Tetrahydroquinolines

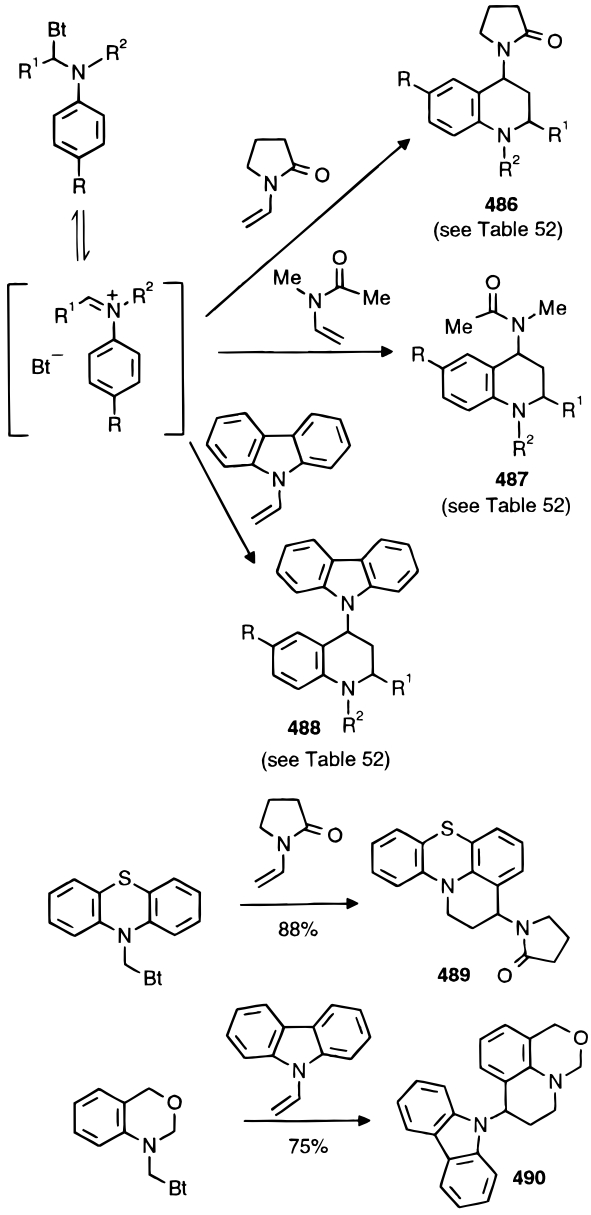
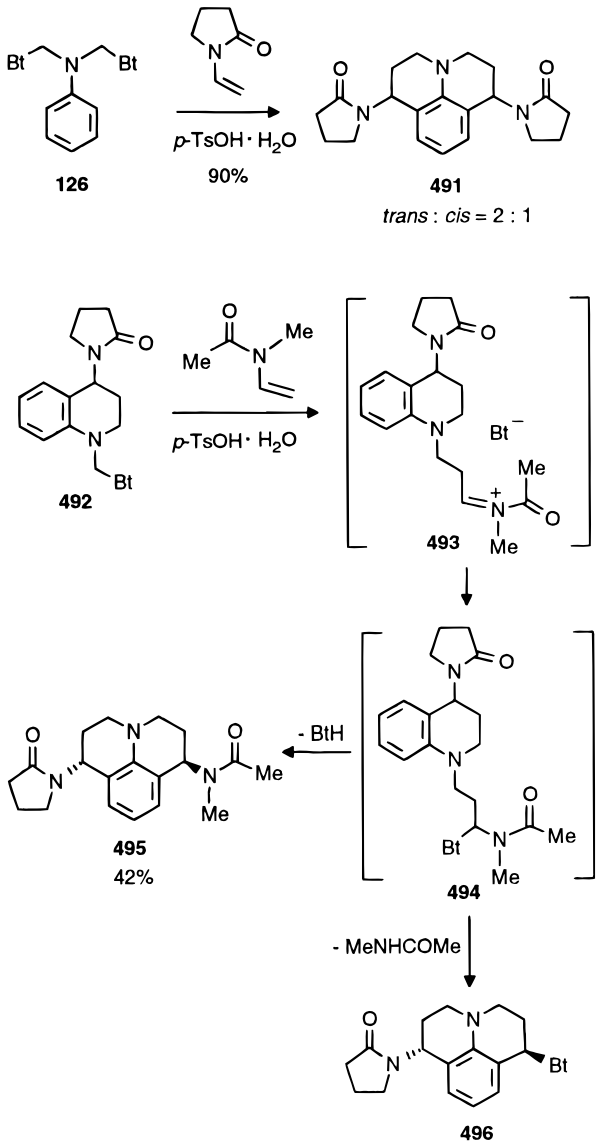


Table 52. Preparation of Tetrahydroquinolines 486−488 from 1-[(Arylamino)alkyl]benzotriazoles and Enamides or *N*-Vinylcarbazole

compound	R	R^1	R^2	yield %	compound	R	R^1	R^2	yield %
486	H	H	Me	90		H	Me	H	38
	H	H	Et	82	**487**	H	H	Et	66
	H	H	$PhCH_2$	92		Me	H	Me	86
	H	Ph	Me	89	**488**	H	Me	H	62
	H	*i*-Pr	Me	64		Me	H	Me	50
	H	H	H	45					

Following a similar pathway, the reaction of *N*,*N*-bis(benzotriazolylmethyl)aniline (**126**, Ar = Ph) (for preparation see section II.B.2.d) with 1-vinyl-2-pyrrolidinone under acid catalysis affords 1,7-bis-amido-substituted julolidine **491** as a mixture of *trans* and *cis* isomers with *trans* isomer predominant (Scheme 162).[101]

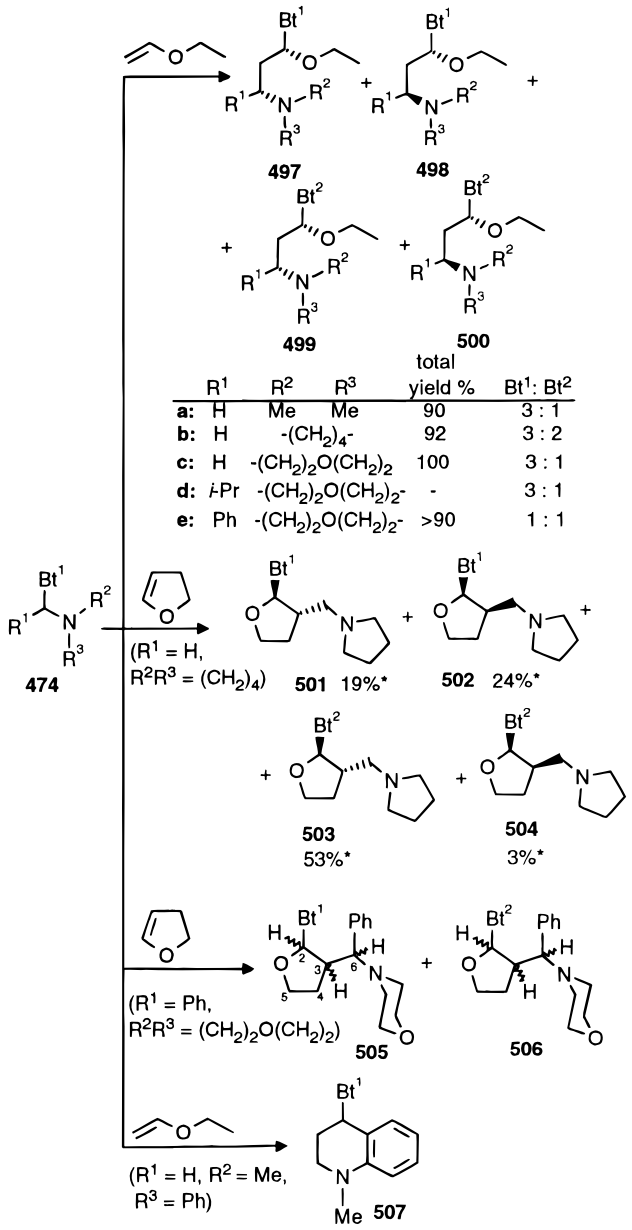
Scheme 162. Preparation of 1,7-Disubstituted Julolidines



N-Benzotriazolylmethyl-substituted tetrahydroquinoline **492**, obtained from **486** (R = R^1 = R^2 = H) and 1-(hydroxymethyl)benzotriazole (see section II.B.2.a), reacts with *N*-vinylacetamide in the presence of *p*-toluenesulfonic acid to give the expected unsymmetrical julolidine **495** in 42% yield and benzotriazolyl-substituted compound **496** as a result of *N*-methylacetamide elimination.[101] Products **495**−**496** are both obtained exclusively as *trans* isomers.

The benzotriazole adduct **474** also adds to enol ethers such as ethyl vinyl ether to give the corresponding 1-benzotriazolyl-3-aminoalkyl ethyl ethers **497**−**500** in high yields (Scheme 163).[267] With R^1 = H, mixtures of benzotriazol-1-yl and -2-yl isomers **497** and **499** are obtained.[102,267,268] In macrocyclic chemistry this method provides a convenient way for synthesis of novel *N*-(alkoxypropyl)-substituted lariat crown ethers.[124] However, when compounds **474** derived from aldehydes other than formaldehyde are used, mixtures of four isomers are resulted, **497**−**500**,**d**,**e**, due to (*R*,*S*) substitutions at the α and γ positions as well as the benzotriazol-1-yl and -2-yl isomers. Additions to other vinyl ethers such as 2,3-dihydrofuran are even more complicated due to the (*R*,*S*) isomers from the furan ring. This complexity intensifies in the case of the addition of **474** (R^1 = Ph, R^2R^3 = morpholin-4-yl) to 2,3-dihydrofuran where eight isomeric adducts are detected by NMR due to three diastereocenters (2, 3, 6) as well as benzotriazol-1-yl and 2-yl isomers. When one of the R^2 or R^3 groups in compound **474** is a phenyl group, a cyclized product **507** is obtained[269] (Scheme 163).

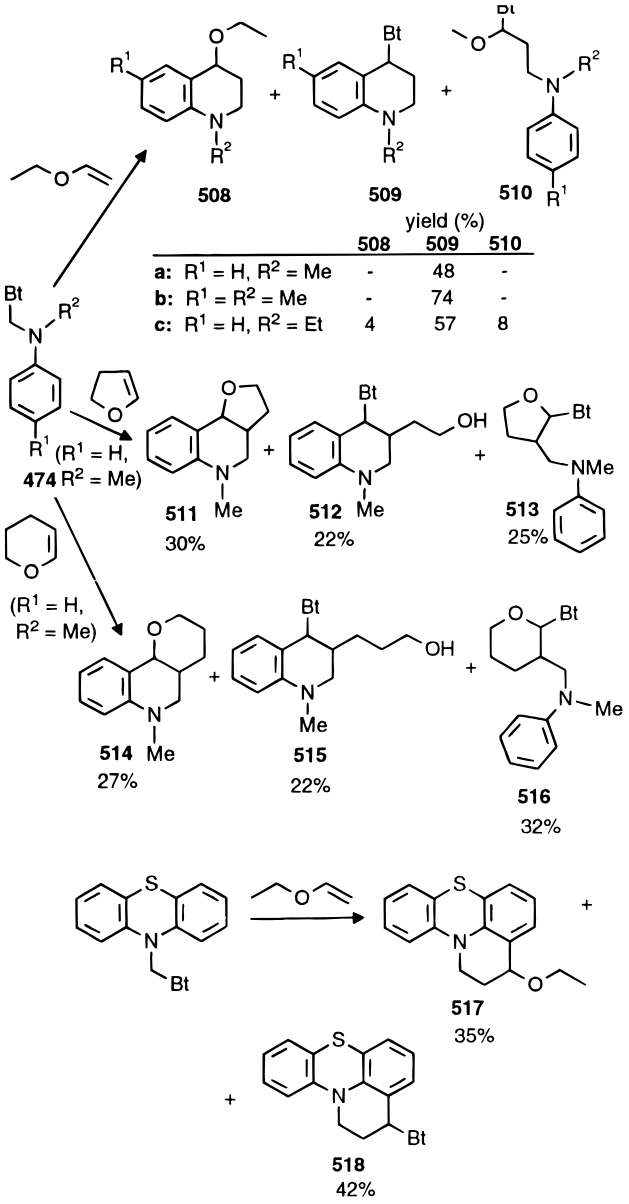
Scheme 163. Additions of 1-(α-Aminoalkyl)benzotriazoles to Vinyl Ethers



* Yields determined by NMR

The fact that both benzotriazole and alkoxy groups are good leaving groups leads to the formation of a mixtures of 4-benzotriazolyl- (**509**, **512**, **515**, **518**) and 4-alkoxytetrahydroquinolines (**508**, **511**, **514**, **517**) along with some uncyclized products (**510**, **513**, **516**) (Scheme 164).

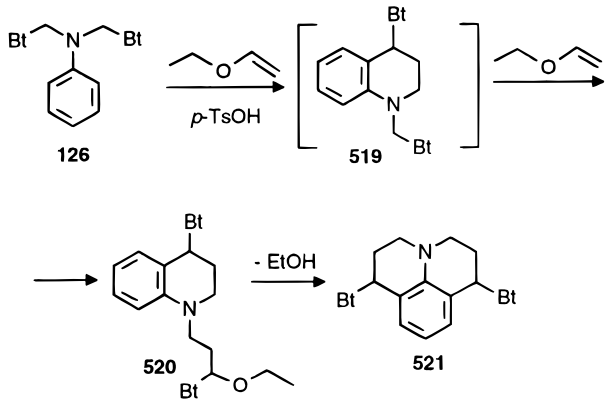
Scheme 164. Addition of *N,N*-Disubstituted (Aminomethyl)benzotriazoles to Vinyl Ethers



Reaction of *N,N*-bis(benzotriazolylmethyl)aniline (**126**, Ar = Ph) with ethyl vinyl ether gives an inseparable mixture of noncyclized product, tetrahydroquinoline **520**, and julolidine **521** (Scheme 165).[101] The suggested reaction mechanism, leading to **521**, involves stepwise reaction of **126** with two molecules of vinyl ether, giving initially tetrahydroquinoline **520** which undergoes intramolecular cyclization with the loss of alkoxy group, no benzotriazolyl group elimination products, analogous to **517**, are detected.

N-[(Arylamino)methyl]benzotriazoles also add to enols generated *in situ* from enolizable aldehydes in the presence of catalytic amounts of *p*-toluenesulfonic acid. The products are solvent dependent: in $CHCl_3$

Scheme 165. Addition of *N,N*-Bis(benzotriazolylmethyl)aniline to Ethyl Vinyl Ether



4-benzotriazolyltetrahydroquinolines **522** are generated as the major products, while in an alcohol 4-alkoxytetrahydroquinolines **523** are formed predominantly[270] (Scheme 166, Table 53). One-pot treatment of *N*-methylaniline with 1 equiv of benzotriazole and 2 equiv of an aldehyde directly yields 4-benzotriazolyltetrahydroquinolines **525**, presumably via intermediate adducts **524**. This method is

Scheme 166. Reactions of *N*-(Benzotriazolylmethyl)anilines and -tetrahydroquinolines with Enolizable Aldehydes

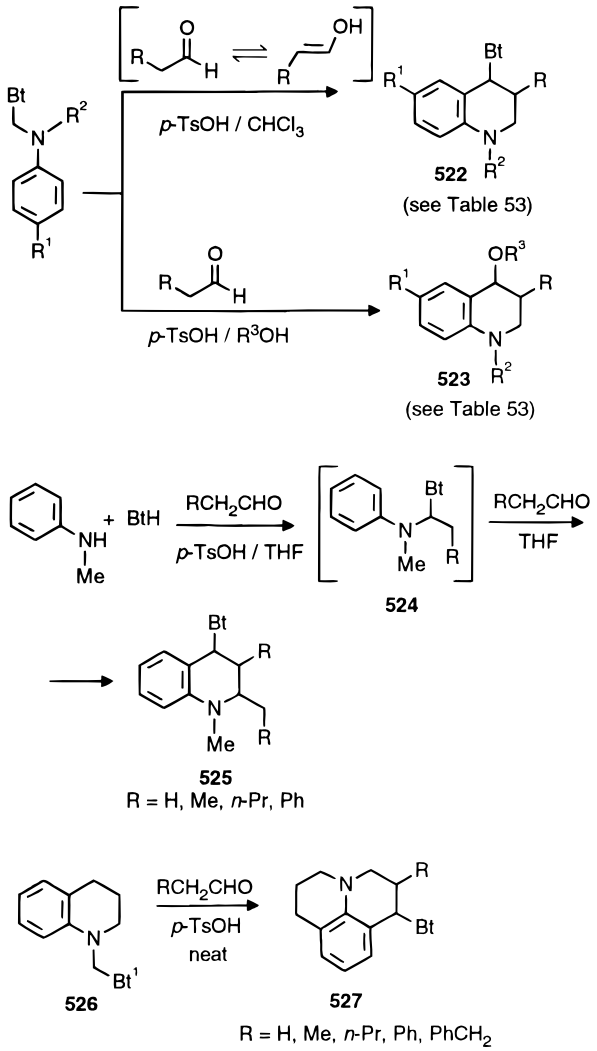


Table 53. Preparation of Tetrahydroquinolines 522 and 523

compound	R^1	R^2	R^3	R	yield %
522	H	Me		H	64
	H	Et		H	65
	Me	Me		H	76
	H	Me		Ph	83
	H	Me		Me	*a*
	H	Me		*n*-Pr	*a*
	H	Me		$PhCH_2$	*a*
523	H	Et	Me	H	50
	H	Et	Et	H	51
	H	Me	Me	*n*-Pr	62

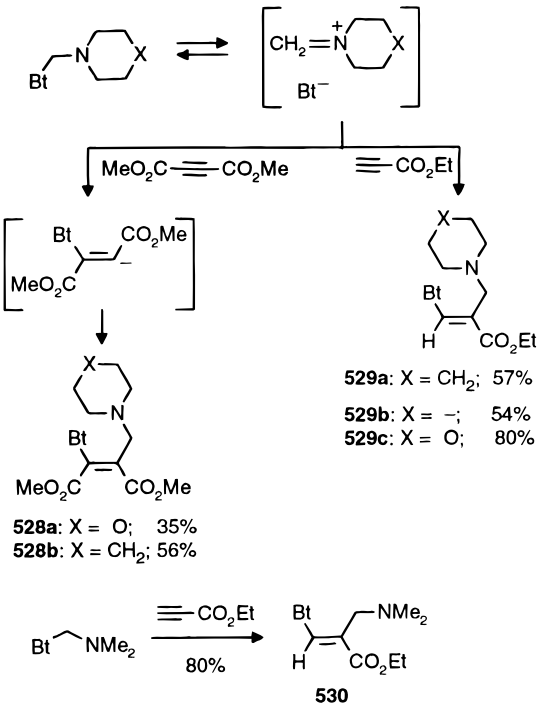
[a] Yields not available; directly used for further transformation (see section IV.B.9.c).

complementary to the two-step procedure described above because the benzotriazole adducts derived from anilines and aldehydes other than formaldehyde are generally not very stable.

The analogous reaction of *N*-(benzotriazol-1-ylmethyl)tetrahydroquinoline **526** with a number of enolizable aldehydes provides a convenient method for the synthesis of unsymmetrical julolidines **527** in almost quantitative yields (Scheme 166).[101] In all cases, the mixtures of *cis* and *trans* isomers of both Bt^1 and Bt^2 derivatives **527** are obtained with *trans*-benzotriazol-1-yl isomer predominating.

The benzotriazolate anion and the immonium cation, the dissociation products of 1-[(dialkylamino)-methyl]benzotriazoles, add to acetylenic esters to form *N*-allylic amine adducts (Scheme 167).[271] The

Scheme 167. Addition of *N*-(α-Aminomethyl)-benzotriazoles to Electron-Deficient Acetylenes

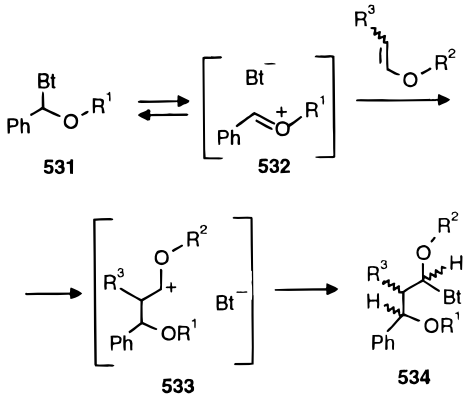


mechanism is different from the addition of such ions to electron-rich olefins. The initial stage is now the Michael addition of benzotriazolate anion to the acetylene which is followed by reaction with the immonium cation. In all cases, the benzotriazole group and the amino methylene group have the *cis* configuration according to their NMR spectra.

2. Additions of Oxonium Benzotriazolides

Like the 1-(α-aminoalkyl)benzotriazoles discussed in the preceding section, 1-(α-alkoxyalkyl)benzotriazoles **531** also exist in solution in equilibrium with benzotriazolyl anion and carboxonium cation ion pairs **532**. However, due to the lesser stabilizing effect of an alkoxy group compared to that of an amino group, an additional stabilizing phenyl group is needed to provide carboxonium cation insufficient concentration to add to enol ethers. Thus, 1-(α-alkoxybenzyl)benzotriazoles **531** react with enol ethers such as ethyl vinyl ether, β-methoxystyrene and 2,3-dihydrofuran to form new α-(benzotriazol-1-yl)alkyl ethers where the carbon chains are extended by an α-ethoxybenzyl group (Scheme 168).[272] Again, the

Scheme 168. Addition of Oxonium Benzotriazolides to Vinyl Ethers

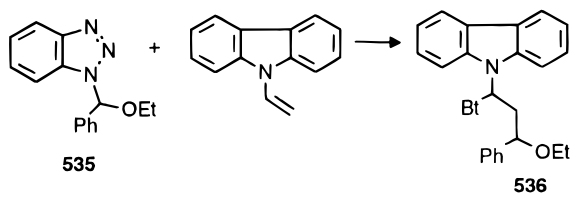


534a: R^1 = Me, R^2 = Et, R^3 = H
534b: R^1 = Et, R^2 = Et, R^3 = H
534c: R^1 = Me, R^2 = Me, R^3 = Ph
534d: R^1 = Et, R^2 = Me, R^3 = Ph
534e: R^1 = Et, R^2 = R^3 = $-CH_2CH_2-$

carboxonium cation adds to the β position of the enol ether to give the cation **533** which then reacts with the benzotriazole anion to yield the final product **534**. Diastereomeric mixtures as well as benzotriazol-1-yl and -2-yl isomers are obtained. Although these products could be isolated, they are usually directly used in subsequent reaction with Grignard reagents (see Scheme 267, section IV.B.6.a).

1-(α-Ethoxybenzyl)benzotriazole (**535**) also adds regiospecifically to 9-vinylcarbazole to afford **536** in moderate yield (Scheme 169).[273]

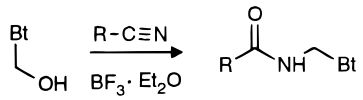
Scheme 169. Addition of 1-(α-Ethoxybenzyl)benzotriazole to 9-Vinylcarbazole



3. Addition of 1-(Hydroxymethyl)benzotriazole to Nitriles

1-(Hydroxymethyl)benzotriazole adds to nitriles in the presence of boron trifluoride etherate to give

Scheme 170. Reactions of 1-(Hydroxymethyl)-benzotriazole with Nitriles



537a: R = *i*-Pr, 32%
537b: R = *n*-C_5H_{11}, 50%
537c: R = *n*-C_9H_{19}, 64%
537d: R = 4-MeC_6H_4, 32%
537e: R = CH=CH_2, 27%
537f: R = C(Me)=CH_2, 28%

N-(benzotriazolylmethyl)amides **537** (Scheme 170).[274] This reaction can be considered as an extension of the Ritter reaction.[275,276] For best results, different reaction conditions are required for aliphatic, aromatic, and α,β-unsaturated nitriles, even so, yields are modest.

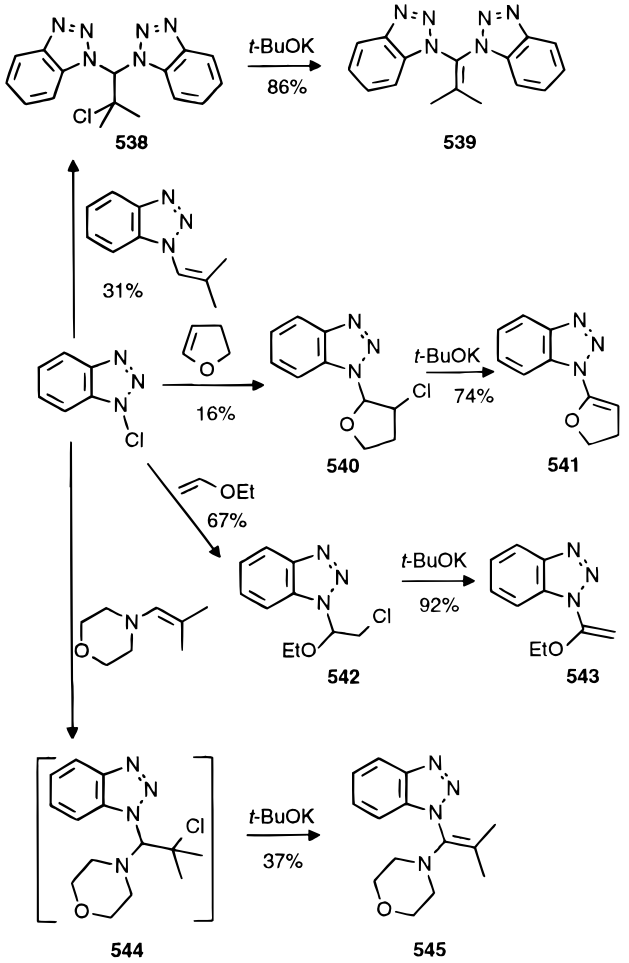
4. Addition of 1-(Benzenesulfonyl)benzotriazole to Aldehydes

The products **459** of such additions (see Scheme 153) are intermediates for α-benzotriazolylbenzylation of arenes (see section III.B.6).

5. Addition of 1-Chlorobenzotriazole to Double Bonds

1-Chlorobenzotriazole adds to electron-rich double bonds to form the corresponding 1-(β-chloroalkyl)-benzotriazoles (Scheme 171).[27] These adducts can be either isolated (**538**, **540**, and **542**), or directly treated with base to give 1-alkenyl benzotriazoles (**539**, **541**, **543**, and **545**) by elimination of hydrogen chloride.

Scheme 171. Addition of 1-Chlorobenzotriazole to C=C Double Bond

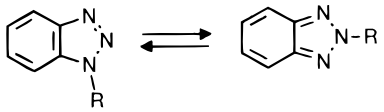


D. Isomerization of Benzotriazole Derivatives

1. 1-Benzotriazole Isomerization with 2-Benzotriazole Analogue

Disubstituted *N*-(aminomethyl)benzotriazoles exist in solution as an equilibrium mixture of the corresponding 1- and 2-benzotriazoles.[96] Such isomerization (Scheme 172) is general for *N*-(amino-alkyl)-,[97,277,278] *N*-(alkoxyalkyl)-,[267] *N*-(alkylthioalkyl)-,[279] and even *N*-trityl- and *N*-(diarylmethyl)-benzotriazoles[18] but not for simple *N*-alkylbenzotriazoles.

Scheme 172. 1- to 2-Substituted Benzotriazole Isomerization

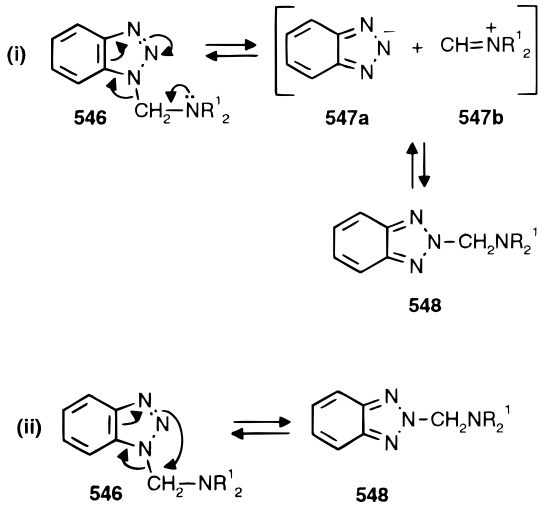


An NMR study shows[88] that when benzotriazole and a carbonyl compound are mixed in a solvent, an equilibrium is established between the benzotriazol-1-yl and the -2-yl adducts (as discussed in section II.B.1).

a. N-(Aminoalkyl)benzotriazoles. A variety of *N*-[(dialkylamino)methyl]benzotriazoles exist in the 1-substituted form **546** in the solid state, but as equilibrium mixtures of the 1 (**546**) and 2 isomers (**548**) in the liquid, melt, solution, and argon matrix phases.[97] *Ab initio* calculations predict an almost equal stability in the gas phase for the 1 (**546**) and 2 isomers (**548**) of *N*-[(dimethylamino)methyl]benzotriazole.[278]

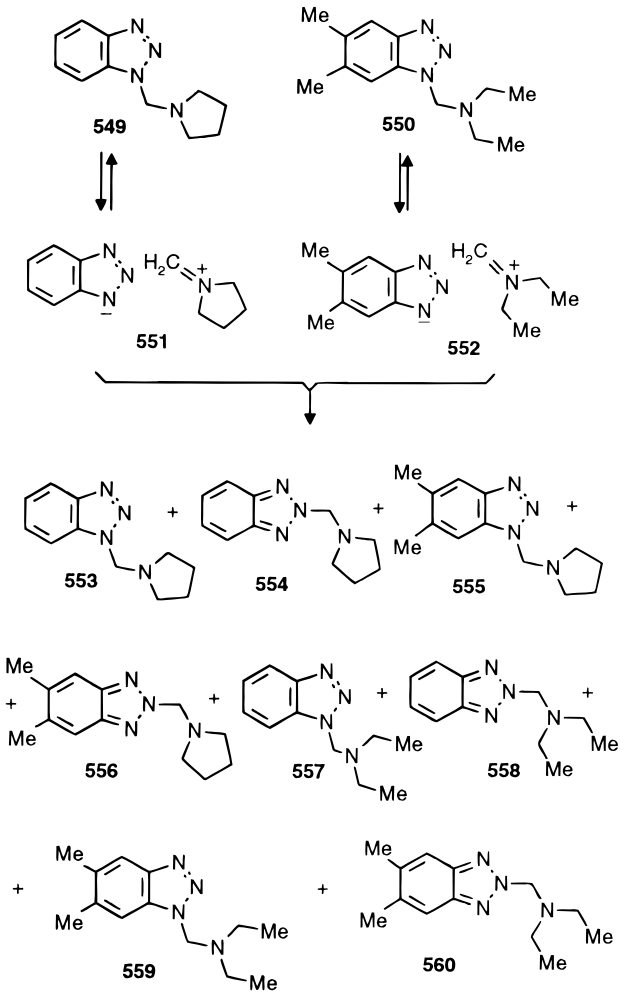
Two mechanisms are possible for the interconversion **546** ⇌ **548** as shown in Scheme 173: (i) a dissociation−recombination process, (ii) a concerted reaction. Cross-over experiments as shown in Scheme

Scheme 173. Possible (i) Intermolecular and (ii) Intramolecular Mechanisms for Isomerizations of *N*-(Aminoalkyl)benzotriazoles



174 have excluded a concerted, intramolecular reaction. Thus, after compounds **549** and **550** were

Scheme 174. Proof of Intermolecular Mechanism for Isomerization by Cross-Over Experiment



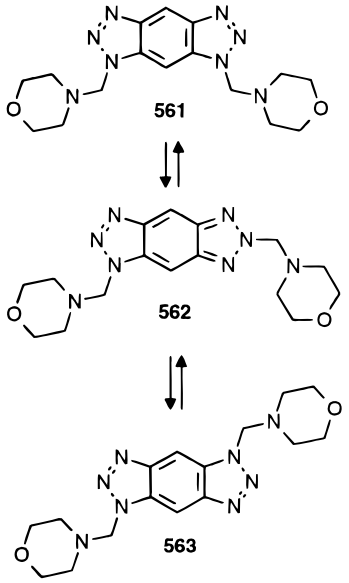
mixed, their $CDCl_3$ or DMSO solutions showed in the NMR spectra the presence of all eight isomers **553**−**560** instead of just the four isomers (**553**, **554**, **559**, and **560**) expected for an intramolecular mechanism.[97] Ionization in solution is supported by the significant conductivity of *N*-(α-aminoalkyl)benzotriazoles in nitromethane solution.[281]

The isomerization between the 1- and 2-substituted benzotriazoles has been studied by NMR spectroscopy. For *N*-(α-aminoalkyl) derivatives, isomerization is normally slow on the NMR time scale at room temperature or slightly below, but on raising the temperature, coalescence often occurs indicating a rapid rearrangement.[277]

On the basis of these studies, the free energies of activation for the isomerizations have been calculated[277] and are found to be greatly dependent on the degree of stabilization of the intermediate ions **547a** or **547b** (Scheme 173). The greater such stabilization, the lower the energy barrier. Also high solvent polarity favors the predominance of the 1-benzotriazolyl isomer. In contrast, the bulkier the (dialkylamino)alkyl (or aryl) substituent, the more abundant the 2 isomers, which in extreme cases can become the predominant components. Ring substitution at the 4 or 4,7 positions of the benzotriazole ring also favors the 2 isomer.[282]

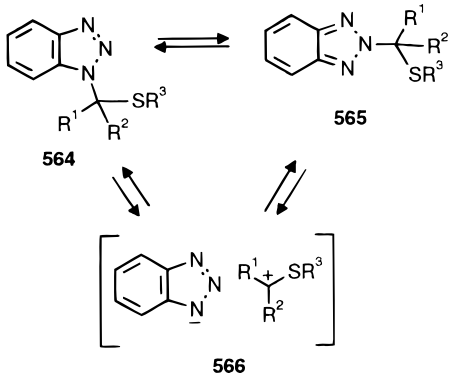
For the benzobistriazole adduct **561**, for which no Kerkule 2,2′ isomer is possible, the 1,3′ isomer **563** predominates in the mixture over the 1,1′ isomer **561** (possibly more hindered by buttressing). The 1,2′ isomer **562** is much less favored[282] (Scheme 175) with the percentage ratio of **561**:**562**:**563** being 33:4:63 in $CDBr_3$.

Scheme 175. Isomerization of Benzobistriazole Derivatives



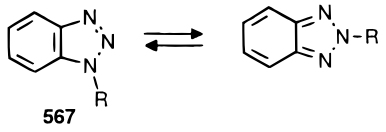
b. N-[(Alkylthio)alkyl]-, N-[(Arylthio)alkyl]-, and N-(Arylmethyl)benzotriazoles. The thermal isomerizations of *N*-[α-(alkylthio)alkyl]- and *N*-[α-(arylthio)-alkyl]benzotriazoles have been investigated[279] under a N_2 atmosphere in a solvent in the presence of a catalyst. Cross-over experiments demonstrate that the isomerization proceeds via an intermolecular reaction by N−C(SR) bond cleavage. Increasing the bulkiness of R^1 and R^2 increases the proportion of the 2*H* isomer at equilibrium (Scheme 176).

Scheme 176. Isomerization of *N*-[α-(Alkylthio)-alkyl]benzotriazoles



Studies on the isomerization of *N*-(arylmethyl)-benzotriazoles **567** and **568** (Scheme 177) showed that **567a**/**568a** and **567f**/**568f** do not interconvert on heating. All the others undergo clean isomerization to afford mixtures of the N-1 and N-2 isomers at

Scheme 177. Isomerization of *N*-(Diarylmethyl)-benzotriazole



567

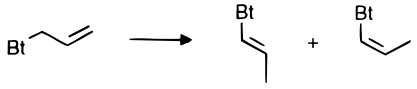
568a: R = CH_2Ph **568d**: R = $CH(C_6H_4NMe_2\text{-}4)_2$
b: R = $CHPh_2$ **e**: R = $CH(C_6H_4OMe\text{-}4)_2$
c: R = CPh_3 **f**: R = $CH(C_6H_4Cl\text{-}4)_2$

175−250 °C with the N-1 isomers being predominant at the equilibrium.[18] Obviously for **567a** and **568a**, the unstable benzyl cation accounts for no isomerization, while for **567f** and **568f** the electronic deactivating effect of the *p*-Cl group compared to the *p*-NMe_2 and *p*-MeO group makes **567f** and **568f** incapable of isomerization on moderate heating.

2. Isomerization of Bt−C−C=C to Bt−C=C−C

1-Allylbenzotriazole (**569a**), upon treatment with potassium *tert*-butoxide isomerizes in 90% yield to a mixture of 1-(*E*)- (**570a**) and 1-(*Z*)-propenylbenzotriazole (**571a**) in a 5:1 ratio[23] (Scheme 178). We later

Scheme 178. Isomerizations of *N*-Allyl- into *N*-Propenylbenzotriazoles



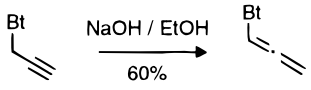
569 570 571

	total yield %	ratio 570 : 571
a: Bt = Bt^1	90	5 : 1
b: Bt = Bt^2	85	4 : 1

found that 2-allylbenzotriazole (**569b**) also undergoes isomerization under similar conditions to yield a mixture of **570b** and **571b** in 4:1 ratio in 85% yield.[24] Attempts to induce thermal rearrangements (i) of **569a** into **569b**, (ii) **570a** into **571a**, and (iii) **570b** into **571b** all failed.

1-Propargylbenzotriazole (**243**) upon heating with ethanolic NaOH solution isomerizes into 1-allenylbenzotriazole (**316**) in 60% yield[283] (Scheme 179). The

Scheme 179. Isomerization of Propargyl- into Allenylbenzotriazoles



243 316

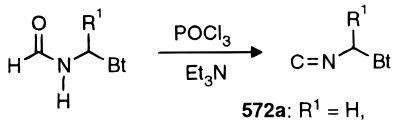
isomerized product is believed to be the intermediate during the transformation to furan and dihydrofuran derivatives (see Scheme 90, section III.A.2.d, and Scheme 266, section IV.B.6.a).

E. Other Reactions with Retention of Bt Group

1. Formation of Benzotriazolylalkyl Isocyanides

N-(α-Benzotriazolylalkyl)formamides are dehydrated with $POCl_3$ in the presence of Et_3N, leading to the corresponding isocyanides **572** (Scheme 180).[284]

Scheme 180. Formation of Benzotriazolylalkyl Isocyanides

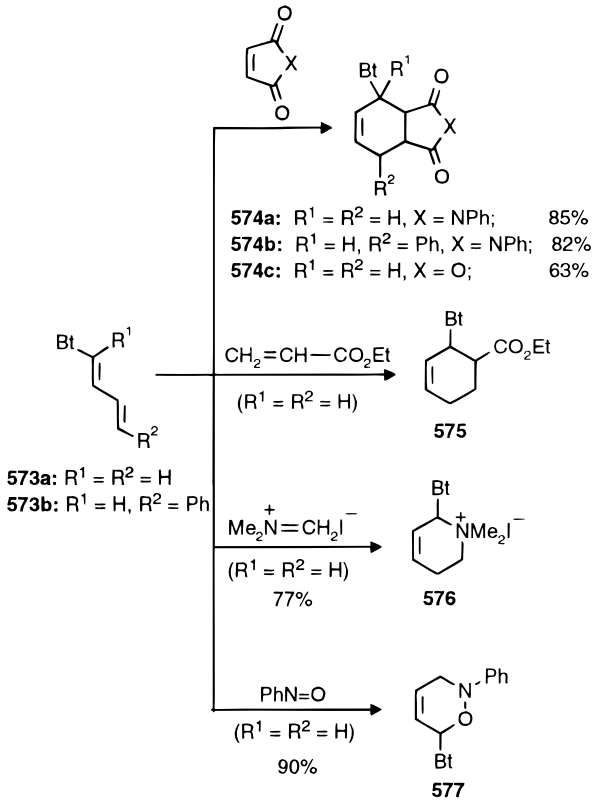


572a: R^1 = H, 66%
572b: R^1 = *n*-Pr, 64%
572c: R^1 = *i*-Pr, 72%
572d: R^1 = Ph, 77%

2. Cycloadditions

1-(1,3-Butadien-1-yl)benzotriazoles **573**, readily available from 1-[α-(phenylthio)alkyl]benzotriazoles through lithiation, alkylation, and dephenylthiolation, undergo Diels−Alder reactions with *N*-phenylmaleimide, maleic anhydride, and ethyl acrylate give compounds **574a**,**b**, **574c**, and **575** respectively[285] (Scheme 181). Compound **573a** also undergoes het-

Scheme 181. Diels−Alder Reactions of 1-Benzotriazolylbutadienes



574a: $R^1 = R^2$ = H, X = NPh; 85%
574b: R^1 = H, R^2 = Ph, X = NPh; 82%
574c: $R^1 = R^2$ = H, X = O; 63%

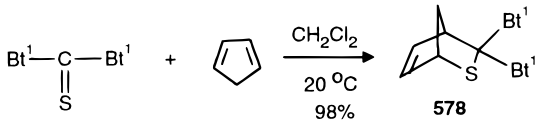
573a: $R^1 = R^2$ = H
573b: R^1 = H, R^2 = Ph

575 576 577

ero Diels−Alder reaction with Eschenmoser's salt and nitrosobenzene to give heterocycles **576** and **577**.

1,1′-Thiocarbonylbisbenzotriazole adds smoothly to cyclopentadiene providing in excellent yield the moisture-stable crystalline adduct **578** (Scheme 182),

Scheme 182. Diels−Alder Addition of 1,1′-Thiocarbonylbisbenzotriazole to Cyclopentadiene

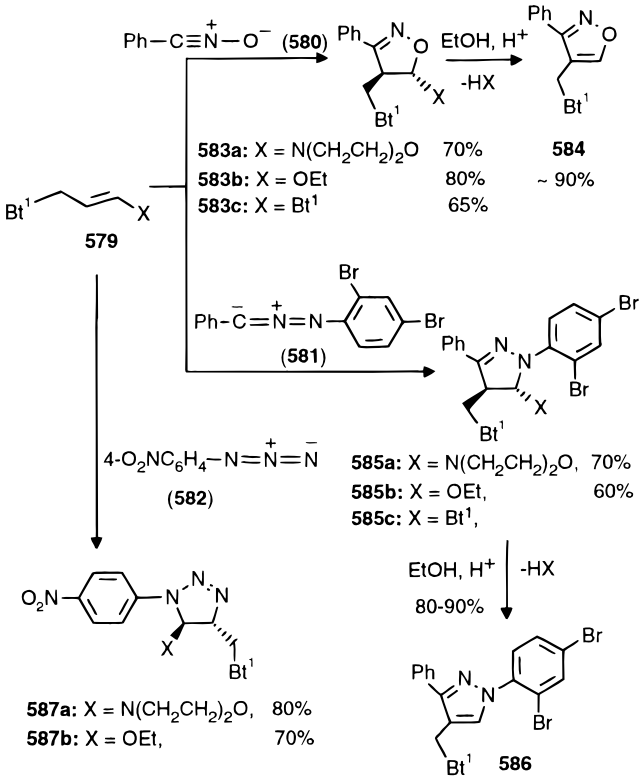


578

an important precursor for the synthesis of *cis*-3,5-fused mercapto esters.[286]

Electron-rich 3-benzotriazolylpropenes **579** undergo 1,3-dipolar cycloaddition reactions with benzonitrile oxide **580**, and **581** (derived from *N*-(2,4-dibromophenyl)phenylhydrazonyl bromide) and 4-nitrophenyl azide (**582**) to afford the corresponding isoxazolines **583**, pyrazolines **585**, and 1,2,3-triazolines **587**, respectively (Scheme 183).[83] Elimination of HX from

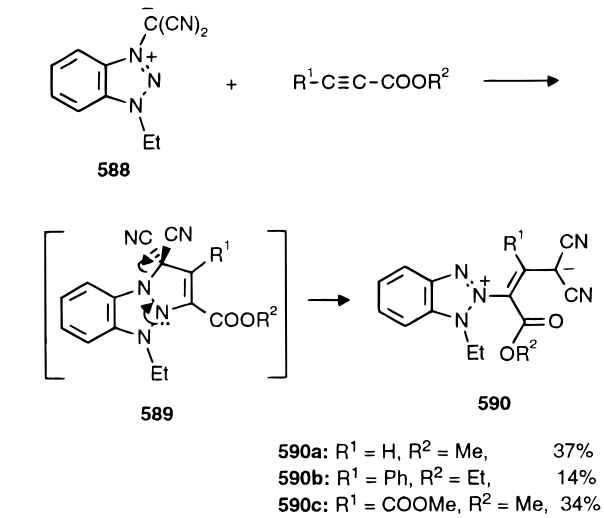
Scheme 183. 1,3-Dipolar Cycloadditions of Electron-Rich 3-Benzotriazolylpropenes



583 and **585** provides benzotriazolylmethyl-substituted isoxazoles **584** and pyrazoles **586** in high yields.

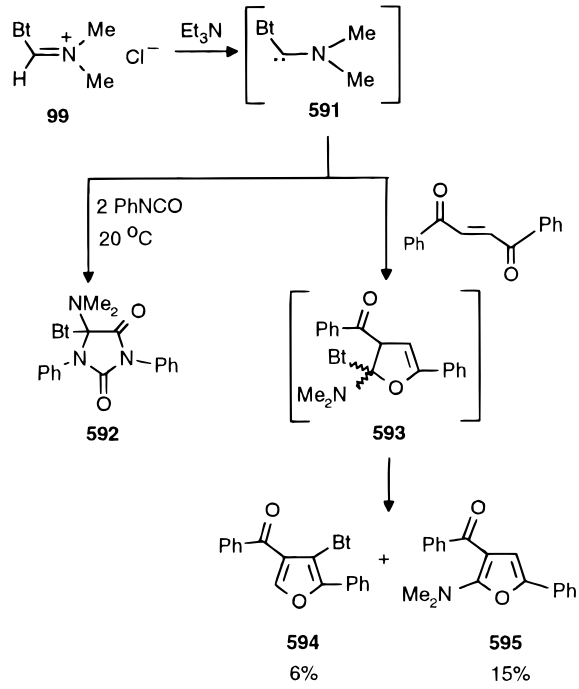
In 1,3-disubstituted benzotriazolium ylides, the benzotriazole ring itself participates as a N=N⁺(R)—C⁻ moiety in 1,3-dipolar cycloaddition reactions. Thus, 3-(dicyanomethyl)-1-ethylbenzotriazolium ylide **588** reacts regioselectively with acetylenic esters in refluxing toluene to produce the corresponding unstable tricyclic adducts **589**, which at reaction conditions undergo the ring opening to give 1,2-disubstituted benzotriazolium ylides **590** (Scheme 184).[287]

Scheme 184. Cycloaddition of Benzotriazolium Ylide with Acetylenic Esters



(*N*,*N*-Dimethylamino)(benzotriazolyl)carbene **591**, easily generated by deprotonation of the corresponding iminium salt **99** (for preparation see section II.A.6) with triethylamine, undergoes a typical [1 + 2 + 2] cycloaddition reaction with phenyl isocyanate to give benzotriazolyl-substituted hydantoin **592** (Scheme 185).[59] However, due to its low stability,

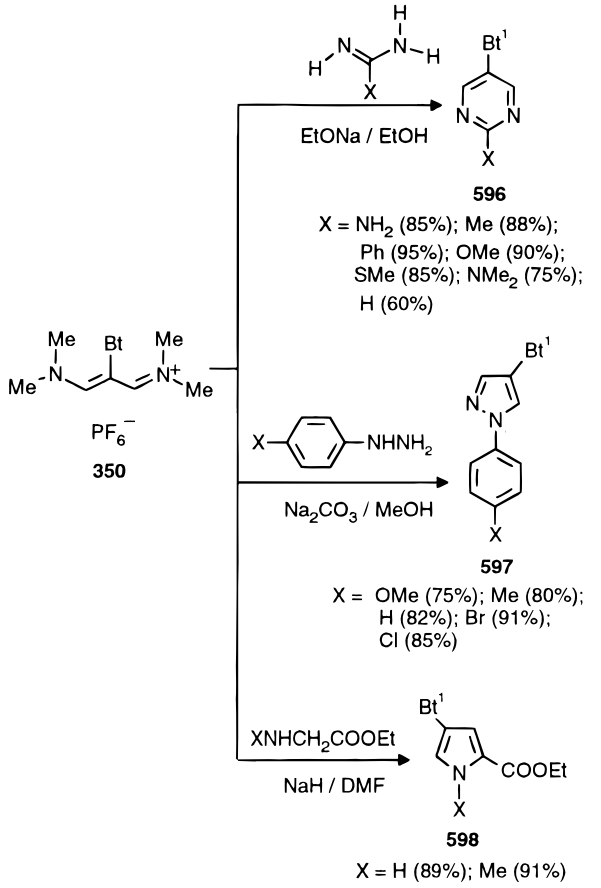
Scheme 185. Generation and Cycloaddition Reactions of (*N*,*N*-Dimethylamino)(benzotriazolyl)-carbene



this hydantoin was not isolated but converted directly into various 5-substituted hydantoins by treatment with different nucleophiles (see sections IV.B.1.a and IV.B.2.a). [1 + 4] cycloaddition reaction of **591** with *trans*-dibenzoylethylene results in a mixture of **594** and the benzotriazole elimination product **595**. The formation of furan **594** is believed to proceed via intermediate **593** ring opening with rearrangement and subsequent ring closure.[59]

Condensation of 2-(benzotriazol-1-yl)vinamidinium salt (**350**; for preparation see section III.A.5.c) with substituted amidines in an ethanol−sodium ethoxide mixture produces the corresponding 5-benzotriazolyl-substituted pyrimidines **596** (Scheme 186) in excellent yields.[21] When X is a good leaving group, the reaction can be carried out under neutral conditions, as exemplified by condensation with methylisothiourea (X = SMe). Similar condensations of **350** with *para*-substituted phenylhydrazines and with ethyl 2-aminoacetates in the presence of a base lead to the formation of a series of benzotriazole-containing pyrazoles **597** and pyrroles **598**, respectively.

Scheme 186. Preparation of Benzotriazolyl-Substituted Pyrimidines, Pyrazoles, and Pyrroles



3. Formation of (Benzotriazol-1-ylmethyl)ammonium Salts and 1-Substituted 3-Alkylbenzotriazolium Iodides

Two routes are possible for the preparation of benzotriazol-1-ylmethylammonium salts[105] (Scheme 187). Reaction of 1-(chloromethyl)benzotriazole with a tertiary amine is facilitated by the addition of 1 equiv of sodium iodide which enables faster reaction and forms less soluble and less hygroscopic ammonium salts compared to the corresponding chloride. Direct quaternization of 1-[(dialkylamino)-methyl]benzotriazoles with a halide is an alternative. However, the halides are generally limited to methyl iodide, ethyl iodide, and 1-(chloromethyl)benzotriazole. Methyl tosylate reacts only with 1-(*N*-pyrrolidylmethyl)benzotriazole. An reasonable explanation for this limitation is that the benzotriazole adduct is in solution in equilibrium with benzotriazole anion and the imminium cation **547**. An alkyl halide alkylates the benzotriazole ring and excess of halide further quaternizes the N-3 of the 1-alkylbenzotriazole giving 1,3-dialkylbenzotriazolium salt **600**. Indeed, when 1-(*N*-pyrrolidylmethyl)benzotriazole is treated with benzyl bromide, 1,3-dibenzylbenzotriazolium bromide is obtained in 65% yield (Table 54).

A separate study has shown that the N-3 of 1-substituted benzotriazoles is nucleophilic enough to react with methyl iodide to form 1-substituted 3-methylbenzotriazolium iodides **601**[240] (Scheme 188).

Scheme 187. Formation of (Benzotriazolyl-methyl)ammonium Salts

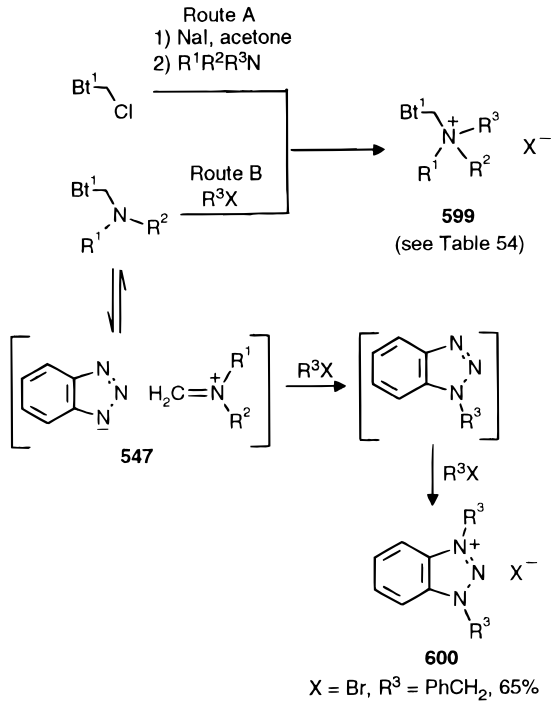
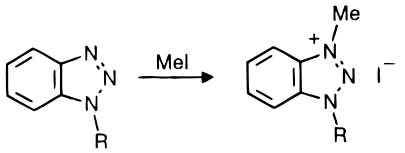


Table 54. Preparation of Trialkyl(benzotriazolyl-methyl)ammonium Salts 599

R^1	R^2	R^3	X	route	yield %
Me	Me	Me	I	A	79
Me	Me	Ph	I	A	34
Et	Et	Et	I	A	96
$-(CH_2)_4-$		Me	I	A	94
$-(CH_2)_4-$		Me	I	B	64
$-(CH_2)_4-$		Me	OTs	B	46
$-(CH_2)_4-$		Et	I	B	60
$-(CH_2)_4-$		$BtCH_2$	Cl	B	53
$-(CH_2)_4-$		$PhCH_2$	I	A	99
$-(CH_2)_4-$		$PhCH_2CH_2$	I	A	100
$-(CH_2)_5-$		Me	I	A	92
$-(CH_2)_2O(CH_2)_2-$		Me	I	B	40
$-CH_2CH_2N(CH_2CH_2)_2-$			I	A	86

Scheme 188. Formation of 1,3-Dialkylbenzotriazolium Salts



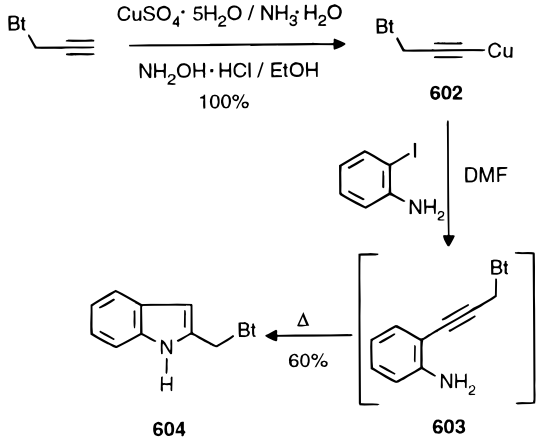
601a: R = CH_2Ph; 65%
601b: R = CH_2SOPh; 82%
601c: R = CH_2SO_2Ph; 35%
601d: R = Me; 26%
601e: R = CH=CHPh; 66%

4. Formation of Bt–C–Heterocyclic Systems by Cyclization

Treatment of 1-propargylbenzotriazole with copper(II) sulfate gives quantitatively the corresponding cupric salt **602**. Subsequent coupling with 2-iodoaniline followed by thermal cyclization affords 2-(benzotriazol-1-ylmethyl)indole **604** in 60% yield[206] (Scheme 189).

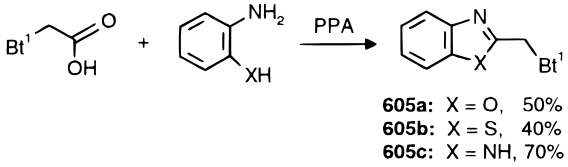
(Benzotriazol-1-yl)acetic acid, readily available from benzotriazole and chloroacetic acid (see section II.A.1),

Scheme 189. Preparation of 2-(Benzotriazolylmethyl)indole from 1-Propargylbenzotriazole



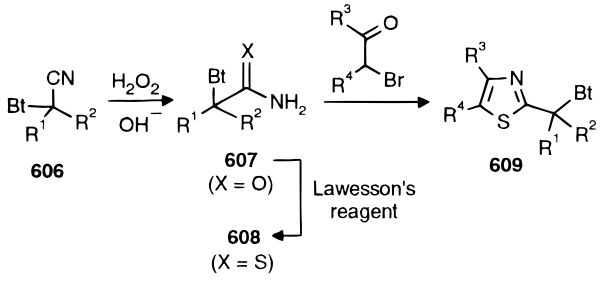
undergoes condensation with *o*-hydroxy-, *o*-mercapto-, or *o*-aminoanilines at 170 °C in the presence of polyphosphoric acid (PPA) to give the corresponding unsymmetrical diazolylmethanes **605** (Scheme 190) in moderate yields.[208]

Scheme 190. Preparation of Unsymmetrical Di(azolyl)methanes from Benzotriazol-1-ylacetic Acid



Treatment of 1-(1-cyanoalkyl)benzotriazoles **606** with 30% hydrogen peroxide and K_2CO_3 in aqueous DMF forms the benzotriazole-substituted amides **607** which are converted to the corresponding thioamides **608** by treatment with Lawesson's reagent (Scheme 191).[207] Condensation of **608** with α-halo carbonyl

Scheme 191. Preparation of 2-(α-Benzotriazol-1-ylalkyl)thiazoles from 1-(1-Cyanoalkyl)-benzotriazoles

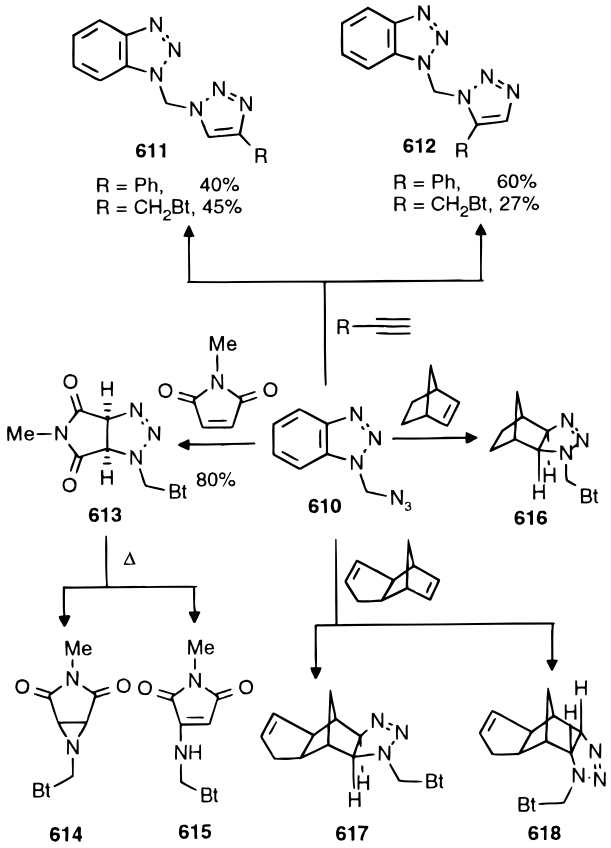


609	R^1	R^2	R^3	R^4	Yield (%)
	H	H	Ph	H	81
	Me	Me	Ph	H	47
	H	H	Ph	Ph	50
	H	H	Ph	Me	59
	H	H	Me	Me	66

compounds leads to 2-(α-benzotriazol-1-ylalkyl)thiazoles **609** in good overall yields.

1-(Azidomethyl)benzotriazole (**610**) undergoes 1,3-dipolar cycloaddition with a number of dienophiles

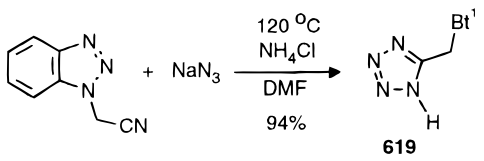
Scheme 192. Reactions of 1,3-Dipolar Cycloaddition of 1-(Azidomethyl)benzotriazole



to yield 1,2,3-triazoles, 1,2,3-triazolines, or aziridines (Scheme 192).[288] Heating **610** with acetylenes in toluene for 2 h produces a mixture of 4- and 5-substituted triazoles **611** and **612**. Reaction with *N*-methylmaleimide for 3 h forms exclusively triazoline **613** while extended reflux leads to a mixture of **613**, aziridine **614** and enamine **615**. Cycloaddition of **610** with norbornene gives exclusively the *exo* isomer **616**. It is noteworthy that reaction of **610** with dicyclopentadiene occurs exclusively at the norbornene double bond, and yet gives a mixture of the *exo* and *endo* isomers.

The general approach to the synthesis of 5-substituted 1,2,3,4-tetrazoles, based on 1,3-cycloaddition of azides to alkyl-, aryl-, or heteroarylnitriles, can also be applied to the preparation of benzotriazolylmethyl-substituted analogues. Thus, 1,3-dipolar addition of sodium azide to 1-(cyanomethyl)benzotriazole gives the corresponding 5-(benzotriazol-1-ylmethyl)-1*H*-tetrazole (**619**, Scheme 193).[208]

Scheme 193. Preparation of 5-(Benzotriazol-1-ylmethyl)-1*H*-tetraazole



5. Formation of α-Benzotriazolyl-α,β-Unsaturated Aldehydes

Reaction of 2-benzotriazol-1-ylvinamidium salt (**350**) with Grignard reagents followed by acid hydrolysis

produces benzotriazolyl-substituted α,β-unsaturated aldehydes **620** which can either be isolated in pure form (even though not very stable) or transformed into the corresponding 2,4-dinitrophenylhydrazones **621** (Scheme 194, Table 55).[289]

Scheme 194. Reactions of 2-Benzotriazol-1-ylvinamidium Salt with Grignard Reagents

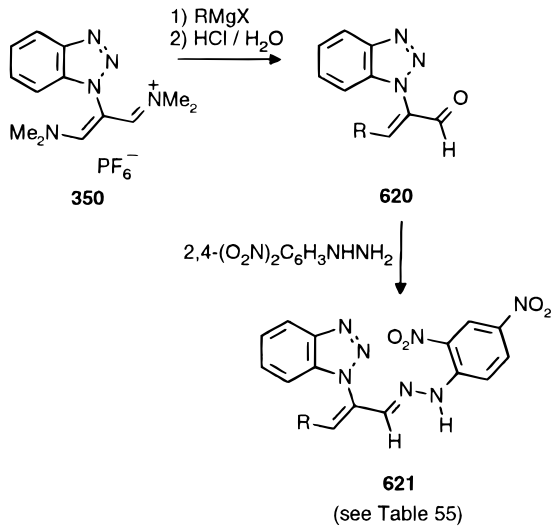


Table 55. Preparation of Benzotriazolyl-Substituted α,β-Unsaturated Aldehydes 620 and Their 2,4-Dinitrophenylhydrazones 621

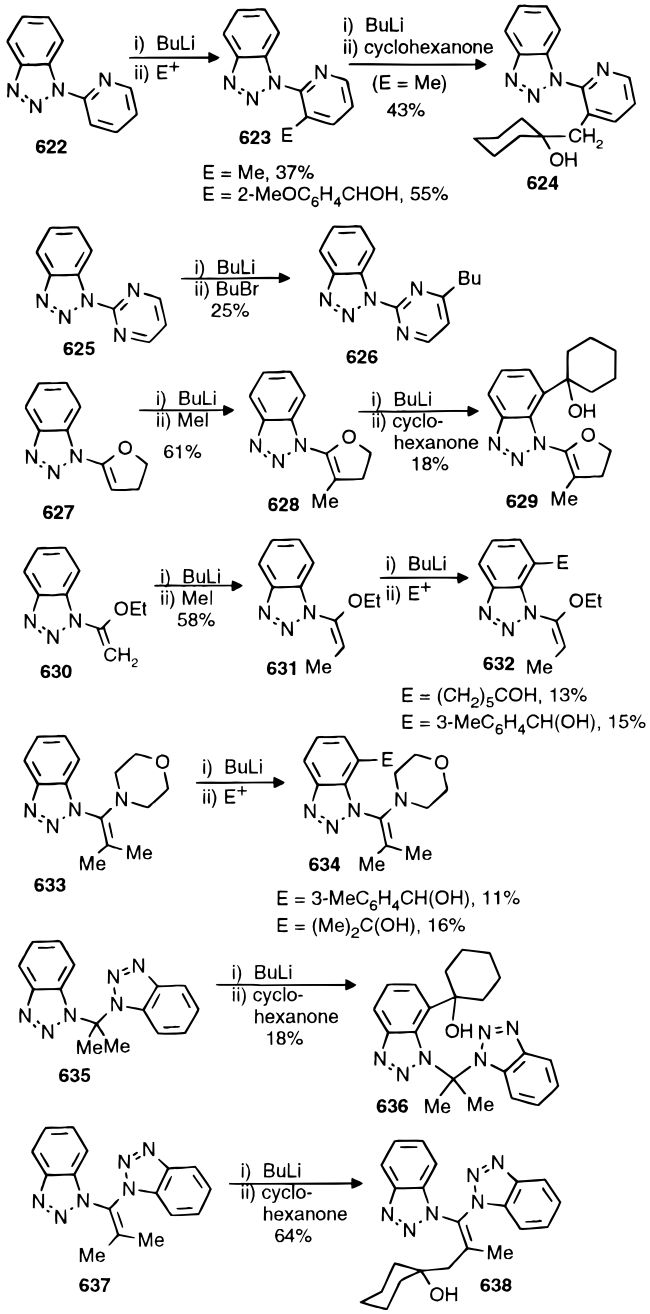
R	yield of **620** (%)	yield of **621** (%)	R	yield of **620** (%)	yield of **621** (%)
Me	92	92	*n*-C_5H_{11}	62	64
Et	58	32	Ph	43	57
i-Pr	48	87	4-ClC_6H_4	66	73
n-Bu	61	68	4-FC_6H_4	63	73
i-Bu	88	67	4-(*t*-Bu)C_6H_4	40	89

6. Heteroatom-Assisted Lithiation of N-Substituted Benzotriazoles

Modification of benzotriazole rings by benzene ring C deprotonation has rarely appeared in the literature. This is due mainly to two reasons: (i) direct ring deprotonation without the assistance of a facilitating group is difficult because of charge repulsion by the nitrogen lone pairs and the low acidity of the ring hydrogens, and (ii) benzotriazole is a good activating group and, as a result, *N*-substituted benzotriazoles containing an α hydrogen most often undergo α deprotonation rather than ring deprotonation.[4] Consequently, it is of significant interest to investigate the lithiation of the benzotriazole systems in which there is no α hydrogen available, but where a heteroatom attached to the α carbon could assist and direct the ring lithiation (Scheme 195).

Treatment of 2-benzotriazol-1-ylpyridine (**622**) with *n*-butyllithium followed by electrophiles gives 3-substituted pyridines **623**, indicating the strong directing effect of the *N*-benzotriazolyl substituent (through the favored five-membered ring intermediate) (Scheme 195).[27] Further lithiation of **623** (R = Me) occurs at the methyl group and quenching with cyclohexanone leads to **624**. A similar reaction out with 2-benzotriazol-1-ylpyrimidine (**625**) where such an assistance

Scheme 195. Heteroatom-Assisted Lithiation of *N*-Substituted Benzotriazoles



is not available, still gave the corresponding 4-substituted pyrimidine **626**. 2-Benzotriazol-1-yl-3,4-dihydrofuran (**627**) treated with *n*-butyllithium and methyl iodide, 3-methyl-3,4-dihydrofuran derivative **628** as a result of the benzotriazole-directing effect.[27] This directing effect is further confirmed by the exclusive formation of *trans*-alkene **631** from 1-ethoxy-1-benzotriazol-1-ylethylene (**630**). Nevertheless, further treatments of **628** and **631** with *n*-butyllithium followed by electrophiles does give the benzotriazole ring-substituted products **629** and **632**, respectively, as a result of the heteroatom-assisting and -directing effects. Similar reactions with 1-benzotriazol-1-yl-1-morpholino-2-methylpropene (**633**) lead to 7-substituted benzotriazoles **634**. Lithiation of 2,2-dibenzotriazol-1-ylpropane (**635**) also occurs at the benzotriazole C-7 position and the resulting anion is

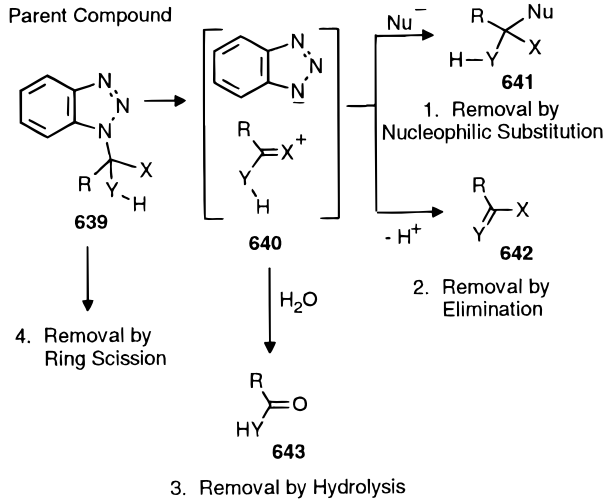
trapped with cyclohexanone to give the 7-substituted product **636**. However in all these cases, the yields of 7-substituted benzotriazoles are low. Lithiation of 1,1-dibenzotriazol-1-yl-2-methylpropene (**637**) takes place exclusively at the methyl group to yield 63% probably because of the dominating inductive effect of the two benzotriazole rings which renders the methyl group more acidic than the ring C-7 hydrogen.

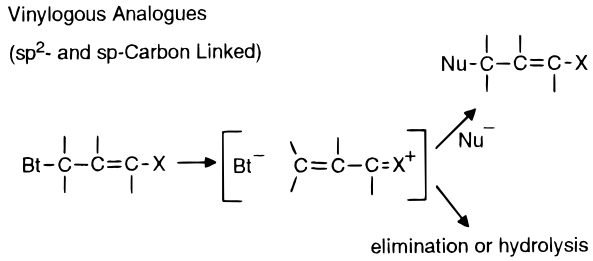
IV. Reactions Involving the Removal of Benzotriazole Groups

A. Introduction

The four major ways in which a benzotriazolyl group is removed from molecule **639** are shown in Scheme 196. The first three modes (1, nucleophilic

Scheme 196. Major Routes by Which a Benzotriazole Group Is Removed from a Molecule

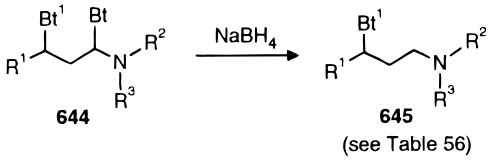




substitution; 2, elimination; 3, hydrolysis) all depend on initial dissociation to Bt^- and a cation **640**. Such dissociation is much assisted by a suitable heteroatom X, and also by proton or Lewis acid catalysis which helps the departure of the benzotriazolyl group. Each of these three modes will be discussed in turn, classified according to the nature of the activating atom X: analogous vinylogous activation is also possible. The fourth mode (ring scission), is of a fundamentally different character, and will be discussed in section V.

It should be emphasized that all these transformations are also highly dependent on the presence of other functionality in the vicinity exemplified by the group Y. Thus, molecules containing Bt groups in different environments can exhibit very different reactivity. An example is shown in Scheme 197

Scheme 197. Example of Different Reactivity of Benzotriazole Groups in the Same Molecule



where the benzotriazole group α to an amino in **644** is easily replaced while the other remains unreacted in product **645**[150] (Table 56).

Table 56. Preparation of Compounds 645 by Reduction of 1,3-Dibenzotriazol-1-ylalkane-1-amines 644 with $NaBH_4$

R^1	R^2	R^3	yield %
H	4-MeC_6H_4	H	76
H	$-(CH_2)_2O(CH_2)_2-$		84
Me	Ph	H	95
Me	4-MeC_6H_4	H	93
Me	4-ClC_6H_4	H	90
Me	4-$MeOC_6H_4$	H	100
Me	4-Py	H	14
Me	$-(CH_2)_2O(CH_2)_2-$		70
Ph	$-(CH_2)_2O(CH_2)_2-$		83

B. Removal by Nucleophilic Substitution

We first consider such reactions of compounds of type Bt−C−X successively where X is N, O, or S. Particularly when X is N there are many subdivisions depending on the type of N, and we consider succeedingly amino-N (aminoalkylations), hydroxylamino- and amidino-N, amido-N (amidoalkylations), thioamido-N, and sulfonamido-N. Activation of the type described in Scheme 196 can occur vinylogously and therefore, systems of type Bt−C−C=C−X, including aryl and heteroaryl cases, will be treated systematically. Finally we deal with Bt groups attached to sp^2 and sp carbon atoms.

1. From Systems of Type Bt–C–N by C- and H-Nucleophiles: Aminoalkylations

Compounds of this type react with a wide variety of nucleophiles, enabling the preparation of a wide variety of compound classes (Scheme 198).

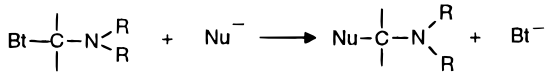
We consider first reactions with unstabilized carbanions (many Grignard reagents and organozinc compounds) and also with sodium borohydride and lithium aluminum hydride which all lead to tertiary and secondary amines, and then continue on to deal with other nucleophiles.

a. With Organometallics or Hydrides To Give Tertiary Amines. Use of an organometallic reagent forms a C−C bond in place of the original Bt−C bond and enables the synthesis of a wide variety of tertiary amines. The preparations of unsymmetrical tertiary amines from secondary amines are illustrated in Scheme 199. The condensation product **113** is treated with a Grignard reagent or $NaBH_4$ to give the

Table 57. Preparation of Tertiary Amines 646

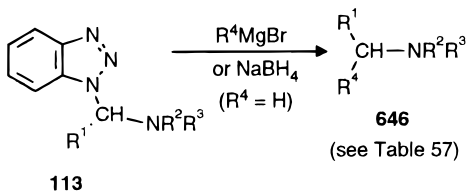
R^1	R^2	R^3	R^4	yield %
H	Me	Ph	H	82[98]
H	Me	Ph	*n*-Bu	73[98]
H	Et	Et	$PhCH_2$	91[98]
H	$PhCH_2$	$PhCH_2$	H	75[98]
H	$PhCH_2$	$PhCH_2$	Me	80[98]
H	$PhCH_2$	$PhCH_2$	Ph	83[98]
H	$PhCH_2$	$PhCH_2$	$PhCH_2$	88[98]
H	*n*-C_8H_{17}	*n*-C_8H_{17}	Ph	58[98]
n-Pr	$-(CH_2)_2O(CH_2)_2-$		*n*-Pr	79[98]
i-Pr	$-(CH_2)_4-$		Ph	64[98]
i-Pr	$-(CH_2)_4-$		$PhCH_2$	76[98]
i-Pr	$PhCH_2$	$PhCH_2$	H	83[98]
i-Pr	$PhCH_2$	$PhCH_2$	Me	78[98]
Ph	$-(CH_2)_5-$		*i*-Pr	59[98]
Ph	$-(CH_2)_2O(CH_2)_2-$		H	91[98]
Ph	$-(CH_2)_2O(CH_2)_2-$		*n*-Bu	82[98]
$HCF_2(CF_2)_3$	$-(CH_2)_5-$		H	65[108]
$HCF_2(CF_2)_3$	$-(CH_2)_2O(CH_2)_2-$		H	54[108]
$ClCF_2(CF_2)_5$	$-(CH_2)_5-$		H	63[108]
$CF_3(CF_2)_2OCFCF_3$	$-(CH_2)_5-$		H	50[108]
C_6F_5	$PhCH_2$	$PhCH_2$	H	81[108]

Scheme 198. Aminoalkylation Reactions by Nucleophilic Replacement of Benzotriazole Groups in *N*-(α-Aminoalkyl)benzotriazoles



Nucleophile	Compounds prepared	Section
Unstabilized Carbanion	Secondary and tertiary amines	IVB1a-d
BH_4^-	Secondary and tertiary amines	IVB1a-d
Unstabilized Carbanion	Primary amines	IVB1e
Acetylene anion	Propargylamine	IVB1f
Stabilized Carbanion	Mannich type bases	IVB1j
Reactive aromatics	Benzylamines	IVB1k
Cyanide anion	Aminonitriles	IVB1l
N-nucleophiles	Aminals	IVB2a
O-nucleophiles	Hemiaminals	IVB2b
S-nucleophiles	Hemithioaminals	IVB2b
P-nucleophiles	Aminomethylphosphonates	IVB2c
Sn-nucleophiles	α-Stannylamines	IVB2d

Scheme 199. Preparation of Tertiary Amines from *N*-(α-Aminoalkyl)benzotriazoles



unsymmetrical tertiary amine **646** usually in good yield (Table 57).[98,122] Perfluoroalkyl tertiary amines are also obtained this way (Table 57).[108] Further examples are given in Scheme 200 and Table 58 for condensation products derived from cyclic ketones.[111]

Scheme 200. Preparation of Cycloalkyl Tertiary Amines and 5-Aminohydantoins

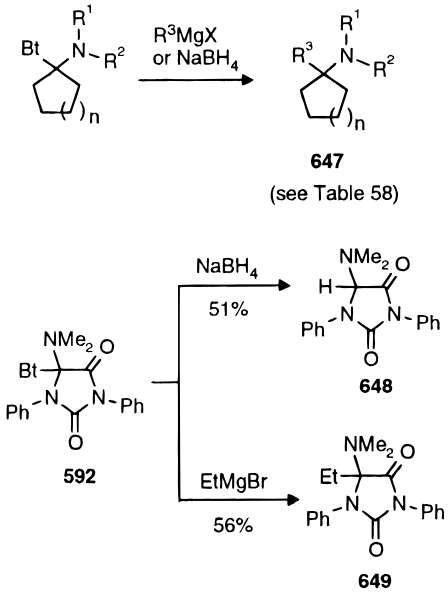


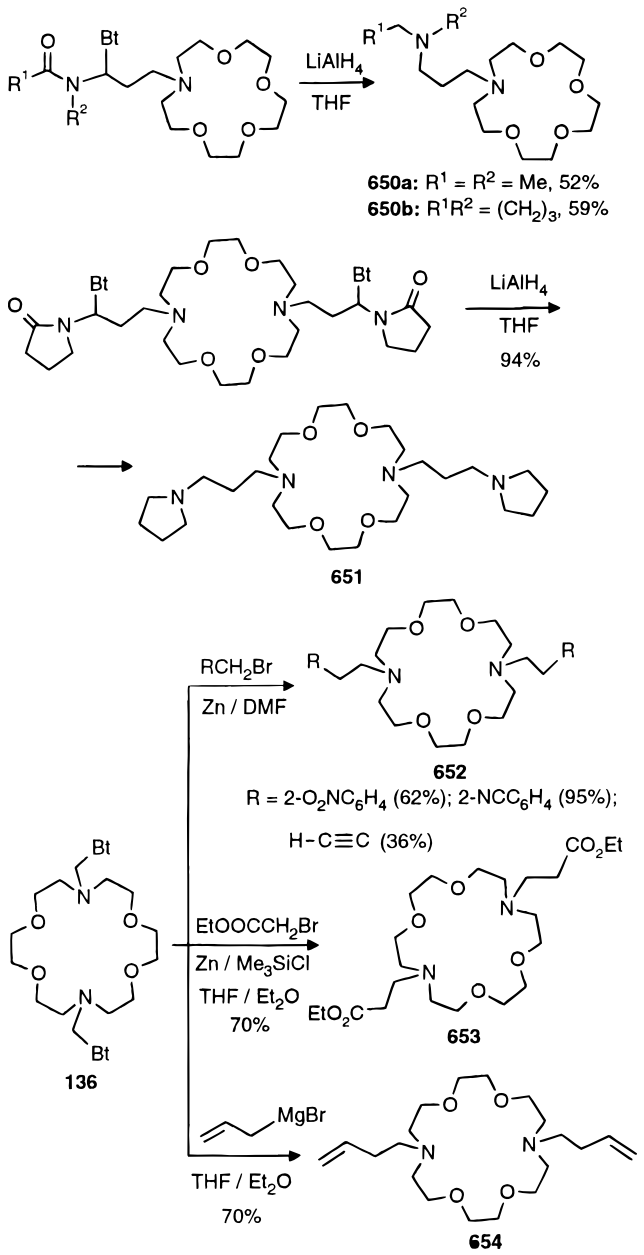
Table 58. Preparation of Cycloalkyl Tertiary Amines 647

R^1	R^2	R^3	n	yield %
$-(CH_2)_4-$		Ph	2	13
$-(CH_2)_5-$		Ph	2	73
$-(CH_2)_2O(CH_2)_2-$		H	2	82
$-(CH_2)_2O(CH_2)_2-$		Ph	2	74
$-(CH_2)_2O(CH_2)_2-$		4-MeC_6H_4	2	85
$-(CH_2)_2O(CH_2)_2-$		4-ClC_6H_4	2	86
$-(CH_2)_2O(CH_2)_2-$		$PhCH_2$	2	72
$-(CH_2)_2O(CH_2)_2-$		Ph	3	13

Unstable 5-benzotriazolyl-5-aminohydantoin **592** (for preparation, see section III.E.2) is converted *in situ* into 5-aminohydantoins **648** and **649** in moderate yields (Scheme 200).[59]

N-(3-Benzotriazolyl-3-amidopropyl)-substituted monoaza-[102] and diaza-[124] crown ethers are reduced with lithium aluminum hydride in refluxing THF to give *N*-(3-aminopropyl) macrocycles **650** and **651**, respectively (Scheme 201). However, a carbazolyl moiety in the α position to benzotriazolyl group

Scheme 201. Preparation of *N*-Pivot Lariat Crown Ethers



deactivates the substrate toward action of lithium aluminum hydride, and the corresponding carbazolyl derivatives were not obtained. *N*,*N*′-Bis(benzotriazolylmethyl)-substituted 4,13-diaza-18-crown-6 **136** reacts with allylmagnesium bromide to afford the functionalized crown ether **654** in 70% yield.[124] Modified Reformatsky reactions of **136** result in the corresponding bis-lariats **652** and **653** (Scheme 201).

Tertiary amines **655** with two identical N substituents can be prepared from the benzotriazole condensation products derived from a primary amine by reactions with a Grignard reagent.[98] Similarly, tertiary amines **656** with three identical substituents are obtained from the tris(benzotriazolylmethyl)-substituted amines [98] (Scheme 202 and Table 59).

1,1-Diaminomethanes **657a**,**b** as well as imidazolidines **658a**−**d** and hexahydropyrimidines **658e**−**f** are prepared from the corresponding benzotriazolyl-

Scheme 202. Preparations of Tertiary Amines with Two or Three Identical Substituents

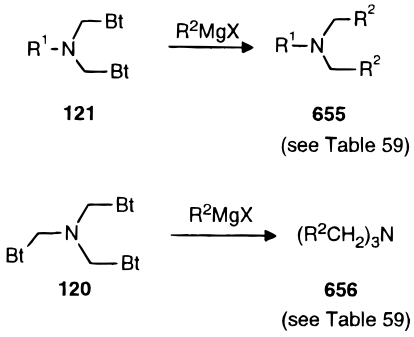
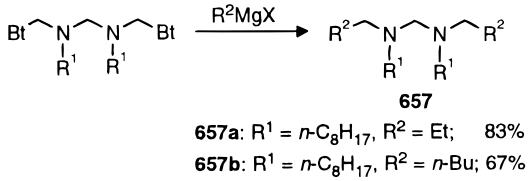


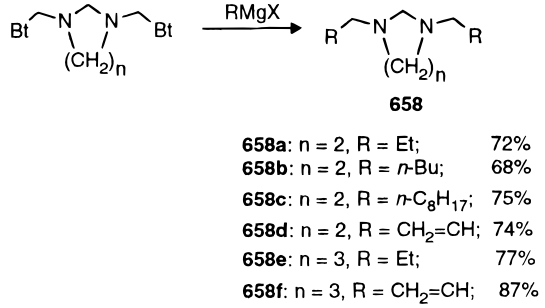
Table 59. Preparation of Tertiary Amines with Two (655) or Three (656) Identical Substituents

compound	R^1	R^2	yield %
655	Me	*i*-Pr	66
	Me	Ph	90
	n-C_8H_{17}	*i*-Pr	88
	n-C_8H_{17}	*n*-C_8H_{17}	95
	OH	*n*-Bu	89
	OH	c-C_6H_{11}	86
	OH	*n*-C_8H_{17}	92
	OH	Ph	94
	OH	PhC/C	87
656		*n*-Pr	75
		n-Bu	40
		c-C_6H_{11}	66
		Ph	74
		4-MeC_6H_4	51
		1-naphthyl	55

containing precursors shown in Scheme 203 by reaction with Grignard reagents.[115]

Scheme 203. Preparation of 1,1-Diaminomethanes, Imidazolines, and Hexahydropyrimidines





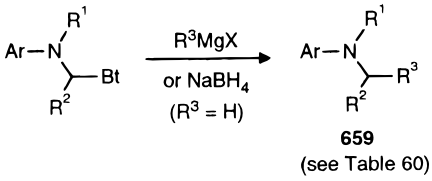
Dialkylarylamines possessing different alkyl groups attached to the nitrogen atom are likewise prepared from an arylalkylamine, benzotriazole, and formaldehyde and subsequent treatment of the product with a Grignard reagent or sodium borohydride.[103] Alternatively the direct dialkylation of aromatic amines can be achieved by reacting the corresponding diben-

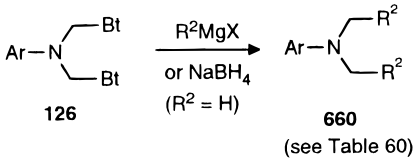
Table 60. Preparation of Tertiary Arylamines 659 and 660

compound	Ar	R^1	R^2	R^3	yield %
659	Ph	Me	H	$PhCH_2$	99[103]
	Ph	Et	H	$PhCH_2$	87[103]
	Ph	*n*-Bu	H	$PhCH_2$	38[103]
	3-$O_2NC_6H_4$	*n*-Bu	$PhCH_2$	H	28[104]
	3-$EtCONHC_6H_4$	*n*-Bu	$PhCH_2$	H	80[104]
660	Ph		*i*-Pr		87[103]
	Ph		c-C_6H_{11}		33[103]
	Ph		$CH_2CH{=}CH_2$		99[103]
	3-ClC_6H_4		$PhCH_2$		56[103]
	4-ClC_6H_4		*i*-Pr		39[103]
	4-MeC_6H_4		$PhCH_2$		85[103]
	4-$MeOC_6H_4$		*i*-Pr		68[103]
	2-EtC_6H_4		H		77[103]
	4-(*n*-Bu)C_6H_4		$PhCH_2$		76[103]
	4-pyridyl		$PhCH_2$		21[103]

zotriazolyl adducts **126** with 2 mol of a Grignard reagent or excess of $NaBH_4$ (Scheme 204, Table 60).[103]

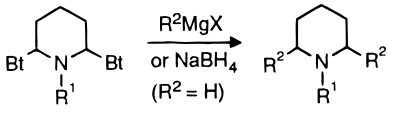
Scheme 204. Preparation of Tertiary Arylamines

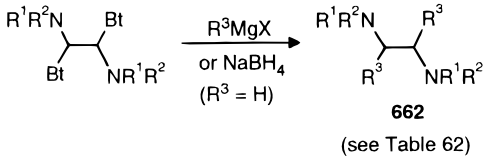




A similar method can be applied to the preparation of *N*-substituted piperidines (**661**, R^2 = H) and *N*,2,6-trisubstituted piperidines **661** (Scheme 205, Table 61).[121] Symmetrical vicinal bis-tertiary amines **662** are obtained analogously (Scheme 205, Table 62).[120]

Scheme 205. Preparation of 1-Mono- and 1,2,6-Trisubstituted Piperidines and Vicinal Bis-Tertiary Amines





An interesting example of this type of reactions is the high yield preparation of 6-aminobicyclo[3,1,0]-hexanes **663a**,**b** (Scheme 206).[159]

Table 61. Preparation of 1-Mono and 1,2,6-Trisubstituted Piperidines 661

R^1	R^2	yield %
i-Pr	H	55
n-Bu	H	59
Ph	H	80
3-MeC_6H_4	H	68
$PhCH_2$	H	78
$PhCH_2$	Me	48
$PhCH_2$	*n*-Bu	45
2-pyridyl	H	64

Table 62. Preparation of Vicinal Bis-tertiary Amines 662

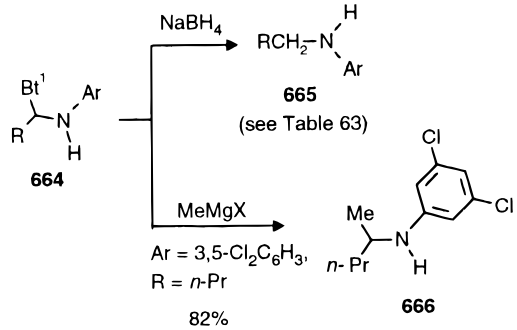
R^1	R^2	R^3	yield %
n-Bu	*n*-Bu	H	70
	$-(CH_2)_5-$	H	79
	$-(CH_2)_5-$	Me	70
	$-(CH_2)_5-$	*n*-Bu	62
	$-(CH_2)_5-$	Ph	78
	$-(CH_2)_5-$	$PhCH_2$	77
	$-(CH_2)_2O(CH_2)_2-$	H	76
	$-(CH_2)_2O(CH_2)_2-$	Me	74
	$-(CH_2)_2O(CH_2)_2-$	*n*-Bu	68
	$-(CH_2)_2O(CH_2)_2-$	Ph	75
	$-(CH_2)_2O(CH_2)_2-$	$PhCH_2$	69
$PhCH_2$	$PhCH_2$	H	87
$PhCH_2$	$PhCH_2$	Me	83
$PhCH_2$	$PhCH_2$	*n*-Bu	68
$PhCH_2$	$PhCH_2$	Ph	81

Scheme 206. Preparation of 6-Aminobicyclo-[3.1.0]hexanes

663a: R = Ph; 91%
663b: R = $PhCH_2$; 98%

b. With Grignards or Borohydride To Give Secondary Amines. Because the corresponding benzotriazole condensation products are readily available, the selective monoalkylation of aromatic amines is easily attained as shown in Scheme 207. The adducts **664**

Scheme 207. Preparation of Secondary Aromatic Amines



react with borohydride or Grignard reagents to give amines of types **665** and **666**, respectively, in high yields (Table 63).[104,116,290]

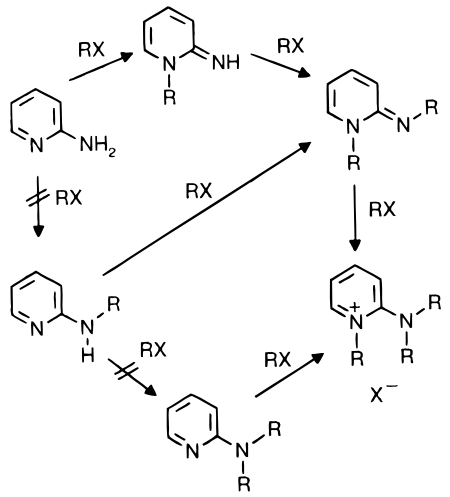
This procedure is highly useful for the preparation of substituted heteroaromatic amines. Direct alkylation of heteroaryl amines at the exocyclic nitrogen

Table 63. Preparation of Secondary Arylamines 665

Ar	R	yield %
4-ClC_6H_4	H	80[290]
4-ClC_6H_4	$PhCH_2$	85[290]
4-$HOOCC_6H_4$	H	91[290]
4-$HOOCC_6H_4$	*n*-Pr	85[290]
3-$O_2NC_6H_4$	Me	93[104]
3-$O_2NC_6H_4$	*n*-Pr	96[104]
3-$O_2NC_6H_4$	$PhCH_2$	98[104]
4-$O_2NC_6H_4$	H	89[290]
3-(MeCONH)C_6H_4	*n*-Pr	95[104]
2-MeC_6H_4	H	87[116]
4-MeC_6H_4	$HCF_2(CF_2)_3$	70[108]
3,5-$Cl_2C_6H_3$	*n*-Pr	68[290]

has been difficult as exemplified by the behavior of 2-aminopyridine is treated with an alkyl halide (Scheme 208). Under normal conditions reaction

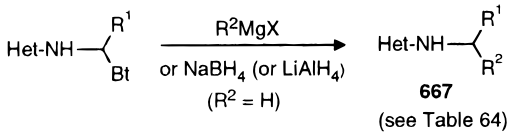
Scheme 208. Classical Alkylation of 2-Aminopyridine



occurs at the pyridine nitrogen instead of at the amino group. In order for the reaction to be directed to the amino group, strongly basic conditions have to be utilized under which one of the amino hydrogens is first removed.

By contrast, using benzotriazole methodology, monoalkylated 2-aminopyridines are prepared directly from 2-aminopyridine in high yields (Scheme 209, Table 64). This methodology can be extended

Scheme 209. Preparation of Secondary Heteroarylamines



to monoalkylation of aminopyrimidines and -adenines. It is noteworthy that adenine is alkylated regiospecifically at the acyclic amino group.[290]

The preparation of symmetrical secondary aliphatic amines is readily achieved using the bis condensation product of ammonia with benzotriazole and formaldehyde **117** (R^1 = H). The secondary amines **668** are formed in high yield as shown in Scheme 210 and Table 65.[98] Later, we found[112] that aldehydes other than formaldehyde can also be used to prepare

Table 64. Alkylation of Primary Heteroarylamines

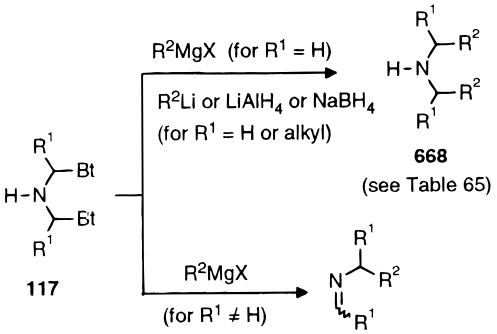
heteroaryl	R^1	R^2	yield %
pyridin-2-yl	H	H	95
pyridin-2-yl	H	$PhCH_2$	82
pyridin-2-yl	Me	CH_2=$CHCH_2$	62
pyridin-2-yl	*i*-Pr	H	81
pyridin-2-yl	*i*-Pr	Me	80
pyridin-2-yl	*t*-Bu	H	96
4-chloropyridin-2-yl	H	H	92
4-chloropyridin-2-yl	$PhCH_2$	H	98
4-nitropyridin-2-yl	H	H	89
4-methylpyridin-2-yl	H	H	95
4-methylpyridin-2-yl	H	$PhCH_2$	78
6-methylpyridin-2-yl	H	Me	76
4,6-dimethylpyridin-2-yl	H	H	85
pyrimidin-2-yl	*n*-Pr	H	98
pyrimidin-2-yl	*n*-Pr	$PhCH_2$	95
pyrimidin-2-yl	4-MeC_6H_4	H	91
adenin-6-yl	H	H	75
adenin-6-yl	H	*n*-Pr	71
adenin-6-yl	H	Ph	80

Table 65. Preparation of Symmetrical Secondary Amines 668

R^1	R^2	yield %
H	*n*-Bu	65[98]
H	Ph	75[98]
H	$PhCH_2$	45[98]
i-Pr	H	90[112]
i-Pr	Ph[a]	91[112]
c-C_6H_{11}	H	91[112]
c-C_6H_{11}	Ph[a]	92[112]
PhCH(Me)	H	93[112]

[a] PhLi is used instead of R^2MgX.

Scheme 210. Preparation of Symmetrical Aliphatic Secondary Amines



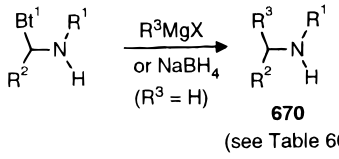
adducts **117** ($R^1 \neq$ H). These adducts, when reduced with $LiAlH_4$ or reacted with phenyllithium, give symmetrical secondary amines **668** (see Table 65). However, with Grignard reagents, adducts **117** ($R^1 \neq$ H) form imines **669** (Scheme 210).

The preparation of unsymmetrical secondary aliphatic amines by this type of method is more tricky as the intermediates tend to disproportionate. However, reasonable yields of the desired secondary amines **670** (Scheme 211) can be obtained as documented in Table 66.[108,114] More recently we found[291,292] that 1-(trimethylsilyl)benzotriazole adds reversibly to an imine to give benzotriazolyl-containing *N*-trimethylsilyl-protected secondary amine intermedi-

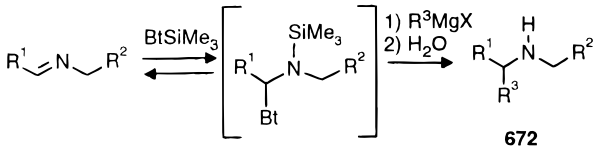
Table 66. Preparation of Unsymmetrical Secondary Amines 670 and 672

compound	R^1	R^2	R^3	yield %
670	*sec*-Bu	H	Ph	55[114]
	t-Bu	H	Ph	49[114]
	t-Bu	H	$PhCH_2$	51[114]
	c-C_5H_9	H	Ph	57[114]
	c-C_6H_{11}	H	Ph	50[114]
	c-C_6H_{11}	H	Et	56[114]
	c-C_6H_{11}	H	$PhCH_2$	64[114]
	n-C_8H_{17}	H	Ph	49[114]
	n-C_8H_{17}	H	$PhCH_2$	46[114]
	$PhCH_2$	$HCF_2(CF_2)_3$	H	59[108]
	PhCHMe	H	Ph	52[114]
	PhCHMe	H	$PhCH_2$	50[114]
672	*n*-Pr	Ph	*n*-Bu	61[291]
	n-Pr	Ph	Ph	70[291]
	i-Pr	*n*-C_7H_{15}	Me	60[291]
	i-Pr	*n*-C_7H_{15}	*n*-Bu	76[291]
	i-Pr	*n*-C_7H_{15}	Ph	78[291]
	i-Pr	*n*-C_7H_{15}	$PhCH_2$	65[291]
	i-Pr	$PhCH_2$	Me	69[291]
	i-Pr	$PhCH_2$	Ph	73[291]
	4-MeC_6H_4	*n*-C_7H_{15}	Me	72[291]
	4-MeC_6H_4	*n*-C_7H_{15}	Ph	93[291]

Scheme 211. Preparation of Unsymmetrical Secondary Aliphatic Amines



670
(see Table 66)

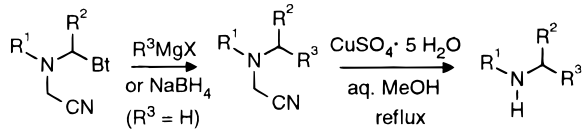


671 **672**
(see Table 66)

ates **671**. Reaction of **671** *in situ* with Grignard reagents followed by hydrolysis to remove the trimethylsilyl group now yields even unhindered secondary aliphatic amines **672** efficiently (Table 66).

An alternative preparation of unsymmetrical secondary amines starts with the quantitative formation of adducts **673** from benzotriazole, an aldehyde, and an *N*-alkylaminoacetonitrile (see section II.B.2.a).[109] Grignard reagents or $NaBH_4$ then displace the benzotriazole group from **673** to give **674** which can be decyanomethylated to form the secondary amines **675** (Scheme 212, Table 67).

Scheme 212. Alternative Preparation of Secondary Aliphatic Amines



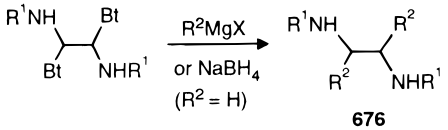
673 **674** **675**
(see Table 67) (see Table 67)

An extension of this methodology to aromatic primary amines allows the synthesis of symmetrical vicinal secondary diamines **676a**−**f** (Scheme 213).[120]

Table 67. Preparation of Tertiary Amines 674 and Unsymmetrical Secondary Amines 675

			yield %	
R^1	R^2	R^3	**674**	**675**
c-C_6H_{11}	H	H	67	not prepared
c-C_6H_{11}	H	$PhCH_2$	63	93
n-C_8H_{17}	H	H	66	90
n-C_8H_{17}	H	Ph	53	not prepared
n-C_8H_{17}	H	$PhCH_2$	65	99
n-C_8H_{17}	Me	H	77	not prepared
n-C_8H_{17}	*n*-Pr	H	70	87
n-C_8H_{17}	*n*-Pr	$PhCH_2$	25	not prepared
n-C_8H_{17}	*i*-Pr	H	73	97
n-C_8H_{17}	Ph	H	77	95
n-C_8H_{17}	Ph	Ph	55	60

Scheme 213. Preparation of Vicinal Secondary Amines

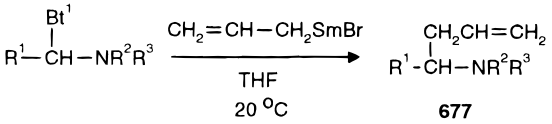


676

676a: R^1 = Ph, R^2 = H; 90%
676b: R^1 = 4-MeC_6H_4, R^2 = H; 93%
676c: R^1 = 3-MeC_6H_4, R^2 = H; 90%
676d: R^1 = R^2 = Ph; 62%
676e: R^1 = Ph, R^2 = $PhCH_2$; 69%
676f: R^1 = Ph, R^2 = Me; 51%

c. With Organosamarium Reagents To Give Tertiary and Secondary Amines. Reactions of *N*-(α-aminoalkyl)benzotriazoles with allylsamarium bromide (Scheme 214) provide a new method for

Scheme 214. Preparation of Homoallyl Amines with Organosamarium Reagents



677
(see Table 68)

preparation of a variety of secondary and tertiary homoallylamines **677** in mild neutral conditions and in good yields (Table 68).[293]

Table 68. Preparation of Homoallyl Amines 677

R^1	R^2	R^3	yield, %
H	H	Ph	90
H	H	3-ClC_6H_4	89
H	H	3-MeC_6H_4	93
H	H	4-MeC_6H_4	91
H	Me	Ph	87
H	H	$PhCH_2$	88
Ph	H	Ph	76
Ph	H	4-ClC_6H_4	72

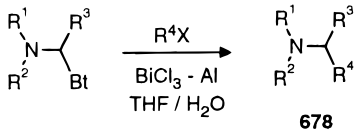
d. With Organobismuth Reagents To Give Tertiary and Secondary Amines in Aqueous Solution. The displacement of benzotriazole involving carbon−carbon formation with organometallic reagents such as Grignards is carried out in strictly anhydrous conditions. Systems utilizing organometallics derived from allyl halides and zinc or tin have been developed for allylation of carbonyl compounds in

Table 69. Preparation of Tertiary and Secondary Amines 678 in Aqueous Solution

R^1	R^2	R^3	R^4	yield %
i-Pr	*i*-Pr	H	Me	78
n-Bu	*n*-Bu	H	$CH_2CH{=}CH_2$	83
i-Bu	*i*-Bu	H	$CH_2CH{=}CH_2$	85
t-Bu	*i*-Bu	H	$PhCH_2$	88
c-C_6H_{11}	H	H	$CH_2CH{=}CH_2$	80
$-(CH_2)_4-$		H	$CH_2CH{=}CH_2$	85
$-(CH_2)_5-$		H	$CH_2CH{=}CH_2$	87
$-(CH_2)_2O(CH_2)_2-$		H	$CH_2CH{=}CH_2$	80
$-(CH_2)_2O(CH_2)_2-$		H	$PhCH_2$	70
Ph	Me	H	$CH_2CH{=}CH_2$	85
Ph	Me	H	$CH_2C{\equiv}CH$	48
Ph	Me	H	$CH{=}C{=}CH_2$	36
Ph	Me	H	$PhCH_2$	75
Ph	Me	H	Ph(Me)CH	75
Ph	Me	c-C_6H_{11}	H	30
Ph	Me	c-C_6H_{11}	Me	60
Ph	Ph	H	Me	75
Ph	Ph	H	$CH_2CH{=}CH_2$	83
Ph	Ph	H	$CH_2C{\equiv}CH$	51
Ph	Ph	H	$CH{=}C{=}CH_2$	41
Ph	Ph	H	$PhCH_2$	79
4-MeC_6H_4	H	H	$CH_2CH{=}CH_2$	35
Ph(Me)CH	H	*i*-Pr	$CH_2CH{=}CH_2$	80
4-(*n*-Bu)C_6H_4	Me	H	$CH_2CH{=}CH_2$	87
MeCO	H	Ph	$CH_2CH{=}CH_2$	78
$PhCH_2OCO$	H	Ph	$CH_2CH{=}CH_2$	85

one- or two-phase media containing water (Barbier reaction).[294−298] Allylations of carbonyl compounds with bismuth(III) chloride promoted by aluminum in THF−water have been reported.[299] We found that *N*-(aminoalkyl)benzotriazoles react with allyl, benzyl, and methyl halides in the presence of bismuth(III) chloride−metallic aluminum at room temperature in THF−water to give the corresponding homoalkylated amines **678** in high yields[300,301] (Scheme 215, Table

Scheme 215. Replacement of Benzotriazole Group Involving C−C Bond Formation in Aqueous Solution



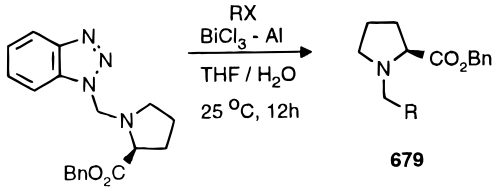
678

(see Table 69)

69). The benzyl and methyl halides constitute an important extension to those used hitherto for such aqueous reactions.

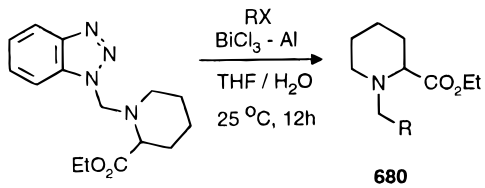
Using this methodology, together with those described in the section II of this review for the formation of the benzotriazolyl adducts in aqueous solution, it becomes feasible to modify aquaphilic amino compounds, without protection of other groups, in aqueous or partially aqueous media. Thus, this method has been successfully extended to include benzotriazole adducts derived from cyclic α-amino esters, as exemplified by *N*-homoalkylation of L-proline benzyl ester and pipecolinic acid ethyl ester[110] (Scheme 216). Methyl, benzyl, allyl, and propargyl halides can all be used, demonstrating the generality of this methodology. Especially noteworthy is that the displacement products **679a**−**d** from L-proline ben9tzotriazole derivatives **114** are ≥98% enantiomerically pure, reflecting the mild reaction conditions used.

Scheme 216. Preparation of *N*-Alkyl-L-proline Benzyl Ester and *N*-Alkylpipecolinic Acid Ethyl Ester in Aqueous Solutions



114 **679**

679a: R = $CH_2CH{=}CH_2$, 70%
679b: R = CH_2Ph, 65%
679c: R = Me, 18%
679d: R = $CH_2C{\equiv}CH$ and $CH{=}C{=}CH_2$ (1:1), 52%



115 **680**

680a: R = $CH_2CH{=}CH_2$, 55%
680b: R = CH_2Ph, 59%
680c: R = $CH_2C{\equiv}CH$ and $CH{=}C{=}CH_2$ (1:1), 33%

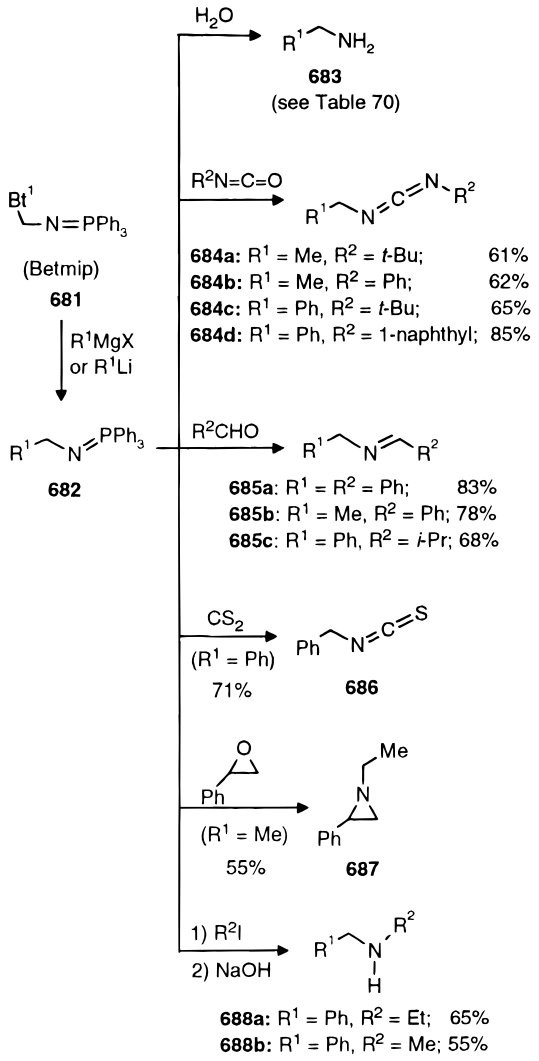
e. With Grignards and with Methylenetriphenylphosphorane To Give Primary and Secondary Amines and Related Products. The preparation of primary amines using benzotriazole as a synthetic auxiliary takes a different approach. Here, a synthon-equivalent "Betmip" $BtCH_2NPPh_3$ (**681**) was developed from the reaction of triphenylphosphine with the easily available 1-(azidomethyl)benzotriazole. Compound **681** reacts with a variety of organometallics, including Grignard and organolithium reagents, with displacement of the benzotriazole moiety to give phosphazenes **682**. Without isolation, intermediates **682** undergo direct hydrolysis to afford primary amines **683**[302−304] (Scheme 217). Thus Betmip represents a novel synthon equivalent to $^+CH_2NH_2$. A similar synthon equivalent was previously reported in the literature in the form of *N*,*N*-bis(trimethylsilyl)methoxymethylamine.[305,306] A direct comparison (Table 70) indicates that our method is advantageous compared to the previous one which (i) requires unpleasant chloromethyl methyl ether for preparation of *N*,*N*-bis(trimethylsilyl)methoxymethylamine, and (ii) affords lower yields.

Table 70. Comparison of Yields of Primary Amines 683 Obtained by Benzotriazole Method with Those from Literature Methods

	yield %	
R^1	benzotriazole method	literature method[a]
c-C_6H_{11}	77	52
Ph	82	75
$PhCH_2$	65	
$PhC{\equiv}C$	86	61
2-thienyl	84	67
2-naphthyl	93	52
n-$C_{12}H_{25}$	87	

[a] Using $MeOCH_2N(SiMe_3)_2$.[305,306]

Scheme 217. Reactions of Betmip To Produce Primary Amines and Derivatives

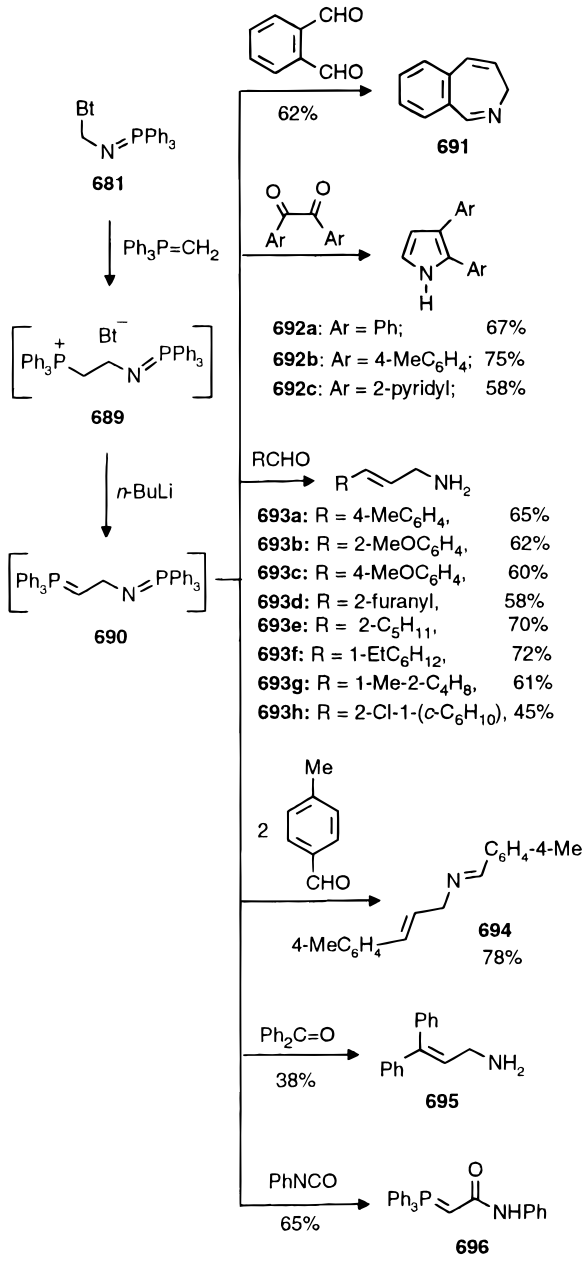


Intermediates **682** undergo normal phosphazene reactions *in situ*[303,304] with isocyanates, aldehydes, carbon disulfide, ethylene oxide, and alkyl halides, giving respectively carbodiimides **684**, Schiff bases **685**, isothiocyanate **686**, aziridine **687**, and secondary amines **688a**,**b** (Scheme 217).

Reaction of Betmip **681** with methylenetriphenylphosphorane gives intermediate **689**, a precursor for the *C*,*N*-1,3-bis ylide **690**. Deprotonation of **689** with *n*-butyllithium leads to the formation of 2(3*H*)-benzazepine (**691**) in 62% yield with phthalic dicarboxaldehyde and of 2,3-diarylpyrroles **692a**−**c** (58−75%) with α-diaryl diketones (Scheme 218). Quenching intermediate with 1 equiv of an aldehyde or a ketone affords primary allylamines **693** and **695**.[304,307] With 2 equiv of an aldehyde, **690** gives an imine **694**, while phenyl isocyanate reacts with intermediate **690** to give (aminocarbonyl)methylene triphenylphosphorane **696** in 65% yield.

This approach has been extended to include benzotriazole adducts **697** derived from benzotriazole, alkyl- or arylaldehydes, and morpholine (for preparation, see section II.B.2.a).[308] Reactions of these adducts with methylenetriphenylphosphorane prepared *in situ* forms salts, which on treatment with

Scheme 218. Betmip−Methylenetriphenylphosphorane Reaction Sequences



n-butyllithium eliminate a molecule of benzotriazole to give new ylides **698**. Finally, Wittig reactions of **698** with aromatic or aliphatic aldehydes affords

Scheme 219. Preparation of *N*-(1,3-Disubstituted-allyl)morpholines

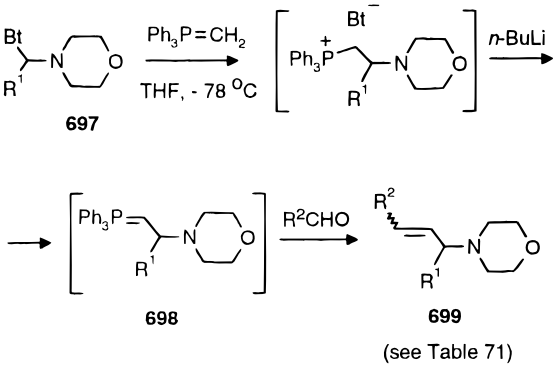


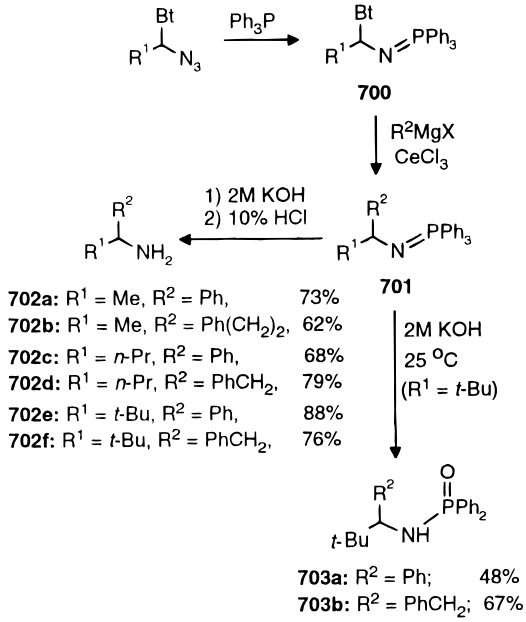
Table 71. Preparation of Substituted *N*-Allylmorpholines 699

R^1	R^2	yield %	ratio *E*:*Z*
Et	*i*-Pr	53	60:40
Et	c-C_6H_{11}	48	80:20
Et	4-MeC_6H_4	68	80:20
Et	*trans*-PhCH=CH−	65	60:40
i-Pr	4-MeC_6H_4	54	60:40
Ph	c-C_6H_{11}	51	100:0
Ph	4-MeC_6H_4	50	60:40
Ph	*trans*-PhCH=CH−	46	60:40

N-allylmorpholines **699**, usually as mixtures of *E* and *Z* isomers with *E* isomers predominant (Scheme 219, Table 71).

The Betmip methodology has also been extended to substituted derivatives **700**, prepared from 1-(α-azidoalkyl)benzotriazoles.[251,252,304] The benzotriazole group in **700** is displaced by a Grignard reagent in the presence of $CeCl_3$ to give intermediates **701** which are hydrolyzed either to secondary alkyl primary amines **702** or to diphenylphosphinic amides **703** (Scheme 220).

Scheme 220. Application of Betmip Methodology for Preparation of Primary Alkylamines

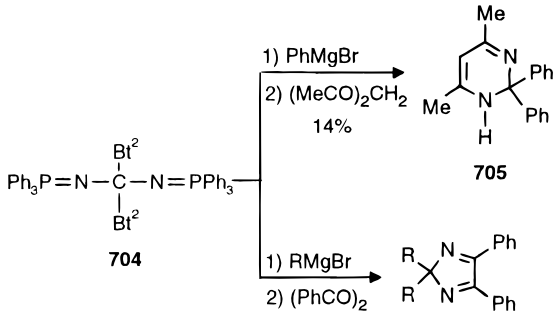


702a: R^1 = Me, R^2 = Ph, 73%
702b: R^1 = Me, R^2 = Ph(CH$_2$)$_2$, 62%
702c: R^1 = *n*-Pr, R^2 = Ph, 68%
702d: R^1 = *n*-Pr, R^2 = PhCH$_2$, 79%
702e: R^1 = *t*-Bu, R^2 = Ph, 88%
702f: R^1 = *t*-Bu, R^2 = PhCH$_2$, 76%

The bisphosphazene **704**, available from the corresponding *gem*-diazido benzotriazole derivative **353c** (see Scheme 114, see section III.A.6.a), reacts with Grignard reagents. The resulting intermediates are treated *in situ* with benzil to give 2*H*-imidazoles **706a**−**c**, and with pentane-2,4-dione to give 1,2-dihydro-4,6-dimethyl-2,2-diphenylpyrimidine (**705**)[224,304] (Scheme 221).

f. With Lithium Acetylides To Give Propargylamines. Using benzotriazole methodology, a wide variety of propargylamines can be obtained in high yields.[309,310] The method involves reactions, *N*-[α-(dialkylamino)alkyl]benzotriazoles with lithium acetylides derived from an alkyne and *n*-butyllithium (Scheme 222, Table 72). This sequence of reactions can also be carried out in a "one-pot" procedure with very acceptable yields. The *N*-furfurylpropargyl-

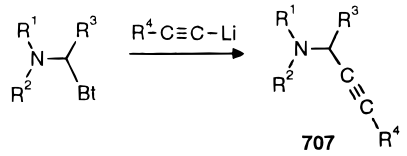
Scheme 221. Reactions of Dibenzotriazolylbis-[(triphenylphosphoranediyl)amino]phosphazenemethane



706a: R = Ph; 16%
706b: R = PhCH$_2$; 21%
706c: R = *n*-Bu; 15%

amines thus obtained undergo intramolecular Diels−Alder cyclizations giving isoindoles.[309]

Scheme 222. Preparation of Propargylamines



(see Table 72)

Table 72. Preparation of Propargylamines 707

R^1	R^2	R^3	R^4	yield %
Me	Me	H	Ph	79[310]
Me	2-furyl-CH_2	H	Ph	89[309]
	−$(CH_2)_4$−	H	Ph	73[310]
	−$(CH_2)_4$−	*i*-Pr	Ph	67[310]
	−$(CH_2)_4$−	*i*-Pr	*n*-C_6H_{13}	71[310]
	−$(CH_2)_5$−	Ph	Ph	73[310]
	−$(CH_2)_2O(CH_2)_2$−	*n*-Pr	Ph	76[310]
	−$(CH_2)_2O(CH_2)_2$−	*n*-Pr	*n*-C_6H_{13}	72[310]
	−$(CH_2)_2O(CH_2)_2$−	Ph	Ph	33[310]
	−$(CH_2)_2O(CH_2)_2$−	*n*-C_7H_{15}	Ph	97[310]
	−$(CH_2)_2O(CH_2)_2$−	*n*-C_7H_{15}	*n*-C_6H_{13}	81[310]
Ph	2-furyl-CH_2	H	Ph	63[309]
Ph	2-furyl-CH_2	H	*n*-C_6H_{13}	38[309]
Ph	2-furyl-CH_2	*i*-Pr	Ph	63[309]
4-MeC_6H_4	2-furyl-CH_2	H	Ph	65[309]
4-MeC_6H_4	2-furyl-CH_2	H	*n*-C_6H_{13}	60[309]
4-MeC_6H_4	2-furyl-CH_2	*i*-Pr	Ph	49[309]
$PhCH_2$	$PhCH_2$	H	Ph	76[310]
$PhCH_2$	$PhCH_2$	*i*-Pr	Ph	95[310]
$PhCH_2$	$PhCH_2$	*i*-Pr	*n*-C_6H_{13}	96[310]
n-C_8H_{17}	*n*-C_8H_{17}	H	*n*-Bu	90[310]

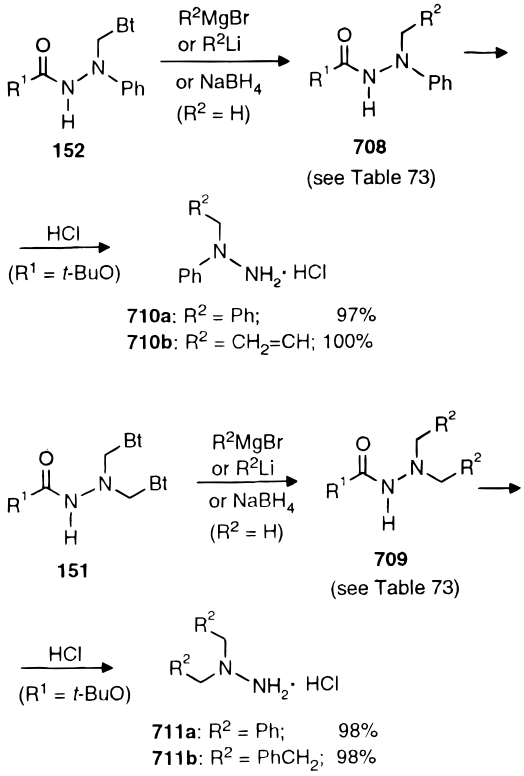
g. With Grignards or Borohydride To Give 2-Substituted 1-Acylhydrazines and Substituted Hydrazines. The benzotriazole moieties in the hydrazine derivatives **152** and **151** are easily replaced by carbanions from Grignard reagents or lithium acetylides or by a hydrogen from $NaBH_4$ to give 2-phenyl-2-alkyl-1-acylhydrazines **708** or 2,2-disubstituted 1-acylhydrazines **709** in high yields[143] (Table 73). The acyl groups in both **708** and **709** can be easily removed by treatment with an acid to allow the preparation of hydrochlorides of 1-phenyl-1-alkyl- (**710**) and 1,1-dialkylhydrazines (**711**) (Scheme 223).

The benzotriazole derivatives **132**, formed from hydrazines, benzotriazole, and glutaraldehyde, react

Table 73. Preparation of Substituted Hydrazines 708 and 709

			yields %	
R^1	R^2	reagent	**708**	**709**
Ph	H	$NaBH_4$	98	95
Ph	Ph	PhMgBr	96	97
Ph	$PhCH_2$	$PhCH_2MgBr$	80	83
Ph	PhC≡C	PhC≡CLi	92	94
EtO	H	$NaBH_4$	98	90
EtO	Ph	PhMgBr	90	95
EtO	$PhCH_2$	$PhCH_2MgBr$	90	94
EtO	PhC≡C	PhC≡CLi	95	92
t-BuO	Et	EtMgBr		80
t-BuO	CH_2=CH	CH_2=CHMgBr	98	
t-BuO	Ph	PhMgBr	95	94
t-BuO	$PhCH_2$	$PhCH_2MgBr$	96	92

Scheme 223. Preparation of Substituted Hydrazines



with $NaBH_4$ and Grignard reagents to give *N*-aminopiperidines **712**[121] (Scheme 224, Table 74).

Scheme 224. Preparation of *N*-Aminopiperidines

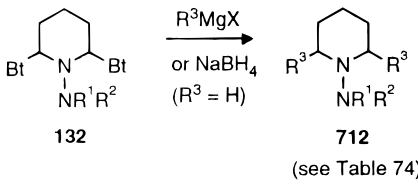


Table 74. Preparation of *N*-Aminopiperidines 712

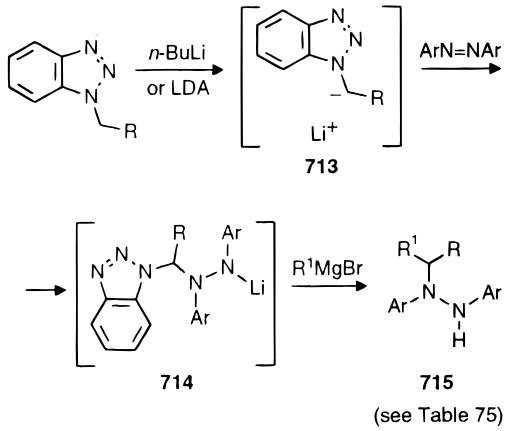
R^1	R^2	R^3	yield %	R^1	R^2	R^3	yield %
Ph	H	H	87	PhCO	H	Ph	49
Me	Me	H	79	EtOOC	H	H	88
MeCO	H	H	84	*t*-BuOOC	H	H	85
PhCO	H	H	82	*t*-BuOOC	H	Ph	75
PhCO	H	Me	70	*t*-BuOOC	H	$PhCH_2$	52
PhCO	H	Et	72	$PhCH_2OOC$	H	H	90

Table 75. Preparation of 1,1,2-Trisubstituted Hydrazines 715

R	R^1	Ar	yield %
H	*n*-Bu	Ph	34
CH=CH_2	*n*-Bu	Ph	32
Ph	Me	Ph	40
Ph	*n*-Bu	Ph	54
Ph	*n*-Bu	4-ClC_6H_4	51
Ph	*n*-Bu	4-MeC_6H_4	48
Ph	Ph	Ph	52
4-MeC_6H_4	*n*-Bu	Ph	57

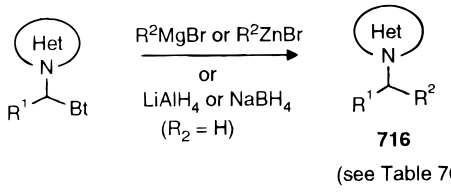
α-Benzotriazolyl carbanions **713** add to azobenzenes to form the *N*-benzotriazol-1-ylalkyl phenylhydrazines **714**, which react *in situ* with Grignard reagents to give the corresponding trisubstituted hydrazines **715** in moderate yields (Scheme 225, Table 75).[201]

Scheme 225. Addition of Lithiated *N*-Substituted Benzotriazoles to Azobenzenes



h. With Grignards or Lithium Aluminum Hydride To Give N-Substituted Heterocycles. *N*-(Benzotriazol-1-ylmethyl)heterocycles react with Grignard reagents, sodium borohydride or lithium aluminum hydride to afford *N*-substituted heterocycles **716** in good yields[119,217] (Scheme 226, Table 76). This method

Scheme 226. Preparation of *N*-Substituted Heterocycles



has led to the synthesis of a series of α-silylalkylated indoles and carbazoles.[198] Noteworthy is the reaction of Grignard or organozinc reagents with derivatives obtained via lithiation and subsequent trapping with cyclohexanone or 4-tolualdehyde to give compounds of **716**, R^1 = RCH(OH) (see Table 76).

An extension of this type of reaction is the displacement of benzotriazole with a Grignard reagent or reduction with a hydride in the adducts formed from addition of *N*-(aminoalkyl)benzotriazoles to 9-vinylcarbazole (Scheme 227, Table 77).[125,265]

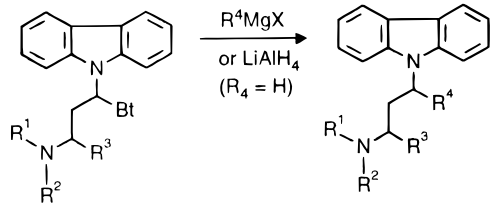
Table 76. Preparation of *N*-Substituted Heterocycles 716

heterocyclic group	R^1	R^2	yield %
pyrrol-1-yl	H	*n*-Bu	42[217]
pyrrol-1-yl	H	Ph	73[217]
pyrrol-1-yl	H	$PhCH_2$	72[217]
pyrrol-1-yl	$PhCH_2$	H	96[217]
pyrrol-1-yl	$(CH_2)_5CH(OH)$	Ph	50[217]
pyrrol-1-yl	4-$MeC_6H_4CH(OH)$	Ph	60[217]
indol-1-yl	H	*n*-Bu	37[217]
indol-1-yl	H	Ph	74[217]
indol-1-yl	*n*-Bu	H	92[217]
indol-1-yl	$PhCH_2$	*n*-Bu	94[217]
indol-1-yl	4-$MeC_6H_4CH(OH)$	Ph	55[217]
indol-1-yl	Me_2(*t*-Bu)Si	Ph	81[198]
indol-1-yl	Me_2(*t*-Bu)Si	*t*-Bu	77[198]
carbazol-9-yl	H	Ph	96[217]
carbazol-9-yl	$PhCH_2$	Ph	45[217]
carbazol-9-yl	$Me_2NCH_2CH_2$	Me	76[265]
carbazol-9-yl	4-$MeC_6H_4CH(OH)$	Ph	50[217]
carbazol-9-yl	Me_3Si	Ph	85[198]
carbazol-9-yl	$(i\text{-}Pr)_3Si$	Ph	94[198]
carbazol-9-yl	$(i\text{-}Pr)_3Si$	*n*-Bu	87[198]
carbazol-9-yl	Ph_3Si	*n*-Bu	81[198]
carbazol-9-yl	Ph_3Si	$PhCH_2$	84[198]
carbazol-9-yl	Me_2(*t*-Bu)Si	$PhCH_2$	77[198]
carbazol-9-yl	$(i\text{-}Bu)_3Si$	$PhCH_2$	75[198]
benzimidazol-1-yl	H	H	75[119]
benzimidazol-1-yl	H	*n*-Bu	56[217]
benzimidazol-1-yl	H	Ph	86[217]

Table 77. Preparation of *N*-Substituted Carbazoles 717

R^1	R^2	R^3	R^4	yield %
Me	Me	H	H	59
Me	Me	H	Me	76
$-(CH_2)_2O(CH_2)_2-$		H	H	53
$-(CH_2)_2O(CH_2)_2-$		H	Ph	73
$-(CH_2)_2O(CH_2)_2-$		Ph	H	35
$-(CH_2)_2O(CH_2)_2-$		Ph	Me	47
$-(CH_2)_2O(CH_2)_2-$		Ph	*n*-Bu	47

Scheme 227. Displacement of Benzotriazole in 9-[1-Benzotriazolyl-3-(*N*,*N*-dialkylamino)alkyl]-carbazoles



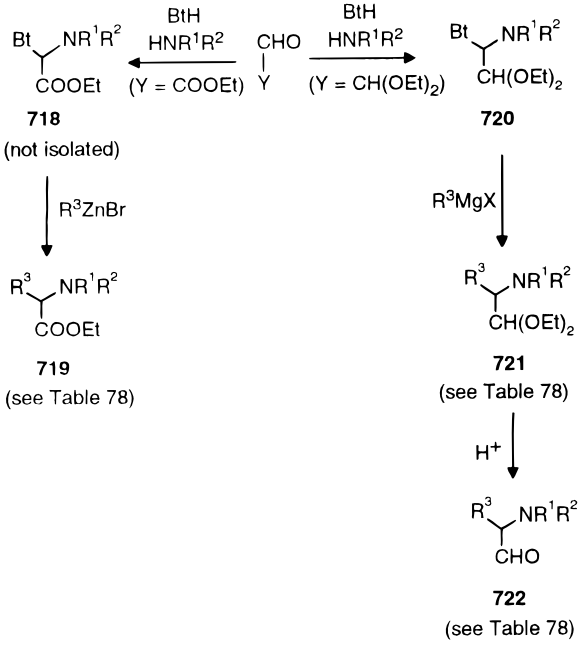
i. Reactions To Give α- and β-Amino Esters and α-Amino Aldehydes. α-Amino esters are frequently prepared by reaction of α-halogeno carboxylic acids (or derivatives) with the appropriate secondary amines.[311,312] Starting from ethyl glyoxylate, α-amino esters can be successfully prepared using the benzotriazole methodology. Thus, the adducts of benzotriazole, ethyl glyoxylate, and dialkylamines **718** (for preparation, see section II.B.2.a) react with organozinc reagents giving α-amino esters **719** in good yields[106] (Grignard reagents are not used due to their reaction with the ester group). This method has the advantage of using readily available starting materials compared to the analogous literature method using α-methoxy-α-dialkylamino esters.[313,314]

Table 78. Preparation of α-Amino Esters 719, Acetals 721, and Aldehydes 722

compound	R^1	R^2	R^3	yield %
719	Et	Et	Ph	75[106]
	$-(CH_2)_4-$		Ph	75[106]
	$-(CH_2)_5-$		Me	55[106]
	$-(CH_2)_5-$		*n*-Bu	50[106]
	$-(CH_2)_5-$		Ph	69[106]
	$-(CH_2)_5-$		4-MeC_6H_4	69[106]
	$-(CH_2)_5-$		$PhCH_2$	75[106]
	$-(CH_2)_2O(CH_2)_2-$		Ph	50[106]
	$-(CH_2)_2N[CH(Ph)CO_2Et](CH_2)_2-$		Ph	60[106]
721	$-(CH_2)_5-$		Me	90[100]
	$-(CH_2)_5-$		Et	98[100]
	$-(CH_2)_5-$		4-MeC_6H_4	85[100]
	$-(CH_2)_2O(CH_2)_2-$		Me	93[100]
	$-(CH_2)_2O(CH_2)_2-$		Et	90[100]
	$-(CH_2)_2O(CH_2)_2-$		$PhCH_2$	72[100]
	Ph	H	Et	75[100]
	Ph	H	Ph	71[100]
	Ph	Me	Et	91[100]
	3-MeC_6H_4	H	Et	80[100]
	$PhCH_2$	$PhCH_2$	Et	96[100]
722	$-(CH_2)_5-$		Me	85[100]
	$-(CH_2)_5-$		Et	91[100]
	$-(CH_2)_2O(CH_2)_2-$		Et	90[100]
	Ph	Me	Et	82[100]
	$PhCH_2$	$PhCH_2$	Et	80[100]

Similarly, glyoxal monoacetal is used for the high-yield preparation of α-amino aldehydes **722**[100] useful intermediates in the preparation of α-functionalized amino compounds[315] (Scheme 228). Thus, the Grignard reaction of benzotriazole derivatives **720**, prepared by reaction of glyoxal monoacetal with benzotriazole and a primary or secondary amine (see section II.B.2.a), gives the expected secondary or tertiary α-amino aldehyde acetals **721** respectively in nearly quantitative yields (Table 78). Acetals **721**

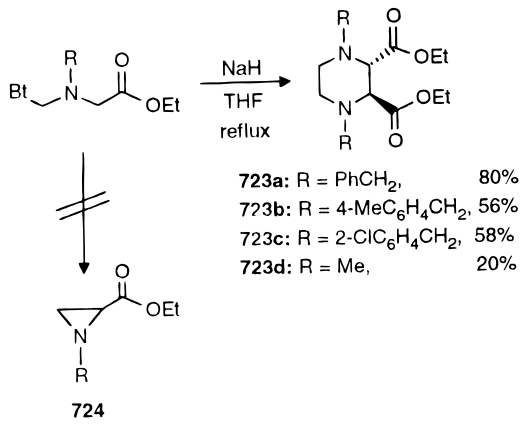
Scheme 228. Preparation of α-Amino Esters and Aldehydes



can be easily hydrolyzed in mild acidic conditions to the corresponding α-amino aldehydes **722**.

Treatment of *N*-(benzotriazolylmethyl)glycine ethyl esters (obtained by Mannich condensation of glycine ethyl esters, see section II.B.2.a) with sodium hydride gives the corresponding diethyl *trans*-2,3-piperazinedicarboxylates **723**[107] (Scheme 229). No products

Scheme 229. Preparation of *trans*-2,3-Piperazinedicarboxylates



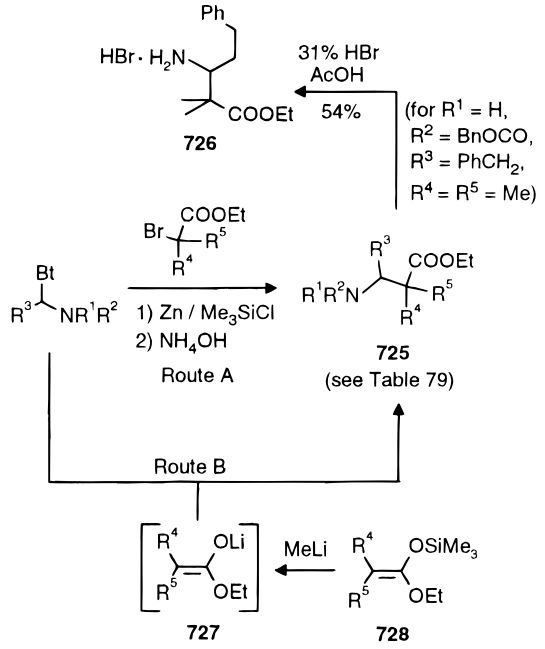
of intramolecular substitution, aziridines **724**, were detected. Nevertheless, the reaction mechanism may involve the intermediate formation of **724** with a subsequent ring opening−dimerization−ring closure sequence.

The dispacement of benzotriazole in *N*-[(dialkylamino)alkyl]benzotriazoles by an α-carboxyalkyl group leads to the formation of *β*-dialkylamino esters **725** (Table 79). One approach, based on an adaptation of the classical Reformatsky reaction, uses α-bromo esters and zinc[135] (route A, Scheme 230). If a carbamate is used as starting material, further elaboration gives *β*-amino esters **726**. Another approach involves reaction of lithium ester enolates **727**, derived from ketene silyl acetals **728**, with *N*-[(alkylamino)alkyl]benzotriazoles[316] (route B, Scheme 230).

Table 79. Preparation of *β*-Amino Esters 725

R^1	R^2	R^3	R^4	R^5	yield %
H	BnOCO	*i*-Bu	H	H	85[135]
H	BnOCO	*i*-Bu	Me	Me	78[135]
H	BnOCO	Bn	Me	Me	56[135]
H	BnOCO	Ph	Me	Me	64[135]
$-(CH_2)_4-$		H	Ph	H	70[316]
$-(CH_2)_4-$		*n*-Pr	H	H	51[135]
$-(CH_2)_4-$		Ph	Me	Me	54[135]
$-(CH_2)_5-$		*i*-Pr	Ph	H	78[316]
$-(CH_2)_5-$		Ph	Me	H	79[135]
$-(CH_2)_5-$		Ph	Me	Me	73[135]
$-(CH_2)_2O(CH_2)_2-$		H	Ph	H	78[316]
$-(CH_2)_2O(CH_2)_2-$		*i*-Pr	H	H	85[135]
$-(CH_2)_2O(CH_2)_2-$		*i*-Pr	Me	H	82[135]
$-(CH_2)_2O(CH_2)_2-$		*i*-Pr	Me	Me	56[135]
$-(CH_2)_2O(CH_2)_2-$		Ph	H	H	84[135]
$-(CH_2)_2O(CH_2)_2-$		Ph	$-(CH_2)_5-$		72[316]
$-(CH_2)_2O(CH_2)_2-$		Ph	Ph	H	75[316]
Ph	H	H	Ph	H	70[316]
Ph	H	H	*n*-Bu	H	78[316]
Ph	Ph	H	Me	Me	88[135]
4-MeC_6H_4	H	H	*n*-Bu	H	75[316]
4-MeC_6H_4	H	H	$-(CH_2)_5-$		78[316]
4-MeC_6H_4	H	H	Ph	H	80[316]

Scheme 230. Preparation of *β*-Amino Esters



j. With Ketones, Ketone Lithium Enolates, Silyl Enolates, and Aliphatic Nitro Compounds: Extension of Mannich-Type Reactions to Aldehydes in General. No general extension of the classical Mannich reaction to include aldehydes other than formaldehyde has previously been achieved. Benzotriazole methodology, utilizing a stabilized carbanion derived from a ketone or aliphatic nitro compound to displace the benzotriazolyl moiety in Bt−C−N-type compounds, allows a significant extension of the Mannich reaction from formaldehyde to most classes of aldehydes. In one case, further extension to the use of a ketone as the central component in a Mannich-type reaction was successful.

Ketones of general type $R^1COCH_2R^2$ (R^1 = Ar, R^2 = H, Me) react easily with *N*-aryl-substituted Mannich bases $BtCH_2NHAr$ under acid catalysis to give the corresponding *β*-amino ketones **729** in moderate to good yields (Scheme 231).[317] Lithium enolates also react with 1-[(alkylamino)alkyl]benzotriazoles yield-

Table 80. Preparation of Mannich-Type Products 729 from Ketone Enolates

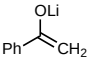
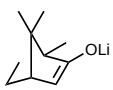
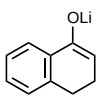
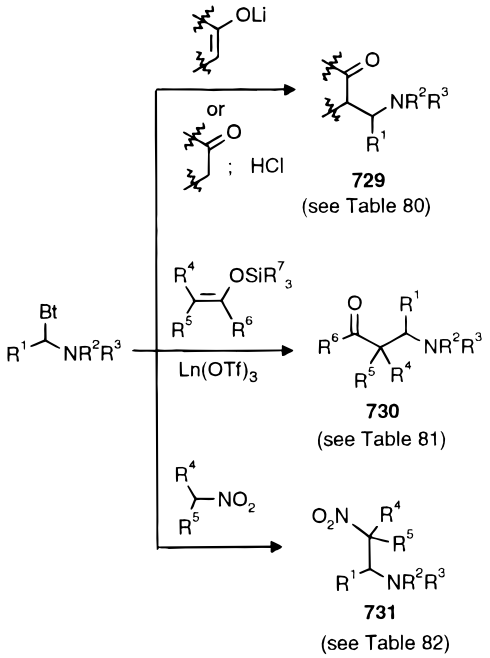
	R^1	R^2	R^3	yield %
	H	H	Ph	85
	H	$-(CH_2)_5-$		67
	Me	$-(CH_2)_2O(CH_2)_2-$		15
	i-Pr	$-(CH_2)_5-$		52
	$-(CH_2)_5-$	$-(CH_2)_2O(CH_2)_2-$		66
	Ph	$-(CH_2)_5-$		48
	H	H	Ph	10
	H	$-(CH_2)_5-$		19
	H	H	Ph	31
	H	$-(CH_2)_5-$		21
	H	H	Ph	29

Table 81. Preparation of Mannich-Type Products 730 from Silyl Enolates

R^1	R^2	R^3	R^4	R^5	R^6	SiR^7_3	yield %
H	H	4-$MeOC_6H_4$	Me	Me	OMe	$SiMe_3$	77
H	H	PhCO	Me	Me	OMe	$SiMe_3$	75
H	$PhCH_2$	$PhCH_2$	H	H	OEt	$SiMe_2$(*t*-Bu)	87
H	$PhCH_2$	$PhCH_2$	Me	H	Ph	$SiMe_3$	75
H	$PhCH_2$	$PhCH_2$	Me	Me	OMe	$SiMe_3$	91
i-Bu	H	PhCO	Me	Me	OMe	$SiMe_3$	81
i-Bu	$-(CH_2)_2O(CH_2)_2-$		Me	Me	OMe	$SiMe_3$	93
i-Bu	$PhCH_2$	$PhCH_2$	Me	Me	OMe	$SiMe_3$	94
i-Bu	$PhCH_2$	$PhCH_2$	$PhCH_2O$	H	OPh	$SiMe_2$(*t*-Bu)	91
Ph	H	PhCO	H	H	Ph	$SiMe_3$	60
Ph	H	PhCO	H	H	SEt	$SiMe_3$	99
Ph	H	PhCO	Me	Me	OMe	$SiMe_3$	98
Ph	$-(CH_2)_2O(CH_2)-$		H	$SiMe_2$(*t*-Bu)	OMe	$SiMe_2$(*t*−Bu)	89
Ph	$-(CH_2)_2O(CH_2)_2-$		Me	Me	OMe	$SiMe_3$	97
Ph	$PhCH_2$	$PhCH_2$	H	H	OEt	$SiMe_2$(*t*-Bu)	99
Ph	$PhCH_2$	$PhCH_2$	H	Me	OMe	$SiMe_3$	99
Ph	$PhCH_2$	$PhCH_2$	H	Me	OMe	$SiMe_2$(*t*-Bu)	72
Ph	$PhCH_2$	$PhCH_2$	H	$SiMe_2$(*t*-Bu)	OMe	$SiMe_2$(*t*-Bu)	~100
Ph	$PhCH_2$	$PhCH_2$	Me	Me	OMe	$SiMe_3$	85
Ph	$PhCH_2$	$PhCH_2$	$SiMe_2$(*t*-Bu)	H	OMe	$SiMe_2$(*t*-Bu)	99
Ph	$PhCH_2$	$PhCH_2$	$PhCH_2O$	H	OMe	$SiMe_2$(*t*-Bu)	97
Ph	$PhCH_2$	$PhCH_2$	$PhCH_2O$	H	OPh	$SiMe_2$(*t*-Bu)	~100
MeO_2C	H	PhCO	Me	Me	OMe	$SiMe_3$	82

ing β-amino ketones of type **729**[318] (Table 80) previously unobtainable under standard Mannich conditions. Such a modification of Mannich-type reaction,

Scheme 231. Reactions with Ketone Lithium Enolates, Ketones, or Silyl Enolates and with Aliphatic Nitro Compounds



carried out under neutral conditions should allow the preparation of β-amino ketones bearing acid- or base-sensitive functional groups. As shown recently, *N*-[(α-alkylamino)alkyl)benzotriazoles react with silyl enolates under neutral conditions in the presence of catalytic amount of lanthanide triflate to provide the corresponding β-amino ketones **730** in excellent yields (Table 81).[319] Several lanthanide triflates are effective in this reaction; they can also be recovered and used repeatedly without decreasing yield. In

Table 82. Preparation of Mannich-Type Products 731 from Nitro Compounds

R^1	R^2	R^3	R^4	R^5	yield %
H	$-(CH_2)_4-$		Me	Me	73
H	$-(CH_2)_2O(CH_2)_2-$		Me	Me	68
H	Ph	H	Me	Me	61
H	c-C_6H_{11}	H	Me	Me	80
H	c-C_6H_{11}	H	$-(CH_2)_5-$		87
Me	Ph	H	Me	Me	63
Me	Ph	H	$-(CH_2)_5-$		39
Me	2-pyridyl	H	Me	Me	64
2-pyridyl	2-pyridyl	H	Me	Me	61

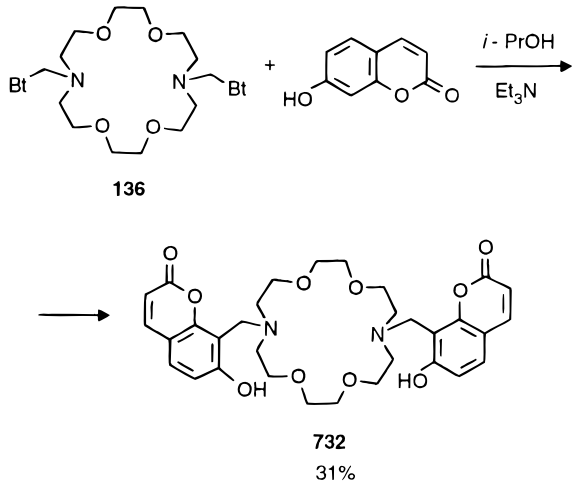
reactions with *cis*- or *trans*-silyl enolates *anti* diastereoisomers are obtained with high selectivity regarless of the geometry of the starting enolates.

N-(β-Nitroalkyl)amines (**731**, R^1 = H) are easily accessible through classical Mannich reactions.[320−323] Using benzotriazole methodology, such *N*-(β-nitroalkyl)amines are now readily available with various types of R^1 by the reaction of *N*-(α-aminoalkyl)-benzotriazoles with the anions of nitroalkanes[324] (Table 82).

k. With Electron-Rich Aromatics and Heteroaromatics To Give Aminoalkylated Derivatives. *N,N′*-Bis(benzotriazolylmethyl)-substituted 4,13-diaza-18-crown-6 **136** (for preparation, see section II.B.2.f) reacts with 7-hydroxycoumarin in the presence of base to give in moderate yield the new bis(lariat) crown ether **732**, containing fluorescent labels on both sides of the macrocycle (Scheme 232).[124]

Electron-rich heteroaromatic compounds such as pyrrole, indole, their *N*-methyl analogues and 2-methylfuran are all aminoalkylated by secondary or tertiary aminoalkylbenzotriazoles in the presence of a Lewis acid (Scheme 233).[325] Yields are good to excellent (Table 83). The secondary amines thus obtained are generally difficult to prepare by the conventional Mannich-type reaction which gives low yields and often leads to the formation of the corresponding tertiary amines as byproducts.[326]

Scheme 232. Aminoalkylation of 7-Hydroxycoumarin



Scheme 233. Aminoalkylation of Electron-Rich Heteroaromatics

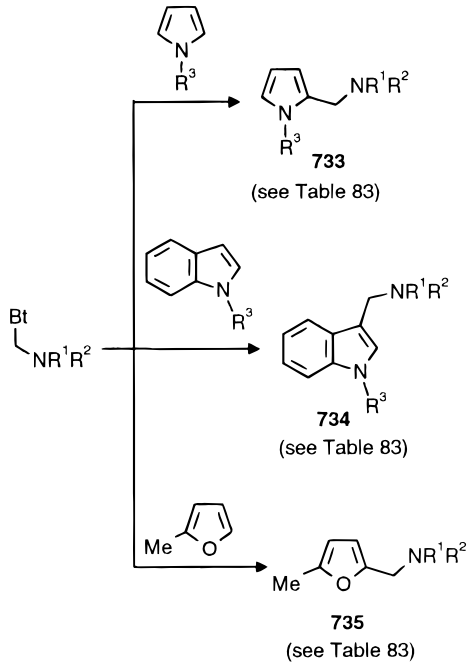


Table 83. Preparation of Aminoalkylated Heteroaromatic Compounds 733−735

compound	R^1	R^2	R^3	yield %
733	H	*n*-Bu	Me	62
	H	c-C_5H_9	Me	71
	H	c-C_6H_{11}	H	64
	H	c-C_6H_{11}	Me	82
	$-(CH_2)_4-$		H	92
	$-(CH_2)_4-$		Me	96
	$-(CH_2)_5-$		Me	70
734	H	*n*-Bu	Me	89
	H	c-C_6H_{11}	H	87
	H	c-C_6H_{11}	Me	93
	$-(CH_2)_4-$		Me	91
	$-(CH_2)_5-$		H	84
735	H	*n*-Bu		58
	H	c-C_5H_9		47
	$-(CH_2)_5-$			87

l. With Cyanide Anion To Give α-Amino Nitriles. α-Amino nitriles are important precursors to α-amino acids and amides. Cyanide anion successfully displaces the benzotriazole moiety in *N*-[(alkylamino)-methyl]benzotriazoles to give (alkylamino)acetonitriles **736** and **737**,[115,122] and in [*N*-(α-benzotriazolyl-alkyl)amino]acetonitriles to give unsymmetrically substituted iminodiacetonitriles **738**[327] which after oxidation afford iminodiacetoamides **739** (Scheme 234, Tables 84 and 85).

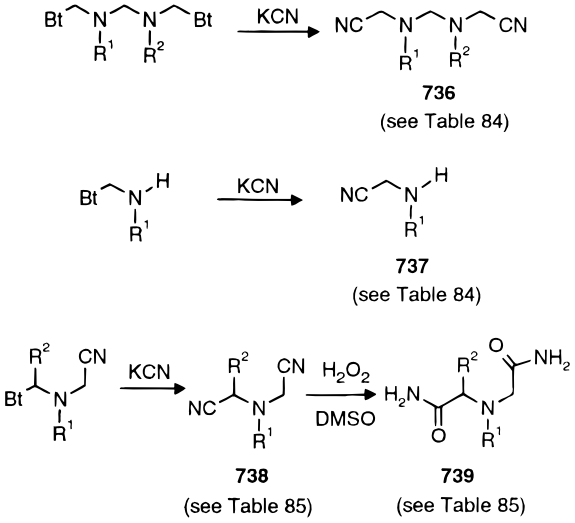
Table 84. Displacement of Benzotriazole by Cyanide Anion To Give α-Aminonitriles 736 and 737

compound	R^1	R^2	yield %
736	*n*-Bu	*n*-Bu	80
	i-Bu	*i*-Bu	72
	n-C_8H_{17}	*n*-C_8H_{17}	89
	$PhCH_2$	$PhCH_2$	85
	$-(CH_2)_2-$		85
	$-(CH_2)_3-$		87
737	*t*-Bu		70
	c-C_6H_{11}		87

Table 85. Displacement of Benzotriazole by Cyanide Anion To Give Iminodiacetonitriles 738 and Iminodiacetamides 739

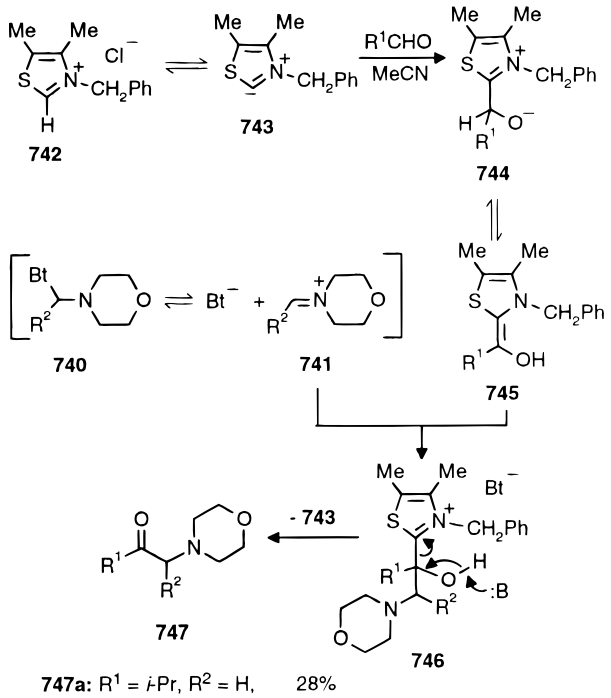
		yield %	
R^1	R^2	**738**	**739**
c-C_6H_{11}	H	91	95
n-C_8H_{17}	H	86	94
n-C_8H_{17}	Me	59	92
n-C_8H_{17}	*n*-Pr	66	97
n-C_8H_{17}	*i*-Pr	60	95
n-C_8H_{17}	Ph	62	94

Scheme 234. Preparation of α-Amino Nitriles



m. With Aldehydes To Give α-Amino Ketones. *N*-(α-Aminoalkyl)benzotriazoles **740** are known to exist in equilibrium with their corresponding iminium ions **741** and benzotriazolyl anion in solution. This property has been successfully used in the synthesis of α-amino ketones.[328] Thus, heating benzotriazole adducts **740**, an aldehyde and 3-benzyl-4,5-dimethylthiazolium chloride (**742**) at reflux in acetonitrile affords the corresponding α-amino ketones **747** in moderate yields[328] (Scheme 235). The mechanism involves initial addition of anion **743** to the aldehyde followed by reversible proton transfer to generate anhydrobase **745**. Intermediate **745** then

Scheme 235. Preparation of α-Amino Ketones



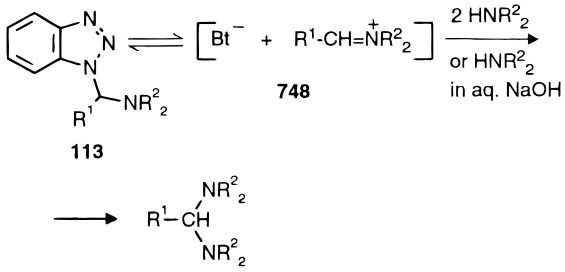
747a: R^1 = *i*-Pr, R^2 = H, 28%
747b: R^1 = Ph, R^2 = H, 58%
747c: R^1 = R^2 = Ph, 44%
747d: R^1 = R^2 = 4-MeC_6H_4, 30%
747e: R^1 = R^2 = 4-ClC_6H_4, 55%
747f: R^1 = 4-NCC_6H_4, R^2 = 4-$MeOC_6H_4$, 42%

reacts with the *in situ* formed iminium ion **741** to afford intermediate **746**, which yields the final product after spinning off the anion **743** (Scheme 235).

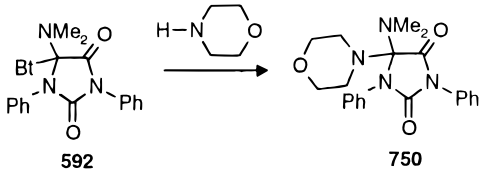
2. From Systems of Type Bt–C–N by N-, O-, S-, Se-, P-, and Sn-Nucleophiles: Other Aminoalkylations

a. N-Nucleophiles. Reactions of 1-[1-(*N*,*N*-dialkylamino)alkyl]benzotriazoles **113** (for preparation, see section II.B.2.a) with the dialkylamine corresponding to the dialkylamino substituent in **113** afford symmetrical aminals **749** in good yields (Scheme 236). Treatment with other dialkylamines gives mixtures of the unsymmetrical and the two symmetrical aminals because of spontaneous disproportionations of unsymmetrical aminals formed initially. The formation of intermediate iminium ions **748** was proposed and confirmed by cross-over experiments with symmetrical aminals.[329] Substitution of the benzotriazolyl moiety in 5-benzotriazolyl-5-aminohydantoin **592** (for preparation, see section III.E.2) with morpholine results in formation of the stable unsymmetrical aminal **750** in moderate yield.[59]

Scheme 236. Aminal Exchange Reactions of 1-[1-(*N*,*N*-Dialkylamino)alkyl]benzotriazoles

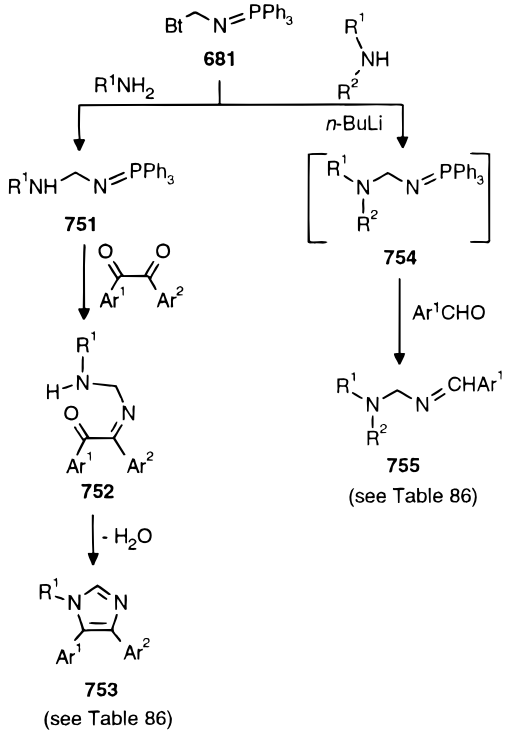


749a: R^1 = Ph, R^2_2 = $(CH_2)_4$, 61%
749b: R^1 = Ph, R^2_2 = $(CH_2)_5$, 65%
749c: R^1 = 4-$MeOC_6H_4$, R^2_2 = $(CH_2)_2O(CH_2)_2$, 89%
749d: R^1 = 4-$MeOC_6H_4$, R^2_2 = $(CH_2)_5$, 79%



The benzotriazole moiety in Betmip (**681**) can also be displaced by amines. With primary amines, the resulting intermediates **751** on further treatment with diaryl α-ketones give 1,4,5-trisubstituted imidazoles **753** in moderate to good yields[330] (Scheme 237, Table 86). When lithiated secondary amines are

Scheme 237. Reactions of Primary and Secondary Amines with Betmip



used, the intermediates **754** react with aromatic aldehydes to afford α-(arylideneamino)alkylamines **755**.[331]

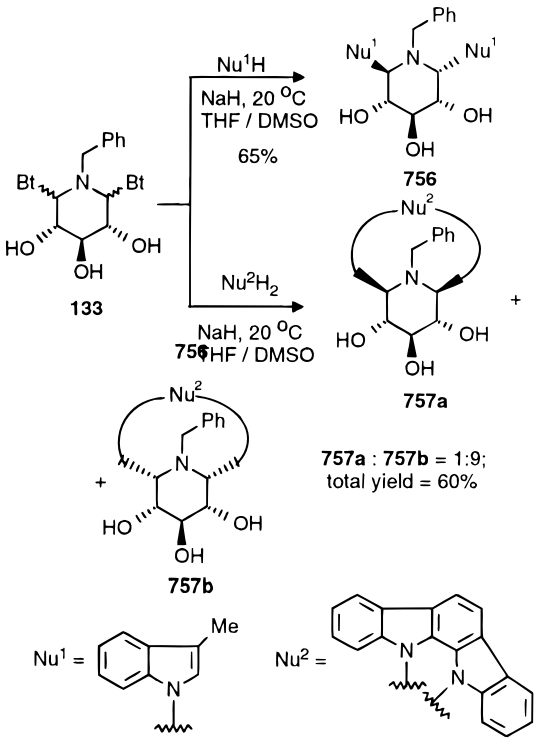
The displacement of benzotriazole moiety by 3-methylindole or indolocarbazole derivatives acting as *N*-nucleophiles in the presence of sodium hydride is applied for the synthesis of some azasugar nucleosides.[122] The stereochemical outcome of this displacement depends on the nature of the nucleophile. Thus, the substitution with 3-methylindole gives exclusively *trans* isomer **756**, while in the case of the bidentate nucleophile indolocarbazole the two *cis* isomers **757a** and **757b** are obtained (Scheme 238).

Treatment of *N*-[(alkylamino)methyl]benzotriazoles **760** with 1,3,5-triphenylformazan (**758**) in the presence of barium hydroxide monohydrate results initially in the displacement of the benzotriazole group

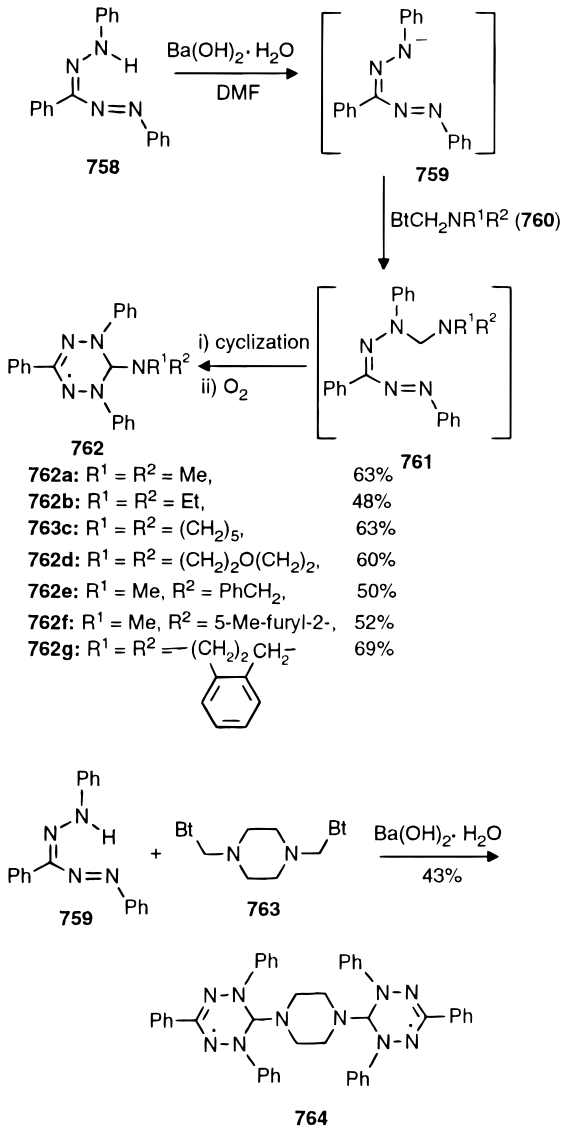
Table 86. Preparation of 1,4,5-Trisubstituted Imidazoles 753 and Imines 755

compound	R^1	R^2	Ar^1	Ar^2	yield %
753	4-$Me_2NC_6H_4$		Ph	Ph	84[330]
	$PhCH_2$		Ph	4-ClC_6H_4	55[330]
	$PhCH_2$		biphenylidine-2,2′-diyl		79[330]
	c-C_7H_{13}		Ph	Ph	81[330]
	n-$C_{10}H_{21}$		biphenylidine-2,2′-diyl		72[330]
	n-$C_{12}H_{25}$		Ph	4-ClC_6H_4	53[330]
	n-$C_{12}H_{25}$		biphenylidine-2,2′-diyl		75[330]
755	Me	Ph	Ph		73[331]
	Me	Ph	4-MeC_6H_4		70[331]
	Me	Ph	2-MeC_6H_4		54[331]
	$-(CH_2)_4-$		2-$MeOC_6H_4$		57[331]
	$-(CH_2)_4-$		4-MeC_6H_4		64[331]
	$-(CH_2)_4-$		4-ClC_6H_4		45[331]
	$-(CH_2)_2O(CH_2)_2-$		Ph		43[331]
	$-(CH_2)_2O(CH_2)_2-$		2-MeC_6H_4		51[331]

Scheme 238. Displacement of Benzotriazole Moiety by Indole Derivatives



Scheme 239. Reactions of *N*-[(Dialkylamino)methyl]benzotriazoles with 1,3,5-Triphenylformazan



by the nitrogen anion **759** to form intermediates **761**. Subsequent cyclization followed by air oxidation affords the corresponding 3-(*N*,*N*-dialkylamino)-2,4,6-triphenylverdazyls **762** in 37−69% yields (Scheme 239).[332] Bis-verdazyl **764**, obtained in 43% yield from *N*,*N*-bis(benzotriazol-1-ylmethyl)piperazine (**763**), represents the first example of compounds of its type.

b. O-, S-, and Se-Nucleophiles. Removal of the benzotriazole group in *N*-[α-(alkylamino)alkyl]benzotriazoles by an alcohol or a thiol is easily achieved in an alcohol at room temperature[333] (Scheme 240). This method can also be applied for the preparation of *N*-(α-alkoxyalkyl)amines and their thio analogues, from the benzotriazole adducts derived from benzaldehyde and pyridine-2-aldehyde. In addition to the mild and nonacidic conditions used and easy workup and purification of products, this procedure also avoids the water formation during the reaction. This is important as *N*,*O*-acetals and *N*,*S*-acetals can be easily hydrolyzed.

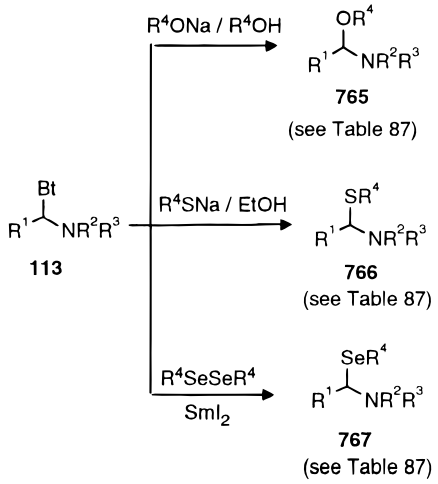
α-Aminomethyl selenides **767**, which are not easily available by other methods, are obtained in high yields by displacement of benzotriazole group in *N*-(α-

Table 87. Preparation of α-Amino Ethers 765, α-Amino Thioethers 766, and α-Amino Selenides 767

compound	R^1	R^2	R^3	R^4	yield %
765	H	H	Ph	Me	80
	H	Et	Ph	Me	90
	H	Et	Ph	Et	98
	H	Et	Ph	*i*-Pr	94
	H	$-(CH_2)_2O(CH_2)_2-$		Et	82
	H	$-CH_2(o\text{-}C_6H_4)CH_2CH_2-$		Et	88
	H	$-CH_2(o\text{-}C_6H_4)CH_2CH_2-$		*sec*-Bu	85
	Ph	$PhCH_2$	$PhCH_2$	*i*-Pr	79
	2-pyridyl	$-(CH_2)_2O(CH_2)_2-$		Me	82
	2-pyridyl	$-(CH_2)_2O(CH_2)_2-$		Et	86
766	H	Et	Ph	*n*-Bu	76
	H	Et	Ph	Ph	83
	i-Pr	$PhCH_2$	$PhCH_2$	*n*-Bu	78
	i-Pr	$PhCH_2$	$PhCH_2$	$n\text{-}C_{10}H_{21}$	80
	Ph	$-(CH_2)_2O(CH_2)_2-$		Ph	95
	Ph	$-(CH_2)_2O(CH_2)_2-$		$PhCH_2$	90
	2-pyridyl	$-(CH_2)_2O(CH_2)_2-$		Ph	84
	2-pyridyl	$-(CH_2)_2O(CH_2)_2-$		$PhCH_2$	80
	2-pyridyl	$-(CH_2)_2O(CH_2)_2-$		$n\text{-}C_8H_{17}$	85
767	H	H	Ph	*n*-Bu	82
	H	H	Ph	$n\text{-}C_5H_{11}$	73
	H	H	3-ClC_6H_4	*n*-Bu	85
	H	H	4-ClC_6H_4	$n\text{-}C_5H_{11}$	76
	H	H	3-MeC_6H_4	Et	80
	H	H	3-MeC_6H_4	*n*-Bu	77
	H	H	4-MeC_6H_4	Et	83
	H	H	4-MeC_6H_4	*n*-Bu	85
	H	Me	Ph	*n*-Bu	75

aminoalkyl)benzotriazoles with selenolate anion, prepared *in situ* from diorganyl diselenides and SmI_2[334] (Scheme 240, Table 87). Although the analogous

Scheme 240. Preparation of *N,O-*, *N,S-*, and *N,Se*-Acetals

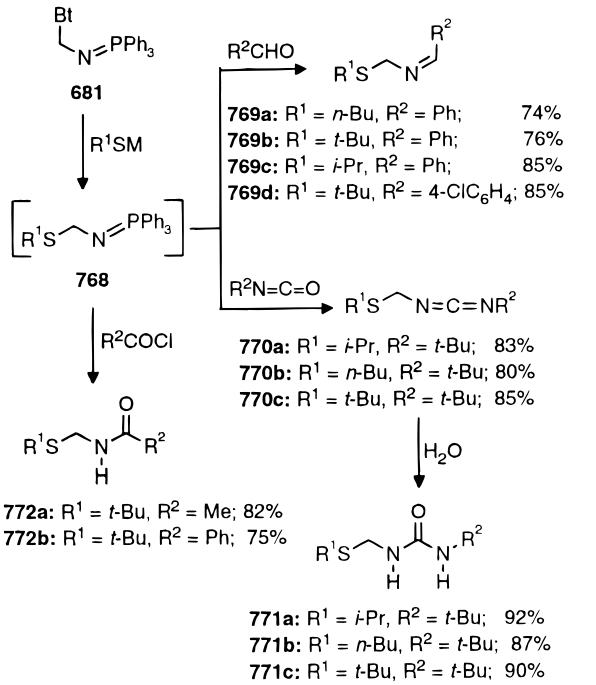


tellurolate anions could be prepared in the same way, the substitution reaction with the benzotriazole adducts failed because of the instability of the targeted *N,Te*-acetals.

Displacement of benzotriazole in Betmip (**681**) by an alkylthio group gives intermediates **768**, which react with aldehydes to afford *N*-[(alkylthio)methyl]-benzalimines **769**, with alkyl isocyanates to urea derivatives **771**, and with acyl chlorides to *N*-[(alkylthio)methyl]amides **772**[335] (Scheme 241).

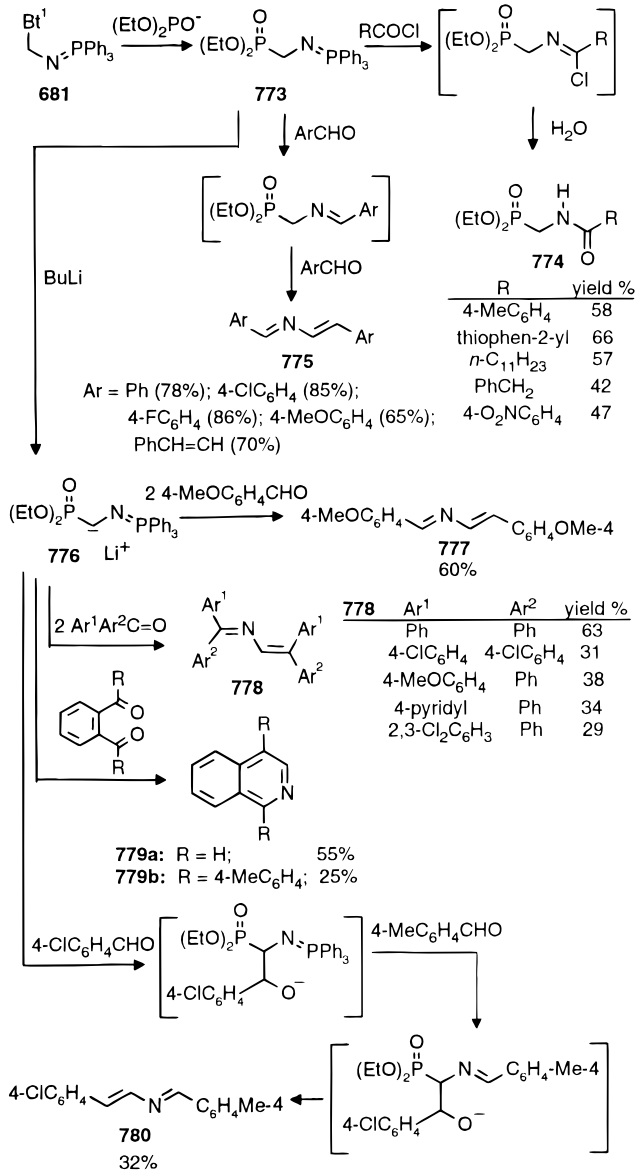
c. P-Nucleophiles. When diethyl phosphite anion is reacted with Betmip **681**, the intermediate **773** is formed initially[336,337] (Scheme 242). Compound **773**

Scheme 241. Displacement of Bt Group in Betmip by RS− and Subsequent Reactions



behaves as a *C,N*-1,2-bis ylide and is of great synthetic utility for introducing the C═N—C═C structural unit. Thus, reactions with acyl chlorides affords diethyl [(acylamino)methyl]phosphonates **774** while with aldehydes yield is 1,4-diaryl-2-azabutadienes **775**. In addition, the methylene carbon in **773** is acidic and can be deprotonated with *n*-BuLi to form the anion **776**. The anion **776** then reacts with 2 equiv of an aldehyde or of a ketone to afford 1,4-diaryl-2-azabutadienes **777** and **778** respectively.

Scheme 242. Reactions of Betmip with Diethyl Phosphite Anion



If 1 equiv of each of two different aldehydes is added stepwise, an unsymmetrical 1,4-diaryl-2-azabutadiene **780** is formed. With *o*-diacylbenzenes, 1,4-disubstituted isoquinolines **779a**,**b** are obtained.

d. Sn-Nucleophiles. The benzotriazole moiety in *N*-[(dialkylamino)alkyl]benzotriazoles is also successfully displaced by tributyltin group to yield *N*-[1-(trialkylstannyl)alkyl]amines **781**[338,339] (Scheme 243,

Scheme 243. Preparation of α-Stannyl Amines

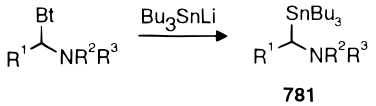


Table 88). This procedure is shorter, more reproducible and operationally simpler than alternatives[340,341] and is particularly useful for preparing compounds highly branched at the α carbon. Products **781** are

Table 88. Preparation of α-Stannyl *N*,*N*-Dialkylamines

R^1	R^2	R^3	yield %	yield %[a]
H	Me	Me	75[338]	81[331]
H	Et	Et	77[338]	80[340]
				83[331]
H	*i*-Bu	*i*-Bu	73[338]	80[340]
H	$-(CH_2)_2O(CH_2)_2-$		78[338]	17[416]
H	$PhCH_2$	$PhCH_2$	76[338]	
H	$PhCH_2$	$PhCH_2$	81[338]	
H	$-(CH_2)_4-$		85[338]	not available[246b]
H	$-(CH_2)_5-$		75[338]	73[340]
				86[331]
H	Me	c-C_6H_{11}	90[338]	71[331]
H	H	indol-1-yl	55[338]	
n-Pr	$-(CH_2)_2O(CH_2)_2-$		89[338]	
i-Pr	$-(CH_2)_2O(CH_2)_2-$		83[338]	
i-Pr	$PhCH_2$	$PhCH_2$	74[338]	
i-Pr	$PhCH_2$	$PhCH_2$	77[338]	
i-Pr	(S)-PhCHMe	$PhCH_2$	38[338]	

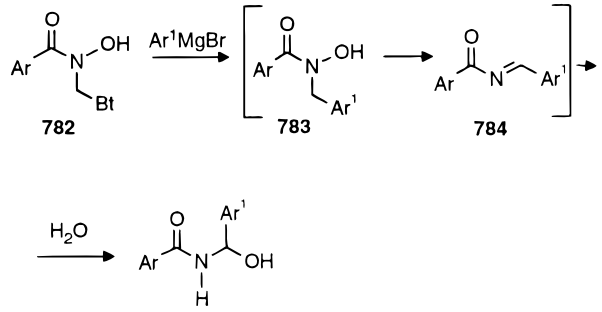
[a] Yields of corresponding compounds obtained by substitution reaction of $(n\text{-Bu})_3SnLi$ with α-(phenylthio)amines.

advantageously used for the preparation of α-lithiated amines.

3. From Systems of Type Bt—C—N—O and Bt—C—N═C—N

a. From Hydroxamic Acid Derivatives: Reaction with Rearrangement. When *N*-hydroxy-*N*-(benzotriazol-1-ylmethyl)arylamides **782** are treated with an aryl Grignard reagent, compounds of type **785** are obtained instead of expected the direct displacement products **783**[142] (Scheme 244). A possible explanation

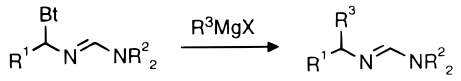
Scheme 244. Preparation of *N*-(α-Hydroxybenzyl) Amides



is that the displacement product **783** is initially formed but undergoes dehydration to **784** which subsequently reacts with a molecule of water to give **785**.

b. Amidine Systems. The benzotriazolyl amidine derivatives **786** (obtained by reaction of a secondary amine with α-(benzotriazol-1-yl)alkyl isocyanides **572**) react with Grignard reagents, yielding unsymmetrical formamidines **787** as shown in Scheme 245.[284]

Scheme 245. Preparation of Formamidines



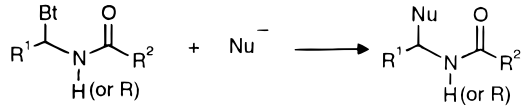
786 **787**

787a: R^1 = H, R^2_2 = $(CH_2)_5$, R^3 = Ph, 80%
787b: R^1 = H, R^2_2 = $(CH_2)_2O(CH_2)_2$, R^3 = Ph, 82%
787c: R^1 = H, R^2_2 = $(CH_2)_4$, R^3 = Ph, 79%
787d: R^1 = H, R^2_2 = $(CH_2)_5$, R^3 = 4-MeC_6H_4, 62%
787e: R^1 = H, R^2_2 = $(CH_2)_5$, R^3 = CH_2=CH, 76%
787f: R^1 = *i*-Pr, R^2_2 = $(CH_2)_5$, R^3 = Ph, 53%

4. From Systems of Type Bt—C—N—C═O: Amidoalkylation

N-(α-Amidoalkyl)benzotriazoles, obtained from benzotriazole, an aldehyde and an amide, are versatile amidoalkylation reagents which act by the loss of benzotriazole during the reaction. The general reactions are summarized in Scheme 246 and include

Scheme 246. Amidoalkylations Mediated by Benzotriazole

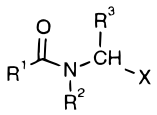


Nucleophile	Compounds Prepared	Section
$NaBH_4$	*N*-alkylamides	IVB4a
RMgBr	*N*-alkylamides	IVB4a
stabilized carbanions	amidoalkylated malonates, acetoacetates, etc.	IVB4b
NaCN	acylated aminonitriles	IVB4c
reactive aromatics	amidoalkylated aromatics	IVB4d
acetylene anions	1,3-oxazines	IVB4e
ammonia, primary and secondary amines	monoacylaminals	IVB4f
RSNa	acylated thioaminals	IVB4g
RONa	acylated hemiaminals	IVB4g
ethyl diphenyl phosphinite anion	α-acylaminophosphine oxides	IVB4h
R_3SnLi	*N*-[1-(trialkylstannyl)alkyl]amides	IVB4i

reactions with carbon nucleophiles (such as Grignard reagents, stabilized carbanions, cyanides, and reactive aromatic compounds), nitrogen nucleophiles (such as ammonia and primary and secondary amines), and other nucleophiles (such as hydride, thiols, and hydroxy compounds).

Amidoalkylation is an important synthetic alternative to the Mannich reaction.[326] Numerous amidoalkylation reactions have been reported.[342−345] Among the previously developed amidoalkylating reagents are **788a**−**e** (X = OH, OR, OCOR, halogen, NHCOR). It is of interest to compare the benzotriazole method with those previously available and a brief summary is given in Scheme 247. In general, all of the previous methods have limitations and disadvantages, as recently reviewed.[128] However, these limitations and disadvantages are largely overcome by the use of the new amidoalkylation reagents incorporating a benzotriazole group (**788f**).

Scheme 247. Comparison of Available Reagents for Amidoalkylation



788

(a) X = OH — strongly acidic conditions needed, and useful only when R^3 = H, CO_2H, CO_2Et and CCl_3 [Zaugg, H.E. *Synthesis*, 85 (1984)]

(b) X = OR — strongly acidic conditions or electrochemistry needed [Barry, J.E.; Mayeda, E.A.; Ross, S.D. *Tetrahedron,* **33**, 369 (1977)]

(c) X = OCOR — prepared by anodic oxidation on N-alkylated amides in organic acids [Nybery, K. *Acta Chem. Scand., (B)* **28**, 825 (1974)]

(d) X = Halogen — very reactive, difficult to prepare, isolate and purify. Low yielding aminoalkylation and the formation of side-product [Schmidt, R.; Schlipf, E. *Chem. Ber.,* **103**, 3783 (1970)]

(e) X = NHCOR — severe aminoalkylation conditions needed and only half a molar equivalent of the amide is utilized [Zaugg, H.E. et al, *J. Heterocyclic Chem.,* **16**, 21 (1979)]

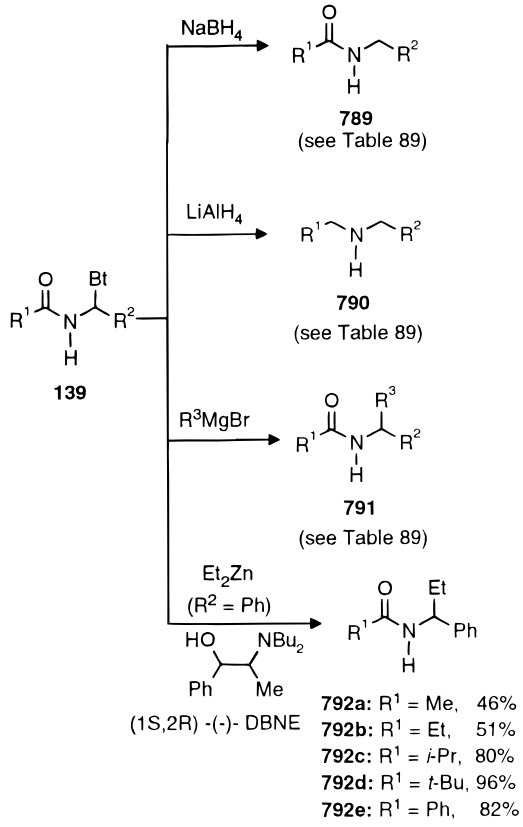
(f) X = Benzotriazolyl — new amidoalkylation reagent, more general, versatile and uses mild conditions

a. Reactions with Borohydride, Lithium Aluminum Hydride, or Grignard Reagents Leading to N-Alkylation of Primary and Secondary Amides. Borohydride reduction replaces the benzotriazolyl group in adducts **139** (Scheme 248, Table 89) by a hydrogen

Table 89. Preparation of *N*-Alkylated Amides 789−791 by Reaction of *N*-(α-Benzotriazolylalkyl) Amides with Grignard Reagents, $NaBH_4$, and $LiAlH_4$

compound	R^1	R^2	R^3	yield %
789	Me	Ph		98[126]
	Ph	H		96[126]
	Ph	*i*-Pr		96[126]
	Ph	*n*-Pr		96[126]
	Ph	*n*-C_5H_{11}		97[126]
	Ph	*n*-C_8H_{17}		99[126]
	Ph	Ph		94[126]
790	Me	Ph		83[126]
	Ph	H		76[126]
	Ph	*i*-Pr		75[126]
	Ph	*n*-Pr		58[126]
	Ph	*n*-C_5H_{11}		66[126]
	Ph	*n*-C_8H_{17}		64[126]
	Ph	Ph		65[126]
791	Me	$(CH_2)_5C(OH)$	Ph	80[228]
	Me	4-MeC_6H_4	Ph	93[137]
	Ph	*i*-Pr	$PhCH_2$	95[137]
	Ph	*i*-Pr	PhC≡C	81[137]
	Ph	*n*-Pr	Ph	92[137]
	Ph	*n*-Pr	PhC≡C	86[137]
	Ph	CH_2=$CHCH_2$	Ph	89[228]
	Ph	Ph	*n*-Bu	85[137]
	Ph	*n*-C_8H_{17}	$PhCH_2$	91[137]

Scheme 248. Preparation of Secondary Amides



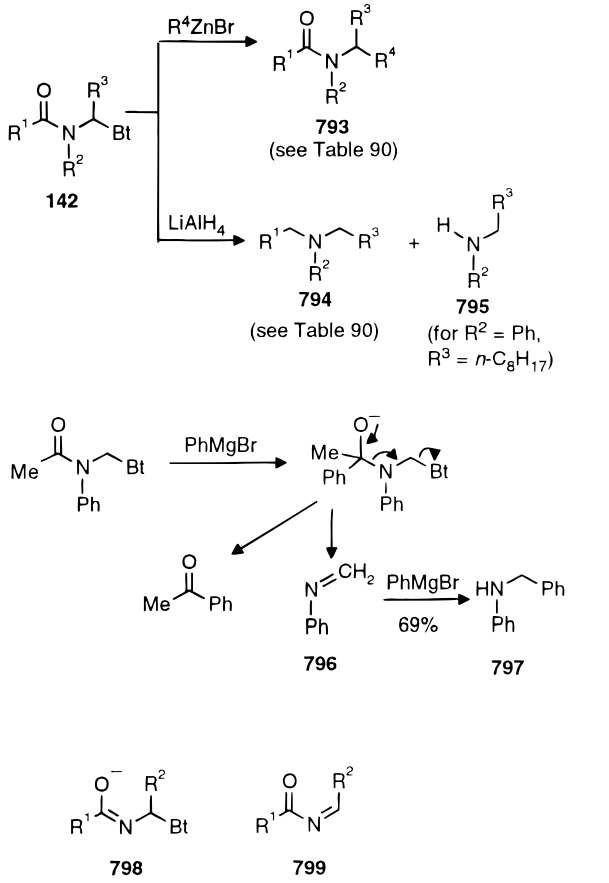
to give *N*-alkylamides **789**, while $LiAlH_4$ leads to complete reduction to secondary amines **790**.[126] The benzotriazole group is also readily replaced by a Grignard reagent to give high yields of secondary amides **791**.[137] Recently, we have found that in the presence of chiral *N*,*N*-dibutylnorephedrine, diethylzinc reacts with the benzotriazole adducts **139** to yield optically active secondary amides **792** with the *R* configuration predominant.[130]

This methodology has been extended to include the benzotriazole adducts **142** ($R^3 \neq H$) derived from secondary amides,[133] but substantial differences in reactivity have been observed compared to the adducts **139** derived from primary amides described above. Organozinc halides have to be used for the removal of the benzotriazole group from **142** to form the tertiary amides **793** (Scheme 249, Table 90). If a phenylmagnesium bromide is used, instead of the regular displacement product **793**, a mixture of compounds is obtained: the phenyl anion attacks the carbonyl first, followed by the elimination of benzotriazole with loss of ketone from the molecule to form an imine **796**. Further reaction with phenylmagnesium bromide then gives secondary amine **797** in 69% yield. Another striking difference is that $NaBH_4$ does not react with the adducts **142**, while $LiAlH_4$ usually affords the expected tertiary amines **794**, but in one case a secondary amine **795** is again obtained. The difference in reactivity is explained as follows: for the adducts derived from primary amides, initial deprotonation gives the anion **798** which expels the benzotriazole anion to give **799**. Such an NH is not available in the adducts **142** derived from a secondary amide. As a result, attack on the carbonyl by Grignard reagent and $LiAlH_4$ is observed. Sodium borohydride, which is known not to reduce an amide group, does not react with **142**.

Table 90. Reaction with Organozinc Reagents and $LiAlH_4$ of Benzotriazole Adducts Derived from Secondary Amides

compound	R^1	R^2	R^3	R^4	yield %
793	H	Me	H	PhC≡C	55
	H	Me	H	Ph	30
	H	Me	H	$PhCH_2$	41
	H	Me	*i*-Pr	Ph	43
	H	Me	Ph	Ph	52
	Me	Ph	H	Ph	64
	Me	Me	*i*-Pr	Ph	44
794	Me	Me	Ph		82
	Me	Ph	H		96
	Me	Ph	n-C_8H_{17}		40

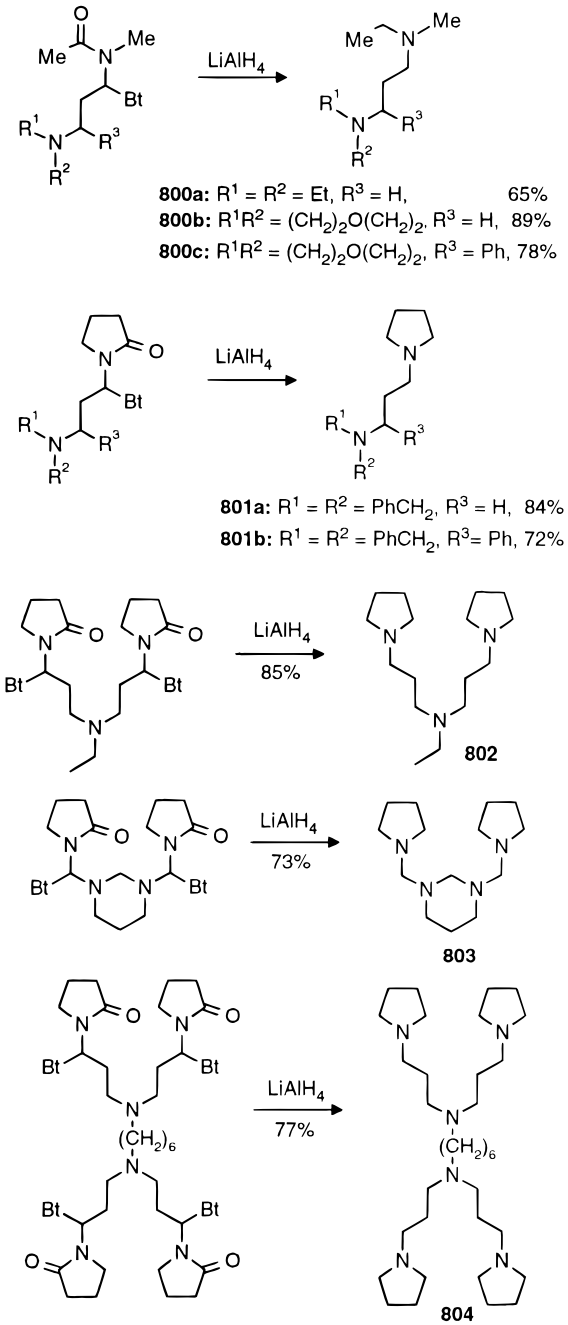
Scheme 249. *N*-Alkylation of Secondary Amides



Reduction with $LiAlH_4$ of the benzotriazole adducts derived from additions of *N*-(alkylamino)benzotriazoles to enamides (see section III.C.1) leads to the synthesis of a variety of polyamines **800**−**804**[125] (Scheme 250).

b. Amidoalkylation of Stabilized Carbanions. Use of a stabilized carbanion as nucleophile leads to the amidoalkylation of acidic CH compounds as shown in Scheme 251 (Table 91) with the formation of products **805** for malonic, **806** from acetoacetic, and **807** from nitroacetic esters.[128] Nitroalkanes afford derivatives **808**.[324]

Scheme 250. Reduction of *N*-[1-Benzotriazolyl-3-(*N*′,*N*′-dialkylamino)alkyl] Amides with $LiAlH_4$



Reactions of *N*-(benzotriazol-1-ylmethyl) amides with allyltrimethylsilane in the presence of a Lewis acid (BF_3·Et_2O) gives *N*-homoallyl amides **809** in good yields (Scheme 252).[132] Under similar conditions, 2-acetoxypropene affords the corresponding *β*-amidoacetone **810** in 33% yield.

Treatment of *N*-(benzotriazol-1-ylmethyl)benzamide (**811**) with 2 equiv of LDA and 1 equiv of 1,1-diphenylethylene gives the *N*-cyclopropyl-substituted amide **813**.[132] The transformation presumably occurs via intermediate dianion **812**, formed by addition of dilithiated amide **811** to 1,1-diphenylethylene, with subsequent intramolecular nucleophilic substitution of benzotriazole (Scheme 253).[132]

c. Amidoalkylation of Cyanide Anion. Cyanide anion, as expected, displaces the benzotriazole anion

Scheme 251. Amidoalkylation of Malonates, Acetoacetates, and Nitroalkanes

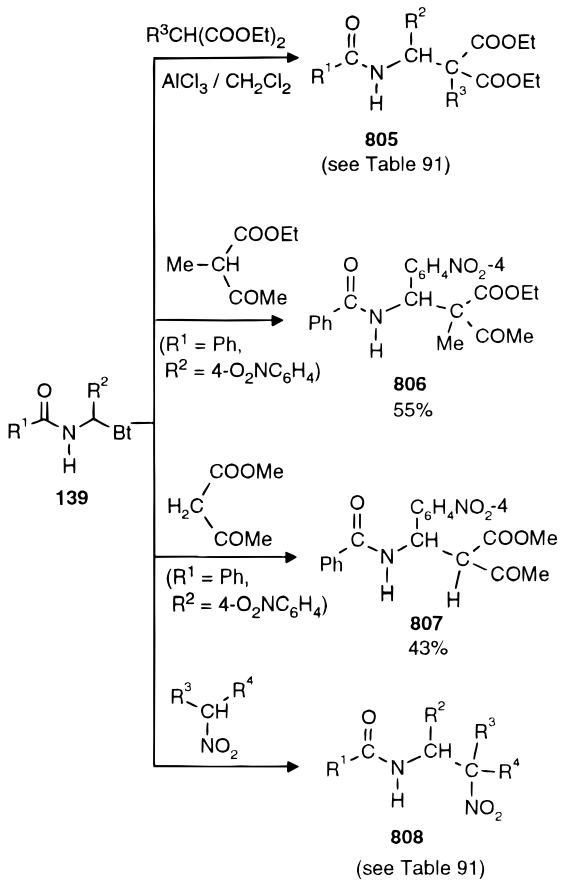
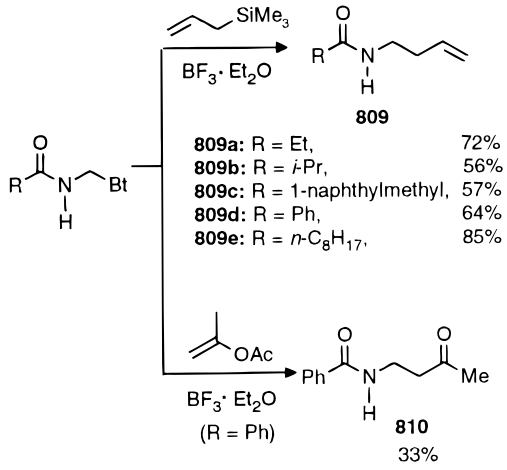


Table 91. Amidoalkylation of Malonates and of Nitroalkanes

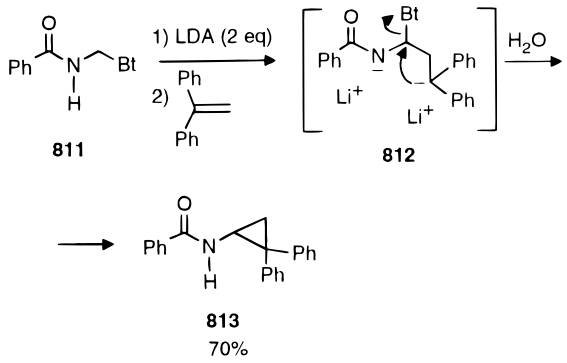
compound	R^1	R^2	R^3	R^4	yield %
805	Me	Ph	Me		59
	Me	Ph	Et		56
	Me	4-$MeOC_6H_4$	Me		62
	Me	4-$MeOC_6H_4$	Et		57
	Ph	Ph	Me		65
	Ph	Ph	Et		58
	Ph	4-$O_2NC_6H_4$	Me		67
	Ph	4-$O_2NC_6H_4$	Et		74
	Ph	4-$MeOC_6H_4$	Me		69
	Ph	4-$MeOC_6H_4$	Et		63
	Ph	$PhCH_2$	Me		72
	Ph	$PhCH_2$	Et		67
	Ph	1-naphthyl	Me		60
	Ph	1-naphthyl	Et		55
808	Me	Ph	Me	Me	79
	Me	Ph	COOEt	H	50
	Me	Ph	$-(CH_2)_5-$		76
	Ph	Ph	Me	H	82
	Ph	Ph	Me	Me	90
	Ph	Ph	$-(CH_2)_5-$		84

giving α-acylamino nitriles **814**.[129,346] In Scheme 254 (Table 92), a novel benzotriazole-assisted method of peptide elongation is shown with the amidoalkylation of the cyanide anion as the key step. This reaction is combined with a smooth hydrolysis of the cyanide group into amide which completes the peptide cycle. However the reaction with cyanide is not stereoselective, and in general, a mixture of diastereomers is obtained. This useful sequence is illustrated by the preparation of [[(benzyloxycarbonyl)phenyl]glycyl]leucine amides (Z-Phg-Leu-NH_2) and [[benzyloxy-

Scheme 252. Preparation of *N*-Homoallylamides and *N*-[1-(3-Oxoalkyl)] Amides



Scheme 253. Preparation of *N*-Cyclopropyl-Substituted Amide



Scheme 254. Amidoalkylation of Cyanide: The Peptide Cycle

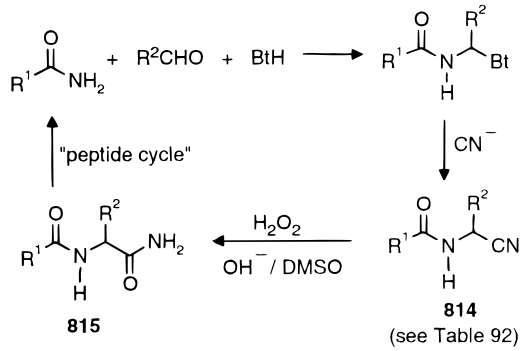


Table 92. Preparation of *N*-(α-Cyanoalkyl) Amides 814 by Displacement of Benzotriazole by Cyanide

R^1CO	R^2	yield %
$PhCH_2OCO$	H	79[346]
$PhCH_2OCO$	*n*-Pr	90[346]
$PhCH_2OCO$	*i*-Pr	90[346]
$PhCH_2OCO$	Ph	79[346]
t-BuOCO	*i*-Pr	90[346]
$PhCH_2OC(O)NHCH(CH_2COOMe)CO$	$PhCH_2$	80[129]
BzGly	*i*-Pr	73[346]
Z-Phe	*i*-Pr	95[346]
Z-L-Val	*i*-Bu	85[346]
Z-Phg	*i*-Bu	87[346]
Z-Ileu	*i*-Pr	86[346]
Z-L-Phe-L-Val	*i*-Bu	94[346]

carbonyl)phenylalanyl]valyl]leucine amide (Z-Phe-Val-Leu-NH_2), starting from benzyl carbamate and Z-Phe-NH_2, respectively.[346]

d. Amidoalkylation of Electron-Rich Aromatics and Heteroaromatics. The amidoalkylation of aromatic compounds is carried out using aluminum chloride as a catalyst and succeeds well on active aromatic rings containing hydroxy, alkoxy, or amino groups as well as heterocycles such as furan to give products **816** (Scheme 255, Table 93).[347] Such amidoalkylation also occurs intramolecularly when arylacetamides are the starting amides to form 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones **817**.[131] Here the ring to be amidoalkylated can be phenyl unsubstituted or substituted with a methoxy group. A naphthyl analogue reacts similarly to form compound **818** in 56% yield. With benzene as solvent, an intermolecular alkylation of the solvent **816** (R^1 = $PhCH_2$, R^2 = Ph) in 81% yield.

Scheme 255. Amidoalkylation of Electron-Rich Aromatics and Heteroaromatics

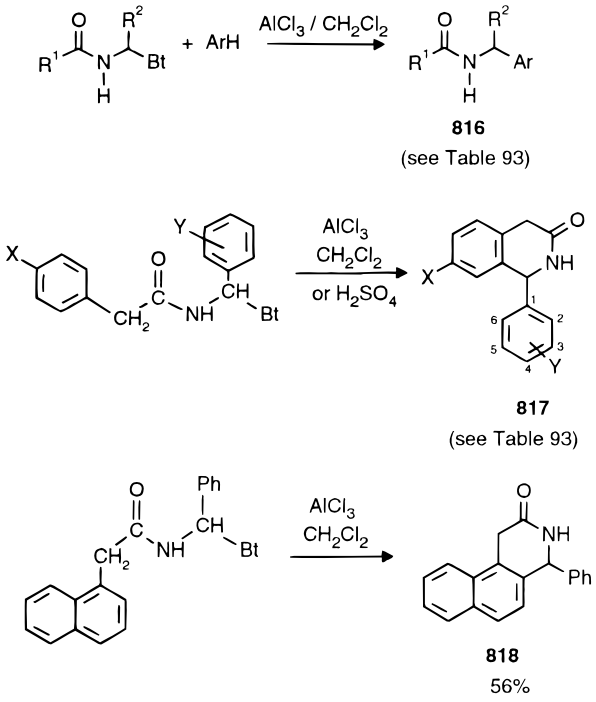


Table 93. Amidoalkylation of Aromatic Rings: Intermolecular To Give 816 and Intramolecular To Give 817

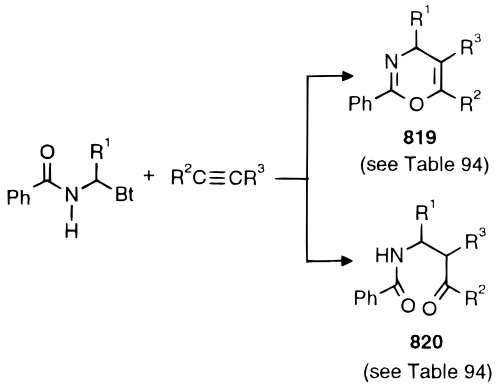
compound	R^1 or X	R^2 or Y	Ar	yield %
816	Me	$4\text{-}MeOC_6H_4$	$4\text{-}HOC_6H_4$	46
	Ph	*t*-Bu	2-hydroxynaphth-1-yl	57
	Ph	Ph	$4\text{-}MeOC_6H_4$	59
	Ph	$4\text{-}ClC_6H_4$	2-furyl	35
	Ph	$3\text{-}O_2NC_6H_4$	$4\text{-}Me_2NC_6H_4$	64
	Ph	$3\text{-}O_2NC_6H_4$	2-furyl	81
	Ph	$4\text{-}MeOC_6H_4$	$2\text{-}HO\text{-}4,6\text{-}Me_2C_6H_2$	65
	Ph	$4\text{-}MeOC_6H_4$	2-hydroxynaphth-1-yl	56
	Ph	1-naphthyl	$2,4\text{-}(MeO)_2C_6H_3$	69
	3-pyridyl	Ph	2-hydroxynaphth-1-yl	100
	$PhCH_2$	Ph	Ph	81
817	H	H		95
	H	2-Me		76
	H	4-Cl		95
	MeO	H		47
	MeO	4-Cl		60

Table 94. Amidoalkylation of Acetylenes

compound	R^1	R^2	R^3	yield %
819	Ph	*n*-Bu	H	83
	Ph	Ph	H	86
	Ph	Ph	Et	94
	4-ClC_6H_4	Ph	H	91
	4-ClC_6H_4	Ph	Et	92
	3-$O_2NC_6H_4$	Ph	Et	76
	4-$MeOC_6H_4$	Ph	H	89
	4-$MeOC_6H_4$	Ph	Et	94
	1-naphthyl	Ph	H	14
820	4-$MeOC_6H_4$	Ph	Et	35
	4-$MeOC_6H_4$	Ph	Ph	75

e. Amidoalkylation of Acetylenes. The amidoalkylation of acetylenes leads to ring closure to form tri- or tetrasubstituted 4*H*-1,3-oxazines **819** mostly in excellent yields (Scheme 256, Table 94).[348] Electrophilic attack of the *N*-acyliminium cation on the triple bond of acetylene is followed by ring closure. Diphenylacetylene yields the open-chain product **820** (R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = Ph) probably due to steric hindrance; however, the formation of a mixture of compounds **819** and **820** (R^1 = 4-$MeOC_6H_4$, R^2 = Ph, R^3 = Et) from 1-phenyl-1-butyne may indicate instability of the oxazine **819** in some cases.

Scheme 256. Amidoalkylation of Acetylenes

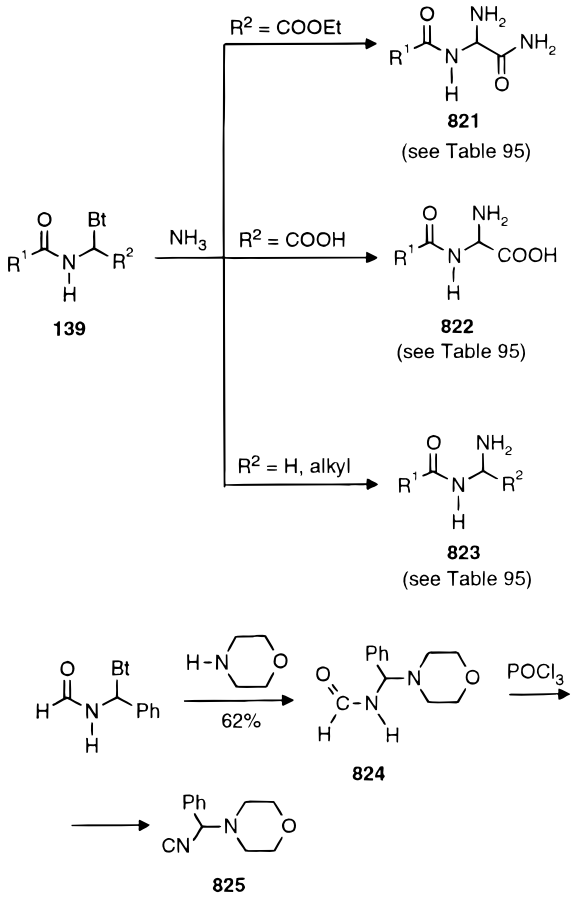


f. Amidoalkylation of Primary and Secondary Amines and Ammonia. The adducts **139** derived from benzotriazole, a primary amide, and ethyl glyoxylate or glyoxylic acid react with ammonia in a novel, convenient route to monoacylated α-aminoglycines **821** and **822**[349] (Scheme 257, Table 95). In the case of ethylglyoxylate, the ester group is also amidated. This amidoalkylation is also general for R^2 = alkyl, allowing synthesis of various monoacylated aminals **823**.[136] If the starting amide is a protected amino acid amide, the above-described reaction sequence leads to the formation of so-called "*gem*-dipeptides". The benzotriazolyl moiety can also be displaced by a secondary amine such as morpholine as in the formation of *N*-[α-(morpholino)benzyl]formamide **824** which can be dehydrated to give the α-amino isocyanide **825**.[357]

Table 95. Preparation of Monoacyl Aminals 821−823

compound	R^1	R^2	yield %
821	Me		91
	Ph		86
	BzlO		37
	Bz-Gly		98
	Z-Gly		85
822	BzlO		70
	Z-Gly		48
823	BzlO	H	77
	BzlO	*n*-Pr	74
	BzlO	*i*-Pr	66
	BzlO	*i*-Bu	77
	BzlO	Bzl	63
	Bz-Gly	*i*-Pr	75
	Z-L-Val	*i*-Bu	86
	Z-iLeu	*i*-Pr	87
	Z-Phg	*i*-Bu	78
	Z-Phe	*i*-Pr	98

Scheme 257. Amidoalkylation of Ammonia and Amines



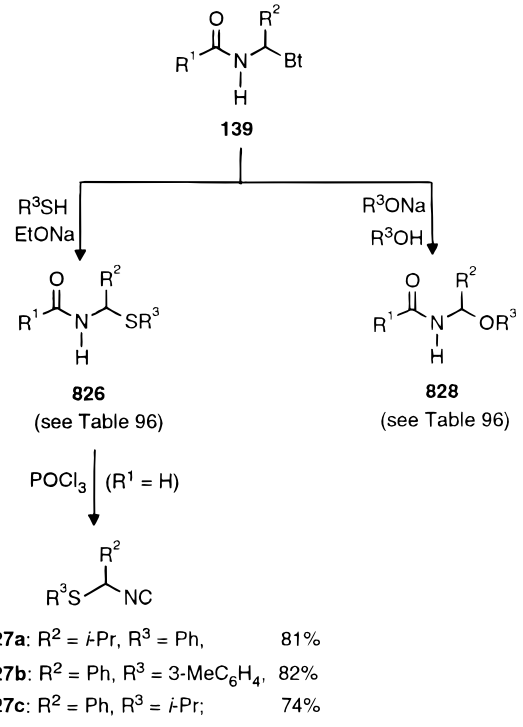
g. Amidoalkylation of Mercaptans and Alcohols. Aromatic as well as aliphatic thiols, and both primary and secondary alcohols all react with *N*-[1-(benzotriazol-1-yl)alkyl]amides **139**, providing a convenient route to *N*-acylhemithioaminals **826**[351] and *N*-(α-alkoxyalkyl)amides **828**[32,352] in good yields (Table 96, Scheme 258). The corresponding formamide derivatives can be dehydrated to α-alkylthioalkyl isocyanides **827**.[350]

h. Amidoalkylation of Ethyl Diphenylphosphinite. *N*-(1-Benzotriazolylalkyl) amides react with ethyl diphenylphosphinite[353] to afford amides **829a−g** which generally possess biological activities[354] (Scheme 259). Alternatively, the starting amides can be prepared *in situ* (see section III.A.6.e) and the reaction can be carried out in one pot.

Table 96. Preparation of *N*-Acyl Hemithioaminals 826 and *N*-(α-Alkoxyalkyl) Amides 828

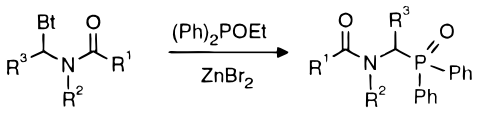
compound	R^1	R^2	R^3	yield %
826	H	*i*-Pr	Ph	74[350]
	H	*n*-C_5H_{11}	*n*-C_8H_{17}	10[351]
	H	Ph	*i*-Pr	80[350]
	H	Ph	3-MeC_6H_4	45[350]
	Me	3-$O_2NC_6H_4$	*n*-Bu	79[351]
	Me	3-$O_2NC_6H_4$	3-MeC_6H_4	90[351]
	Ph	H	*n*-Bu	78[351]
	Ph	H	Ph	87[351]
	Ph	*n*-Pr	1-naphthyl	92[351]
	Ph	*i*-Pr	3-MeC_6H_4	84[351]
	Ph	CH_2=$CHCH_2$	Ph	88[228]
	Ph	CH_2=$CHCH_2$	$Ph(CH_2)_2$	93[228]
	Ph	$(CH_2)_5C(OH)$	$Ph(CH_2)_2$	94[228]
	Ph	Ph	*i*-Pr	75[351]
	Ph	Ph	$PhCH_2$	82[351]
	Ph	$PhCH_2$	*n*-C_8H_{17}	99[351]
	Ph	1-naphthyl	*n*-C_8H_{17}	94[351]
	PhNH	Ph	*n*-C_8H_{17}	57[351]
828	Me	4-ClC_6H_4	*i*-Pr	78[352]
	Me	4-ClC_6H_4	*i*-Bu	75[352]
	Me	4-$MeOC_6H_4$	*i*-Pr	56[352]
	Et	H	*i*-Pr	94[132]
	i-Pr	H	Et	76[132]
	Ph	H	Et	67[352]
	Ph	H	*i*-Pr	64[352]
	Ph	CH_2=$CHCH_2$	Me	89[228]
	Ph	CH_2=$CHCH_2$	Et	76[228]
	Ph	Ph	Me	69[352]
	Ph	Ph	MeEt	91[352]
	Ph	Ph	*i*-Pr	94[352]
	Ph	4-$MeOC_6H_4$	Me	86[352]
	Ph	4-$MeOC_6H_4$	Et	88[352]
	Ph	$PhCH_2$	Et	92[352]
	3-pyridyl	H	*i*-Pr	89[132]

Scheme 258. Amidoalkylation of Alcohols and Thiols



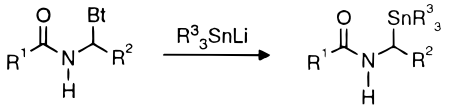
i. Amidoalkylation of Trialkylstannanes. Secondary *N*-(1-benzotriazolylalkyl) amides react smoothly with (trialkylstannyl)lithium reagents to give in good yields the corresponding *N*-[1-(trialkylstannyl)alkyl] amides **830** (Scheme 260), which are important precursors to nitrogen-substituted organolithium reagents.[338]

Scheme 259. Amidoalkylation of Ethyl Diphenylphosphinite



829a: $R^1R^2 = (CH_2)_3$, R^3 = H, 46%
829b: $R^1R^2 = (CH_2)_3$, R^3 = *i*-Pr, 64%
829c: $R^1R^2 = (CH_2)_3$, R^3 = *t*-Bu, 61%
829d: $R^1R^2 = (CH_2)_3$, R^3 = Ph, 79%
829e: R^1 = Ph, R^2 = H, R^3 = 4-ClC_6H_4, 55%
829f: R^1 = Ph, R^2 = Me, R^3 = H, 58%
829g: R^1 = 2-MeC_6H_4, $R^2 = R^3$ = H, 78%

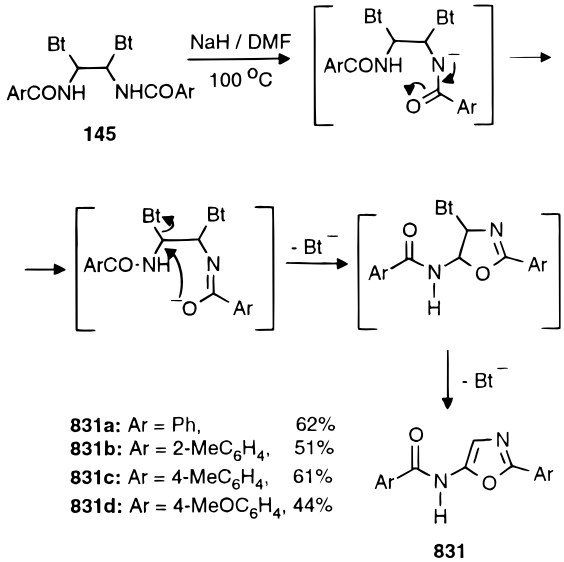
Scheme 260. Amidoalkylation of Trialkylstannanes



830a: R^1 = Me, R^2 = *i*-Pr, R^3 = Me, 42%
830b: R^1 = Me, R^2 = *i*-Pr, R^3 = *n*-Bu, 85%
830c: $R^1 = R^2$ = *i*-Pr, R^3 = *n*-Bu, 84%
830d: R^1 = Ph, R^2 = H, R^3 = *n*-Bu, 39%
830e: R^1 = Ph, R^2 = *i*-Pr, R^3 = *n*-Bu, 54%
830f: R^1 = Ph, R^2 = *n*-C_5H_{11}, R^3 = *n*-Bu, 41%
830g: R^1 = 4-MeC_6H_4, R^2 = *i*-Pr, R^3 = *n*-Bu, 67%

j. Preparation of Oxazoles. 1,2-(Diacylamino)-1,2-di(benzotriazolyl)ethanes **145** (for preparation, see section II.B.2.h) react with sodium hydride in DMF at 100 °C to give 5-(acylamino)oxazoles **831** in moderate yields (Scheme 261).[134] The reaction is believed to proceed via the intramolecular displacement of one benzotriazolyl group, followed by elimination of the second molecule of benzotriazole.

Scheme 261. Preparation of Oxazoles



831a: Ar = Ph, 62%
831b: Ar = 2-MeC_6H_4, 51%
831c: Ar = 4-MeC_6H_4, 61%
831d: Ar = 4-$MeOC_6H_4$, 44%

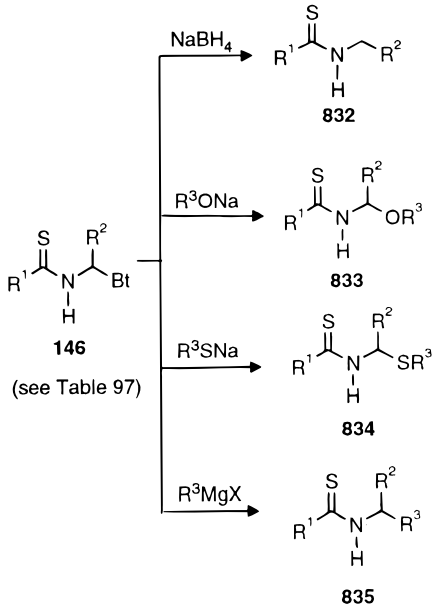
Table 97. Preparation of Secondary Thioamides and Functionalized Derivatives

compound	R^1	R^2	R^3	yield %
832	Ph	H		98[138]
	Ph	*i*-Pr		99[138]
	Ph	*n*-C_5H_{11}		92[138]
	Ph	*n*-C_7H_{15}		95[138]
	Ph	*n*-C_8H_{17}		97[138]
	NH_2	*i*-Pr		60[138]
	NH_2	*n*-C_7H_{15}		60[138]
833	Ph	CH_2=$CHCH_2$	Me	75[233]
	Ph	CH_2=$CHCH_2$	Et	77[233]
	Ph	*n*-Bu	Me	99[233]
	4-ClC_6H_4	CH_2=$CHCH_2$	Et	74[233]
834	Ph	CH_2=$CHCH_2$	*i*-Pr	41[233]
	Ph	CH_2=$CHCH_2$	*n*-Bu	45[233]
	Ph	*n*-C_7H_{15}	*i*-Pr	98[233]
	4-ClC_6H_4	*n*-Bu	*i*-Pr	70[233]
835	Ph	H	$PhCH_2$	84[137]
	Ph	*n*-Pr	*n*-Bu	89[137]
	Ph	*i*-Pr	$PhCH_2$	87[137]
	Ph	CH_2=$CHCH_2$	*n*-Bu	70[233]
	Ph	CH_2=$CHCH_2$	Ph	83[233]
	Ph	*n*-C_5H_{11}	Ph	88[137]
	Ph	*n*-$C_{11}H_{23}$	$PhCH_2$	81[137]

5. From Systems of Type Bt—C—N—C=S and Bt—C—N—SO_2R

a. N-Alkylation of Thioamides. Similar to the corresponding amides, secondary thioamides **835** can be prepared by reaction of *N*-[(thiocarboamido)alkyl]-benzotriazoles **146** with Grignard reagents (Table 97, Scheme 262).[137,233] The benzotriazole group in the

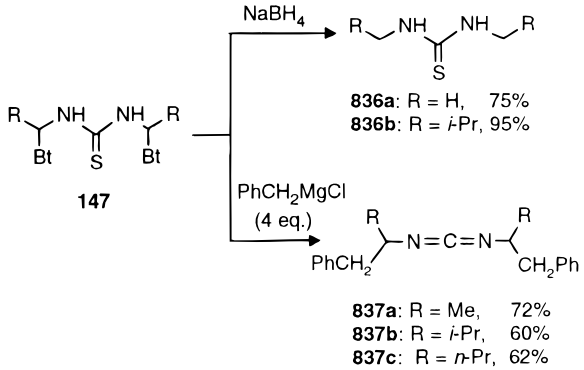
Scheme 262. Preparation of Secondary Thioamides and Functionalized Derivatives



N-[(thiocarboamido)alkyl]benzotriazoles is also replaced by a hydrogen on treatment with borohydride to give **832**[138] or by an alkoxy or alkylthio group to give **833** and **834** respectively (Table 97).[233]

Reactions of thiourea benzotriazole derivatives **147** with $NaBH_4$ afford *N*,*N*-dialkylthioureas **836** (Scheme 263). However, the reactions of **147** with benzylmagnesium chloride result in the formation of carbodiimides **837**.[139]

Scheme 263. Preparation of Dialkylthioureas and Carbodiimides



b. N-Alkylation of Sulfonamides. Reactions of this type can be futher extended to sulfonamides **838** as shown in Scheme 264 although the preparation of **841** by this route is of less synthetic interest as the

Scheme 264. *N*-Alkylation of Sulfonamides

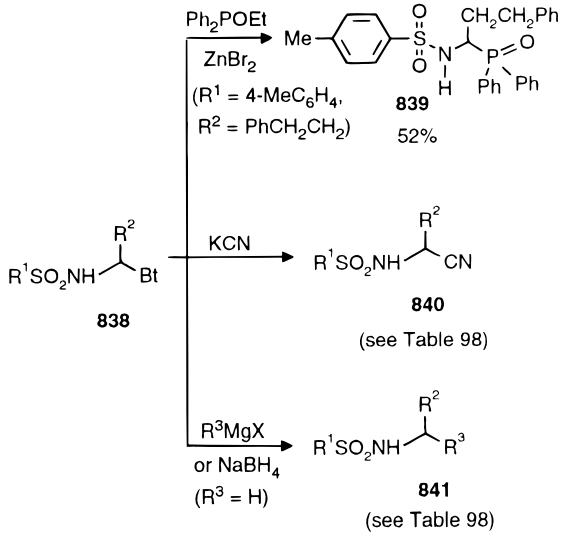


Table 98. Preparation of *N*-Alkyl Sulfonamides 840 and 841

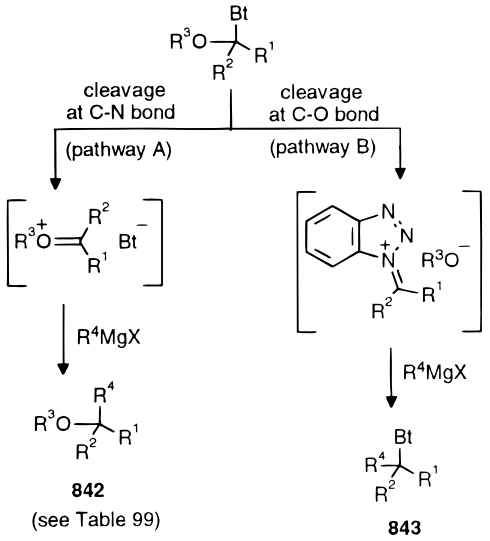
compound	R^1	R^2	R^3	yield %
840	Me	H		~100
	Ph	*i*-Pr		90
	4-MeC_6H_4	H		80
	4-MeC_6H_4	Me		94
	4-MeC_6H_4	Et		98
	4-MeC_6H_4	Ph		98
	4-MeC_6H_4	4-MeC_6H_4		95
	4-MeC_6H_4	1-naphthyl		65
841	Ph	H	H	97
	Ph	H	Ph	94
	Ph	H	*n*-$C_{12}H_{25}$	65
	Ph	*i*-Pr	H	71
	Ph	*i*-Pr	Ph	96
	Ph	*i*-Pr	$PhCH_2$	48
	Ph	Ph	H	49
	Ph	Ph	Ph	88
	Ph	Ph	$PhCH_2$	68
	Ph	Ph	*n*-$C_{12}H_{25}$	40
	Ph	*n*-C_7H_{15}	H	77
	Ph	*n*-C_7H_{15}	Ph	55
	Ph	*n*-C_7H_{15}	*n*-$C_{12}H_{25}$	84
	Ph	pyridin-2-yl	H	96
	4-MeC_6H_4	*i*-Pr	Ph	38
	4-MeC_6H_4	Ph	H	75

N-alkylation of sulfonamides by classical methods is usually quite easy.[27] *N*-(Benzotriazolylalkyl)sulfonamides react also with ethyl diphenylphosphinite to give *N*-[(1-diphenyloxophosphoranyl)alkyl]sulfonamides **839**. Displacement of benzotriazolyl moiety with cyano group provides a convenient approach to the synthesis of *N*-(1-cyanoalkyl)sulfonamides **840**[141] (Table 98).

6. From Systems of Type Bt—C—O: Alkoxyalkylations and Acyloxyalkylations

a. Alkoxyalkylation. Compared to the corresponding amino derivatives, α-benzotriazolylalkyl alkyl ethers are more stable and less reactive. The removal of the benzotriazole group in the latter (pathway A) (Scheme 265) requires higher temperature

Scheme 265. Preparation of Ethers



than for the amino analogues. Cleavages of C−O instead of C−N bonds (pathway B) and benzotriazole ring opening (see section V.A) are also found. Nevertheless, under suitable conditions dialkyl and alkyl aryl ethers can be obtained in high yields provided at least R^1 or R^2 is not hydrogen (Table 99).[75]

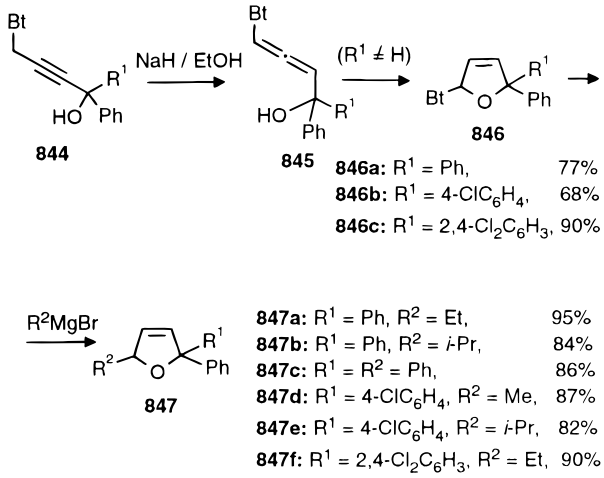
Table 99. Preparation of Dialkyl and Alkyl Aryl Ethers 842

R^1	R^2	R^3	R^4	yield %
Me	Me	Me	Et	60[75]
Me	Me	Me	$PhCH_2$	73[75]
Me	Me	*n*-C_6H_{13}	$PhCH_2$	96[75]
i-Pr	H	*i*-Pr	Me	75[75]
i-Pr	H	*i*-Pr	Et	76[75]
i-Pr	H	*i*-Pr	c-C_6H_{11}	40[75]
i-Pr	H	*i*-Pr	Ph	73[75]
i-Pr	H	*i*-Pr	$PhCH_2$	95[75]
i-Pr	H	c-C_6H_{11}	$PhCH_2$	95[75]
i-Pr	H	Ph	Me	86[75]
i-Pr	H	2-naphthyl	Me	45[75]
n-Bu	H	Me	*n*-C_8H_{17}	60[234]
$-(CH_2)_5-$		*n*-Pr	$PhCH_2$	93[75]
$-(CH_2)_5-$		$PhCH_2$	$PhCH_2$	68[75]
Ph	H	*i*-Pr	Ph	80[75]
Ph	H	*i*-Pr	$PhCH_2$	85[75]
4-MeC_6H_4	H	$Cl(CH_2)_3$	Ph	25[75]
$PhCH_2$	H	Me	*n*-Bu	68[234]
n-C_8H_{17}	H	Me	*n*-Bu	57[234]
n-$C_{10}H_{21}$	H	Me	*n*-Bu	64[234]
n-$C_{10}H_{21}$	H	Me	$PhCH_2$	50[234]

However α-benzotriazolylalkyl ethers, derived from formaldehyde ($R^1 = R^2 = H$) (for preparation, see section III.B.2), under the same conditions provide only 1-alkylbenzotriazoles **843**, and no traces of expected ethers **842** are detected.[75] 1-(α-Methoxyalkyl)benzotriazoles, obtained by lithiation of 1-(methoxymethyl)benzotriazole and quenching with electrophiles (see section III.A.7), react as expected with Grignard reagents to afford the expected ethers.[234] The method works best for the preparation of corresponding ethers **842** where R^1 and R^2 are not both hydrogen, and is thus especially suitable for the preparation of hindered ethers which cannot be easily prepared using the well-known Williamson reaction. The Williamson ether synthesis is good for primary alkyl halides, poor for secondary halides, and fails completely for tertiary alkyl halides. Hence, these two ether syntheses, the Williamson and our new method, are complementary.

Cyclic ethers can be used successfully as substrates. Thus, 2-benzotriazolyl-2,5-dihydrofurans **846**, which are easily prepared from 1-hydroxy-4-benzotriazolyl-2-alkynes **844** (for preparation of **844**, see section III.A.2.d), react readily with Grignard reagents to give the corresponding 2,5,5-trisubstituted 2,5-dihydrofurans **847** (Scheme 266).[283]

Scheme 266. Preparation of 2,5-Dihydrofurans from 1-Hydroxy-4-benzotriazolyl-2-alkynes



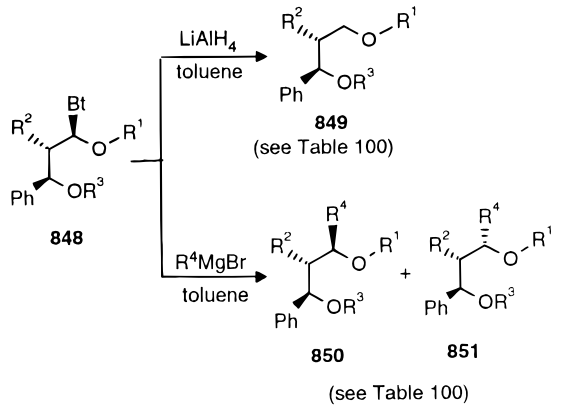
This method has been extended[272] to the preparation of 1,3-diethers **849**−**851** (Table 100, Scheme 267) using the benzotriazole adducts **848** obtained by the addition of 1-(α-alkoxybenzyl)benzotriazoles to enol ethers (see section III.C.2).

Table 100. Preparation of 1,3-Diethers

compound	R^1	R^2	R^3	R^4	yield %	ratio **850**:**851**
849	Et	H	Me		30	
	Et	H	Et		43	
	Me	Ph	Me		61	
850 and **851**	Me	H	Me	Me	86	44:56
	Me	Ph	Et	Me	94	50:50
	Et	H	Me	Ph	80	50:50
	Et	H	Et	Ph	91	44:56
	Et	H	Et	*n*-BuC≡C	80	67:33
	$-(CH_2)_2-$		Et	Me	70	*a*

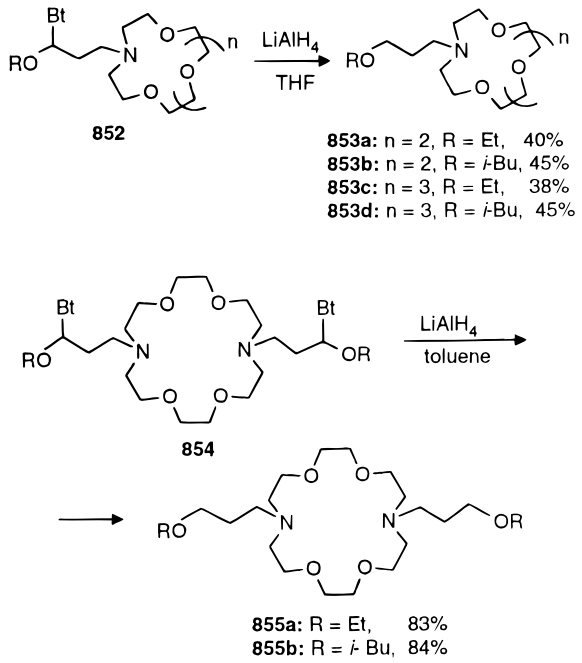
[a] Mixture of 4 isomers in ratio 32:2:18:48 obtained.

Scheme 267. Preparation of 1,3-Diethers



Reductions of *N*-(3-alkoxy-3-benzotriazolylpropyl)-substituted monoaza- (**852**)[102] and diaza- (**854**)[124] crown ethers with lithium aluminum hydride in refluxing THF or toluene give lariat crown ethers **853** and **855**, respectively (Scheme 268). Toluene as a solvent seems to be superior to THF as it inhibits the side reaction of alkoxy group displacement.

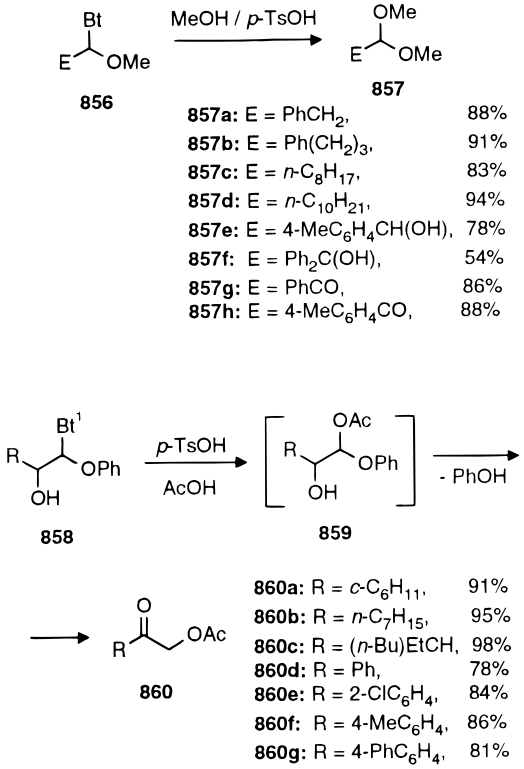
Scheme 268. Preparation of *N*-(3-Alkoxypropyl)-Substituted Crown Ethers



Treatment of 1-(α-methoxyalkyl)benzotriazoles **856** with methanol in the presence of *p*-toluenesulfonic acid affords (Scheme 269) the corresponding dimethyl acetals **857**[235] which are important organic intermediates and synthetic equivalents of the corresponding aldehydes.[355] 1-(1-Phenoxy-2-hydroxyalkyl)benzotriazoles **858** are acetoxylated in acetic acid providing acetoxymethyl ketones **860** presumably via intermediate α-hydroxyaldehyde acetals **859** which then eliminate a molecule of phenol to give.[236]

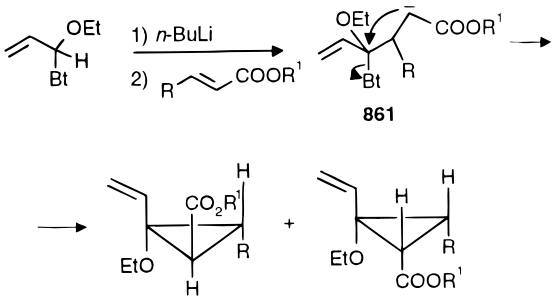
As discussed in section III.A.7, unstable intermediates **389**, obtained from reaction of lithiated 1-(α-ethoxyallyl)benzotriazoles with nonhindered aliphatic ketones (see Scheme 126, Table 40), undergo intramolecular cyclization in the presence of zinc bromide to give the corresponding 1-ethoxy-1-vinyloxiranes.[78] These oxiranes are reasonably stable under neutral and basic conditions but can be easily hydrolyzed in acidic media to give the corresponding α-hydroxy ketones.

Scheme 269. Preparation of Dimethyl Acetals and Acetoxymethyl Ketones



When α,β-unsaturated esters are used as electrophiles with the same lithiated 1-(α-ethoxylallyl)-benzotriazoles (Scheme 270), the initially formed intermediates **861** cyclize intramolecularly with the elimination of benzotriazole to produce a mixture of two stereoisomers of 1-ethoxy-1-vinylcyclopropanes **862a**,**b** (Scheme 270).[78,356a] The size of the R^1 group in **861** is critical for smooth cyclization; for example, all attempts to prepare cyclopropane derivatives from ethyl acrylate (R = H) failed.

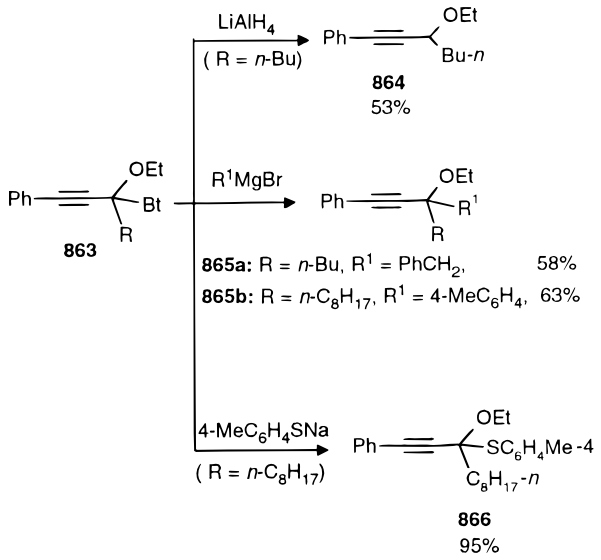
Scheme 270. Preparation of Vinylcyclopropanes from *N*-(α-Ethoxyallyl)benzotriazole



R^1	R	total yield %
Me	Me	58
Et	Me	51
Et	n-C_7H_{15}	54

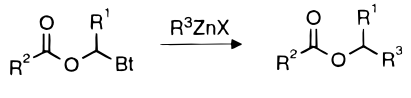
The benzotriazolyl group in 1-benzotriazolylpropargyl ethyl ethers **863** (for preparation, see section III.A.2.d) can be reduced out by treatment with lithium aluminum hydride to yield **864** or replaced by C- and S-nucleophiles giving **865** and **866**, respectively (Scheme 271).[187]

Scheme 271. Displacement of Benzotriazole in 1-Benzotriazolylpropargyl Ethyl Ethers



b. Acyloxyalkylation. Carboxylic acid esters can also be made by benzotriazole methodology using 1-[α-(acyloxy)alkyl]benzotriazoles as shown in Scheme 272.[82] Benzotriazole derivatives **867** react smoothly

Scheme 272. Preparation of Esters



867 **868**

(see Table 101)

Table 101. Preparation of Esters 868

R^1	R^2	R^3	yield %
H	Ph	$PhCH_2$	64
H	Ph	$PhCH_2CH_2$	38
H	Ph	*n*-BuC≡C	85
H	Ph	PhC≡C	70
n-Pr	Me	Ph	74
n-Pr	Me	$PhCH_2$	94
n-Pr	Me	PhC≡C	87
n-Pr	*n*-C_5H_{11}	$PhCH_2$	95
n-Pr	Ph	*n*-BuC≡C	90
Ph	Me	*n*-Bu	96
Ph	Me	$PhCH_2$	98
Ph	Me	4-MeC_6H_4	98

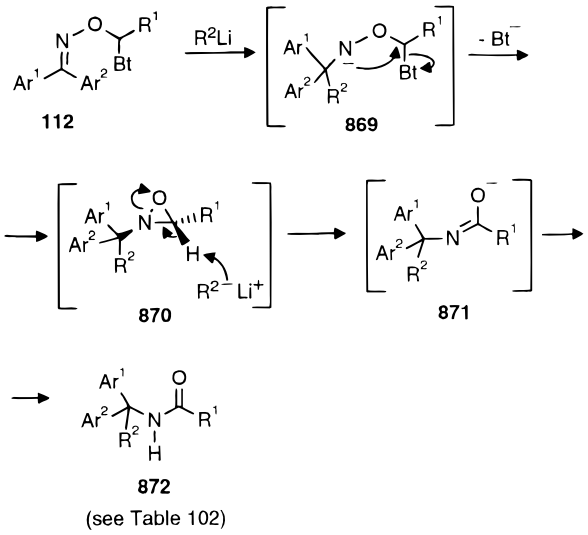
with organozinc reagents in refluxing toluene to give **868** usually in good to quantitative yields (Table 101) by substitution of the benzotriazolyl moiety with an alkyl, aryl or alkynyl group. The reaction requires use of organozinc reagents to prevent competitive attack on the carbonyl group.

c. Intramolecular Rearrangement of N−O−CH−Bt Derivatives. Treatment of the benzotriazolyl adducts **112**, derived from oximes (see sections II.B.1.b and III.B.2) with organolithium reagents leads directly to amides **872** (Table 102, Scheme 273).[94] The mechanism is believed to involve initial addition of an alkyllithium to the oxime C=N bond followed by intramolecular cyclization to form the oxaziridine **870**. Deprotonation by the second equivalent of the alkyllithium is accompanied by ring opening to give enol form **871** of amide **872**. This reaction sequence allows nonoxidative conversion of aldehydes into amides.

Table 102. Preparation of Amides 872 from Oximes 112

Ar^1	Ar^2	R^1	R^2	yield %
Ph	Ph	H	H	55
Ph	Ph	*i*-Pr	Me	87
Ph	Ph	*i*-Pr	*n*-Bu	90
Ph	Ph	*i*-Pr	*sec*-Bu	78
Ph	Ph	*i*-Pr	Ph	82
Ph	Ph	c-C_6H_{11}	Me	95
Ph	Ph	c-C_6H_{11}	*n*-Bu	93
Ph	Ph	(*n*-Bu)EtCH	Me	75
−(2-C_6H_4)-(2-C_6H_4)−		c-C_6H_{11}	*n*-Bu	58

Scheme 273. Rearrangement of Hydroxylamines into Amides



(see Table 102)

7. From Systems of Type BtC(OR)−C=C and Bt−C−C=C−OR by S_N2' Reactions

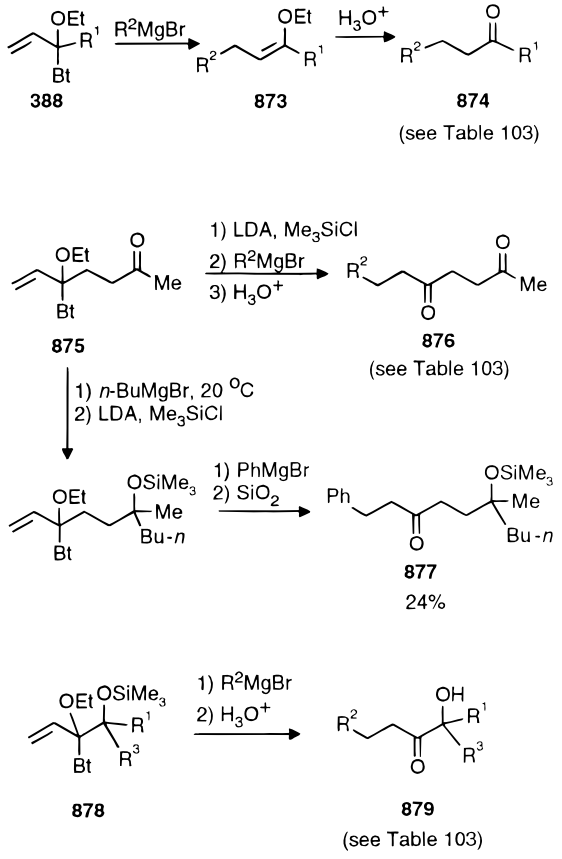
Substituted *N*-(α-ethoxyallyl)benzotriazoles **388** react with Grignard reagents in S_N2' displacement

Table 103. Addition of Grignard Reagents to *N*-(α-Ethoxyallyl)benzotriazoles Followed by Hydrolysis. Preparation of Ketones 874, 876, and 879

compound	R^1	R^2	R^3	yield %
874	Et	4-MeC_6H_4		81
	i-Pr	3-MeBu		33
	i-Pr	Ph		40
	n-Bu	4-MeC_6H_4		76
	3-MeBu	*i*-Pr		49
	3-MeBu	Ph		55
	3-MeBu	4-MeC_6H_4		79
	c-C_6H_{11}	Ph		31
	n-C_8H_{17}	4-MeC_6H_4		67
876		Ph		51
		4-MeC_6H_4		56
879	Ph	Me	Me	20
	4-MeC_6H_4	Me	H	25
	4-MeC_6H_4	Ph	H	47

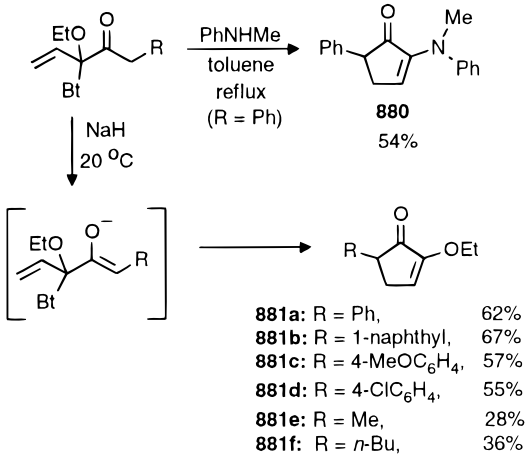
to give vinyl ethers of type **873**, which in most cases are directly hydrolyzed to the corresponding ketones **874** (Scheme 274, Table 103).[238] The reaction has been extended to **875** and **878** as starting materials to produce γ-diketones **876**, γ-hydroxy ketones **877**, and an α-hydroxy ketone **879**.

Scheme 274. Preparation of *β*-Substituted Ethyl Ketones from *N*-(α-Ethoxyallyl)benzotriazoles



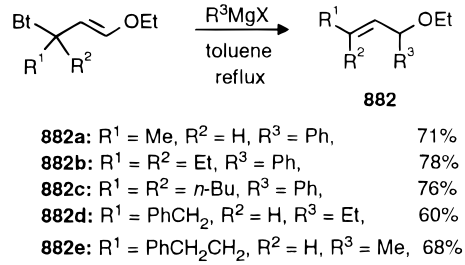
When a nucleophilic species is generated and properly positioned within the molecule, such reactions lead to the formation of carbocycles, as exemplified by the synthesis of 2-cyclopentenones **880** and **881** (Scheme 275).[238] The mechanism is believed to involve initial addition of the carbanion to the double bond followed by the elimination of benzotriazole.

Scheme 275. Preparation of 2-Amino- and 2-Ethoxycyclopent-2-enones from Substituted *N*-(α-Ethoxyallyl)benzotriazoles



Treatment of substituted 1-ethoxy-3-benzotriazol-1-ylpropenes with Grignard reagents in refluxing toluene results in the formation of 3-ethoxypropenes **882** (Scheme 276).[181]

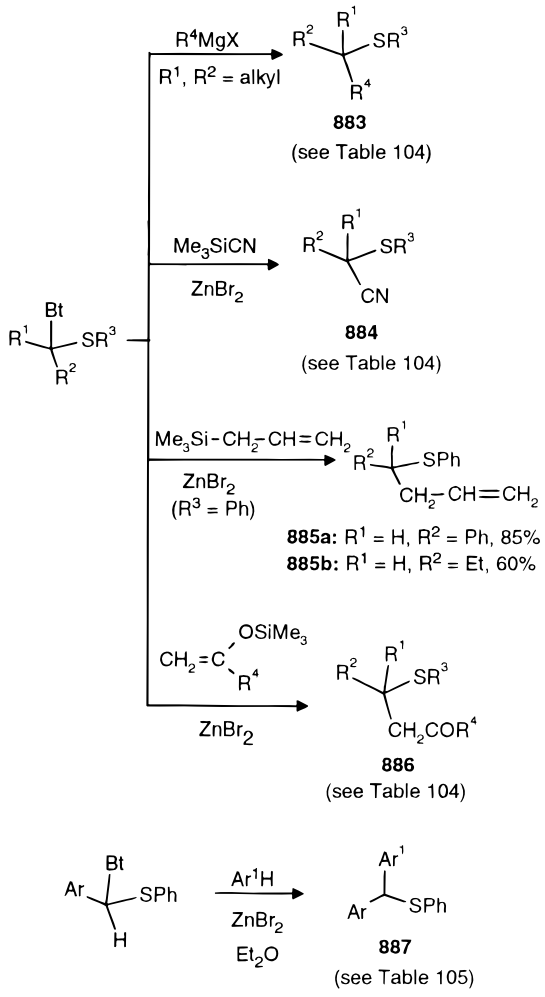
Scheme 276. Reactions of Substituted 1-Ethoxy-3-(benzotriazol-1-yl)propenes with Grignard Reagents



8. From Systems of Type Bt–C–S: Thioalkylations

1-[α-(Alkylthio)alkyl]benzotriazoles react with Grignard reagents to give thioethers **883** in good yields (Table 104) provided both R^1 and R^2 (Scheme 277)

Scheme 277. Preparation of Thioethers



are alkyl groups.[146] Thus this method is applicable for the synthesis of tertiary alkyl thioethers which

Table 104. Preparation of Thioethers 883, 884, and 886

compound	R^1	R^2	R^3	R^4	yield %
883	Me	Me	Ph	$PhCH_2$	58
	n-Pr	Me	Ph	$PhCH_2$	64
	i-Pr	Me	Ph	$PhCH_2$	64
	i-Pr	*n*-Bu	Ph	$PhCH_2$	75
	i-Pr	$PhCH_2$	Ph	$PhCH_2$	64
	$-(CH_2)_4-$		Ph	$PhCH_2$	54
	$-(CH_2)_4-$		*n*-C_8H_{17}	$PhCH_2$	61
	$-(CH_2)_4-$		*n*-C_8H_{17}	4-$MeC_6H_4CH_2$	53
	$-(CH_2)_5-$		Ph	$PhCH_2$	69
	$-(CH_2)_5-$		$PhCH_2$	$PhCH_2$	51
	$-(CH_2)_5-$		*n*-C_8H_{17}	$PhCH_2$	77
	$-(CH_2)_5-$		*n*-C_8H_{17}	$CH_2{=}CHCH_2$	65
884	H	Et	Ph		43
	H	Ph	Ph		81
	Me	Me	Ph		58
886	H	Et	Ph	Ph	48
	H	Ph	Ph	Ph	83
	H	Ph	Ph	4-MeC_6H_4	83

Table 105. Preparation of Diarylmethyl Thioethers 887

Ar	Ar^1	yield %
Ph	4-HOC_6H_4	40
Ph	4-$MeOC_6H_4$	50
Ph	3,4-$(MeO)_2C_6H_3$	51
Ph	2-Me-4-HOC_6H_3	52
Ph	4-$HOC_{10}H_6$	41
Ph	1-$MeOC_{10}H_6$	9
Ph	2-$MeOC_{10}H_6$	30
Ph	4-$MeOC_{10}H_6$	56
4-MeC_6H_4	3,4-$(MeO)_2C_6H_3$	40

are not available by the classical Williamson synthesis, and the two procedures are again complementary.

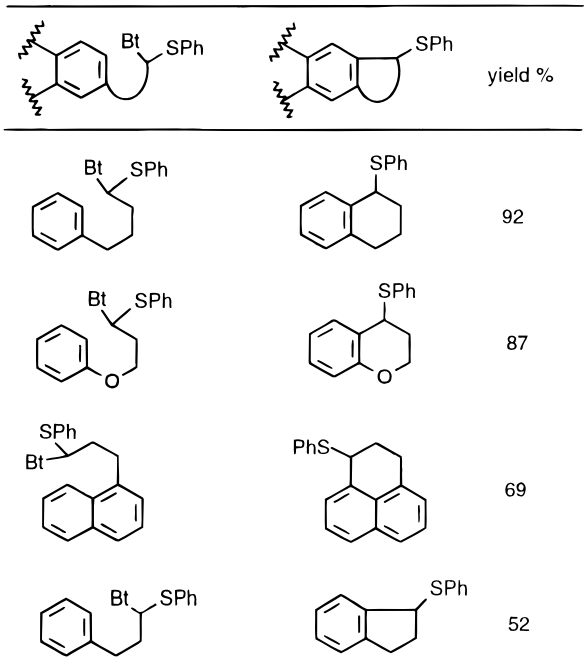
Displacement of benzotriazole moiety from α-benzotriazolyl thioether substrates can also be achieved with carbanions generated from organosilicon compounds under Lewis acid catalysis. Thus, reactions of α-benzotriazolylmethyl thioethers with trimethylsilyl cyanide or with trimethylallylsilane in the presence of zinc bromide result in α-cyano thioethers **884** and homoallyl thioethers **885**, respectively (Scheme 277, Table 104).[356b] α-Phenylthioalkylation of trimethylsilyl enol ethers gives *β*-substituted *β*-(phenylthio)ethyl aryl ketones **886**.

1-[α-(Phenylthio)benzyl]benzotriazoles react under mild conditions with electron-rich aromatic compounds including anisole, dimethoxybenzene, methoxynaphthalenes, phenols and naphthols to afford thioalkylation products **887** (Scheme 277, Table 105).[148] If the ring size is favorable, such thioalkylations occur intramolecularly to form fused aromatics (Chart 3).[242]

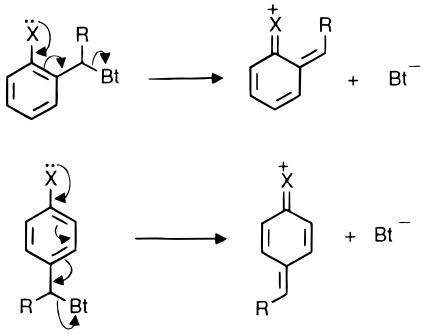
9. From Vinylogous Systems of Type Bt—C—C═C—X and Analogous

In this type of reaction heteroatom activation is nearly always needed, although aryl cases do occur where no heteroatom is present in the side chain. Similar to the vinylogous systems, suitable *ortho*- and *para*-substituted aromatics can show this type of reactivity (Scheme 278). The activation for the departure of the benzotriazolyl anion is through the benzene ring. The reactive cations formed then react with nucleophiles to yield the final products.

Chart 3. Intramolecular Thioalkylation



Scheme 278. Activation through Benzene Ring



a. From Systems of Type Bt—C—C═C—N and Bt—C—C═N—N. 1,3-Dibenzotriazolylpropylamines **888** provide an entry (Scheme 279) as the two benzotriazolyl residues are of different lability in that the benzotriazolyl residue at the C-1 is activated by the amino group.[150] When this Bt is removed by the action of sodium hydride, the resulting enamine **235**, can undergo vinylogous ionization to give benzotriazolyl anion and the mesomeric cation **889**.[357] This cation is susceptible to nucleophilic attack of a Grignard reagent. With phenylmagnesium bromide, a mixture of products **890** and **891** from attack on both C-1 and C-3 is obtained. Benzylmagnesium bromide gives, along with **890** and **891**, tertiary amine **892**, product of further Grignard addition to **890**. The more sterically hindered cyclohexylmagnesium chloride attacks exclusively at the C-3, while the weakly nucleophilic phenylethynylmagnesium bromide attacks exclusively at the C-1. Solvent plays an important role in the product distribution. With the strongly complexing dioxane, the Grignard reagent tends to be less reactive, and more product from attack on C-1 is obtained. Cyanide ion attacks **889** at the C-1 followed by a series of further transformations (see Scheme 279) to give finally compound **894** in 93% yield as a mixture of *Z* and *E* isomers (Table 106).

Scheme 279. Reactions of 1,3-Dibenzotriazolylpropylamine

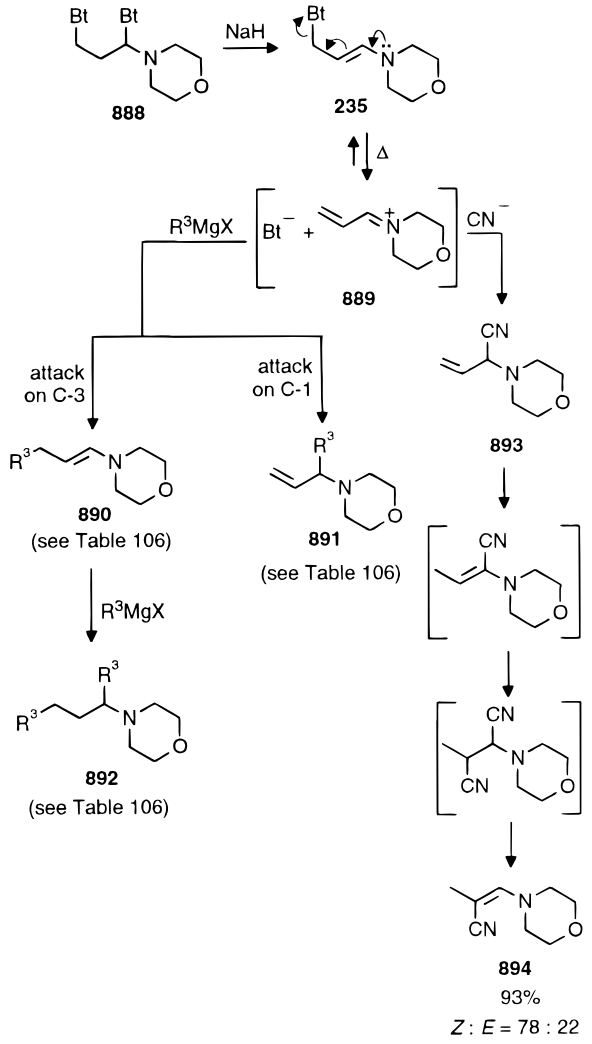


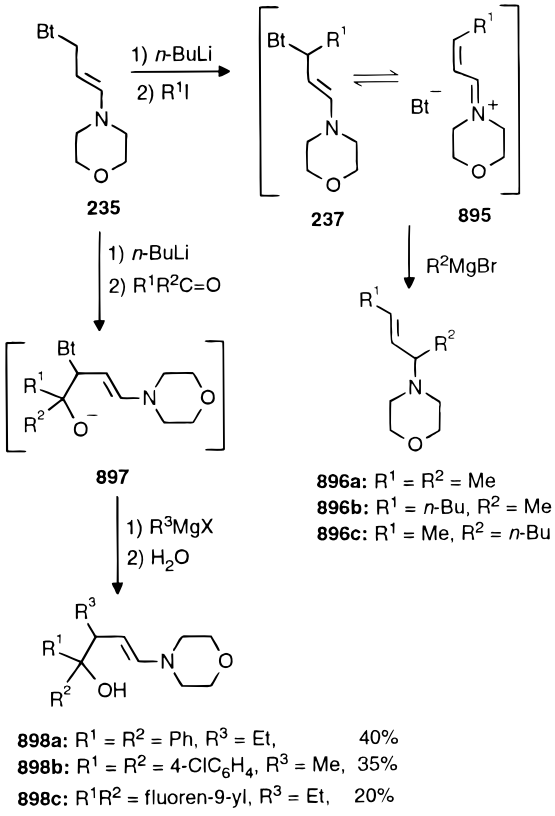
Table 106. Displacement of Benzotriazole in *N*-(1,3-Dibenzotriazolylpropyl)morpholine

		yield %		
R^3MgX	solvent	**890**	**891**	**892**
n-BuMgI	THF	19	0	0
PhMgBr	ether	11	39	0[a]
PhMgBr	THF	40	34	0
PhMgBr	toluene	13	23	0
PhMgBr	dioxane	19	67	0
$PhCH_2MgCl$	THF	25	18	5
$PhCH_2MgBr$	toluene/ether	41	30	16
PhC≡CMgBr	THF	0	41	0
c-$C_6H_{11}MgCl$	THF	63	0	0

[a] Compound **888** is recovered in 24% yield.

Intermediates **237**, prepared by lithiation of 1-(3-morpholinoprop-2-enyl)benzotriazole (**235**) and subsequent quenching with alkyl halides (see Scheme 85, section III.A.2.b), react *in situ* with Grignard reagents to give the corresponding allylamines **896** in 64−73% yields (Scheme 280).[179] As **237** exist in equilibrium with ionic pairs **895**, this reaction is related to known preparations of allylamines by the addition of nucleophiles to α,β-unsaturated imines and iminium salts. Treatment of adducts **897**,

Scheme 280. Preparation of 3-Substituted 4-Hydroxy-1-enamines and 1,3-Disubstituted Allylamines from 1-(3-Morpholinoprop-2-enyl)-benzotriazole



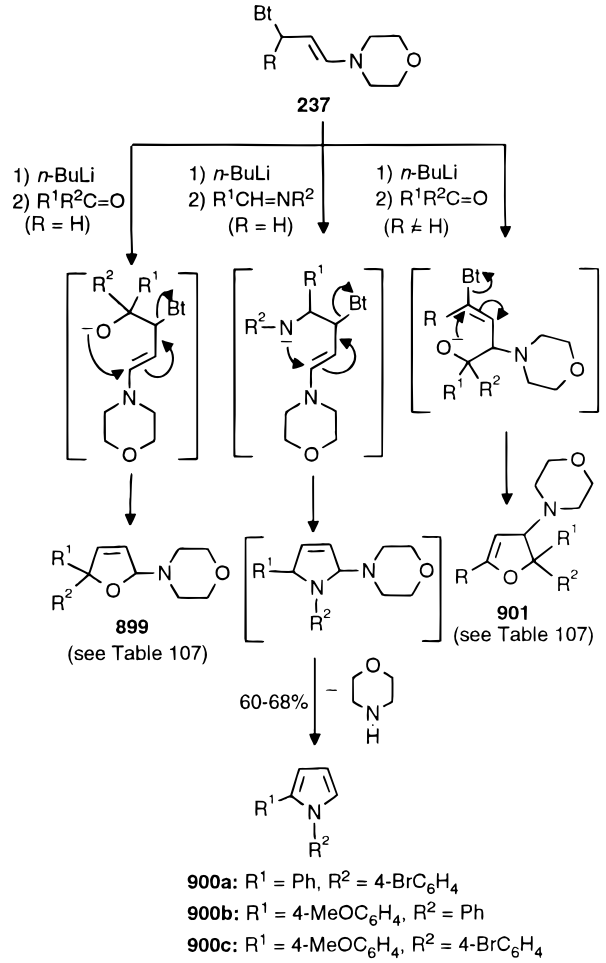
prepared from **235** and ketones *in situ*, with Grignard reagents yields enamines **898** exclusively as the result of nucleophilic attack at C-3 (Scheme 280).[180]

Treatment of 1-(3-morpholinoprop-2-enyl)benzotriazole (**237**, R = H) with *n*-butyllithium forms the analogous α-benzotriazolyl carbanion which, upon treatment with carbonyl compounds, directly gives 2,5-dihydrofurans **899** (Scheme 281, Table 107).[180] Following the same procedure, aromatic imines afford 1,2-disubstituted pyrroles **900** as a result of the further elimination of a molecule of morpholine.[179] Interestingly, when an alkyl derivative of 1-(3-morpholinoprop-2-enyl)benzotriazole (**237**, R ≠ H) is treated with butyllithium followed by carbonyl compounds, 2,3-dihydrofurans **901** are obtained.[180] This is believed to be the result of the steric hindrance caused by the alkyl group which promotes initial attack at the γ position to the benzotriazolyl residue.

Table 107. Preparation of 2,5-Dihydrofurans 899 and 2,3-Dihydrofurans 901

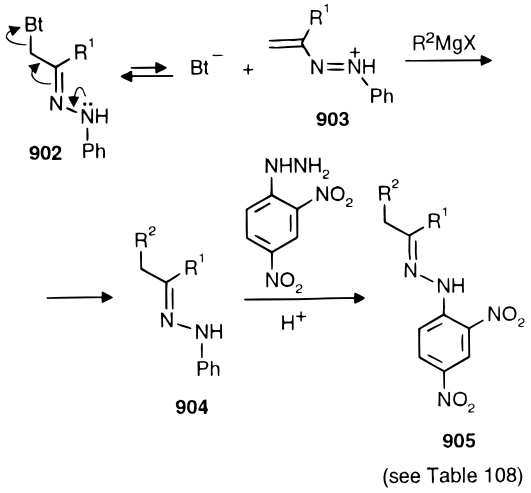
compound	R^1	R^2	R	yield %
899	Ph	Ph		50
	Ph	2-ClC_6H_4		63
	Ph	2,4-$Cl_2C_6H_3$		70
	4-ClC_6H_4	4-ClC_6H_4		80
901	Ph	Ph	*n*-Bu	65
	Ph	Ph	*n*-C_8H_{17}	70
	Ph	2,4-$Cl_2C_6H_3$	*n*-Bu	55
	fluorene-9-diyl		*n*-Bu	50

Scheme 281. Preparation of Pyrroles and Dihydrofurans from 1-(3-Morpholinoprop-2-enyl)benzotriazole



A conceptionally similar transformation is the conversion (Table 108, Scheme 282) of benzotriazolyl

Scheme 282. Displacement of Benzotriazole in α-Benzotriazolyl Ketone Hydrazones



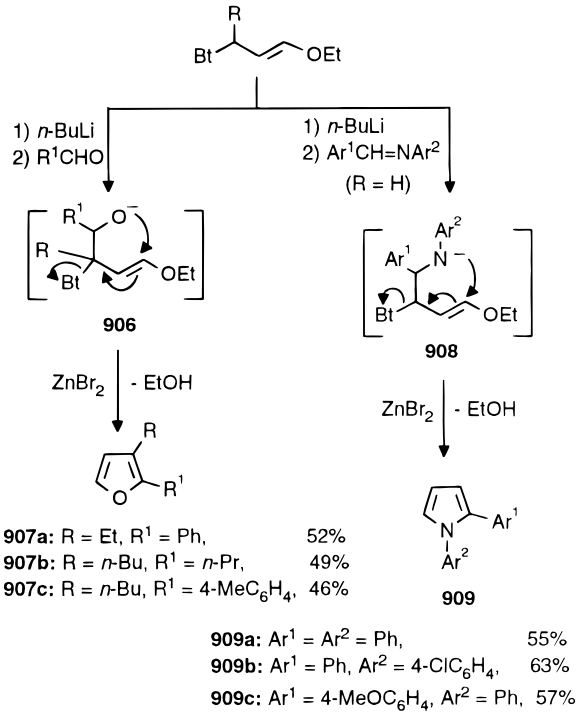
hydrazone derivatives into ketone hydrazones.[358] The carbanions from the Grignard reagents attack the C-3 exclusively to afford the phenylhydrazones **904** which are isolated as the corresponding 2,4-dinitrophenylhydrazones **905**.

Table 108. Preparation of 2,4-Dinitrophenylhydrazones 905

R^1	R^2	yield %
Ph	Et	78
Ph	*n*-Bu	31
Ph	*t*-Bu	27
Ph	Ph	72
Ph	$PhCH_2$	64
Ph	*n*-C_7H_{15}	72
Ph	*n*-C_8H_{17}	75
2-naphthyl	Et	56
2-naphthyl	Ph	76
biphenyl-4-yl	Et	67
biphenyl-4-yl	*i*-Pr	62

b. From Systems of Type Bt—C—C═C—O. 1-(Ethoxyallyl)benzotriazoles undergo lithiation and subsequent reactions with aldehydes to give the initial adducts **906**, which cyclize *in situ* upon treatment with $ZnBr_2$ to form 2,3-disubstituted furans **907** (Scheme 283).[181] Following the same procedure, aromatic imines yield 1,2-disubstituted pyrroles **909**.

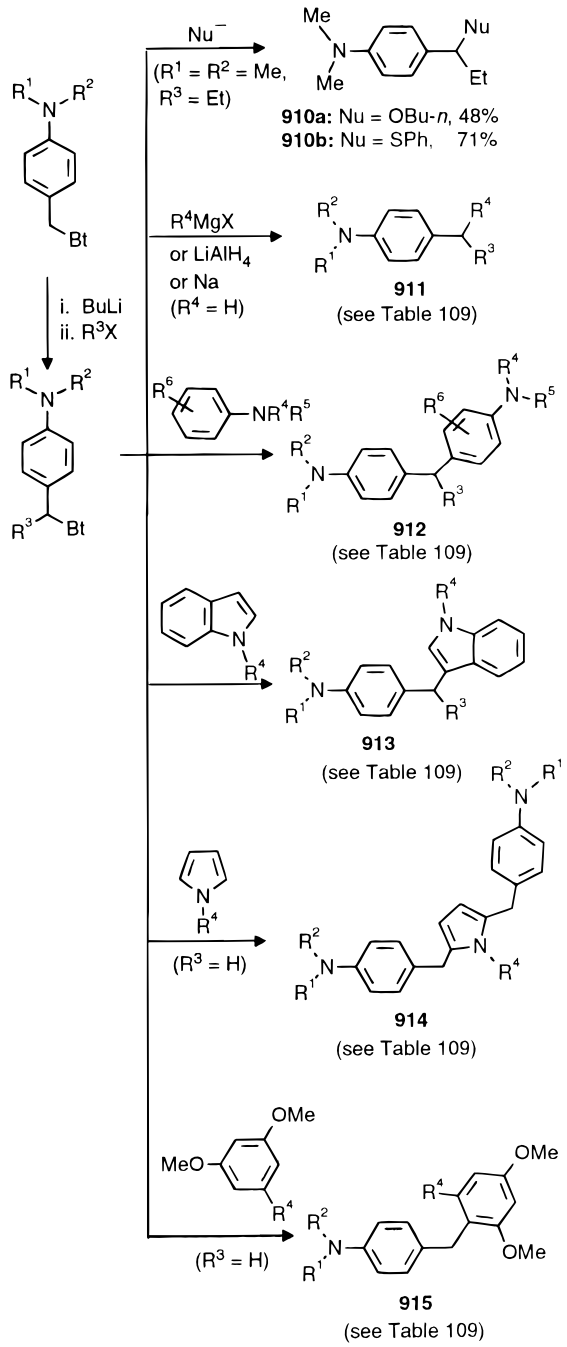
Scheme 283. Preparation of Furans and Pyrroles from 1-(Ethoxyallyl)benzotriazoles



c. From Systems of Type Bt—C—(o/p-Aromatic)—N. Grignard reagents or lithium aluminum hydride or sodium in piperidine react with *N*-[α-(4-aminophenyl)alkyl]benzotriazoles allowing (Scheme 284, Table 109) introduction of normal as well as branched alkyl substituents at the *para* position of *N*,*N*-dialkylanilines, *N*-alkylanilines, and anilines and affording **911**.[192,198,199] The method is versatile compared to classical methods and allows introduction of α-hydroxyalkyl groups. The introduction of group R^3 is achieved through lithiation of the corresponding methylene compounds (see section III.A.3.a), and the starting *p*-(benzotriazolylmethyl)anilines are readily available (see section III.B.3).

N-[α-(4-Aminophenyl)alkyl]benzotriazoles can ionize to benzotriazolyl anion and an immonium cation

Scheme 284. Preparation of 4-Substituted Anilines (Part 1)



which can attack another molecule of the same or a different aniline to give a diarylmethane **912**.[250] Such diarylmethanes are relatively easy to prepare when they are symmetrical, but very difficult when they are unsymmetrical. The present method is equally applicable to both types of compounds as shown in Scheme 284. These 1-[α-(4-aminophenyl)-alkyl]benzotriazoles also alkylate other electron-rich aromatic compounds such as indoles (giving **913**), pyrroles (to **914**), methoxy-substituted benzenes (to **915**) and 2-naphthol (to **916**) as shown in Schemes 284 and 285.[197] They also react with diacylmethanes. When anhydrous conditions are used, compound **917** from displacement of benzotriazole by the carbanion is obtained. In aqueous conditions, one of the carbonyl group is hydrolyzed to give **918**. Reactions with alcohol and thiophenol allow introduction of ether or thioether group affording **910**.

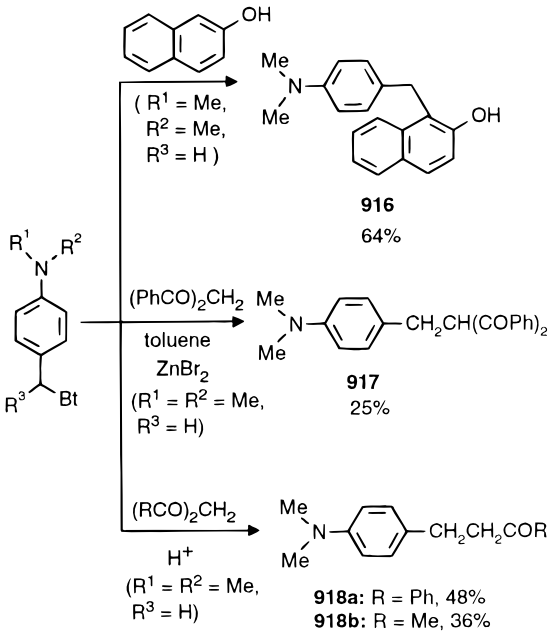
Substituents at the methylene carbon as in compound **919** do not appear to hinder the reaction. Thus, α-disubstituted benzotriazole derivative **919** reacts with sodium in piperidine, sodium ethoxide, or thiophenol to allow displacement of benzotriazole by these nucleophiles (Scheme 285).[192]

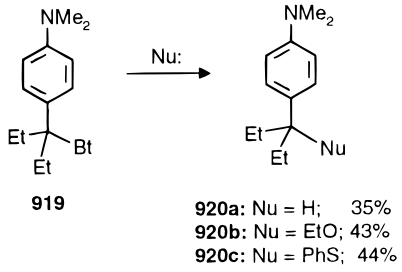
4-Benzotriazol-1-yltetrahydroquinolines **921** (for preparation, see Scheme 166, section III.C.1) react with $LiAlH_4$ to give **922** or with Grignard reagents to give **923**[266,269,270] (Scheme 286, Table 110). Treatment of **921** with alkoxides produces the corresponding 4-alkoxytetrahydroquinolines **924** in good yields.[270]

Table 109. Preparation of 4-Substituted Anilines 911 and Diaryl- and Arylheteroarylmethanes 912−915

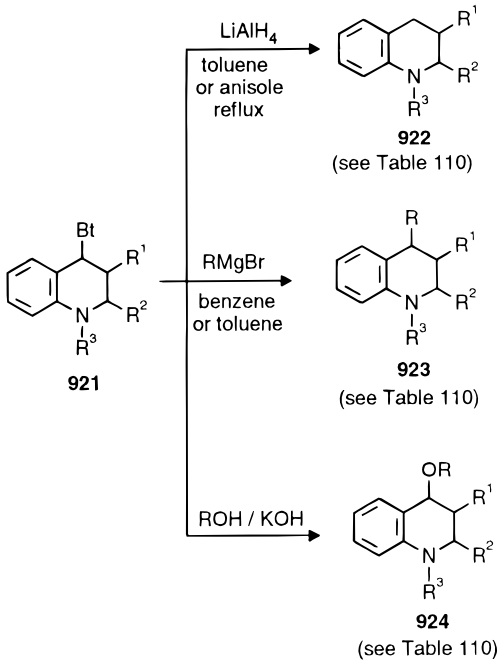
compound	R^1	R^2	R^3	R^4	R^5	R^6	yield %
911	H	H	H	*n*-Bu			55[199]
	H	H	H	Ph			48[199]
	H	H	$PhCH_2$	Ph			68[199]
	Me	H	H	*n*-Bu			30[199]
	Me	H	H	Ph			36[199]
	Me	H	*n*-Bu	H			95[199]
	Me	H	*n*-Bu	Ph			35[199]
	Me	Me	H	*n*-Bu			52[199]
	Me	Me	H	Ph			97[199]
	Me	H	4-$MeC_6H_4CH(OH)$	Ph			60[199]
	Me	Me	Me	Ph			82[199]
	Me	Me	Et	H			45[192]
	Me	Me	$PhCH_2$	H			78[199]
	Me	Me	$PhCH_2$	Ph			91[199]
	Me	Me	$(CH_2)_5C(OH)$	Ph			81[199]
	Me	Me	PhCH(OH)	Ph			69[199]
	Me	Me	Me_3Si	Me			88[198]
	Me	Me	Me_3Si	Ph			81[198]
	Me	Me	Me_2(*t*-Bu)Si	Ph			85[198]
	Et	Et	H	*n*-Bu			78[199]
	Et	Et	H	Ph			92[199]
	Et	Et	Me	H			77[199]
912	H	H	H	H	H	H	80[256]
	H	H	H	H	H	2-Me	78[256]
	H	H	H	H	H	2-Cl	72[256]
	H	H	H	Me	Me	H	70[256]
	H	H	H	H	Me	H	66[256]
	Me	Me	H	Me	Me	H	97[256]
	Me	Me	H	H	H	H	83[256]
	Me	Me	H	Me	Et	H	96[256]
	Me	Me	H	Et	Et	H	99[256]
	Me	Me	Me	Et	Et	H	67[256]
	Et	Et	H	Me	Me	H	100[256]
	Et	Et	H	Me	Et	H	96[256]
	Et	Et	H	Et	Et	H	90[256]
913	H	H	H	H			92[197]
	H	H	H	Me			85[197]
	Me	Me	H	H			96[197]
	Me	Me	H	Me			98[197]
	Me	Me	Me	H			91[197]
	Me	Me	$PhCH_2$	H			82[197]
	Me	Me	$(CH_2)_5C(OH)$	H			86[197]
	Me	Me	4-$MeC_6H_4CH(OH)$	H			38[197]
	Me	Me	pyridyl-4-CH(OH)	H			70[197]
	Me	Me	$Ph_2C(OH)$	H			26[197]
	Et	Et	H	H			95[197]
	Et	Et	H	Me			82[197]
914	H	H		H			29[197]
	Me	Me		H			52[197]
	Me	Me		Me			45[197]
	Et	Et		H			41[197]
915	H	H		H			53[197]
	H	H		OMe			80[197]
	Me	Me		H			50[197]
	Me	Me		OMe			73[197]
	Et	Et		H			68[197]
	Et	Et		OMe			72[197]

Scheme 285. Preparation of 4-Substituted Anilines (Part 2)





Scheme 286. Preparation of 1,2,3,4-Substituted Tetrahydroquinolines



Similarly, reduction of 1-benzotriazolyl-substituted julolidines **527** (see section III.C.1) with lithium aluminum hydride gives the corresponding mono-substituted julolidines **925** in high yields (Scheme 287).[101] Interestingly, treatment of **527**, in the form of a mixture of *cis*- and *trans*-Bt[1] and Bt[2] isomers, with Grignard reagents produces exclusively *trans*-1,2-disubstituted julolidines **926a**−**c** regardless of the size of the R group, while the reaction of dibenzotriazolyl derivative **521** with phenylmagnesium bromide affords **928** as a mixture of diastereomers.

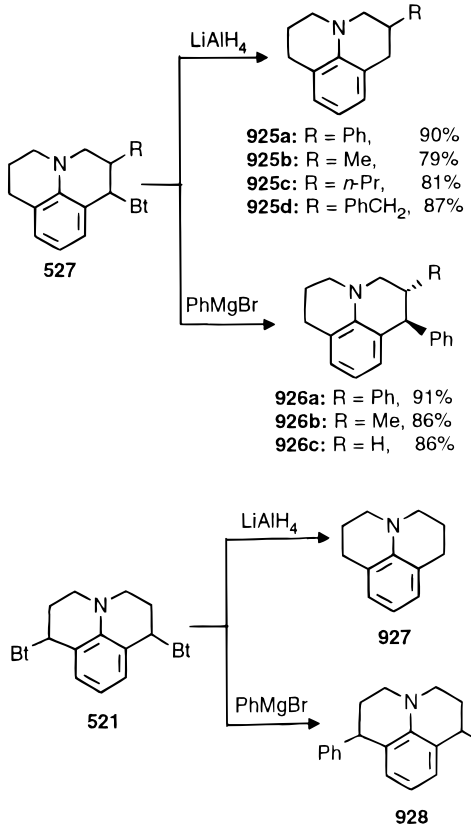
In the absence of electron-donor substituents, pyridine rings are electron deficient in nature. Therefore, the benzotriazolyl groups in most (benzotriazol-

Table 110. Preparation of Substituted Tetrahydroquinolines 922−924

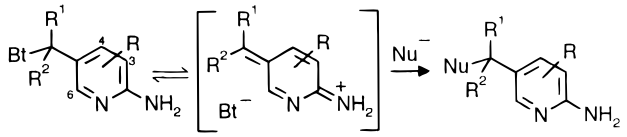
compound	R^1	R^2	R^3	R	yield %
922	H	Me	Me		88
	Me	H	Me		96
	Me	Et	Me		80[a]
	n-Pr	H	Me		68
	n-Pr	*n*-Bu	Me		88[a]
	Ph	H	Me		92
	Ph	$PhCH_2$	Me		78
	$PhCH_2$	H	Me		75
923	H	H	Me	*n*-C_8H_{17}	92
	H	H	Et	Ph	77
	Me	H	Me	Ph	80
	Ph	H	Me	Me	79
	Ph	H	Me	Ph	95
	Ph	$PhCH_2$	Me	Ph	90
924	H	H	Me	c-C_6H_{11}	83
	H	H	Me	$(CH_2)_2O(CH_2)_2OH$	61
	H	H	Me	*n*-$C_{10}H_{21}$	79
	H	H	Et	Me	50
	H	H	Et	Et	51

[a] Separable mixtures of *cis* and *trans* isomers were obtained.

Scheme 287. Preparation of Julolidines



Scheme 288. Substitution of Benzotriazole in 5-(1-Benzotriazolylalkyl)-2-aminopyridines



929 **930** (see Table 111)

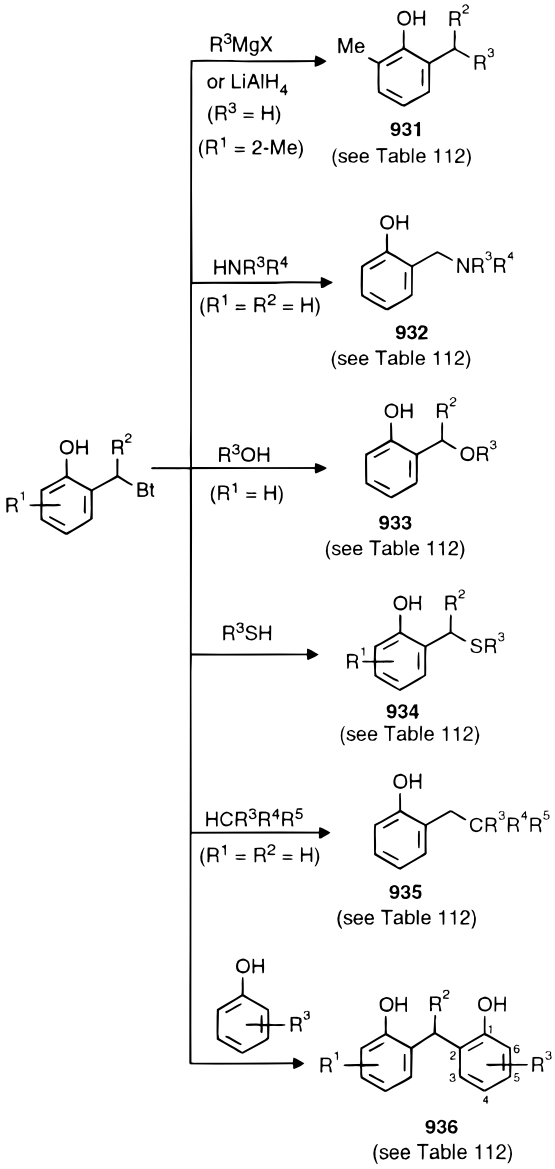
Table 111. Preparation of 5-Substituted 2-Aminopyridines 930

R	R^1	R^2	Nu	yield %
3-Me	H	H	*n*-Bu	77
3-Me	H	H	*n*-BuS	48
3-Me	H	Et	*n*-Bu	65
3-Me	H	$Ph_2C(OH)$	*n*-Bu	70
3-Me	Et	Et	*n*-Bu	83
3-Me	Et	Et	OEt	72
4-Me	H	H	SPh	94
6-Me	H	H	Ph	49
6-Me	H	H	*n*-BuO	70

1-ylalkyl)pyridines are not activated and thus cannot be displaced by nucleophiles.[359] However, when a strong electron-donating group is attached to the pyridine ring, such a displacement becomes highly feasible. Thus, 2-amino-5-(benzotriazol-1-ylalkyl)-pyridines **929** react with various nucleophiles, such as Grignard reagents, alkoxides or thiolates, to afford the corresponding displacement products **930**[209] (Scheme 288, Table 111). These highly functionalized 3-substituted pyridines were not previously easily accessible due to the limited methods for the direct substitution at the 3 position of a pyridine ring.

d. From Systems of Type Bt−C−(o/p-Aromatic)−O. Transformations of *o*-(α-benzotriazolylalkyl)phenols are shown in Schemes 289 (Table 112) and 290. The Bt group is readily replaced by H or an alkyl/aryl group (to give **931**),[196] by amines and amides (to **932**), by alcohols (to **933**) and thiols (to **934**),[202] by active methylene compounds (to **935**),[202] by substituted phenols (to **936**) and naphthols (to **937** and **938**), and by indole (to **939**).[203] The displacement by phenols is of particular interest since both symmetrical and unsymmetrical methylenebisphenols can be prepared. 4-(Benzotriazol-1-ylmethyl)-2,6-di-

Scheme 289. Transformations of *o*-[α-Benzotriazolylalkyl]phenols



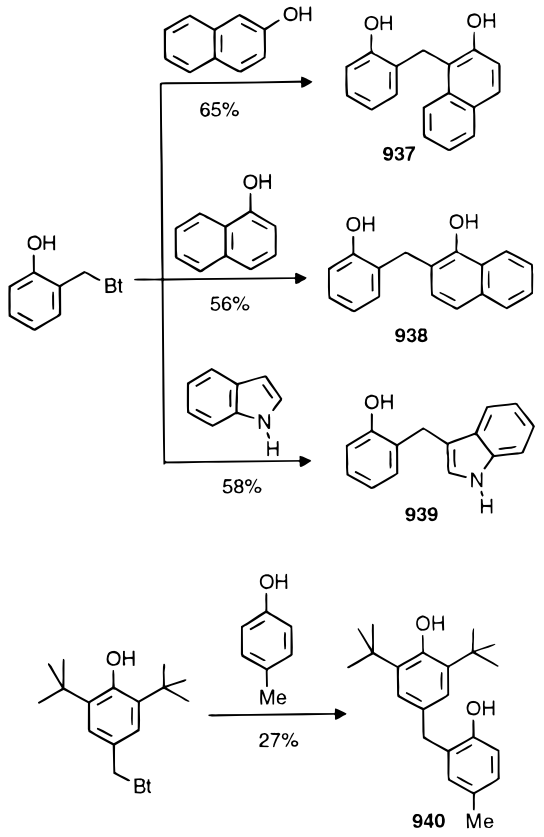
931 (see Table 112) **932** (see Table 112) **933** (see Table 112) **934** (see Table 112) **935** (see Table 112) **936** (see Table 112)

tert-butylphenol reacts similarly with *p*-cresol to form 2,4′-methylenebisphenol **940** (Scheme 290).[203]

Table 112. Preparation of *ortho*-Substituted Phenols 931−936

compound	R^1	R^2	R^3	R^4	R^5	yield %	compound	R^1	R^2	R^3	R^4	R^5	yield %
931		H	H			50[196]		H	4-$MeC_6H_4CH(OH)$	*n*-C_8H_{17}			78[202]
		H	*n*-Bu			29[196]		2-Me	H	*n*-C_8H_{17}			74[202]
		H	Ph			45[196]		2-(*t*-Bu)	H	*n*-C_8H_{17}			74[202]
		Me	H			59[196]	**935**			H	Ph	NO_2	22[202]
		Me	Ph			80[196]				Me	Me	PhCO	53[202]
		Me	$PhCH_2$			66[196]				Me	CO_2Pr	CO_2Pr	62[202]
		n-Bu	H			62[196]	**936**	H	H	H			40[203]
932			H	PhCO		24[202]		H	H	4-Me			57[203]
			$-(CH_2)_2O(CH_2)_2-$			66[202]		H	H	4-(*t*-Bu)			39[203]
			Ph	Me		33[202]		H	H	4-Ph			40[203]
933		H	Et			26[202]		H	H	4-Cl			27[203]
		H	*i*-Pr			60[202]		H	H	3-Me			51[203]
		H	*n*-Bu			58[202]		H	H	5-Me			51[203]
		PhCH(OH)	*i*-Pr			72[202]		H	H	$3,5-(Me)_2$			55[203]
934	H	H	Ph			55[202]		H	Me	4-Me			43[203]
	H	H	*n*-C_8H_{17}			69[202]		4-(*t*-Bu)	H	4-Me			62[203]
	H	*n*-Bu	Ph			83[202]		2-(*t*-Bu)-4-Me	H	4-Me			53[203]
	H	*n*-Bu	*n*-C_8H_{17}			77[202]							

Scheme 290. Preparation of 2-Arylmethyl- and 2-Heteroarylmethyl-Substituted Phenols



Similar reactions are used for the preparation of substituted naphthols **941**[202,257,258] (Scheme 291, Table 113). The naphthol derivatives also react with

Table 113. Preparation of Substituted Naphthols 941

R^1	R^2	yield %
H	PhS	68[202]
Ph	H	90[257]
Ph	Ph	66[257]
Ph	$PhCH_2$	86[257]
4-$Me_2NC_6H_4$	H	94[257]
4-$Me_2NC_6H_4$	Ph	68[257]
4-$Me_2NC_6H_4$	$PhCH_2$	90[257]
4-$Me_2NC_6H_4$	n-$C_8H_{17}S$	89[202]

substituted phenols to give **943**[203] and thiols to give **944**. When diethyl malonate is used as the nucleophile, intramolecularly cyclized product **942** is obtained. An interesting example is given in Scheme 291 relates to the preparation of compound **947**.

Phenol ethers (Scheme 292) show similar reactivity and undergo replacement reactions with Grignard reagents (to give **948**),[192,196] alcohols (to **949**) and thiols (to **950**),[192] electron-rich aromatic compounds including anilines (to **951**), indoles (to **952**), and methoxy-substituted benzenes (to **953**−**955**)[196,261] (see Table 114).

The same reactivity pattern is found for analogous naphthol ethers which have been used to prepare compounds **956**−**960** (Scheme 293).[196]

e. From Systems of Type Bt−C−Aryl. The benzotriazole group can act as a leaving group without assistance of a heteroatom, provided the α carbon is

Scheme 291. Preparation of Substituted Naphthols

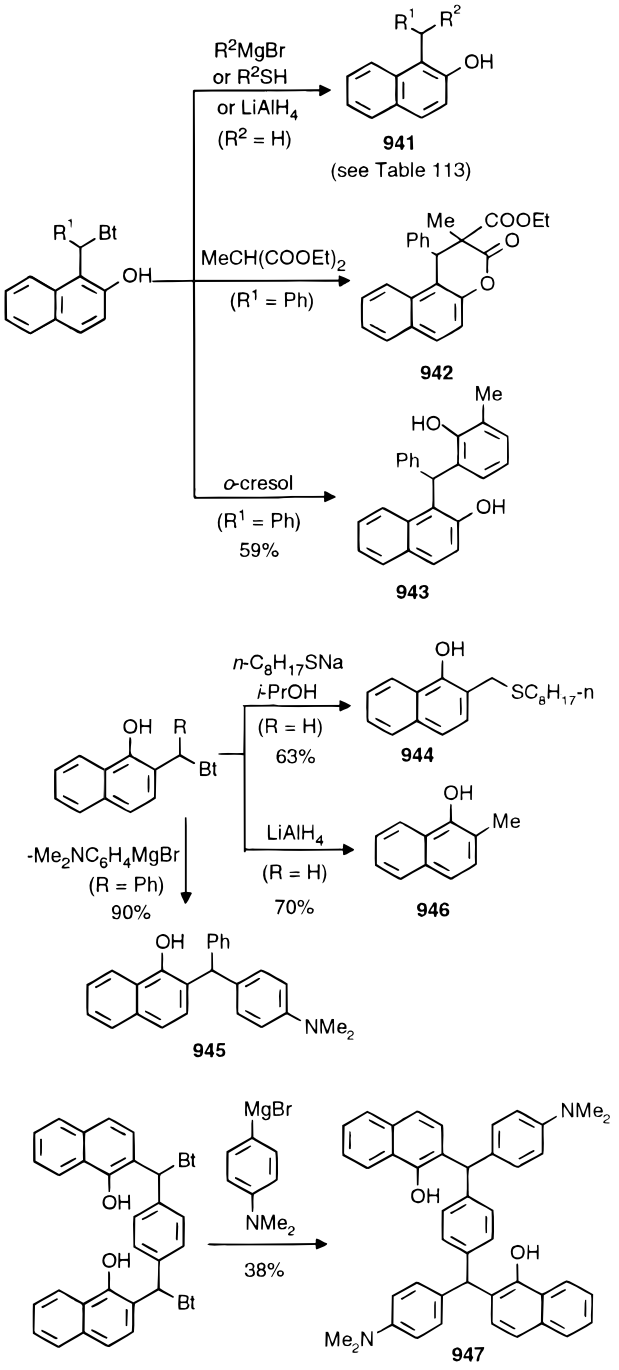
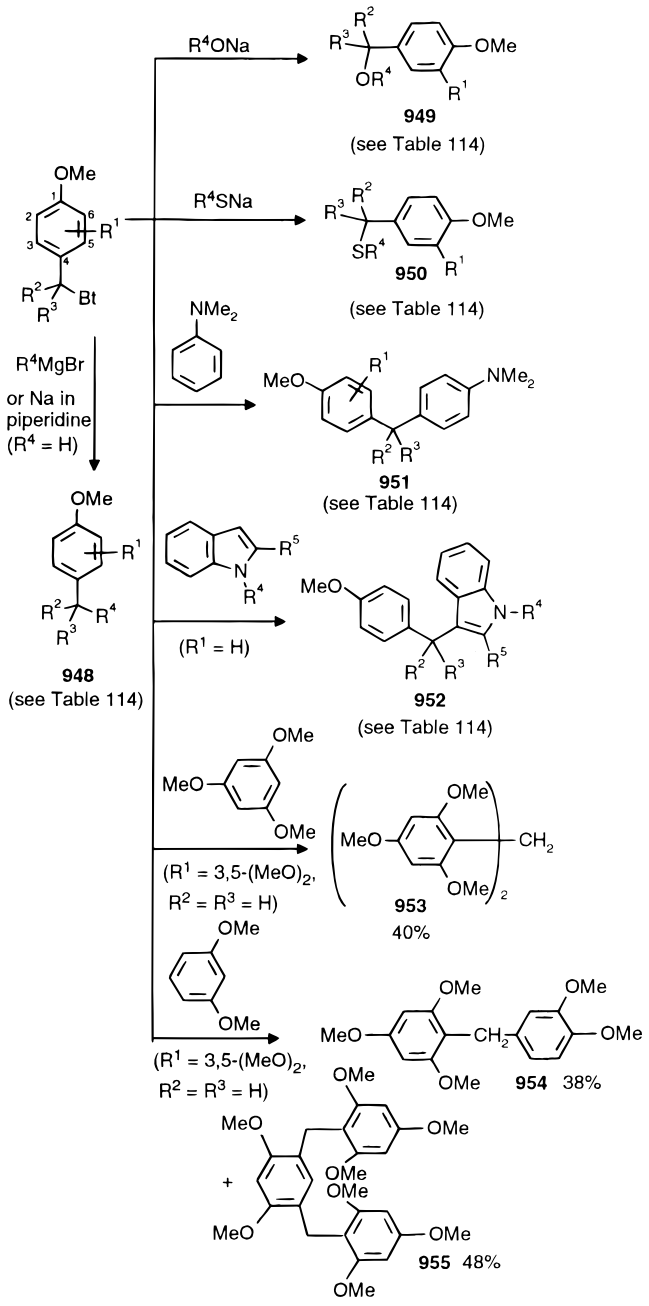


Table 114. Preparation of Substituted Phenol Ethers

compound	R^1	R^2	R^3	R^4	R^5	yield %
948	2-MeO	Et	H	H		54[192]
	3,5-$(MeO)_2$	H	H	Ph		56[196]
	3,5-$(MeO)_2$	H	H	$PhCH_2$		13[196]
949	H	Et	H	Ph		35[192]
	H	Et	Et	Ph		33[192]
	MeO	Et	H	Ph		27[192]
950	H	Et	H	Ph		48[192]
	H	Et	Et	Ph		45[192]
	MeO	Et	H	Ph		56[192]
951	H	2,4,6-$Me_3C_6H_2$	H			55[261]
	3,5-$(MeO)_2$	H	H			70[196]
952		2,4,6-$Me_3C_6H_2$	H	H	H	57[261]
		2,4,6-$Me_3C_6H_2$	H	H	Me	70[261]
		2,4,6-$Me_3C_6H_2$	H	Me	H	85[261]

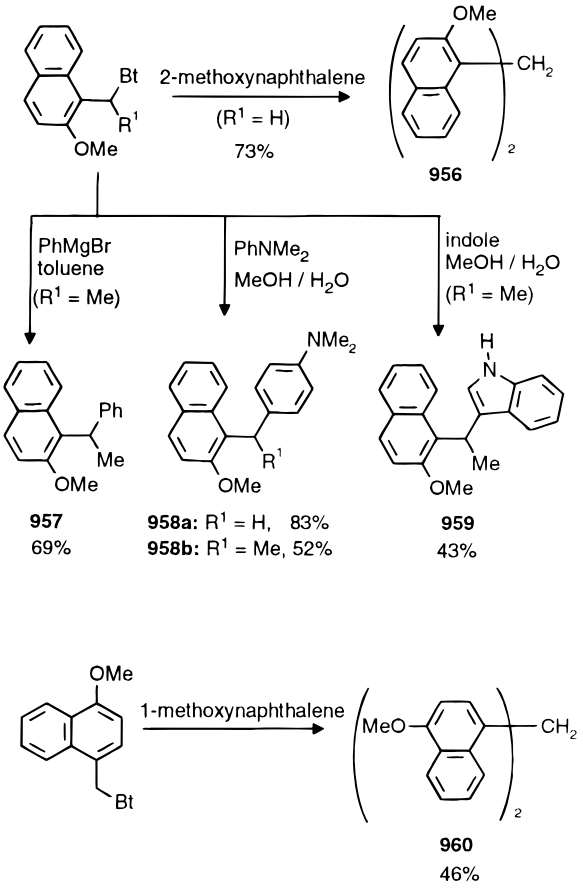
Scheme 292. Reactions of (Benzotriazolylalkyl)-aryl Methyl Ethers



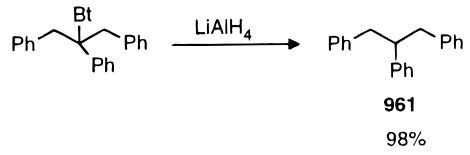
both tetrasubstituted and benzylic. Thus, 1-(α,α-dibenzylbenzyl)benzotriazole is reduced with $LiAlH_4$ yielding compound **961** in 98% yield[190] (Scheme 294).

Benzotriazolyl groups can be displaced intramolecularly by a stabilized carbanion center, as shown in Scheme 295. Thus, 1-(arylmethyl)benzotriazoles and 1-propylbenzotriazole undergo lithiation with LDA to give carbanions **962**. These add to 1,1-diarylethylenes to generate new anions **963**, which cyclize with simultaneous elimination of benzotriazolyl anion, leading to 1,1,2-trisubstituted cyclopropanes **964a**−**e** in high yields (Scheme 295).[195] Stabilization of carbanion **963** with two aryl groups is necessary for these successful cyclopropanation reaction. For example, when styrene or 1-aryl-1-alkylethylenes were used in this reaction, no cyclopropanes were detected. This method provides a new

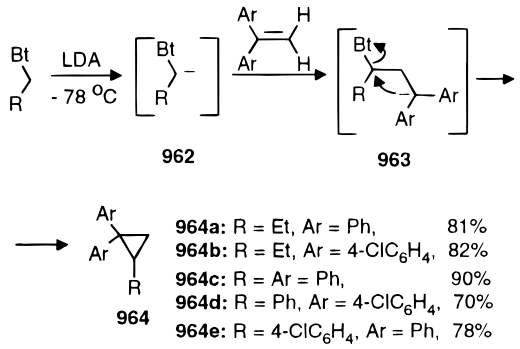
Scheme 293. Reactions of (Benzotriazolylalkyl)-naphthyl Methyl Ethers



Scheme 294. Removal of Benzotriazole Residue without Heteroatom Activation



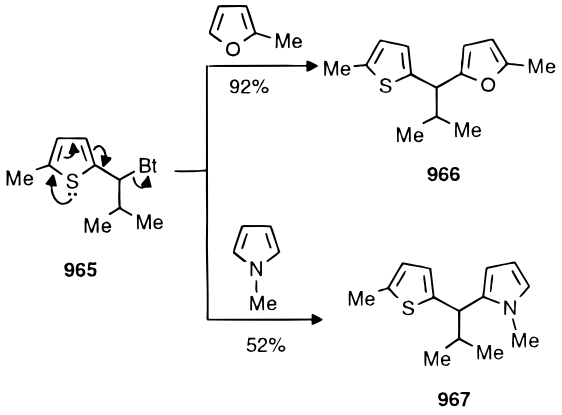
Scheme 295. Preparation of Cyclopropanes from Alkylbenzotriazoles and 1,1-Diarylethenes



and convenient alternative to the known cyclopropanations of 1,1-diarylethylenes using diazomethane.

f. From Systems of Type Bt−C−Heteroaryl. The activation of the benzotriazole group can also be achieved through a heteroatom in an electron-rich heterocycle as shown in compound **965** (Scheme 296). This compound thus heteroalkylates other electron-rich heteroaromatic compounds including furans and

Scheme 296. Reactions of 2-(α-Benzotriazolylalkyl)thiophenes



pyrroles to afford 1,1-diheteroarylalkanes **966** and **967**.[263] Analogous 1,1-diheteroarylalkanes **968** and **969** are formed in reactions of 2-(α-benzotriazol-1-ylalkyl)furans with furan, thiophene, and indole[183] (Scheme 297, Table 115).

Scheme 297. Reactions of 2-(α-Benzotriazolylalkyl)furans

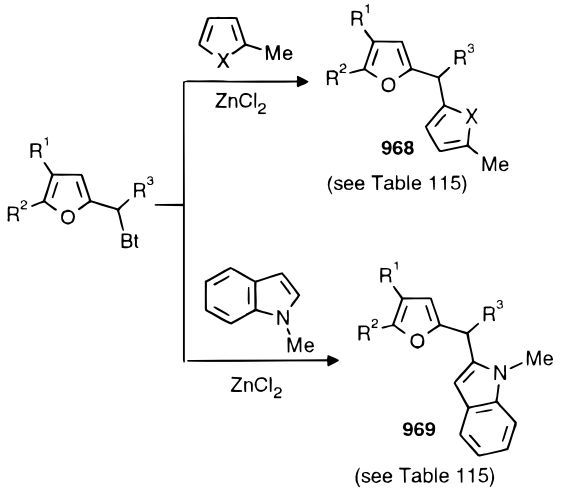


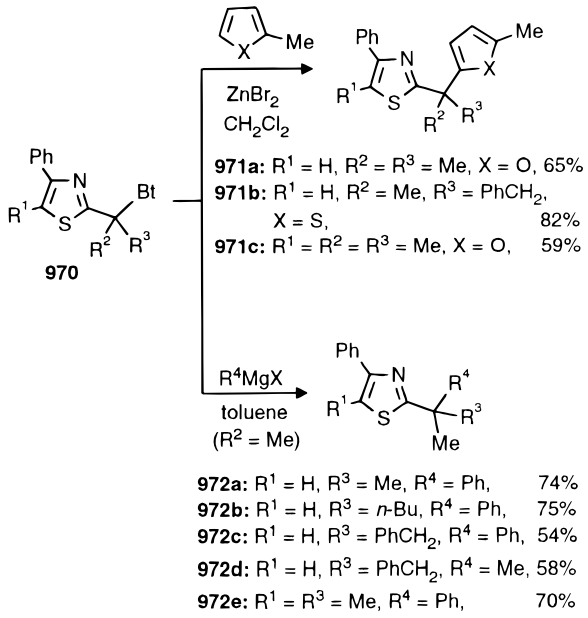
Table 115. Preparation of 1,1-Diheteroarylalkanes

compound	R^1	R^2	R^3	X	yield %
968	Me	Me	H	S	67
	Ph	Me	*n*-Bu	O	95
	Ph	Me	H	O	57
	Ph	Me	H	S	86
	Ph	H	$PhCH_2$	S	61
	2-naphthyl	H	*i*-Pr	O	68
969	Me	Me	H		63
	Me	Me	Me		79
	Ph	H	$PhCH_2$		57

2-(Benzotriazol-1-ylalkyl)thiazoles **970** undergo similar reactions with electron-rich heterocycles, such as 2-methylfuran and 2-methylthiophene, to give the corresponding 1,1-diheteroarylalkanes **971** (Scheme 298).[207]

The benzotriazole moiety in such heterocyclic systems is also displaced by other nucleophiles. Thus, 2-(benzotriazol-1-ylalkyl)thiazoles **970** react with Grignard reagents to give the displacement products **972**.[207]

Scheme 298. Preparation of 1,1-Diheteroarylalkanes and 2-Alkylthiazoles

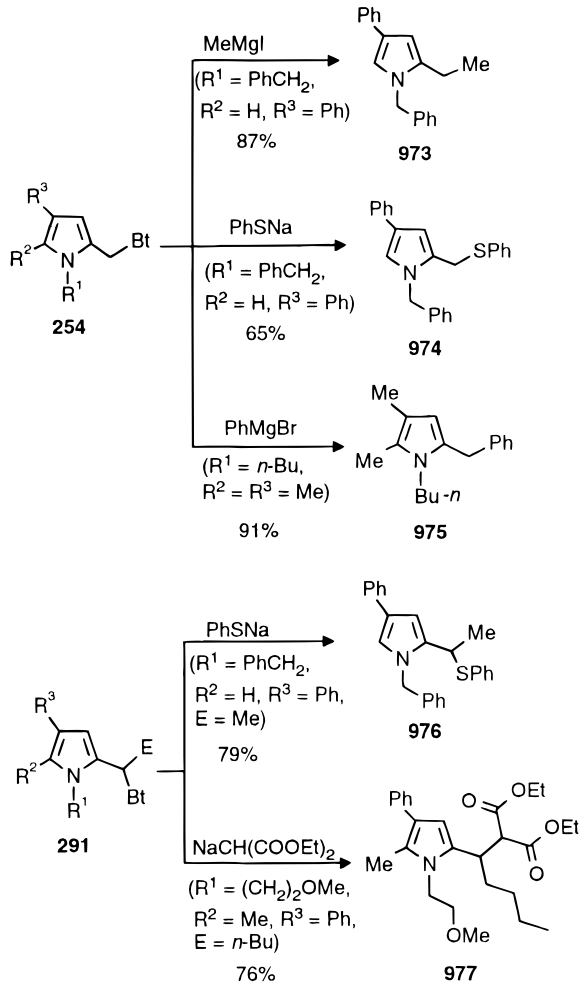


971a: R^1 = H, R^2 = R^3 = Me, X = O, 65%
971b: R^1 = H, R^2 = Me, R^3 = $PhCH_2$, X = S, 82%
971c: R^1 = R^2 = R^3 = Me, X = O, 59%

972a: R^1 = H, R^3 = Me, R^4 = Ph, 74%
972b: R^1 = H, R^3 = *n*-Bu, R^4 = Ph, 75%
972c: R^1 = H, R^3 = $PhCH_2$, R^4 = Ph, 54%
972d: R^1 = H, R^3 = $PhCH_2$, R^4 = Me, 58%
972e: R^1 = R^3 = Me, R^4 = Ph, 70%

However, all attempts to displace the benzotriazole group in the benzo analogues **298**−**301** (see section III.A.3.b) in reactions with sodium phenolate or with thiophenol in the presence of zinc bromide, or with

Scheme 299. Displacement of Benzotriazole in 2-(Benzotriazolylalkyl)pyrroles

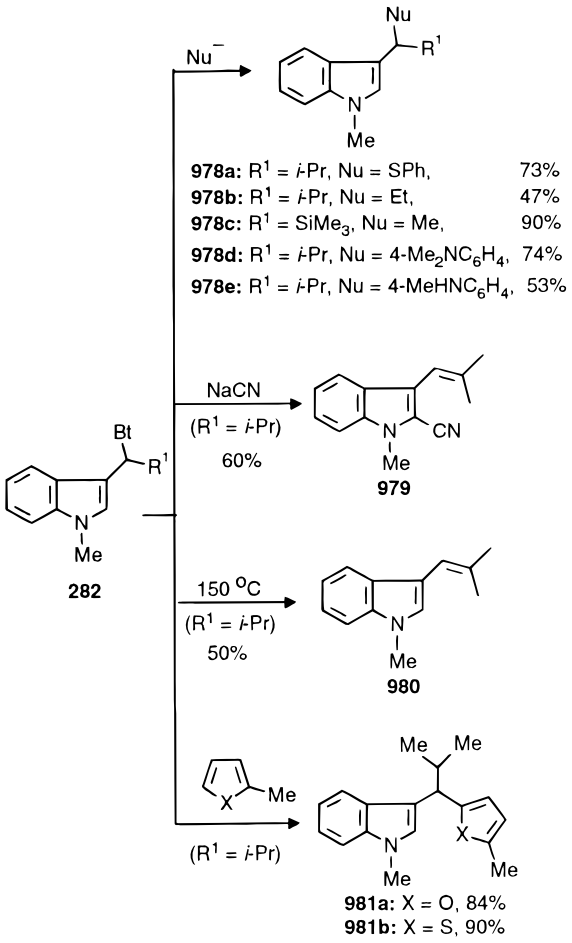


Grignard reagents failed.[208] This implies that benzannelation of a thiazole, oxazole, or imidazole ring has a strong enough electron-withdrawing effect to suppress the carbocation formation in such benzazolyl(benzotriazol-1-yl)methanes.

The benzotriazolyl moiety in *N*-substituted 2-(benzotriazolylalkyl)pyrroles **254** and **291** is displaced successfully by a number of C- and N-nucleophiles (Scheme 299).[184] The presence of an alkyl group in the α position to benzotriazolyl group in **291** facilitates the substitution reaction with sodium thiophenolate, providing the corresponding α-(phenylthioalkyl)pyrrole **976** in high yield.

3-(Benzotriazol-1-ylalkyl)-1-methylindoles **282** react with thiolates (to give **978a**), Grignard reagents (to **978b**,**c**), and anilines (to **978d**,**e**) (Scheme 300).[204]

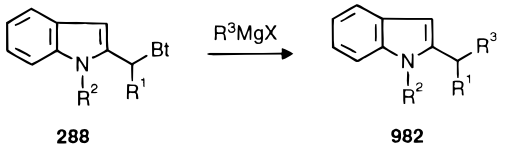
Scheme 300. Reactions of 3-(α-Benzotriazolylalkyl)indoles



Cyanide undergoes S_N2' attack on the indole 2 position to give **979**. On heating, a molecule of benzotriazole is eliminated at the side alkyl chain to form an alkene **980**. Substitution with 2-methylfuran and 2-methylthiophene yields **981a**,**b**.

The benzotriazole group in 2-(α-benzotriazol-1-ylalkyl)indoles **288** is also activated, as illustrated by the displacement with Grignard reagents forming **982**[206] (Scheme 301). Compounds **288** also undergo Lewis acid-promoted dissociation and subsequent dimerization[206] to give either 6,12-dihydroindolo[3,2-*b*]carbazoles **983** or indolo[3,2-*b*]carbazoles **984**, depending on the nature of the R^2 group (Scheme 302).

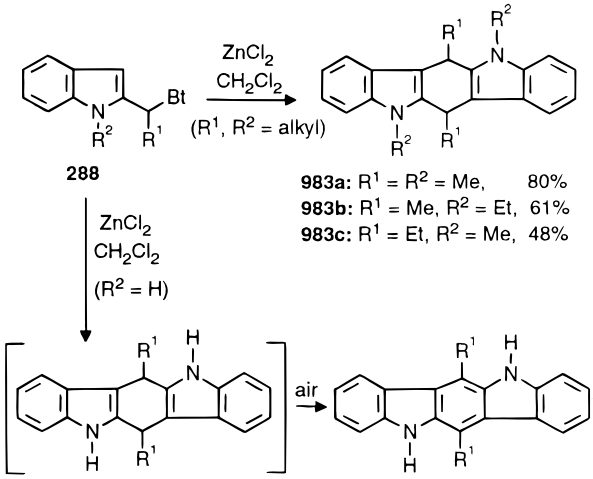
Scheme 301. Reaction of 2-(α-Benzotriazol-1-ylalkyl)indoles with Grignard Reagents



288 **982**

982a: $R^1 = R^2 = R^3$ = Me, 90%
982b: R^1 = *i*-Pr, $R^2 = R^3$ = Me, 88%
982c: $R^1 = R^2$ = *n*-Bu, R^3 = Et, 68%
982d: R^1 = *n*-Bu, R^2 = $PhCH_2$, R^3 = Et, 62%
982e: R^1 = $PhCH_2$, R^2 = *n*-Bu, R^3 = Ph, 70%
982f: $R^1 = R^2$ = $PhCH_2$, R^3 = Ph, 78%

Scheme 302. Lewis Acid-Promoted Dimerization of 2-(α-Benzotriazolyl-1-alkyl)indoles



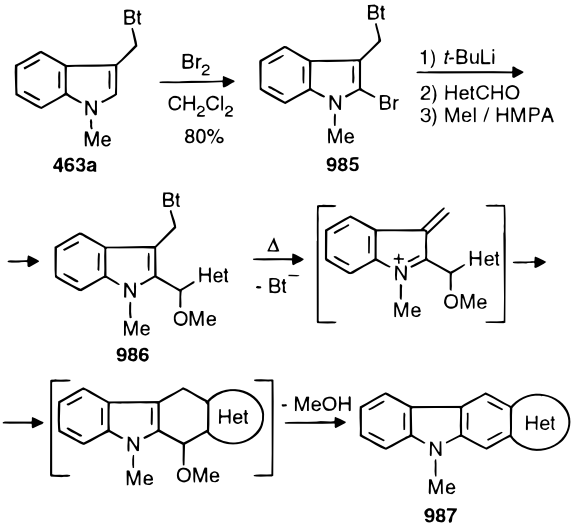
288

983a: $R^1 = R^2$ = Me, 80%
983b: R^1 = Me, R^2 = Et, 61%
983c: R^1 = Et, R^2 = Me, 48%

$ZnCl_2$, CH_2Cl_2, (R^2 = H)

984a: R^1 = *n*-Bu, 63%
984b: R^1 = *n*-C_5H_{11}, 57%
984c: R^1 = *n*-C_6H_{13}, 64%

Scheme 303. Preparation of Heterocyclo[*b*]-Fused Carbazoles from 3-(Benzotriazolylmethyl)-1-methylindole



463a **985** **986** **987**

Het	yield % 986	987
thien-3-yl	81	55
furan-3-yl	86	67
thien-2-yl	88	56
furan-2-yl	84	43
1-methylindol-3-yl	88	31

The leaving ability of benzotriazolyl group in such systems has enabled a novel synthesis of heterocyclo-[*b*]-fused carbazoles **987** from readily prepared (see Scheme 154, section III.B.7) 3-(benzotriazolylmethyl)-1-methylindole **463a**[262a] (Scheme 303). The method is high yielding and appears to be quite general.

10. From Systems of Type Bt—C═X and Analogous

a. Acylbenzotriazoles Bt—C═O. In his comprehensive review in 1962, Staab introduced *N*-acylazoles as powerful acylating reagents, suitable for the acylation of different classes of proton-labile compounds, such as amines, alcohols, acids, peroxides and so on.[280] Although almost all those reactions were developed for *N*-acylimidazoles and *N*-acyltriazoles, the corresponding *N*-acylbenzotriazoles can also be used and are advantageous in some cases.

1-(Trifluoroacetyl)benzotriazole (**55**) (see section II.A.2) has been demonstrated to be an effective reagent for the trifluoroacetylation of amides and alcohols[55] compound **55** reacts smoothly with both primary and secondary, alkyl- and arylamines to give trifluoroacetamides **988** in excellent yields (Scheme 304, Table 116). Optically active amines are converted into the corresponding optically pure trifluoroacetamides without racemization. If a substrate contains both primary and secondary amino groups, trifluoroacetylation occurs only at the primary amino group.

Scheme 304. Trifluoroacetylation of Amines and Alcohols

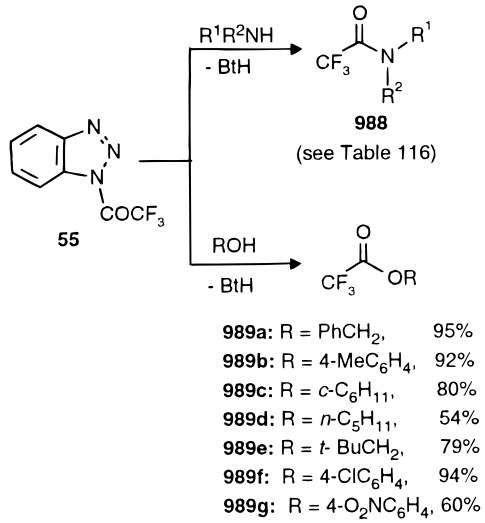


Table 116. Preparation of Trifluoroacetamides 988

R^1	R^2	solvent	yield %
H	*t*-Bu	THF	95
H	$EtCH(Me)CH_2$	THF	97
H	$4\text{-}O_2NC_6H_4$	THF	90
H	$2\text{-}(i\text{-}Pr)C_6H_4$	THF	92
H	$4\text{-}(PhNH)C_6H_4$	THF	92
H	$PhCH_2CH_2$	THF	~100
H	$PhCH_2CH(OH)$	THF	90
H	$4\text{-}MeC_6H_4CH_2$	THF	92
H	2-naphthyl	THF	93
Et	Ph	Et_2O	85
	$-(CH_2)_5-$	Et_2O	89

Aliphatic and benzylic alcohols and phenols all react with **55** to give the corresponding esters **989** in good yields.[55]

N-Acetylbenzotriazole is an important reagent for the acetylation of proteins, superior in many ways to the other widely used acetylating reagents, such as acetic anhydride or acetylimidazole.[262b] It acetylates both the amino and the phenolic groups of proteins in mild conditions, stable at acidic pH, and being aromatic, responsible for optical properties of modified proteins. Later the reactivity of oligomeric *N*-acylbenzotriazoles **58** (for preparation, see section II.A.2, Scheme 16) toward aromatic and aliphatic alcohols and secondary aliphatic amines was investigated.[57] In these reactions the formation of the corresponding esters and amides occurs to a fairly high degree of conversion, which can be increased in the presence of triethylamine. The ability of polymers with *N*-acylbenzotriazole end groups **58** to undergo easy benzotriazolyl group exchange reactions allows these compounds to be used in medicinal chemistry as matrices for binding pharmacologically active substrates bearing hydroxyl or amino groups.

Transformations of *N*-acylbenzotriazoles **990** into unsymmetrical ketones **992** is achieved by treatment with alkylaluminum chlorides (Scheme 305, Table 117). This procedure requires either use of 2 equiv of organoaluminum compound (method A) or the preliminary preparation of *N*-acylbenzotriazole·$AlCl_3$ complex *in situ* (method B).[360]

Scheme 305. Ketone Synthesis Using Organoaluminum Compounds

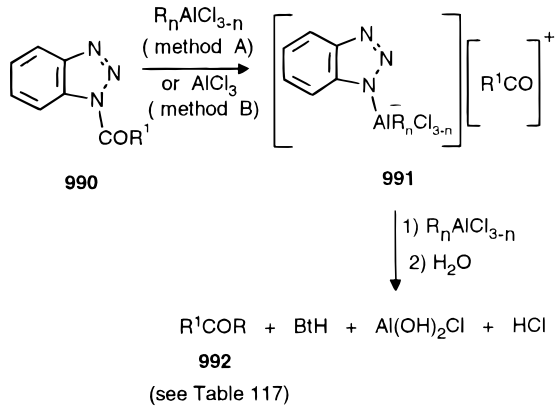


Table 117. Preparation of Ketones 992 from 1-Acylbenzotriazoles

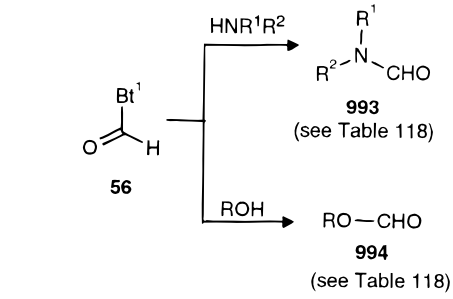
R	R^1	n	method	yield %
Et	Ph	1	A	73
Et	*n*-Bu	2	A	75
Et	Ph	1	B	76
$n\text{-}C_6H_{13}$	*n*-Bu	3	B	66
$n\text{-}C_6H_{13}$	Ph	3	B	64

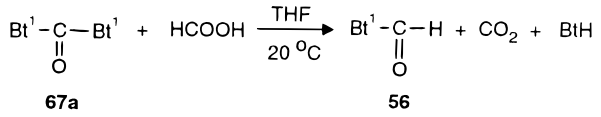
1-Formylbenzotriazole **56**, readily available from benzotriazole and formic acid (see section II.A.2), is a stable and convenient *N*- and *O*-formylating agent.[56] Thus, it reacts with amines and alcohols to form formamides **993** and formates **994**, respectively (Scheme 306, Table 118). Alternatively **56** can be prepared by treatment of 1,1′-carbonyldibenzotriazole (**67a**) with formic acid.[361]

Table 118. Preparation of Formamides 993 and Formates 994

compound	R^1	R^2	yield %
993	Et	Et	78
	Ph	H	59
	2-$O_2NC_6H_4$	H	78
	4-$O_2NC_6H_4$	H	82
	$PhCH_2$	H	84
	2-pyridyl	H	70
	2-thiazolyl	H	78
994	*n*-Bu		88
	$PhCH_2$		90
	1,2,3,4-tetrahydronaphth-1-yl		70
	naphth-1-yl		75
	(−)-menthyl		90

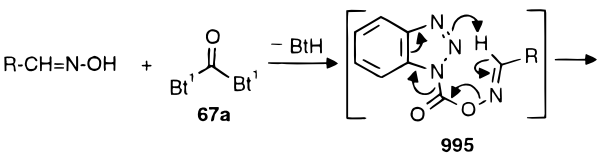
Scheme 306. Reactions of 1-Formylbenzotriazole and Its Preparation from 1,1′-Carbonyldibenzotriazole



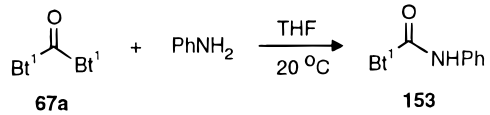


1,1′-Carbonyldibenzotriazole (**67a**) can be used for the dehydration of aldoximes under mild and neutral conditions.[362] As shown in Scheme 307, the reaction

Scheme 307. Reactions of 1,1′-Carbonyldibenzotriazole with Aldoximes and Aniline



996a: R = Ph, 64%
996b: R = 4-ClC_6H_4, 84%
996c: R = 4-$MeOC_6H_4$, 75%
996d: R = 3-pyridyl, 71%

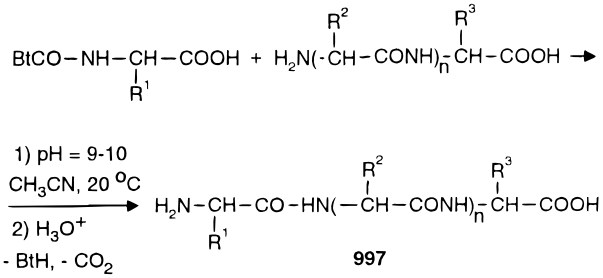


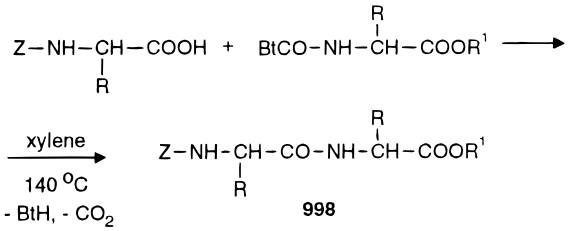
involves the initial formation of the intermediate **995** followed by the elimination of carbon dioxide and benzotriazole to give nitriles **996**.

In its reaction with aniline, 1,1′-carbonyldibenzotriazole (**67a**) behaves differently from the corresponding benzimidazole analogue. While 1,1′-carbonyldibenzimidazole reacts with 2 equiv of aniline providing 1,3-diphenylurea, only one benzotriazole moiety in **67a** is substituted by the amino group with formation of benzotriazolecarboxanilide **153** (Scheme 307).[61]

The remarkable stability of benzotriazolecarboxamides toward action of primary and secondary amines has found wide application in the peptide chemistry.[363,364] The 1-benzotriazolylcarbonyl group is a convenient protective group for primary amines; which can be introduced into an amino acid molecule and subsequently removed under mild conditions and in high yield. The stability of 1-benzotriazolylcarbonyl protection toward carboxylate anions at ambient temperature allows the successful synthesis of terminal peptides **997**[363] (Scheme 308). 1-Benzotri-

Scheme 308. Synthesis of Low Peptides Using 1-Benzotriazolylcarbonyl Protecting Group





azolylcarbonyl group can be displaced with carboxylic acid by heating in xylene to afford a variety of small peptides **998**.[364]

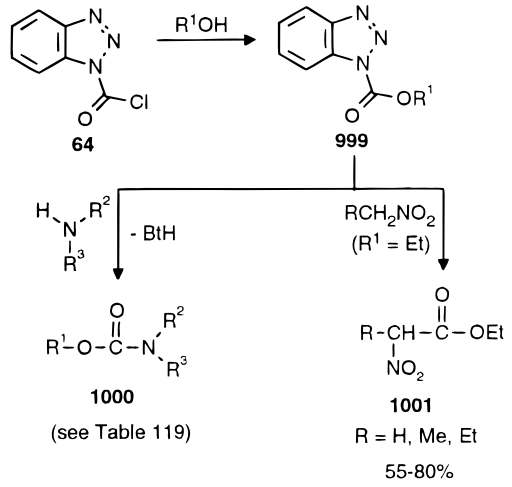
1-(Alkoxycarbonyl)benzotriazoles **999**, prepared from 1-(chlorocarbonyl)benzotriazole (**64**) (for preparation of **64**, see section II.A.2) and alcohols,[265] are effective *N*- and *C*-carboxylating reagents. They react readily with primary and secondary amines or hydrazines to give the corresponding carbamates **1000** in high yields which provides a convenient two-step procedure for the conversion of a wide range of primary

Table 119. Preparation of Carbamates 1000 from 1-(Alkoxycarbonyl)benzotriazoles

R^1	R^2	R^3	yield %
Et	H	c-C_6H_{11}	67
Et	H	*n*-$C_{18}H_{37}$	85
Et	H	$-(CH_2)_2-$[a]	76
Et	H	PhNH	86
Et	Et	Et	49
Ph	H	c-C_6H_{11}	95
$PhCH_2$	H	*n*-Pr	90
$PhCH_2$	H	c-C_6H_{11}	74
$PhCH_2$	H	$-(CH_2)_2-$ [a]	69

[a] 1,2-Ethylenediamine is used to give the corresponding dicarbamates.

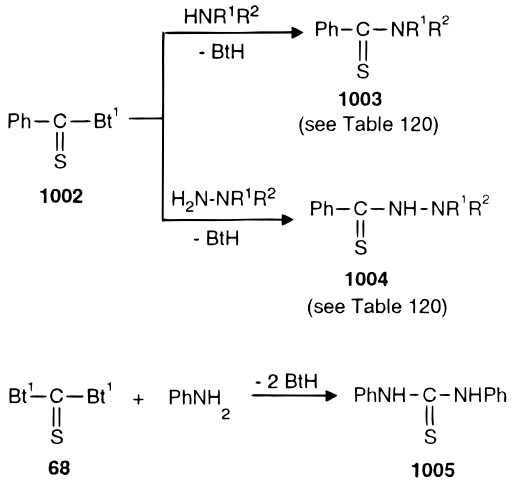
Scheme 309. Preparation and Properties of 1-(Alkoxycarbonyl)benzotriazoles



alcohols into carbamates (Scheme 309, Table 119). 1-(Ethoxycarbonyl)benzotriazole (**999**, R^1 = Er) reacts with nitroalkanes in the presence of sodium hydride to afford the corresponding α-nitro esters **1001** in 55−80% yields. Nitro(aryl)methanes cannot be carboxylated in this way.[366]

b. Thioacylbenzotriazoles Bt−C═S. 1-Thiobenzoylbenzotriazole (**1002**), which prepared from benzotriazole and thiobenzoyl chloride (see section II.A.2), is powerful thioacylating agent. It reacts at ambient temperature with ammonia, primary and secondary amines to afford the corresponding phenyl thioamides **1003** in moderate yields[54] (Scheme 310, Table 120).

Scheme 310. Reactions of 1-Thiobenzoylbenzotriazole and 1,1′-Thiocarbonyldibenzotriazole with Amines and Hydrazines



A similar reaction with *N*,*N*-disubstituted hydrazines gives phenylthiohydrazides **1004**.

1,1′-Thiocarbonyldibenzotriazole (**68**) (for preparation, see section II.A.2) is significantly more reactive toward proton-labile compounds than its oxygen analogue (see section IV.B.10.a) and undergoes double substitution with aniline to give 1,3-diphenylthiourea **1005** (Scheme 310).[62] It can be used for thioacylation of amines, but shows no particular advantages compared to other known thiocarbonyldiazoles, such as thiocarbonyldiimidazole.

Table 120. Preparation of Phenyl Thioamides 1003 and Phenyl Thiohydrazides 1004

compound	R^1	R^2	yield %
1003	H	H	47
	H	Me	
	H	Ph	55
	H	2-MeC_6H_4	72
	Et	Et	44
		$-(CH_2)_5-$	58
		$-(CH_2)_2O(CH_2)_2-$	39
	Me	Ph	
1004	Me	Me	39
	Me	Ph	27

c. (Methyl-, (Trifluoromethyl-, and (Arylsulfonyl)-benzotriazoles $BtSO_2R$. 1-(Trifluoromethylsulfonyl)-benzotriazole is successfully employed in the transformation of thiol acid salt **1006**[367] or dithio acid salt **1007**[368,369] to the corresponding amides **1010** or thioamides **1008**. Triflic anhydride functions similarly.[368] 1-Acyl- (**1009**) or 1-thiocarbonylbenzotriazoles are presumably formed as the intermediates which subsequently react with amines to yield amides **1010** and thioamides **1008** (Scheme 311, Table 121).

Scheme 311. Preparations of Amides and Thioamides

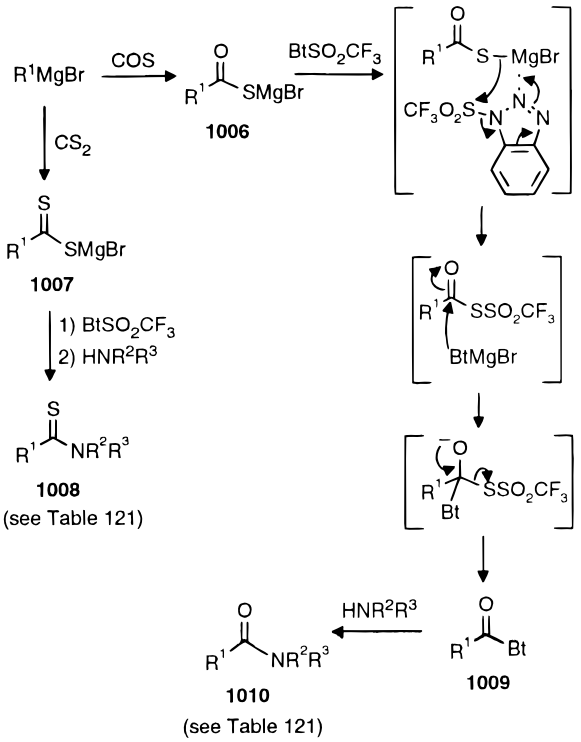


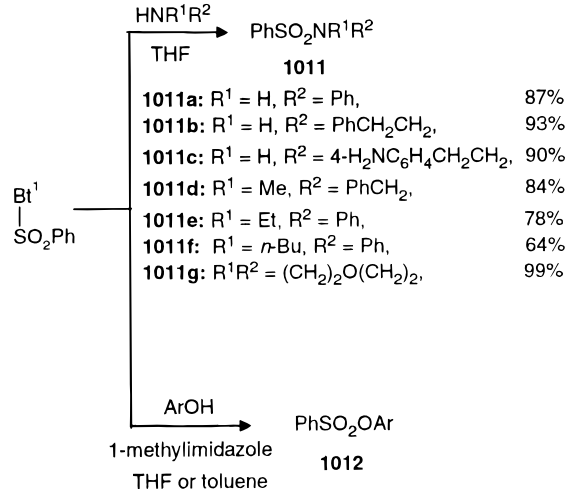
Table 121. Preparation of Thioamides 1008 and Amides 1010

compound	R^1	R^2	R^3	yield %
1008	*n*-Bu	H	$PhCH_2$	61
	n-Bu	$-(CH_2)_2O(CH_2)_2-$		64
	n-C_7H_{15}	H	Ph	79
	n-C_7H_{15}	H	$PhCH_2CH_2$	72
	n-C_7H_{15}	H	2-Py	45
	n-C_7H_{15}	$-(CH_2)_2O(CH_2)_2-$		78
	Ph	H	*n*-Bu	63
	Ph	H	$PhCH_2CH_2$	62
	$PhCH_2$	H	*n*-Bu	68
	$PhCH_2$	H	$PhCH_2CH_2$	79
1010	*n*-Bu	H	$PhCH_2$	68
	n-C_7H_{15}	$-(CH_2)_2O(CH_2)_2-$		75

1-(Methylsulfonyl)-6-(trifluoromethyl)benzotriazole has been successfully used as an activating agent for the multistep synthesis of antibacterial cephalosporines.[370]

The benzotriazole group in 1-(phenylsulfonyl)benzotriazole (for preparation, see section II.A.2) is readily displaced by amines and phenols allowing the preparation of benzenesulfonamides **1011** and benzenesulfonates **1012** in good yields[371] (Scheme 312).

Scheme 312. Preparations of Sulfonamides and Sulfonates



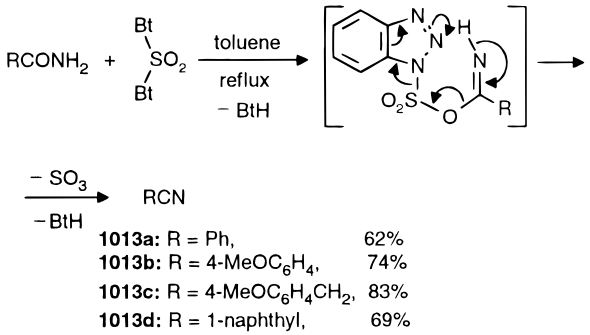
1011a: R^1 = H, R^2 = Ph, 87%
1011b: R^1 = H, R^2 = $PhCH_2CH_2$, 93%
1011c: R^1 = H, R^2 = 4-$H_2NC_6H_4CH_2CH_2$, 90%
1011d: R^1 = Me, R^2 = $PhCH_2$, 84%
1011e: R^1 = Et, R^2 = Ph, 78%
1011f: R^1 = *n*-Bu, R^2 = Ph, 64%
1011g: R^1R^2 = $(CH_2)_2O(CH_2)_2$, 99%

1012a: Ar = 4-ClC_6H_4, 88%
1012b: Ar = 3-$MeOC_6H_4$, 91%
1012c: Ar = 4-$MeOC_6H_4$, 99%
1012d: Ar = 2,6-$Me_2C_6H_3$, 62%
1012e: Ar = 3,4-$Me_2C_6H_3$, 96%
1012f: Ar = 1,2-$(HO)_2C_6H_3$, 83%
1012g: Ar = 1,3,5-$(HO)_3C_6H_2$, 80%
1012h: Ar = 1-naphthyl, 51%

In the cases of aliphatic amines this method does not require the use of a base and thus reduces the chance of possible side reactions which may occur in the sulfonylation with sulfonyl chloride. Moreover, 1-(phenylsulfonyl)benzotriazole is less reactive than phenylsulfonyl chloride and therefore is more selective toward primary and secondary amines or toward aliphatic and aromatic amines.[371]

1,1′-Sulfonyldibenzotriazole effects the dehydration of amides into nitriles **1013** as shown in Scheme 313.[362]

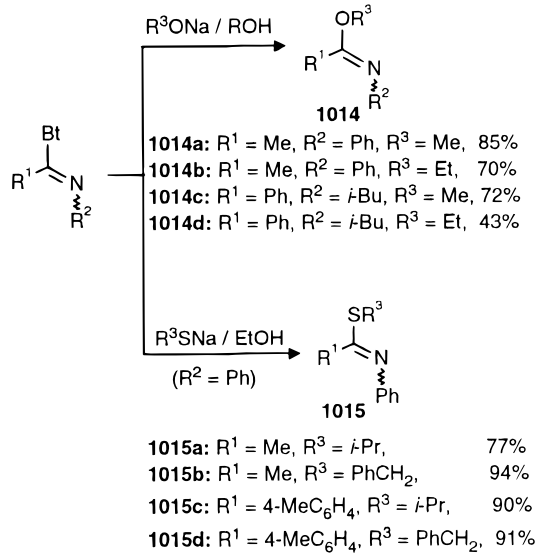
Scheme 313. Dehydration of Amides to Nitriles



1013a: R = Ph, 62%
1013b: R = 4-$MeOC_6H_4$, 74%
1013c: R = 4-$MeOC_6H_4CH_2$, 83%
1013d: R = 1-naphthyl, 69%

d. Imidoylbenzotriazoles Bt—C═N. Through an addition−elimination mechanism, alkoxides or thiolates add to the C═N bond in 1-imidoylbenzotriazoles **73** (for preparation, see section II.A.3) with subsequent elimination of a molecule of benzotriazole to give imidates **1014** or thioimidates **1015**[68] (Scheme 314).

Scheme 314. Preparation of Imidates and Thioimidates



1014a: R^1 = Me, R^2 = Ph, R^3 = Me, 85%
1014b: R^1 = Me, R^2 = Ph, R^3 = Et, 70%
1014c: R^1 = Ph, R^2 = *i*-Bu, R^3 = Me, 72%
1014d: R^1 = Ph, R^2 = *i*-Bu, R^3 = Et, 43%

1015a: R^1 = Me, R^3 = *i*-Pr, 77%
1015b: R^1 = Me, R^3 = $PhCH_2$, 94%
1015c: R^1 = 4-MeC_6H_4, R^3 = *i*-Pr, 90%
1015d: R^1 = 4-MeC_6H_4, R^3 = $PhCH_2$, 91%

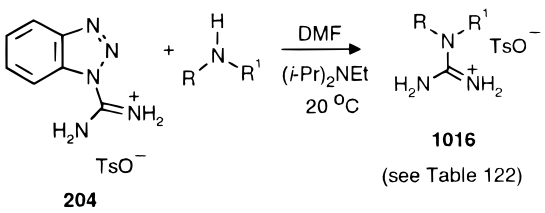
Reactions of imidoylbenzotriazoles **73** with Grignards are discussed in section V.A because, in addition to the expected Bt replacement to form the corresponding amines, attack of Grignard reagents occurs on the benzotriazole ring nitrogen atoms.[73]

Treatment of benzotriazole-1-carboxamidinium tosylate **204** with primary or secondary amines at room temperature produces in good yields the substituted guanidines which are isolated and characterized as their tosylate salts **1016** (Table 122, Scheme 315).[160]

Table 122. Preparation of Tosylate Salts of Substituted Guanidines 1016

R	R^1	yield %
H	*n*-Bu	55
H	*n*-C_6H_{13}	67
H	Ph	68
H	4-$MeOC_6H_4$	68
Me	Me	69
	$-(CH_2)_4-$	71
	$-(CH_2)_5-$	84
	$-(CH_2)_2O(CH_2)_2-$	86

Scheme 315. Preparation of Tosylate Salts of Substituted Guanidines



e. Cyanobenzotriazoles Bt—C≡N. 1-Cyanobenzotriazole is a convenient and safe source of positive cyanogen and has been used to cyanate various primary and secondary amines (Scheme 316, Table

Scheme 316. Reactions of 1-Cyanobenzotriazole

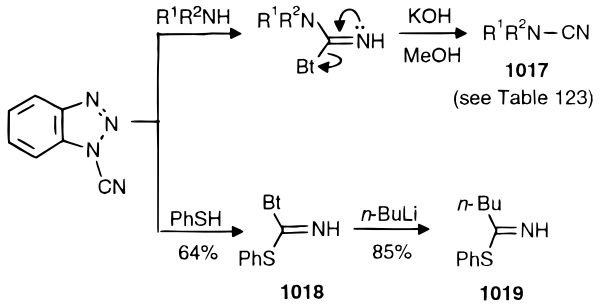


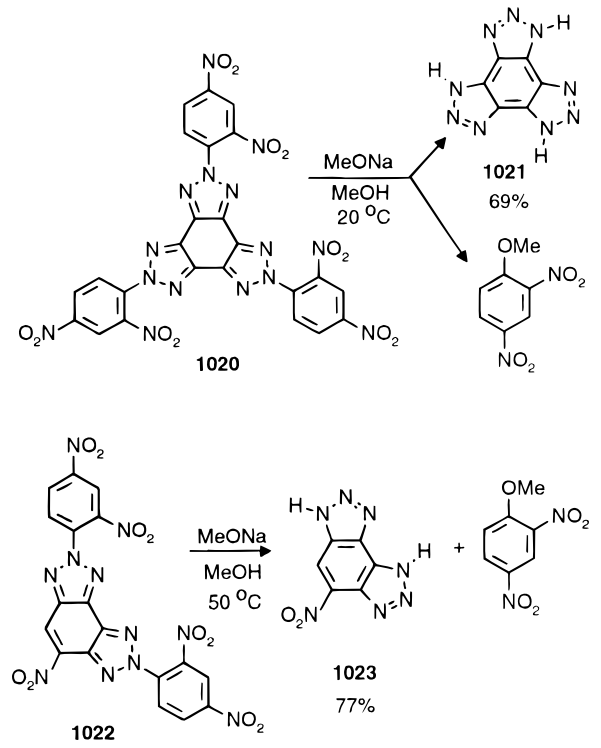
Table 123. Preparation of Cyanamides 1017

R^1	R^2	yield %
i-Bu	H	84
i-Bu	*i*-Bu	83
c-C_6H_{11}	*i*-Pr	87
c-C_6H_{11}	c-C_6H_{11}	90
$PhCH_2$	$PhCH_2$	90
n-C_8H_{17}	*n*-C_8H_{17}	96
$-(CH_2)_5-$		91

123).[71] The initial step is the addition of amine to the cyano group, which is followed by elimination of benzotriazole. Similarly, thiophenol adds to the cyano group of 1-cyanobenzotriazole to give compound **1018** where the benzotriazole group can be displaced by *n*-butyllithium to give imino thioester **1019** (Scheme 316).

f. Aryl- and Vinylbenzotriazoles Bt−C=C. Cleavage of the Bt−Ar bonds in 2,5,8-tris(2,4-dinitrophenyl)benzotriazole (**1020**, Scheme 317) occurs under

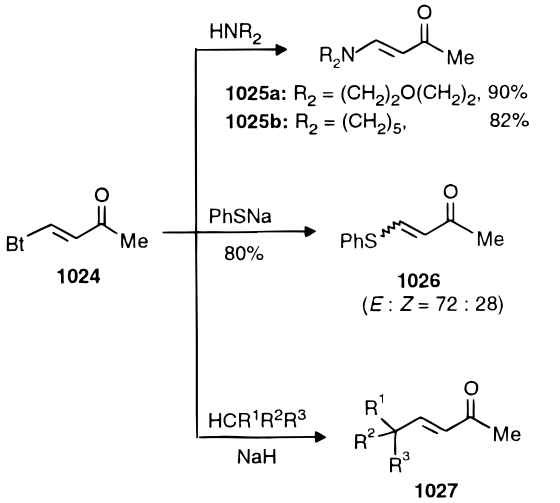
Scheme 317. Cleavage of Bt−Ar Bonds



very mild conditions: treatment with methanolic MeONa at room temperature provides benzotristriazole (**1021**) in 69% yield.[372] An analogous reaction with benzobistriazole derivative **1022** yields the corresponding nitrobenzobistriazole **1023**.

Although nucleophilic substitution of the benzotriazole moiety does not occur in nonactivated vinylbenzotriazoles, β-benzotriazole-substituted α,β-unsaturated ketones undergo easy displacement with various *N*-, *S*-, and *C*-nucleophiles (Scheme 318).[81]

Scheme 318. Displacement of Vinylic Benzotriazolyl Group

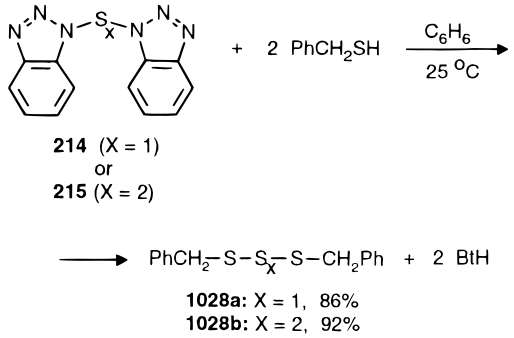


β-Benzotriazolylvinyl ketone **1024** reacts with secondary amines at ambient temperature without addition of any other base to give enamines **1025** and with thiolate anion to form **1026**. Reaction of **1024** with C−H acids requires their preliminary deprotonation with sodium hydride and affords α,β-unsaturated ketones **1027** exclusively as *E* isomers.

11. From Systems Bt–X

The utility of 1,1′-thio- and 1,1′-dithiobisbenzotriazoles (**214** and **215**, respectively) as sulfur-transfer reagents is demonstrated in the synthesis of dibenzyl polysulfides.[165] Thus, **214** and **215** react with benzyl mercaptan to afford the corresponding tri- and tetrasulfides **1028a**,**b** in high yields (Scheme 319).

Scheme 319. Preparation of Polysulfides

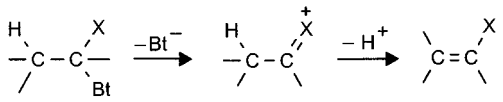


C. Removal by Elimination To Give a Multiple Bond

Important classes of elimination reactions together with the section where they are treated are shown in Scheme 320. (i) If there is a hydrogen β to an activated benzotriazole group as in **1029**, elimination of a molecule of benzotriazole is possible to form a double bond. This allows the synthesis of enamines, enamides, enol ethers, and vinyl sulfides (Scheme 320). (ii) If two suitably activated Bt groups are present, dienamines and dienol ethers **1032** are obtained by vinylogous reactions. (iii) Elimination to form C=X bonds and (iv) reverse Michael reactions are also important.

Scheme 320. Overview of Elimination Reactions

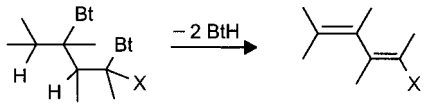
(i) Initial ionisation followed by deprotonation



1029 **1030**

Nature of X	Compound Formed	Section
NR_2	enamine	IVC1a
NRCOR'	enamide	IVC1b
OR	enol ether	IVC1c
SR	vinyl sulfide	IVC1d

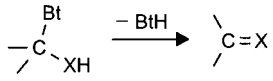
(ii) Initial ionisation in vinylogous situation



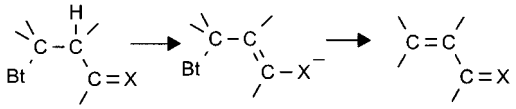
1031 **1032**

Nature of X	Compound Formed	Section
NR_2	dienamine	IVC2
OR	dienyl ether	IVC2

(iii) Elimination to give C=O, C=N or C=S



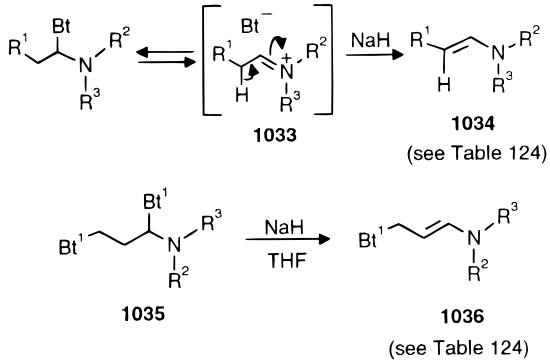
(iv) Initial deprotonation followed by loss of Bt^-: Reverse Michael Reaction



1. Ionization of Activated Bt Followed by Deprotonation: Preparation of Enamines, Enamides, Vinyl Ethers, Vinyl Sulfides, etc.

a. Preparation of Enamines. The preparation of enamines is shown in Scheme 321 (Table 124) by treatment of the easily available (see section II.B.3) *N*-(α-aminoalkyl)benzotriazoles with sodium hydride in THF.[373] The initial ionization to cation **1033** is followed by deprotonation and elimination to give enamines **1034**. *E* isomers are obtained exclusively. Enamines are easy to prepare from aldehydes and amines using a suitable catalyst or reagent, but in the previously published methods at least 2 mol of amine were used per mole of aldehyde and the yields were always "calculated on the aldehyde". Calculating the yields in previous methods with respect to amines gives much poorer results. The benzotriazole method utilizes strictly 1 mol of amine and 1 mol of aldehyde and gives high yields on the basis amount of amine taken.

Scheme 321. Preparation of Enamines



1033 **1034** (see Table 124)

1035 **1036** (see Table 124)

Table 124. Preparation of Enamines 1034 and 1036

compound	R^1	R^2	R^3	yield %
1034	H	$-(CH_2)_2O(CH_2)_2-$		83
	Me	$-(CH_2)_5-$		61
	Me	$-(CH_2)_2O(CH_2)_2-$		75
	Et	Me	Ph	90
	Et	$-(CH_2)_4-$		92
	Et	$-(CH_2)_5-$		84
	Et	$-(CH_2)_2O(CH_2)_2-$		81
	Et	$-CH_2CH_2N(Me)CH_2CH_2-$		64
	n-Pr	$-(CH_2)_2O(CH_2)_2-$		83
	n-Bu	$-(CH_2)_5-$		90
	n-Bu	$-(CH_2)_2O(CH_2)_2-$		92
	n-Bu	$-CH_2CH_2N(Me)CH_2CH_2-$		80
1036		$-(CH_2)_2O(CH_2)_2-$		74
		$-CH_2CH_2$-C_6H_4(1,2)$-$		75
		$PhCH_2$	$PhCH_2$	88

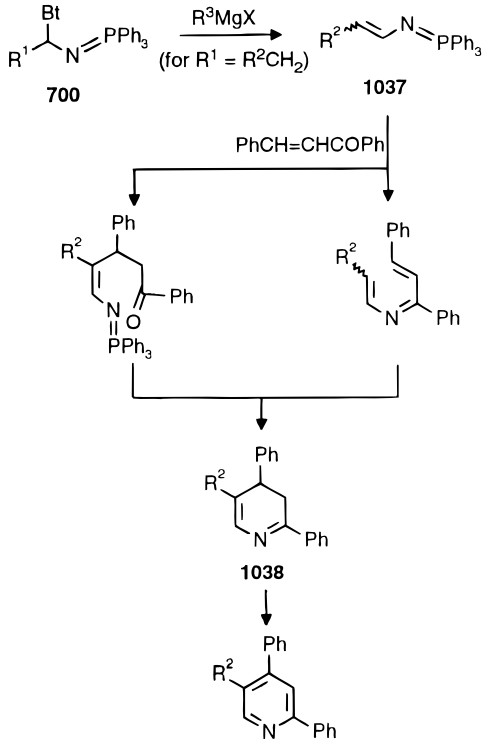
The presence of unactivated benzotriazole moiety does not affect the course of the reaction and by this procedure 3-(benzotriazol-1-yl)enamines **1036** can easily be prepared.[357]

When a β-hydrogen is available in an α-substituted Betmip **700** (Scheme 322), elimination of a molecule of benzotriazole on treatment with a Grignard reagent results in compounds **1037**. Subsequent condensation of **1037** with an α,β-unsaturated ketone followed by cyclization and oxidation of the intermediate 3,4-dihydropyridines **1038** yields 2,4-di- or 2,4,5-trisubstituted pyridines **1039**.[257]

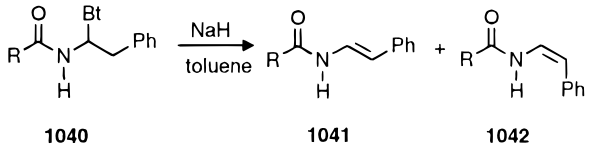
b. Preparation of Enamides. *N*-(1-Benzotriazol-1-ylphenethyl) amides **1040** on treatment with sodium hydride eliminate a molecule of benzotriazole (Scheme 323) to form mixtures of (*E*)- (**1041**) and (*Z*)-enamides (**1042**) with the *E* isomer predominant.[274]

c. Preparation of Enol Ethers. Similar methodology is also applicable to *N*-(α-alkoxyalkyl)benzotri-

Scheme 322. Preparation of 2,4,5-Trisubstituted Pyridines



Scheme 323. Preparation of Enamides



R	total yield (%)
Ph	93
4-MeC_6H_4	91
4-$MeOC_6H_4$	94
$PhCH_2$	84
Et	89
3-pyridyl	95

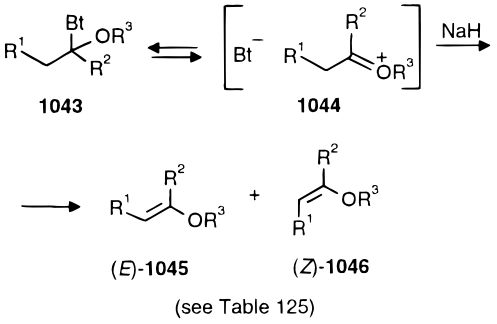
azoles **1043** for the formation of enol ethers.[76] Again, the initial ionized product **1044** is deprotonated. For $R^1 = H$, only one isomer is possible, and for derivatives from cyclohexanone only the *E* isomers are obtained. But for other adducts **1043** mixtures of *E* (**1045**) and *Z* isomers (**1046**) are formed with the *E* isomers predominant (Scheme 324, Table 125). This method allows preparation from ketones of enol ethers containing both primary and secondary alkoxy groups. The latter are not readily available by previously reported methods.

d. Preparation of Vinyl Sulfides. The elimination of a molecule of benzotriazole from *tert*-alkyl sulfides **1047** is achieved by treatment with $BF_3{\cdot}Et_2O$ instead

Table 125. Preparation of Enol Ethers 1045 and 1046

R^1	R^2	R^3	yield %	ratio **1045**:**1046**
H	Me	c-C_6H_{11}	90	
H	Ph	Me	92	
Me	Et	*i*-Pr	89	60:40
Me	Et	*n*-C_6H_{13}	80	62:38
Me	Et	$PhCH_2$	80	58:42
$-(CH_2)_4-$		*i*-Pr	91	100:0
$-(CH_2)_4-$		$PhCH_2$	75	100:0

Scheme 324. Preparation of Enol Ethers



of sodium hydride.[147,241] When two different methylene groups are available, the reaction affords a mixture of two isomeric compounds **1048** and **1049**, each as a mixture of the *E* and *Z* isomers (Scheme 325, Table 126).

Scheme 325. Preparation of Vinyl Sulfides

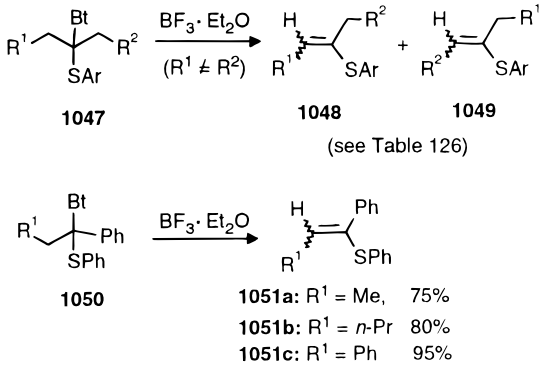


Table 126. Preparation of Vinyl Sulfides 1048 and 1049

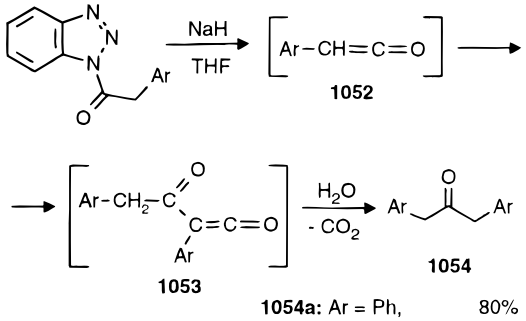
Ar	R^1 [a]	R^2 [a]	yield %
Ph	Ph	H	60
Ph	Ph	Me	75
Ph	Ph	*n*-Pr	62
Ph	Ph	*n*-C_6H_{13}	70
Ph	Ph	Ph	85
Ph	Ph	4-MeC_6H_4	83
Ph	4-MeC_6H_4	4-MeC_6H_4	80
4-MeC_6H_4	Ph	H	52
4-MeC_6H_4	Ph	Ph	91
4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	90

[a] When $R^1 \neq R^2$, mixtures of regioisomers are obtained.

e. Preparation of 1,3-Diarylacetones and Aryl Benzyl Sulfoxides via Ketene Intermediates. On treatment with sodium hydride at ambient temperature, *N*-(arylacetyl)benzotriazoles (easily available from benzotriazole and appropriate acyl chlorides, see section II.A.2) eliminate a molecule of benzotriazole

to give aryl ketenes **1052**, which dimerize spontaneously to **1053**. Subsequent hydrolysis *in situ* followed by loss of carbon dioxide produces symmetrical ketones **1054** in good yields (Scheme 326).[375] When

Scheme 326. Preparation of 1,3-Diarylacetones via Ketene Intermediates



such a dimerization is hindered (for example, in case of disubstituted *N*-acylbenzotriazoles BtC(O)CHR^{1}R^2), the corresponding carboxylic acids R^{1}R^{2}CHCOOH are obtained.

Elimination of benzotriazole from *N*-(arylacetyl)-benzotriazoles with the generation of ketene intermediates can be achieved even with such a weak base as DMF. Thus, refluxing a solution of *N*-(arylacetyl)-benzotriazoles in DMF in the presence of sulfinate anions as nucleophilic ketene trapping agents gives aryl benzyl sulfoxides **1057** in good yields (Scheme 327, Table 127).[376] The suggested mechanism in-

Scheme 327. Preparation of Aryl Benzyl Sulfoxides via Ketene Intermediates

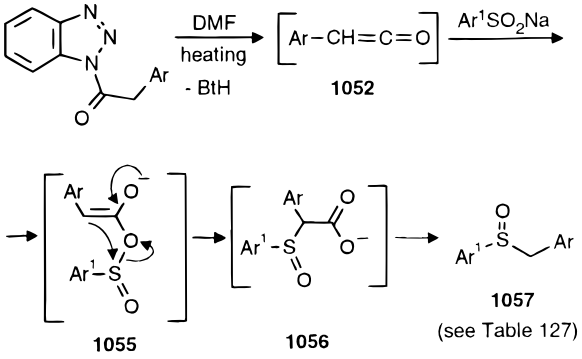


Table 127. Preparation of Aryl Benzyl Sulfoxides 1057

Ar	Ar^1	yield %
Ph	Ph	75
Ph	4-MeC$_6$H$_4$	90
3-MeC$_6$H$_4$	Ph	70
4-MeC$_6$H$_4$	Ph	75
2-MeOC$_6$H$_4$	Ph	68
4-MeOC$_6$H$_4$	4-MeC$_6$H$_4$	85
4-PhC$_6$H$_4$	Ph	75

volves the addition of sulfinate anion to the ketene intermediate **1052** to give enolate **1055**. Subsequent intramolecular rearrangement with C–S bond formation followed by decarboxylation affords sulfoxides **1057**.

2. Ionization of Vinylogously Activated Bt: Preparation of Dienamines, Dienamides and Dienyl Ethers

Dienamines **1059** are obtained by the elimination methodology (Scheme 328, Table 128)[377] from **1058**

Scheme 328. Preparation of Dienamines

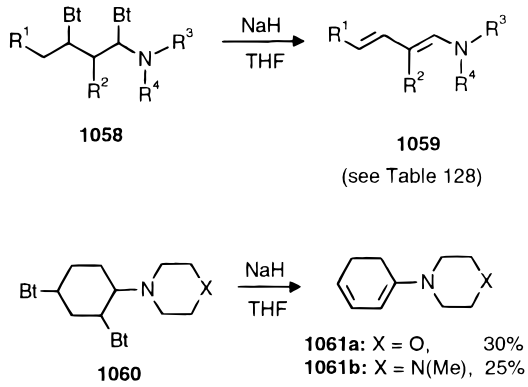


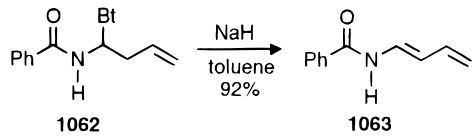
Table 128. Preparation of Dienamines 1059

R^1	R^2	R^3	R^4	yield %
H	H	–(CH$_2$)$_4$–		58
H	H	–(CH$_2$)$_5$–		68
H	H	–(CH$_2$)$_2$O(CH$_2$)$_2$–		51
H	H	–(CH$_2$)$_2$N(Me)(CH$_2$)$_2$–		61
H	H	Ph	Ph	41
Me	Me	–(CH$_2$)$_2$O(CH$_2$)$_2$–		45
Me	Me	–(CH$_2$)$_2$N(Me)(CH$_2$)$_2$–		28
Et	H	–(CH$_2$)$_2$O(CH$_2$)$_2$–		54
Et	H	–(CH$_2$)$_5$–		51

(readily available from α,β-unsaturated aldehydes or ketones, benzotriazole and a secondary amine, see section II.B.2). Compared to previous methods using the unsaturated aldehyde and amine, our method does not require excess of the amine, and affords comparable yields of the dienamines.

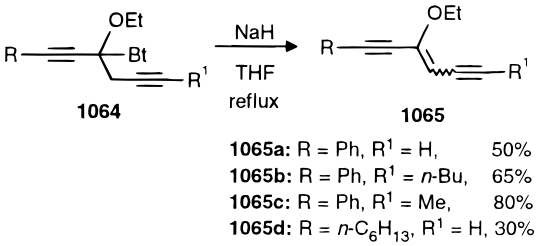
A similar reaction of benzotriazole adduct **1062** with sodium hydride affords *N*-butadienyl amide **1063** in 92% yield (Scheme 329).[132]

Scheme 329. Preparation of *N*-Butadienyl Amide

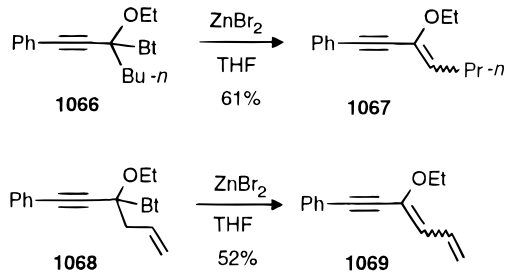


3-Benzotriazolyl-3-ethoxy-1,5-alkadiynes **1064** (for preparation, see section III.A.2.d) readily eliminate a molecule of benzotriazole on treament with sodium hydride in toluene to give the corresponding conjugated enediynes **1065** as mixtures of *E* and *Z* isomers in moderate yields (Scheme 330).[187] The analogous 1-benzotriazolylpropargyl ethyl ether (**1066**) and 4-benzotriazolyl-4-ethoxy-6-phenyl-1-hexene-5-yne (**1068**) undergo benzotriazole elimination in the presence of the Lewis acid ZnBr$_2$, to form enyne **1067** and dienyne **1069**, respectively.

Scheme 330. Preparation of Dienyl Ethers



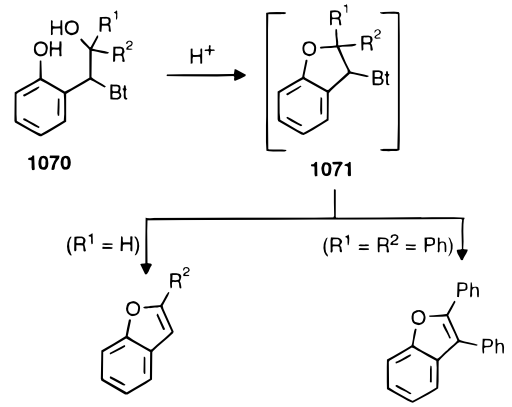
1065a: R = Ph, R^1 = H, 50%
1065b: R = Ph, R^1 = *n*-Bu, 65%
1065c: R = Ph, R^1 = Me, 80%
1065d: R = *n*-C_6H_{13}, R^1 = H, 30%

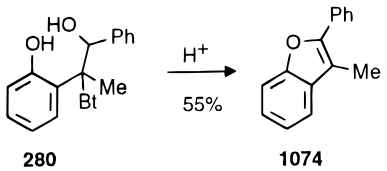


3. Preparation of Heterocycles by Ionization of Activated Benzotriazole

a. Preparation of Benzofurans and Furans. Compounds **1070**, obtained from lithiation of *o*-(benzotriazolylmethyl)phenol and subsequent treatment with aldehydes or ketones (see section III.A.3.a), undergo cyclization to give the benzotriazolyl-substituted dihydrobenzofuran derivatives **1071**, which eliminate *in situ* a molecule of benzotriazole (for R^1 = H) to give 2-substituted benzofurans **1072a**−**c** (Scheme 331). With $R^1 = R^2$ = Ph, the departure of the benzotriazole group is followed by migration of a phenyl group to yield 2,3-diphenylbenzofuran (**1073**). A similar route allows the preparation of 2-phenyl-3-methylbenzofuran (**1074**).[131]

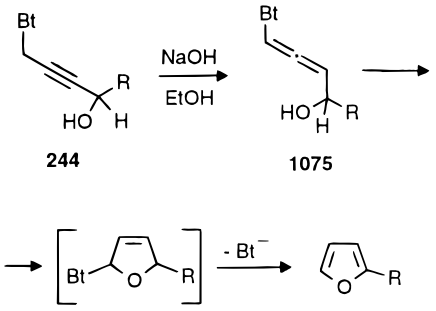
Scheme 331. Elimination of Benzotriazole from Dihydrobenzofurans Prepared *in Situ*





1-Hydroxy-4-benzotriazolyl-1-alkynes **244**, obtained from 1-propargylbenzotriazole and the appropriate aromatic aldehydes (see Scheme 88, section III.A.2.d), undergo base-promoted isomerization into allenes **1075**. Subsequent intramolecular cyclization of **1075** gives 2,5-dihydrofurans **1076** which are aromatized under the reaction conditions with elimination of a benzotriazole molecule to give furans **1077a**−**c** (Scheme 332).[283]

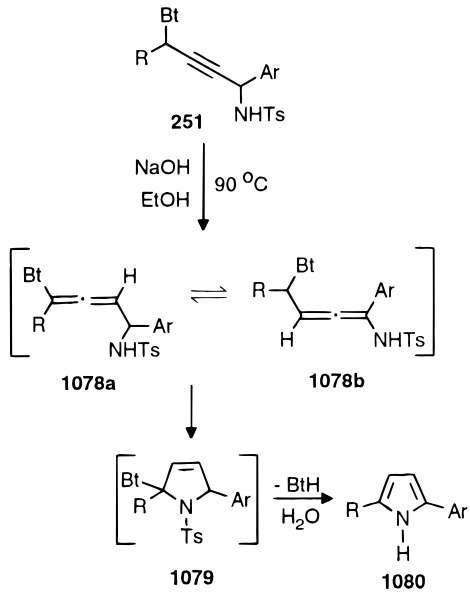
Scheme 332. Preparation of Furans from 1-Hydroxy-4-benzotriazolyl-2-alkynes



1077a: R = Ph, 81%
1077b: R = 4-ClC_6H_4, 62%
1077c: R = 2-furanyl, 53%

b. Preparation of Pyrroles, Imidazoles, Indoles, and Carbazoles. Upon heating with an ethanolic solution of NaOH, 1-benzotriazolyl-4-(*N*-tosylamino)-2-butynes **251** (for preparation see Scheme 89, section III.A.2.d) undergo a similar isomerization into the corresponding allenes **1078**. Subsequent with following cyclization gives unstable *N*-tosyl-2,5-dihydropyrroles **1079**, which under the reaction conditions eliminate benzotriazole and lose the tosyl group

Scheme 333. Preparation of Pyrroles from 1-Benzotriazolyl-4-((*N*-tosylamino)-2-butynes

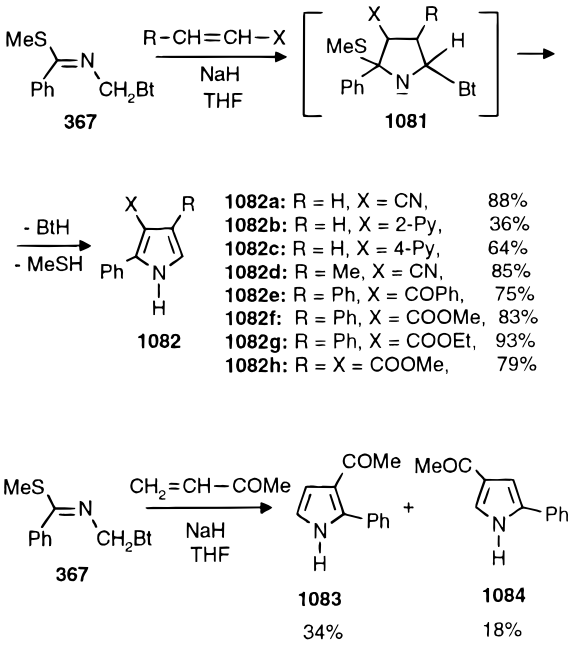


1080a: R = H, Ar = Ph, 51%
1080b: R = H, Ar = 4-ClC_6H_4, 47%
1080c: R = H, Ar = 4-MeC_6H_4, 45%
1080d: R = H, Ar = 2-thienyl, 60%
1080e: R = H, Ar = 1-naphthyl, 58%
1080f: R = Me, Ar = 1-naphthyl, 56%
1080g: R = Et, Ar = 1-naphthyl, 43%

to produce 2-substituted pyrroles **1080** in moderate yields[182] (Scheme 333).

N-(Benzotriazolylmethyl) thioimidate **367** (easily available from *N*-(benzotriazolylmethyl)thiobenzamide, undergoes regiospecific [2 + 3] cycloadditions with α,β-unsaturated esters, ketones, and nitriles in the presence of sodium hydride to give intermediates **1081**, which under the reaction conditions eliminate benzotriazole and methanethiol to provide the corresponding 2,3-di- or 2,3,4-trisubstituted pyrroles **1082**[227] (Scheme 334). An exception was observed

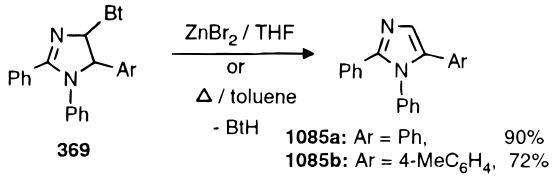
Scheme 334. Preparation of Pyrroles from *N*-(Benzotriazolylmethyl) Thioimidates



with methyl vinyl ketone which gave a mixture of regioisomers **1083** and **1084** in ratio ~3:2.

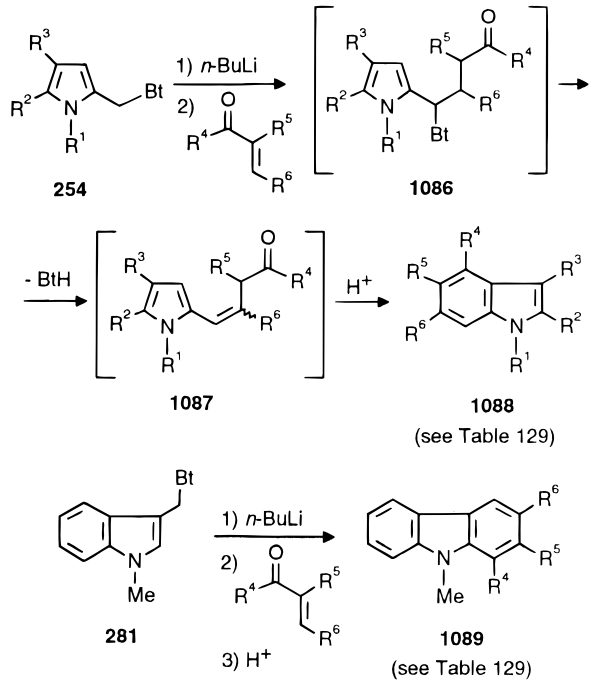
[2 + 3] cycloaddition of **367** to imines does not occur under these conditions, but the corresponding 1,2,5-trisubstituted imidazoles **1085a**,**b** can be prepared by benzotriazole elimination from 4,5-dihydroimidazoles **369** (for preparation of **369**, see section III.A.6.d) on heating or in the presence of Lewis acid (Scheme 335).[227]

Scheme 335. Preparation of Imidazoles



γ-Benzotriazolyl-substituted ketones **1086** (available from pyrroles **254** and α,β-unsaturated aldehydes and ketones, see section III.A.3.b) eliminate a molecule of benzotriazole upon heating with acid catalyst (Amberlyst-15) to give β,γ-unsaturated ketones **1087**, which under the reaction conditions

Scheme 336. Preparation of Indoles and Carbazoles via [3 + 3] Annulation of Benzotriazolylmethyl-Substituted Heterocycles



undergo cyclocondensation with the formation of polysubstituted indoles **1088** in good yields (Table 129, Scheme 336).[185]

Table 129. Preparation of Indoles 1088 and Carbazoles 1089

compound	R^1	R^2	R^3	R^4	R^5	R^6	yield %
1088	H	H	Ph	Me	H	H	56
	n-Bu	Me	Me	Ph	H	Ph	54
	t-Bu	H	Ph	Me	H	H	60
	$MeO(CH_2)_2$	Me	Me	H	Ph	Et	75
	$MeO(CH_2)_2$	Me	Me	Ph	H	Ph	52
	$PhCH_2$	Me	Ph	H	Ph	Et	76
	$PhCH_2$	Me	Ph	Ph	H	Ph	56
	4-$MeOC_6H_4CH_2$	Me	Me	Ph	H	Ph	51
1089				H	Me	Ph	31
				H	Ph	Me	62
				H	Ph	Et	60
				H	Ph	*i*-Bu[a]	67
				Me	H	Ph	80
				Me	CO_2Et	*n*-Pr	36
				Me	CO_2Et	Ph	38
				Ph	H	Ph	83
				Ph	CN	Ph	45
				PhCH=CH	H	Ph	66
				H			

[a] As a mixture with regioisomer (R^5 = *i*-Bu, R^6 = Ph) in ratio 2:3.

Similar reactions with *N*-methyl-3-(benzotriazolylmethyl)indole (**281**) provide a convenient approach to the synthesis of various *N*-methylcarbazoles **1089**.[205]

4. Elimination To Give C=X (X is O, N, or S) or C≡N with Subsequent Reactions

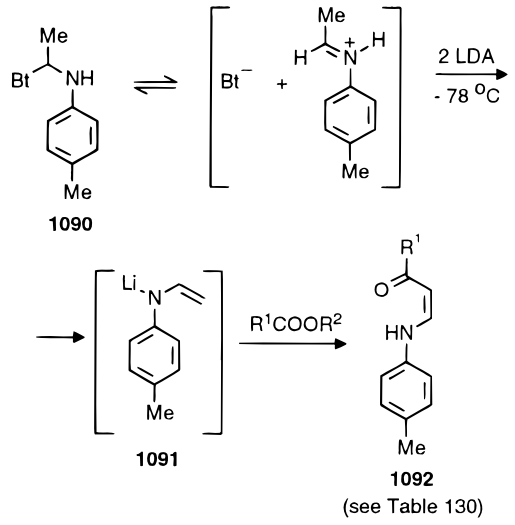
Dissociation of RCH(OH)Bt into RCHO + BtH is the reverse of the equilibrium reaction of formation of hemiaminals (see section II.B.1). In many cases reactions of these types are important synthetically especially when the products can be trapped.

a. Preparation of Enaminones and Dienaminones. *N*-(1-Benzotriazolylethyl)-4-methylaniline (**1090**), when treated with 2.5 equiv of LDA, affords an enamine lithium derivative **1091**. Trapping species **1091** with esters results in the formation of enaminones **1092** as their *cis* isomers (due to internal hydrogen bonding)[378,379] (Table 130, Scheme 337).

Table 130. Preparation of Enaminones 1092

R^1	R^2	yield %
n-Pr	Me	47[378]
c-C_6H_{11}	Me	65[378]
Ph	Me	84[378]
3-$MeOOCC_6H_4$	Me	35[379]
2-$EtOOCC_6H_4$	Et	40[379]
PhCH=CH	Et	50[379]
1-naphthyl	Me	64[378]
OEt	Et	75[378]

Scheme 337. Preparation of Enaminones

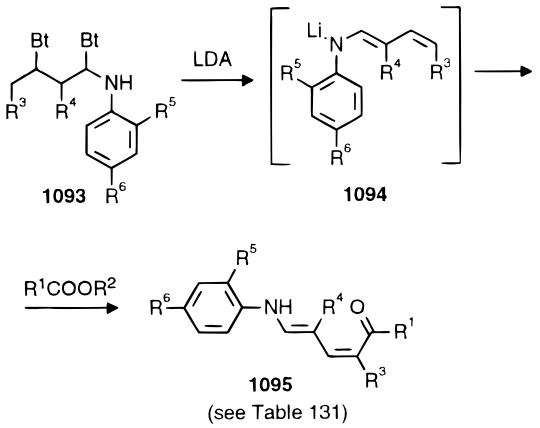


Similar treatment of the dibenzotriazole derivative **1093** with 3 equiv of LDA, followed by 1 equiv of an ester, gives dienaminones **1095**[378] (Table 131, Scheme 338).

Table 131. Preparation of Dienaminones 1095

R^1	R^3	R^4	R^5	R^6	yield %
c-C_6H_{11}	H	H	H	H	45
OEt	H	H	H	H	61
OEt	H	H	H	Me	67
OEt	H	H	H	OMe	63
OEt	H	H	Me	Me	58
OEt	Me	Me	H	H	62

Scheme 338. Preparation of Dienaminones

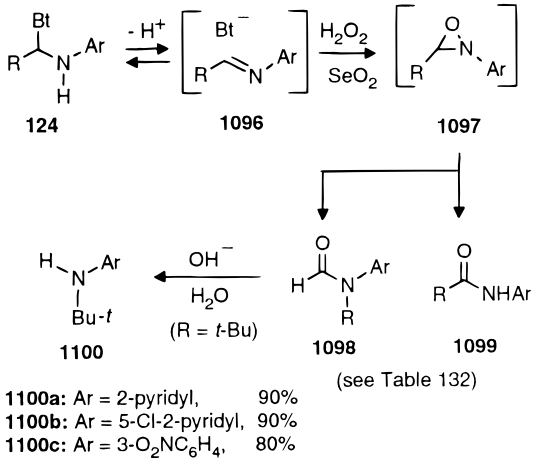


b. Formation of Imines Followed by Oxidation and Rearrangement or Diels−Alder Reaction. Adducts **124** formed from benzotriazole, an aldehyde, and an aromatic or heteroaromatic amine (see section II.B.2.d) are converted by oxidation with H_2O_2/SeO_2 into formamides or other amides (Scheme 339, Table 132).[380] The reaction sequence presumably involves

Table 132. Preparation of Amides 1098 and 1099

		yield %		
Ar	R	**1098**	**1099**	ratio **1098**:**1099**
Ph	*t*-Bu	24	<2	>10:1
3-ClC_6H_4	*t*-Bu	34	<2	>10:1
3-$O_2NC_6H_4$	*t*-Bu	29	<2	>10:1
4-$O_2NC_6H_4$	*t*-Bu	34	<2	>10:1
2-pyridyl	*n*-Pr	20	20	1:1
2-pyridyl	*i*-Pr	20	5	4:1
2-pyridyl	*t*-Bu	29	<2	>10:1
3-pyridyl	*i*-Pr	20	5	4:1
3-pyridyl	*t*-Bu	34	<2	>10:1
4-methyl-2-pyridyl	*t*-Bu	29	<2	>10:1
5-chloro-2-pyridyl	*t*-Bu	39	<2	>10:1

Scheme 339. Trapping Imines by Oxidation and Rearrangement



formation of the imine **1096** and its oxidation to oxaziridine **1097**. The N−O bond scission in **1097** is accompanied by a 1,2-shift of either the alkyl group resulting in formamides **1098** or of a hydrogen atom, giving secondary amides **1099**. The ratio of **1098** and **1099** depends strongly on the bulkiness of group R: with R = *tert*-butyl product **1098** predominates. As

Scheme 340. Trapping Iminium Ions by Diels–Alder Reaction

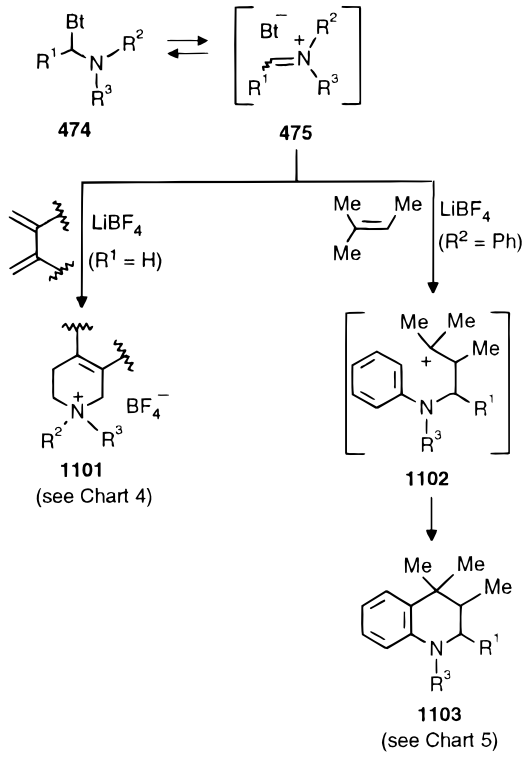
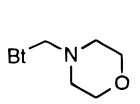
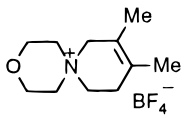
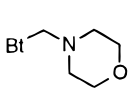
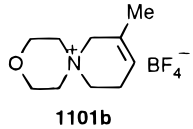
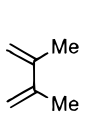
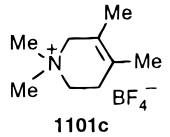
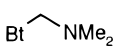
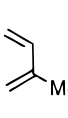
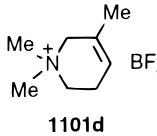


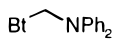
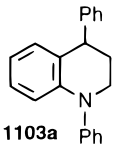
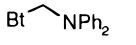
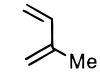
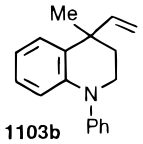
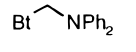
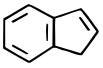
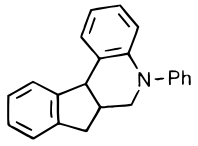
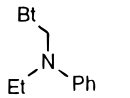
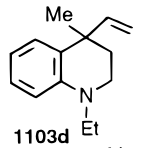
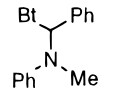
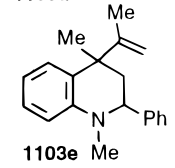
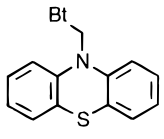
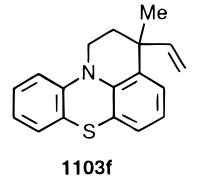
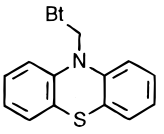
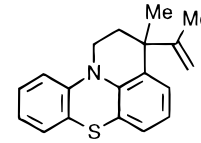
Chart 4. Hetero-Diels–Alder Addition of Immonium Cations from 1-(α-Aminoalkyl)-benzotriazoles to 1,3-Dienes

Aminal **474**	Substrate	Product	Yield %
		 **1101a**	90
		 **1101b**	79
		 **1101c**	35
		 **1101d**	70

hydrolysis of **1098** to **1100** is facile, this sequence provides a useful method for the mono-*N*-*tert*-butylation of aromatic and heteroaromatic amines. Previously, such mono-*N*-*tert*-butylations were at best difficult.

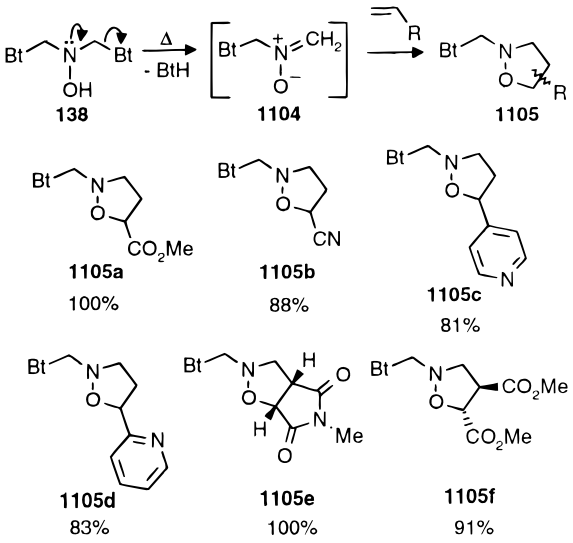
The ionization of 1-(α-aminoalkyl)benzotriazoles **474** is assisted by lithium tetrafluoroborate to generate the reactive iminium intermediates, which can be trapped by electron-rich olefins and by 1,3-dienes.[268] Thus, the iminium intermediates **475** undergo hetero-Diels–Alder cycloaddition with 1,3-dienes to give 1,2,5,6-tetrahydropyridinium salts **1101** (Scheme 340 and Chart 4). When an aniline derivative **474** is used (one of R^2 or R^3 is a phenyl group), the initially formed cation **1102** attacks the electron-rich aniline ring to afford substituted 1,2,3,4-tetrahydroquinolines **1103** (Scheme 340 and Chart 5).

Chart 5. Hetero-Diels–Alder Addition of Immonium Cations from 1-(α-Aminoalkyl)-benzotriazoles to 1,3-Dienes

Aminal **474**	Substrate	Product	Yield %
		 **1103a**	45
		 **1103b**	60
		 **1103c**	40
		 **1103d**	53
		 **1103e**	58
		 **1103f**	85
		 **1103g**	80

c. Trapping Nitrones by 1,3-Dipolar Addition: Preparation of Isoxazolidines. Nitrone **1104**, formed by elimination of a molecule of benzotriazole from the hydroxylamine derivative **138**[381] undergoes *in situ* 1,3-dipolar addition with methyl acrylate, acrylonitrile, 4-vinylpyridine, and 2-vinylpyridine to afford regiospecifically the corresponding 5-substituted isoxazolidines **1105a–d** (Scheme 341). With *N*-methylmaleimide and dimethyl fumarate, the addition products **1105e,f** obtained retain the stereochemistry of the reactants.

Scheme 341. Preparation of Isoxazolidines



d. Formation and Trapping of Azomethine Ylides. The 1,3-dipole **1107**, formed from *N*-[(trimethylsilyl)-methyl]-*N*-(benzotriazol-1-ylmethyl)amine **1106**, is trapped with electron-deficient alkenes in refluxing toluene to give pyrrolidine products **1108** (Scheme 342, Table 133).[382] The cycloaddition proceeds ste-

Scheme 342. Preparation of 3,4-Disubstituted Pyrrolidines

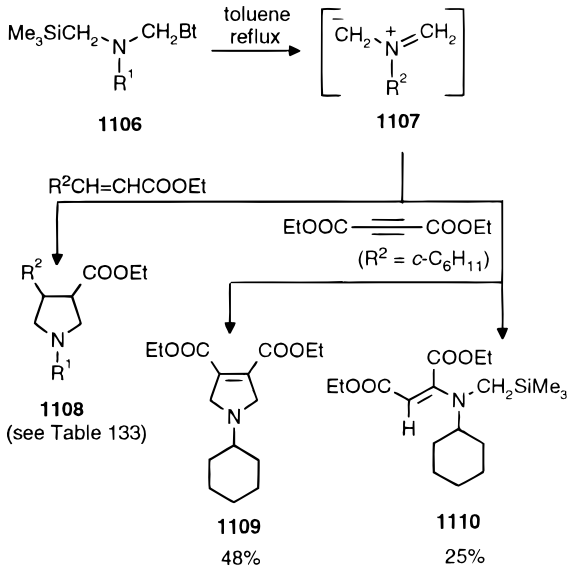


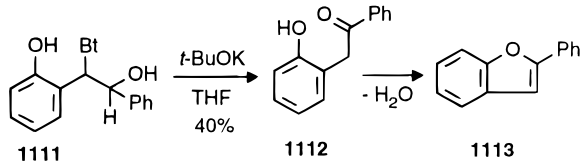
Table 133. Preparation of 3,4-Disubstituted Pyrrolidines 1108

R^1	R^2	yield %
CH_2=$CHCH_2$	Ph (*Z*)	90
sec-Bu	COOEt (*Z*)	88
c-C_6H_{11}	COOEt (*Z*)	84
c-C_6H_{11}	Ph (*Z*)	71
n-C_6H_{13}	COOEt (*E*)	87
n-C_6H_{13}	COOEt (*Z*)	89

reospecifically with retention of the olefinic dipolarophile configuration. With diethyl acetylenedicarboxylate as the dipolarophile, the expected 2,5-dihydropyrrole **1109** is obtained as the major product along with the noncyclized product **1110**.

e. Formation and Trapping of β-Arylalkyl Ketones. 1-(β-Hydroxyalkyl)benzotriazole **1111** on treatment with potassium *tert*-butoxide eliminates a molecule of benzotriazole to give ketone **1112** (Scheme 343),

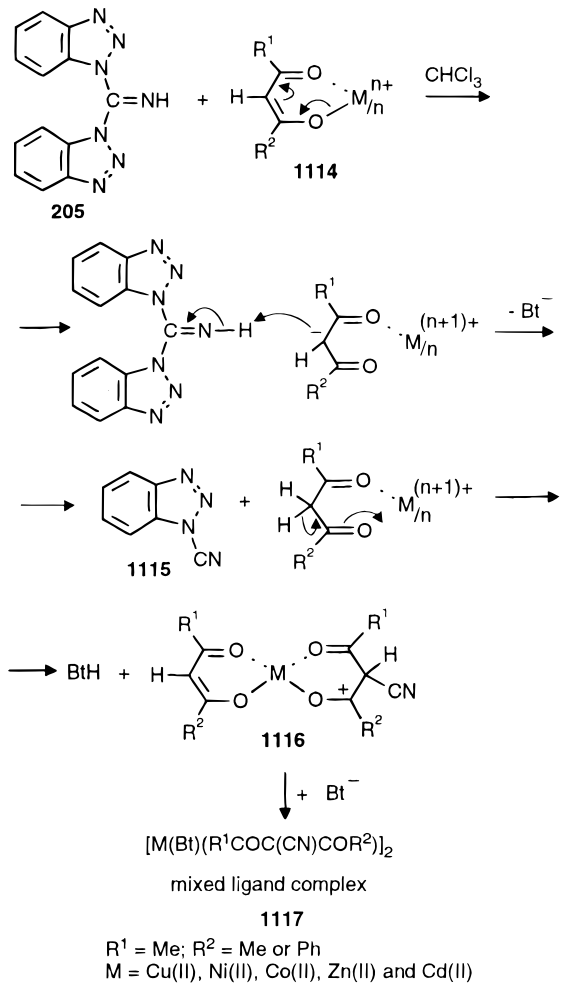
Scheme 343. Formation and Trapping of β-Arylalkyl Ketone



which on standing undergoes slow intramolecular cyclization to 2-phenylbenzofuran **1113**.[202]

f. Formation of 1-Cyanobenzotriazole. Dibenzotriazol-1-ylmethylimine (**205**) undergoes debenzotriazolation in the presence of labile β-diketonates **1114** (M = Cu(II), Ni(II), etc.) to generate *in situ* 1-cyanobenzotriazole **1115**.[161] This reaction is possibly induced by labile metal−oxygen bond in chelates **1114** (Scheme 344), because it does not occur with

Scheme 344. Formation of 1-Cyanobenzotriazole *in Situ*

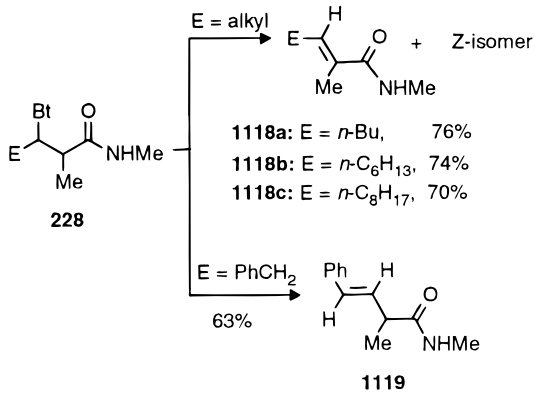


inert or less labile β-diketonates. The resulting 1-cyanobenzotriazole **1115** cyanates the 3 position of the chelate ring to give intermediate **1116**, which undergoes further transformation to afford the final mixed benzotriazole-containing complex **1117**.

5. Formation of C=C by Reverse Michael Reaction

a. Preparation of α,β- and β,γ-Unsaturated Amides. As discussed in sections II.B.4.a and III.A.1, Michael addition of benzotriazole to *N*-methylmethacrylamides gives **162** (see Scheme 64), which undergoes lithiation and subsequent reactions with electrophiles affording compounds of type **228** (see Scheme 82). With E = alkyl, treatment of **228** with a base affords a mixture of the *E* and *Z* α,β-unsaturated amides **1118a**−**c**[151] (Scheme 345). With E = $PhCH_2$, the

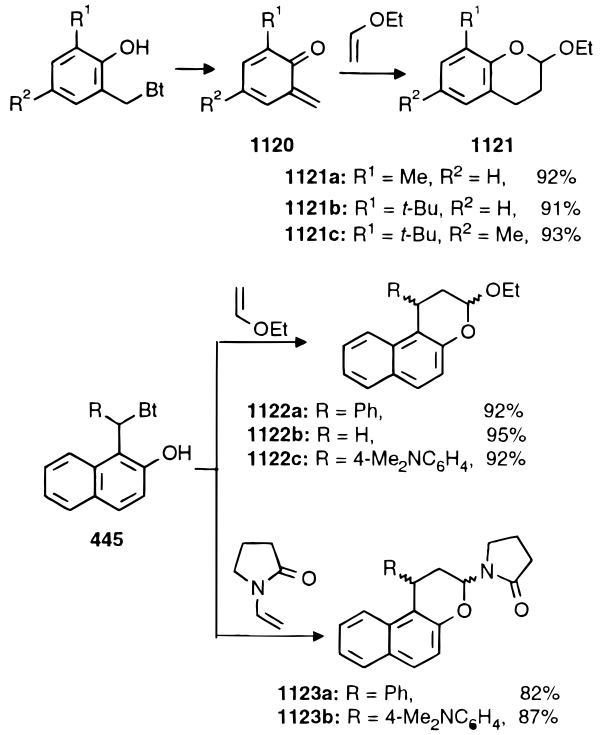
Scheme 345. Preparation of α,β- or β,γ-Unsaturated Amides



deprotonation occurs at the benzylic proton and as a result, the elimination of benzotriazole leads to the β,γ-unsaturated amide **1119**.

b. Formation and Trapping of o-Quinone Methides. The quinone methide intermediates **1120**, obtained by treatment of *o*-(benzotriazolylalkyl)phenols with base, can be trapped by dienophiles such as ethyl vinyl ether or 1-vinyl-2-pyrrolidinone affording chroman derivatives **1121**[383] (Scheme 346). Similar trans-

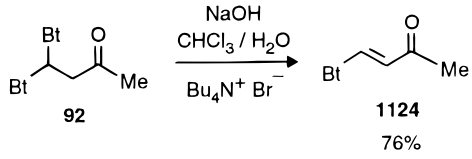
Scheme 346. Trapping *o*-Quinone Methide Intermediates



formations occur for naphthol analogues yield 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans **1122** and **1123** as mixtures of diastereomers.

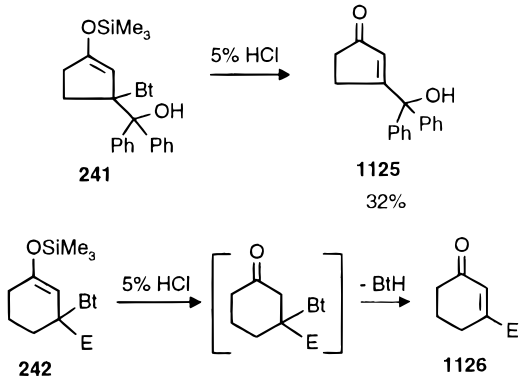
c. Preparation of Substituted α,β-Unsaturated Ketones and Aldehydes. On treatment with sodium hydroxide in two-phase $CHCl_3$/water system in the presence of a phase-transfer catalyst, 4,4-dibenzotriazol-1-yl-2-butanone **92** (for preparation, see section II.A.5) eliminates one molecule of benzotriazole stereospecifically to give (*E*)-β-benzotriazolylvinyl ketone **1124** in good yield (Scheme 347).[81]

Scheme 347. Preparation of β-Benzotriazolylvinyl Ketone

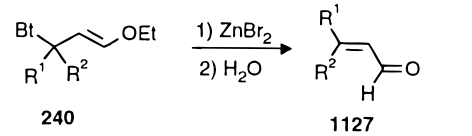


Treatment of 3-substituted 3-benzotriazol-1-yl-1-(trimethylsiloxy)cyclopentenes (**241**) and -cyclohexenes (**242**) with 5% aqueous hydrochloric acid affords the corresponding 3-substituted cyclopentenones **1125** and cyclohexenones **1126** via reverse Michael elimination of benzotriazole[152] (Scheme 348). The overall

Scheme 348. Preparation of 3-Substituted Cyclohexenones and Cyclopentenones



Scheme 349. Preparation of α,β-Unsaturated Aldehydes from Substituted 1-Ethoxy-3-benzotriazol-1-ylpropenes



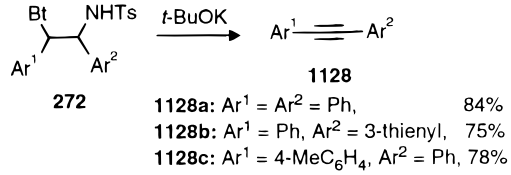
yields for this one-pot preparation are good to moderate.

Treatment of substituted *N*-(1-ethoxyallyl)benzotriazoles **240** with zinc bromide followed by water provides α,β-unsaturated aldehydes **1127a**−**e** (Scheme 349).[181]

6. Formation of Acetylenes

The benzotriazole adducts **272** (see Scheme 95, section III.A.3.a) on treatment with potassium *tert*-butoxide eliminate one molecule of tosylamide and one of benzotriazole to form diarylalkynes **1128**[191] (Scheme 350).

Scheme 350. Preparation of Diarylacetylenes



α-Benzotriazolyl-substituted ketones **1129** are converted into the corresponding tosylhydrazones **1130** in high yields. Hydrazones **1130** on treatment with excess of *n*-butyllithium undergo elimination of the tosyl group to form the intermediates **1131** which then quickly lose a molecule of nitrogen and benzotriazolyl anion to give the unsymmetrical acetylenes **1132** (Scheme 351, Table 134).[384] When R^1 is an *N*-linked pyrrole group (for preparation see Scheme 114, section III.A.6.a), an analogous elimination affords the *N*-alkyn-1-yl-substituted pyrrole in moderate yield (see Table 134). Interestingly, the presence of the good leaving group, phenoxy as the α position to benzotriazolyl moiety **1133** (for preparation, see section III.A.7) leads to initial elimination of phenoxide anion with formation, presumably, of carbene **1135** which couples with a molecule of the organolithium reagent. Subsequent elimination of the tosyl and benzotriazolyl groups then gives unsymmetrical acetylenes of type **1137** in moderate yields (Scheme 351, Table 134).

Scheme 351. Preparation of Acetylenes from Ketone Tosylhydrazones

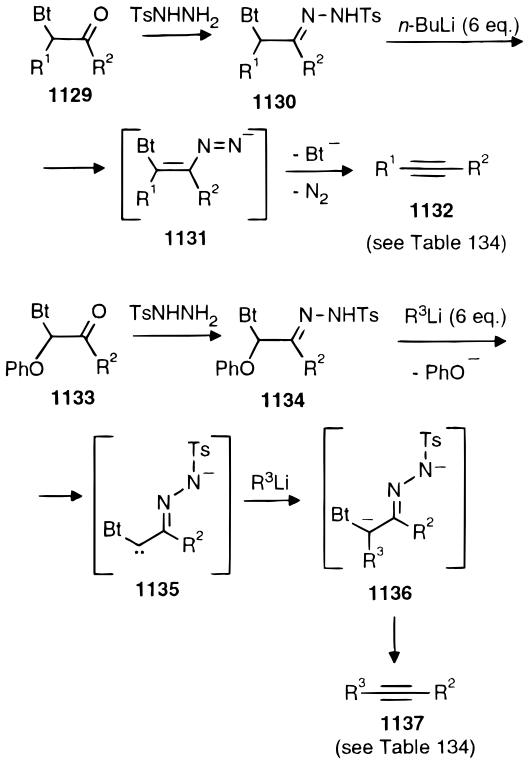


Table 134. Preparation of Acetylenes 1132 and 1137

compound	R^1	R^2	R^3	yield %
1132	H	*n*-C_5H_{11}		73
	H	*n*-C_8H_{17}		76
	H	*n*-C_9H_{19}		82
	Me	Ph		72
	Et	$PhCH_2$		18
	Ph	Ph		85
	pyrrol-1-yl	*n*-$C_{16}H_{33}$		42
1137		4-MeC_6H_4	*n*-Bu	63
		n-C_7H_{15}	Me	68
		n-C_7H_{15}	*n*-Bu	72
		n-C_7H_{15}	Ph	83

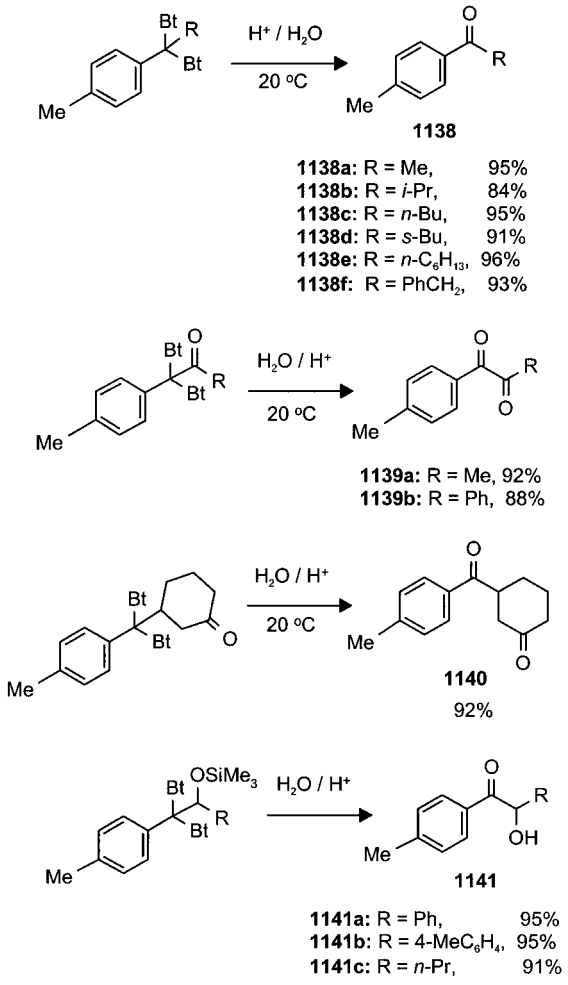
D. Removal by Hydrolysis To Give a C=O Bond

This type of reaction normally involves nucleophilic substitution to give an OH derivative followed by elimination to form the C=O bond.

1. gem-Di-Bt Derivatives

The two benzotriazole groups of (dibenzotriazolylmethyl)aryl derivatives are cleaved under mild acidic hydrolysis (Scheme 352) affording aromatic ketones

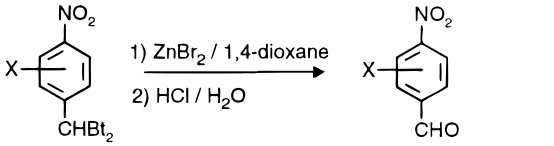
Scheme 352. Hydrolysis of *gem*-Dibenzotriazole Derivatives



1138, α-diketones **1139**, γ-diketone **1140**, and α-hydroxy ketones **1141**.[223] This method offers the advantages of milder conditions compared to methods using other acyl anion equivalents. However, hydrolysis of analogues of structure $RC(Bt)_2R^1$ with an alkyl group instead of an aryl was not successful. The aryl group is evidently needed to stabilize the intermediate cation formed.

p-(Dibenzotriazolylmethyl)nitroarenes **455**, prepared from the corresponding nitroarenes and tribenzotriazol-1-ylmethane (see section III.B.6), undergo mild hydrolysis with hydrochloric acid in the presence of zinc bromide to provide *p*-nitrophenylcarboxaldehydes **1142a**−**f** in high yields (Scheme 353).[259]

Scheme 353. Preparation of Aldehydes from *gem*-Dibenzotriazole Derivatives



455

1142a: X = H, 90%
1142b: X = 2-Ph, 92%
1142c: X = 2-NO_2, 69%*
1142d: X = 2-Br, 71%*
1142e: X = 3-F, 41%*
1142f: X = 2-Cl, 84%*

* Overall yields of aldehydes **1142** from nitroarenes and tris(benzotriazolyl)methane (see also Scheme 151)

2. Bt–C–Carbazole Derivatives

Unlike the *gem*-dibenzotriazole derivatives which require the presence of an aryl group, 9-(α-benzotriazolylalkyl)carbazoles (for preparation, see section III.A.6.a) undergo mild acidic hydrolysis for a much broader range of structural types to give aldehydes (Scheme 354, Table 135) or ketones (Scheme 355, Table 136).[218,219,221] The 9-carbazolyl group, a better electron donor than a benzotriazolyl group, facilitates the initial cleavage of the benzotriazolyl group to form the intermediates **1143** which hydrolyze to give aldehydes **1144**. The aldehydes are isolated in the form of 2,4-dinitrophenylhydrazones **1146**.

Scheme 354. Preparation of Aldehydes from 9-(Benzotriazolylmethyl)carbazoles

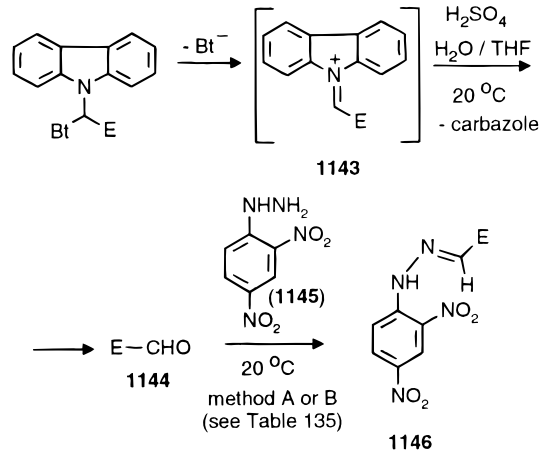


Table 135. Preparation of Aldehyde 2,4-Dinitrophenylhydrazones 1146

E	method[a]	yield %
n-Bu	B	83
$PhCH_2$	A	78
4-$BrC_6H_4CH_2$	B	81
n-C_8H_{17}	A	67
i-PrCH(OH)	B	76
t-BuCH(OH)	B	71
$Et_2C(OH)$	B	73
$(CH_2)_4C(OH)$	B	61
$(CH_2)_5C(OH)$	B	71
4-$MeC_6H_4CH(OH)$	B	42
PHNHC(O)	A	68
PhNHC(S)	B	70
Me_3Si	A	48
(*t*-Bu)Me_2Si	A	81
(*i*-Pr)$_3$Si	A	79
(*i*-Bu)$_3$Si	A	84
(*t*-Bu)Ph_2Si	A	61
Ph_3Si	A	58

[a] Method A: (i) H_2SO_4/H_2O/THF, 30 min; (ii) **1145**. Method B: (i) H_2SO_4/H_2O/THF, 24 h; (ii) **1145** in 10% $HClO_4$.

When two substituents are present at the benzotriazolyl α carbon, as in the compounds shown in Scheme 355, hydrolysis gives classes of various ketones. The following were thus obtained simple ketones **1147** (See Table 136), α-hydroxy ketones **1148a**,**b**, α-keto amides **1149a**,**b**, and γ-diketones **1150a**,**b**. This method was extended to the preparation of β-dialkylamino ketones[220] starting from 9-vinylcarbazole (Table 136).

Scheme 355. Preparation of Ketones from 9-(Benzotriazolylmethyl)carbazoles

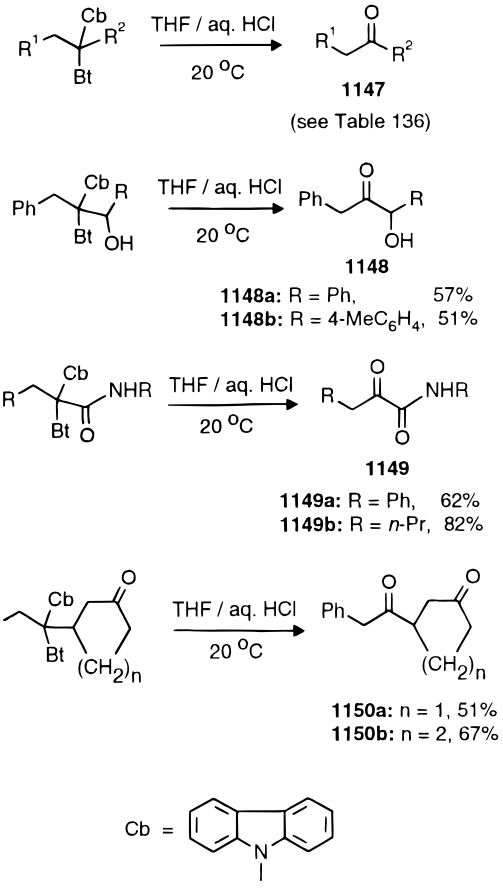


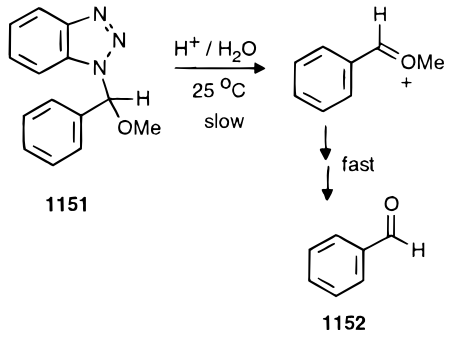
Table 136. Preparation of Ketones 1147

R^1	R^2	yield %
n-Pr	Me	86[219]
n-Pr	*n*-Bu	89[219]
Ph	Me	77[219]
Ph	*n*-Bu	82[219]
Ph	$PhCH_2$	63[219]
$(CH_2)_5NCH_2CH_2$	$PhCH_2$	69[220]
$(CH_2)_5NCH_2CH_2$	*n*-C_8H_{17}	71[220]
$O(CH_2CH_2)_2NCH_2CH_2$	*n*-C_6H_{13}	86[220]
$O(CH_2CH_2)_2NCH_2CH_2$	$PhCH_2$	78[220]
$O(CH_2CH_2)_2NCH_2CH_2$	4-$MeC_6H_4CH_2$	74[220]
$O(CH_2CH_2)_2NCH_2CH_2$	*n*-C_8H_{17}	82[220]
$O(CH_2CH_2)_2NCH_2CH_2$	c-$C_6H_{11}CH(OH)$	57[220]
$O(CH_2CH_2)_2NCH_2CH_2$	PhCH(OH)	61[220]
$O(CH_2CH_2)_2NCH_2CH_2$	4-$MeC_6H_4CH(OH)$	68[220]

3. Bt–C–OR Derivatives

α-Functionalized benzotriazol-1-ylmethoxymethanes undergo hydrolysis under rather mild acidic conditions to give the corresponding carbonyl compounds. The mechanism is similar to that proposed for the hydrolysis of (benzotriazol-1-yl)(carbazol-9-yl)methanes.[218] Further detailed studies of the hydrolysis of α-benzotriazol-1-yl-α-methoxytoluene **1151** → **1152** have shown that the reaction is of pseudo-first orderwith the rate-determining step being the elimination of the benzotriazolyl group[385] (Scheme 356).

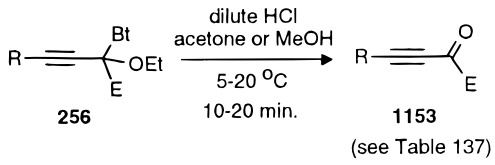
Scheme 356. Hydrolysis of α-Substituted (Benzotriazol-1-yl)methoxymethane



Due to the diverse preparatiove routes for this type of compound, their hydrolysis has made easily accessible a wide range of highly functionalized ketones and esters to be.

1-(α-Ethoxy-α-substituted propargyl)benzotriazoles **256** are easily hydrolyzed under acidic conditions to form acetylenic ketones **1153** (Scheme 357, Table

Scheme 357. Preparation of Acetylenic Ketones



E = alkyl, α-hydroxyalkyl, α-aminoalkyl,

RCO, CO_2Et, CONHR, SiR_3

137).[79] The hydrolysis is further facilitated by the stabilization of the acetylenic cation by the triple bond. This method forms that of choice for the

Table 137. Preparation of Acetylenic Ketones 1153

R	E	yield %
H	*n*-C_7H_{15}	92
H	*n*-C_8H_{17}	94
n-C_6H_{13}	Et	92
n-C_6H_{13}	PhCH(OH)	98
n-C_6H_{13}	$SiMe_3$	88
Ph	Et	90
Ph	3-MeBu	93
Ph	$PhCH_2$	86
Ph	*n*-$C_{16}H_{33}$	88
Ph	4-$MeC_6H_4CH(OH)$	84
Ph	4-$MeC_6H_4CHNH(4'-C_6H_4)$	90
Ph	MeCO	92
Ph	$Ph_2C(OH)$	98
Ph	$Me_2C(OH)$	100
Ph	EtOC(O)	90
Ph	*t*-BuNHC(O)	99
c-$C_6H_{10}(OH)$	PhNHCH(Ph)	98
PhCH(OH)	4-$MeC_6H_4CH(OH)$	98
4-$MeC_6H_4CH(OH)$	*n*-C_8H_{17}	99

preparation of α-hyrdroxy- and α-aminoacetylenic ketones, acetylenic α-diketones, acetylenic keto acids and amides, and silyl alkynyl ketones (for example, see Table 137).

α-Substituted *N*-(α-ethoxyallyl)benzotriazoles are hydrolyzed at ambient temperature (Scheme 358) by treatment with $H_2C_2O_4/SiO_2/H_2O$[27,28] or with dilute HCl[118] enabling convenient syntheses of a variety of functionalized vinyl ketones including simple (**1154**), α-hydroxy (**1155**), γ-keto (**1156** and **1157**), and γ-alkoxycarbonyl (**1158**) vinyl ketones (Scheme 358, Table 138).

Scheme 358. Preparation of α,β-Unsaturated Ketones from *N*-(α-Ethoxyallyl)benzotriazoles

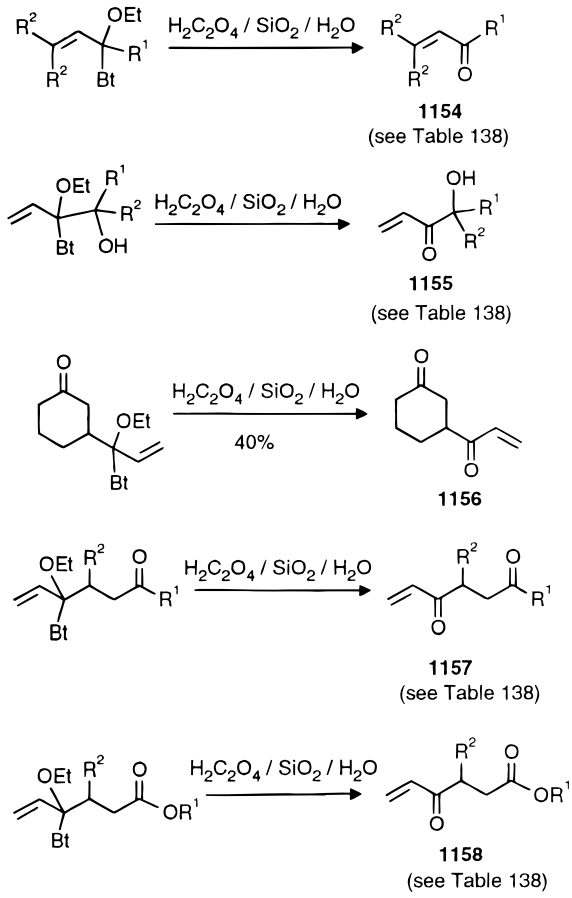


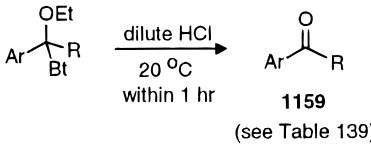
Table 138. Hydrolysis of *N*-(α-Ethoxyallyl)benzotriazoles To Give Vinyl Ketones 1154, 1155, 1157, and 1158

compound	R^1	R^2	yield %
1154	*n*-C_5H_{11}	*n*-Bu	50[181]
	c-C_6H_{11}	H	48[77]
	n-C_7H_{15}	H	64[77]
	$PhCH_2CH_2$	H	71[77]
	n-$C_{12}H_{25}$	H	66[77]
	n-$C_{16}H_{33}$	H	69[77]
	$Me_2Si(n\text{-}C_8H_{17})$	*n*-Bu	66[181]
1155	$-(CH_2)_5-$		81[78]
	Ph	Me	48[78]
	4-ClC_6H_4	H	43[77]
	4-MeC_6H_4	H	70[77]
	4-$MeOC_6H_4$	H	61[77]
	$PhCH_2$	H	30[77]
1157	Me	H	62[77]
	Et	Me	44[77]
1158	Et	H	63[77]
	Me	Me	70[77]

Among the few exceptions to this behavior are cyclic compounds **263** and **264**, obtained from 3-substituted 1-propargylbenzotriazoles (see Scheme 94, section III.A.2.d) which could not be hydrolyzed by dilute acid.[79]

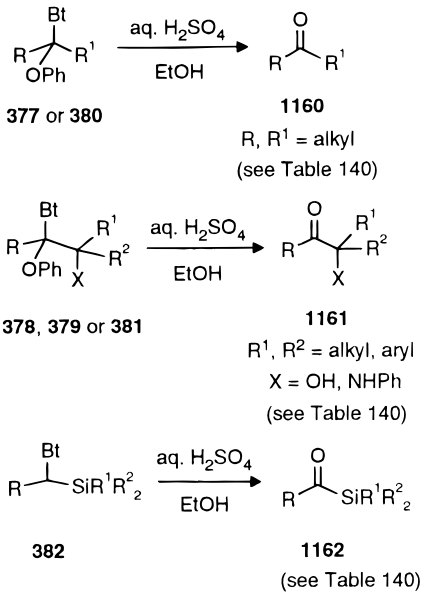
Substituted α-benzotriazol-1-yl-α-arylalkyl ethyl ethers undergo even more facile hydrolysis: the reaction is generally effected with dilute hydrochloric acid at room temperature within 1 h and affords the corresponding aromatic ketones **1159** in good to excellent yields (Scheme 359, Table 139).[80,188] This sequence provides an efficient conversion of aldehydes to aromatic ketones and aryl- and heteroarylacylsilanes.

Scheme 359. Hydrolysis of α-Benzotriazol-1-yl-α-aryl Alkyl Ethyl Ethers



1159
(see Table 139)

Scheme 360. Preparation of Ketones and Functionalized Ketones by Hydrolysis of α-Benzotriazolyl-α-phenoxyalkanes



377 or **380**

1160
R, R^1 = alkyl
(see Table 140)

378, **379** or **381**

1161
R^1, R^2 = alkyl, aryl
X = OH, NHPh
(see Table 140)

382

1162
(see Table 140)

Table 139. Hydrolysis of α-(Benzotriazol-1-yl)arylmethyl Ethyl Ethers. Preparation of Aromatic Ketones 1159

Ar	R	yield %
Ph	Et	94
Ph	4-$MeC_6H_4CH(OH)$	57
Ph	Me_3Si	80
Ph	$Me_2(n\text{-}C_8H_{17})Si$	90
2-ClC_6H_4	3-MeBu	84
2-ClC_6H_4	Me_3Si	97
2-ClC_6H_4	$Me_2(n\text{-}C_8H_{17})Si$	96
4-MeC_6H_4	$CH_2{=}CHCH_2$	65
4-MeC_6H_4	Me_3Si	81
4-MeC_6H_4	$Me_2(n\text{-}C_8H_{17})Si$	81
2-$MeOC_6H_4$	*n*-Bu	80
2-$MeOC_6H_4$	Me_3Si	82
2-$MeOC_6H_4$	$Me_2(n\text{-}C_8H_{17})Si$	84
3-$MeOC_6H_4$	*n*-C_8H_{17}	80
2-furyl	$CH_2{=}CHCH_2$	90
2-furyl	*n*-Bu	94
2-furyl	$Br(CH_2)_3$	71
2-furyl	$Br(CH_2)_4$	95
2-furyl	*n*-C_8H_{17}	96
2-furyl	*i*-PrCH(OH)	67
2-furyl	PhCH(OH)	55
2-furyl	4-$MeC_6H_4CH(OH)$	60
2-furyl	Me_3Si	75
2-furyl	$Me_2(n\text{-}C_8H_{17})Si$	89
3-furyl	*n*-Bu	84
3-furyl	3-MeBu	99
2-thiophenyl	*n*-C_8H_{17}	90
2-thiophenyl	PhCH(OH)	93
2-thiophenyl	Me_3Si	76
2-thiophenyl	$Me_2(n\text{-}C_8H_{17})Si$	57
3-thiophenyl	Et	82
3-thiophenyl	*n*-Bu	84
2-pyridyl	*n*-C_8H_{17}	75
1-naphthyl	*i*-PrCH(OH)	82
1-naphthyl	Me_3Si	86
1-naphthyl	$Me_2(n\text{-}C_8H_{17})Si$	86

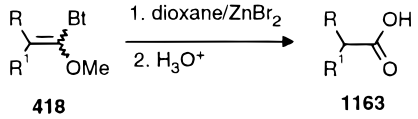
Table 140. Hydrolysis of α-Benzotriazolyl-α-phenoxyalkanes. Preparation of Ketones and Functionalized Ketones

compound	R	R^1	R^2	X	yield %
1160	*n*-$C_{11}H_{23}$	Et			88
	n-$C_{11}H_{23}$	*n*-Bu			90
	n-C_5H_{11}	*n*-C_8H_{17}			81
	n-C_5H_{11}	$Ph(CH_3)_3$			80
1161	C_5H_{11}	Ph		OH	65
	C_5H_{11}	4-$CH_3C_6H_4$		OH	76
	C_5H_{19}	Ph	Ph	OH	76
	$C_{11}H_{23}$	Ph	H	NHPh	74
1162	$PhCH_2$	Me	Me		84
	C_8H_{17}	Me	Me		82
	C_7H_{15}	Ph	Me		96
	Et	Ph	Me		85
	Et	C_8H_{17}	Me		71
	C_8H_{17}	*t*-Bu	Me		56
	Et	*i*-Pr	*i*-Pr		46

Compared to α-benzotriazolyl-α-arylalkyl ethyl ethers, hydrolysis of α-benzotriazolylalkyl ethers is more difficult. Nevertheless, the hydrolysis of the phenyl ethers **377**−**382**[237] proceeds smoothly with 5% H_2SO_4 in aqueous ethanol to produce the corresponding simple ketones **1160**, α-hydroxy and α-amino ketones **1161** and acylsilanes **1162** in high yields (Scheme 360, Table 140).

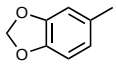
1-Benzotriazolyl-1-methoxyalkenes **418** (R^1 = OMe) are hydrolyzed easily with aqueous HCl in the presence of zinc bromide affording the corresponding

Scheme 361. Preparation of Carboxylic Acids



418 1163

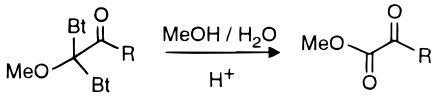
Table 141. Preparation of Carboxylic Acids

R	R^1	yield %
Me	Ph	80
Et	Ph	55
Me	4-$MeOC_6H_4$	53
Ph	4-BrC_6H_4	43
	$-C_5H_{10}-$	55
H		57
H	4-(n-$C_7H_{13}O$)C_6H_4	45
H	4-PhC_6H_4	45
H	4-MeC_6H_4	56
H	α-$C_{10}H_7$	57
H	Ph(Me)CH	54

carboxylic acids **1163** (Scheme 361, Table 141) in good yields. Although **418** (R^1 = OMe) are isolable and moderately stable, generally, they are subjected to hydrolysis directly once formed from 1-[1-methoxy-1-(trimethylsilyl)methyl]benzotriazoles **416** (R^1 = OMe) (see Scheme 135, section III.A.10) providing a one-pot transformation of aldehydes and ketones into one carbon homologated carboxylic.[246a]

Treatment of α,α-dibenzotriazol-1-yl-α-methoxy ketones **1164** with Amberlite H^+ ion exchange resin in aqueous methanol affords the corresponding α-keto esters **1165a**−**f** in excellent yields[239] (Scheme 362).

Scheme 362. Preparation of α-Keto Esters



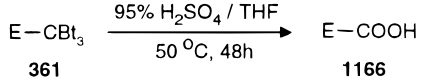
1164 1165

1165a: R = *t*-Bu, 88%
1165b: R = Ph, 87%
1165c: R = 4-ClC_6H_4, 79%
1165d: R = 2-MeC_6H_4, 92%
1165e: R = 4-$MeOC_6H_4$, 81%
1165f: R = 2-naphthyl, 81%

4. Bt_3C Derivatives

The hydrolysis of tribenzotriazolylmethanes requires somewhat stronger conditions (heating with stronger H_2SO_4 at 50 °C for 48 h) compared to that of the dibenzotriazolylaryl and of (benzotriazolyl)-(carbazolyl) derivatives. Nevertheless, compounds of type **361** hydrolyze yielding the corresponding carboxylic acids **1166**.[225] Simple as well as α-keto, α-hydroxy, and other α-functionalized carboxylic acids are thus prepared including compounds of type RNHC(S)COOH which were previously unknown (Scheme 363, Table 142).

Scheme 363. Preparation of Carboxylic Acids



361 1166

(see Table 142)

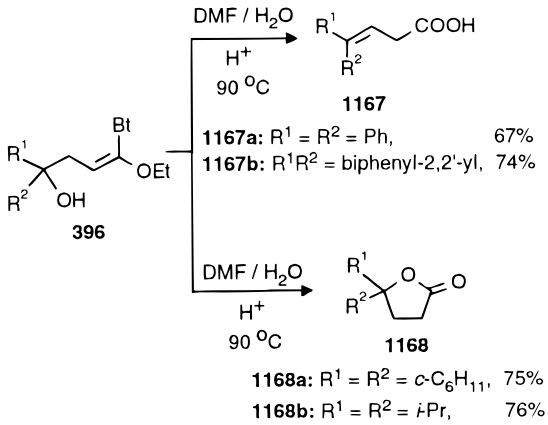
Table 142. Preparation of Carboxylic Acids 1166

E	yield %	E	yield %
n-Bu	79	PhCO	81
$PhCH_2$	92	4-MeC_6H_4CO	83
$PhCH{=}CHCH_2$	73	PhNHCS	82
PhCH(OH)	78	$PhCH_2NHCS$	74
4-$MeC_6H_4CH(OH)$	76	1-naphthyl-NHCS	87

5. Electron-Rich Vinylbenzotriazoles

1-(Ethoxyvinyl)benzotriazoles of type **396** (for preparation see Scheme 128, section III.A.7) are hydrolyzed in aqueous DMF to yield either β,γ-unsaturated carboxylic acids **1167a**,**b** (when R^1 and R^2 are aryl) or γ-lactones **1168a**,**b** (when R^1 and R^2 are alkyl) via hydrolysis and subsequent cyclization (Scheme 364).[78]

Scheme 364. Preparation of β,γ-Unsaturated Carboxylic Acids



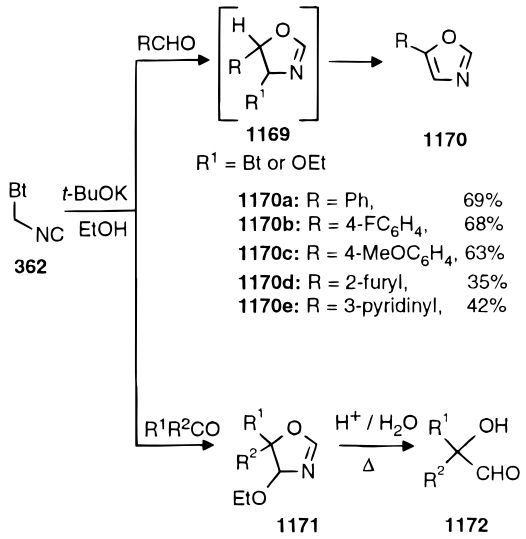
E. Removal by Cyclization

Benzotriazol-1-ylmethyl isocyanide (Betmic, **362**) reacts under mild conditions with aldehydes and ketones in THF/ethanol in the presence of potassium *tert*-butoxide to afford the cyclized products. In the reactions with aldehydes the benzotriazole group is eliminated from intermediates **1169** during the reaction[127] to form the oxazoles **1170** (Scheme 365). With ketones, the benzotriazole group is displaced by an ethoxy group to form **1171**, as elimination is not possible. Hydrolysis of **1171**[386] affords synthetically useful α-hydroxy aldehydes **1172**.

Betmic and its α-substituted derivatives undergo similar 1,3-dipolar cycloadditions with imines and electron-deficient alkenes in the presence of potassium *tert*-butoxide to give corresponding benzotriazolyl-containing cyclic adducts, which under the reaction conditions eliminate benzotriazole to afford imidazoles **1173** and pyrroles **1174**, respectively (Scheme 366, Table 143).[226] For cyclizations with diaryl aldimines without electron-withdrawing groups and with acrylonitrile derivatives, Betmic is superior to Tosmic (*p*-tosylmethyl isocyanide), providing much better yields of the corresponding imidazoles and pyrroles.

Upon treatment with *n*-butyllithium, *N*-(benzotriazolylalkyl) imines **1175** generate 1,3-dipoles **1176** which react stereoselectively with a number of dipolarophiles to give, after benzotriazole elimination, the

Scheme 365. Preparation of Oxazoles, Oxazolines, and α-Hydroxy Aldehydes



Scheme 366. Preparation of Imidazoles and Pyrroles

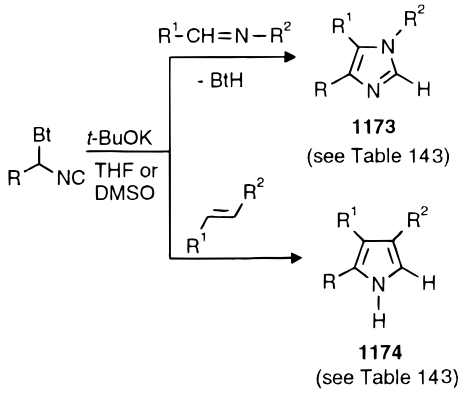
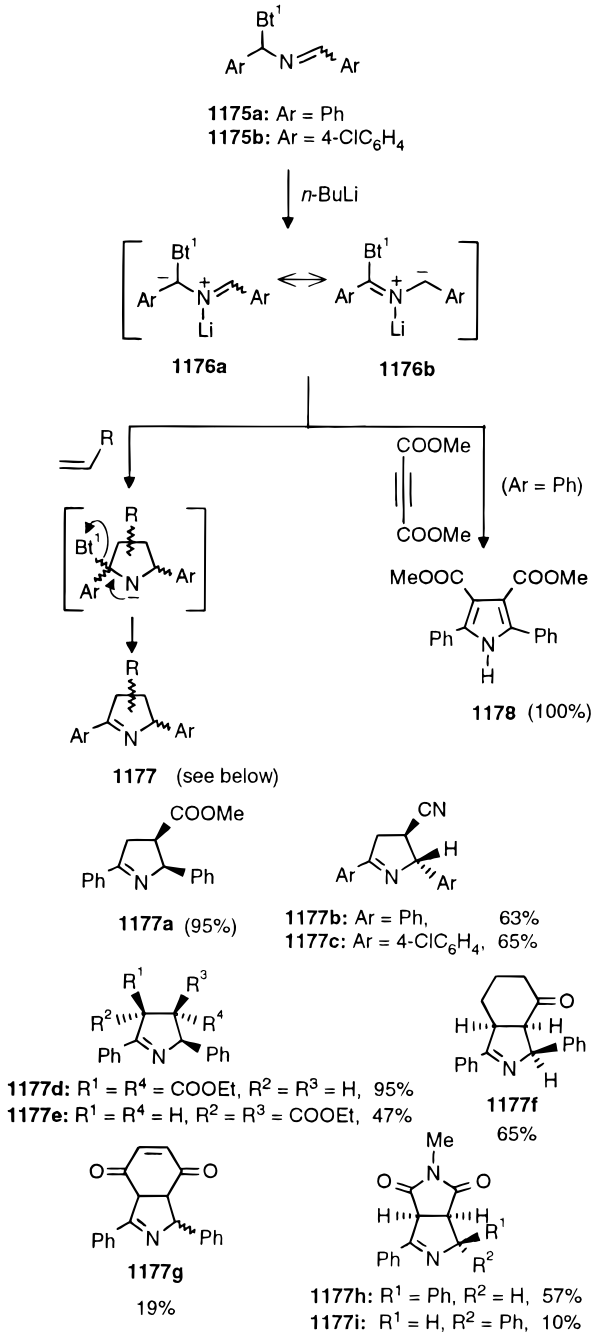


Table 143. Preparation of Imidazoles 1173 and Pyrroles 1174

compound	R	R^1	R^2	yield %
1173	H	Ph	Me	10
	H	Ph	Ph	85
	Me	Ph	Ph	67
	Ph	Ph	Ph	23
	$PhCH_2$	Ph	Me	0
	$PhCH_2$	4-$MeOC_6H_4$	Ph	73
1174	H	H	COMe	0
	H	H	COOMe	45
	H	H	CN	63
	H	Me	CN	92
	H	Ph	COOMe	40
	H	Ph	CN	81
	Me	H	COOMe	30

corresponding pyrrolines **1177a**−**i** or pyrrole **1178** (Scheme 367).[387]

Scheme 367. Preparation of Pyrrolines and Pyrroles

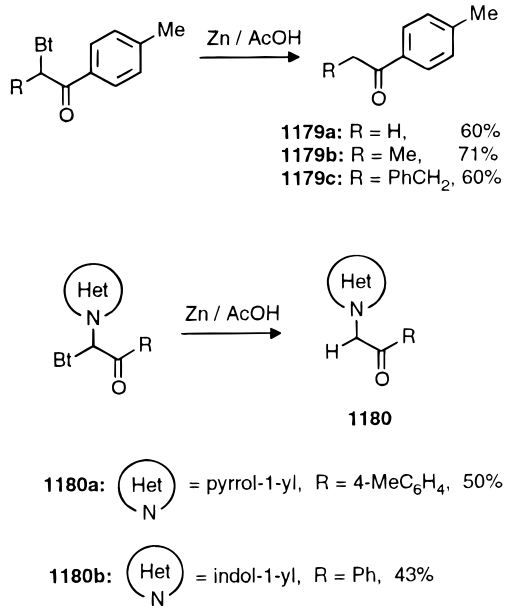


F. Removal by Reduction

N-(α-Ketoalkyl)benzotriazoles lose the benzotriazole group on zinc/AcOH reduction[189,216] (Scheme 368). Simple as well as heterocyclic alkyl ketones are obtained by contrast, treatment of *N*-(α-ketoalkyl)benzotriazoles with sodium borohydride in ethanol[216] or with palladium on carbon or ammonium formate[189] leads to the reduction of the carbonyl group to hydroxy group while the benzotriazole moiety is left intact.

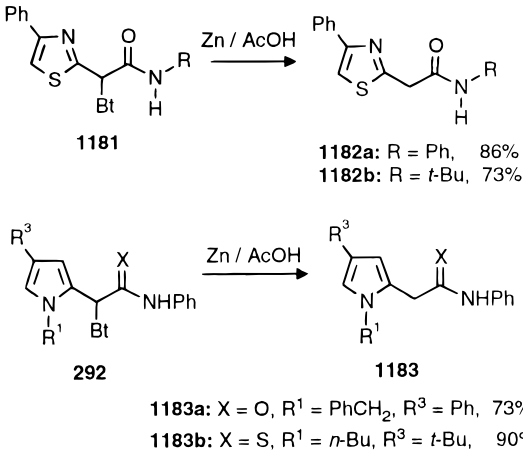
This reaction has been extended to α-benzotriazolyl substituted amides and thioamides, as exemplified by the reduction of benzotriazole derivatives of thiazole **1181**[207] and pyrrole **292**[184] to the corresponding

Scheme 368. Reductive Elimination of Benzotriazole



amides **1182** and **1183a**, and thioamide **1183b**, respectively (Scheme 369).

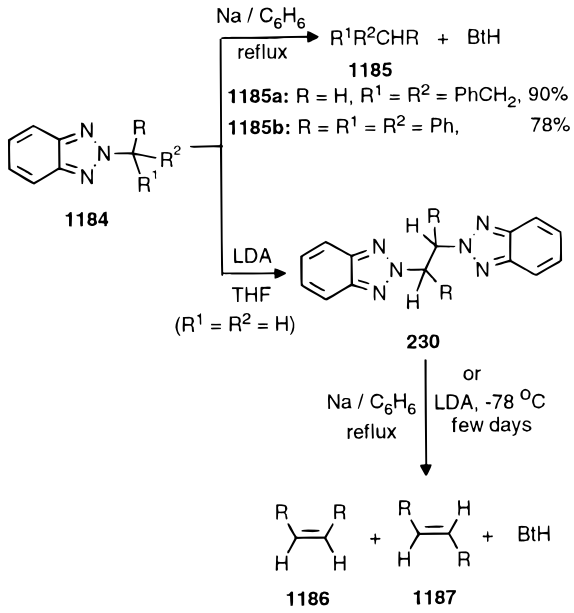
Scheme 369. Reduction of α-Benzotriazolyl-Substituted Amides



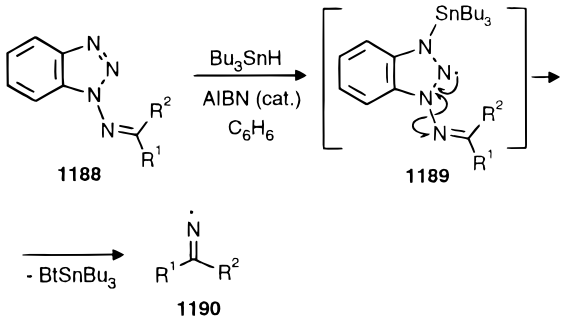
2-Alkylbenzotriazoles **1184** are readily reduced to the corresponding alkanes **1185** in high yields by treatment with excess of sodium metal in benzene (Scheme 370).[177] Under similar conditions, the dimers **230** (for preparation, see section III.A.1) produce mixtures of (*Z*)- (**1186**) and (*E*)- (**1187**) olefins, with the *E* isomers predominant. The elimination of benzotriazole is also observed when the solutions of **230** are kept in the presence of LDA at low temperature for a prolonged time; however, in this case the formation of (*Z*)-alkenes **1186** is favored.

Tributylstannyl radical *n*-$Bu_3Sn^•$, generated *in situ* from Bu_3SnH, reacts smoothly with *N*-benzotriazolylimines **1188** to generate the corresponding iminyl radicals **1190** (Scheme 371), a new class of interesting intermediates in synthetic radical chemistry, which can be trapped with formation of Δ^1-pyrrolines or various substituted nitriles.[388] The mechanism of

Scheme 370. Reduction of 2-Alkylbenzotriazoles and the Dimers 230 with Sodium Metal or LDA



Scheme 371. Generation of Iminyl Radicals from 1-Benzotriazolylimines



this reaction involves the initial attack of $Bu_3Sn^•$ on the N-3 atom of the benzotriazole ring to give the intermediate **1189** with subsequent elimination of 1-(tributylstannyl)benzotriazole.

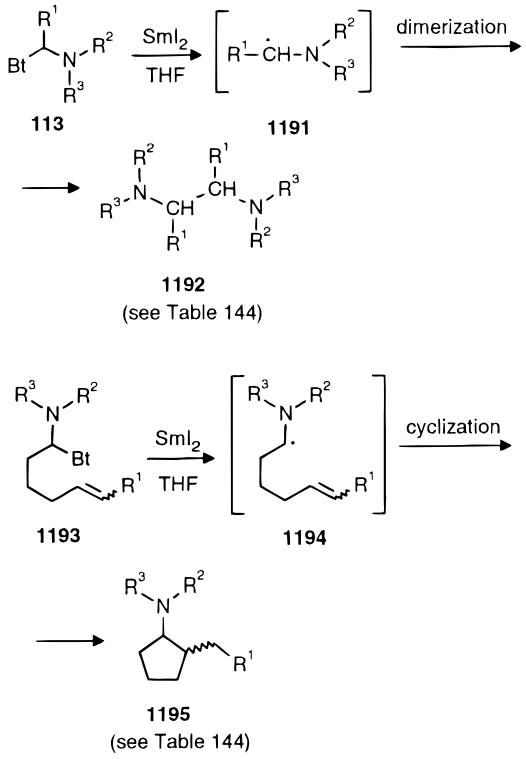
One-electron reducing agent SmI_2 causes the smooth elimination of benzotriazolyl radical Bt$^•$ from a wide variety of *N*-[(*N*,*N*-dialkylamino)alkyl]benzotriazoles **113** with the generation of α-amino radicals **1191**, which under the reaction conditions dimerize to give the corresponding vicinal diamines **1192** (Scheme 372) as mixtures of diastereomers in high yields (Table 144).[389] This procedure is successful for the benzotriazole adducts derived from formaldehyde and aliphatic and aromatic aldehydes. However, adducts derived from ketones failed to give any diamine products. When a benzotriazole adduct, such as **113**, contains in an appropriate position a double bond activated by alkoxycarbonyl or cyano groups, the resulting radical **1194** undergoes intramolecular addition to this double bond to form *N*-cycloalkylamines **1195** (Scheme 372, Table 144).[390] Activation of the multiple bond by a phenyl group is insufficient and adducts **1193** (R^1 = Ph) give only dimerization products of type **1192**.

Table 144. Preparation of Vicinal Diamines 1192 and *N*-Cyclopentylamines 1195

compound	R^1	R^2	R^3	yield %
1192	H	$-(CH_2)_4-$		82
	H	$PhCH_2$	$PhCH_2$	55
	n-Pr	$-(CH_2)_4-$		85
	i-Pr	$-(CH_2)_4-$		87
	i-Pr	$-(CH_2)_2O(CH_2)_2-$		61
	Ph	$-(CH_2)_4-$		75
	Ph	$PhCH_2$	$PhCH_2$	80
	2-$(PhCH{=}CHCH_2O)C_6H_4$	$-(CH_2)_2O(CH_2)_2-$		70
1195	CN	$-(CH_2)_2O(CH_2)_2-$		60
	CN	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	65
	CN	$PhCH_2$	$PhCH_2$	63
	trans-COOEt	$-(CH_2)_4-$		70[a]
	trans-COOEt	$-(CH_2)_2O(CH_2)_2-$		58[a]
	trans-COOEt	$PhCH_2$	$PhCH_2$	39

[a] Exclusively *cis* isomer obtained.

Scheme 372. Reductive Elimination of Benzotriazolyl Group from [(*N*,*N*-Dialkylamino)-alkyl]benzotriazoles



G. Elimination Followed by Rearrangement: A Novel Carbon Insertion

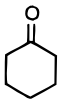
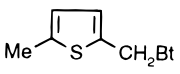
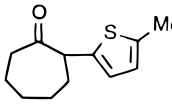
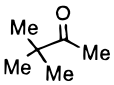
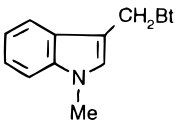
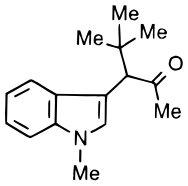
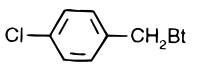
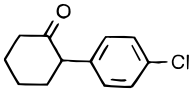
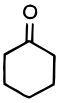
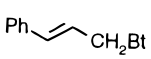
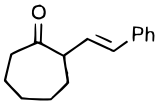
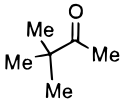
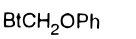
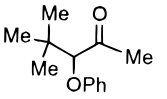
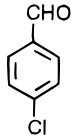
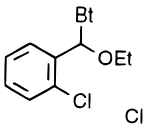
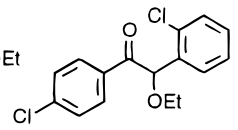
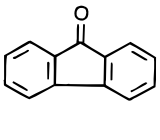
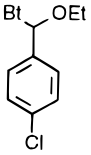
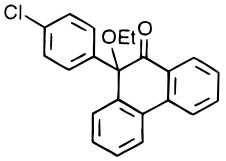
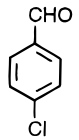
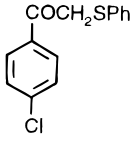
The ability of benzotriazole to stabilize an α carbanion and to function as a leaving group has led to a general carbon insertion route to one carbon homologated α-aryl, α-heteroaryl, α-alkenyl, α-alkoxy-, and α-(phenylthio)alkyl ketones (Scheme 373, Table 145).[391−393] The role of a Lewis acid, such as zinc bromide, is vital as the initial adducts **1197** are resistant to thermal rearrangement in its absence. The regioselectivity is in accordance with the general pattern of the reactions of this type where the group which can best stabilize an electron deficiency in the transition state migrates, for example, H > Ar > alkyl; *tert*-alkyl > *sec*-alkyl > *n*-alkyl. Generally the ketones **1200** are obtained as single regioisomers. In a few cases (see Table 145), mixtures of two regioisomers are formed with one isomer strongly predominating.[392,393] The reaction temperatures needed for rearrangement vary with the nature of the R

Table 145. Preparation of Ketones 1200 by Carbon Insertion

X	R	R^1	R^2	yield %
MeO	H	H	Ph	82[392]
MeO	H	H	$PhCH_2CH_2$	50[391]
MeO	H	Ph	Me	60[392]
MeO	H	Ph	Ph	62[392]
MeO	H	Ph	4-Py	78[392]
EtO	2-ClC_6H_4	H	4-ClC_6H_4	91[391]
EtO	4-ClC_6H_4	−2-C_6H_4-C_6H_4-2−		51[391]
PhO	H	*t*-Bu	Me	47[391]
PhO	H	Ph	Ph	53[392]
PhO	*n*-C_5H_{11}	H	4-MeC_6H_4	81[392]
MeS	H	H	Ph	84[392]
MeS	H	$PhCH_2$	Ph	80[a,392]
PhS	H	H	Ph	70[392]
PhS	H	H	4-ClC_6H_4	86[392]
PhS	H	H	$PhCH_2CH_2$	65[392]
PhS	H	Ph	Me	65[391]
PhS	H	Ph	Ph	78[392]
PhS	Me	H	Ph	84[392]
PhS	Ph	H	Ph	56[392]
4-ClC_6H_4	H	$-(CH_2)_4-$		85[393]
4-MeC_6H_4	H	H	$PhCH_2CH_2$	65[391]
4-MeC_6H_4	H	Ph	Me	32[393]
4-$MeOC_6H_4$	H	*t*-Bu	Me	63[393]
4-$MeOC_6H_4$	H	$-(CH_2)_5-$		40[393]
4-$MeOC_6H_4$	H	Ph	Me	79[393]
4-$MeOC_6H_4$	H	Ph	4-$CF_3C_6H_4$	35[393]
4-$Me_2NC_6H_4$	H	H	$PhCH_2CH_2$	63[393]
4-$Me_2NC_6H_4$	H	H	*t*-Bu	76[393]
4-$Me_2NC_6H_4$	H	H	Ph	40[393]
4-$Me_2NC_6H_4$	H	$-(CH_2)_5-$		40[393]
trans-PhCH=CH	H	$-(CH_2)_5-$		60[391]
5-methyl-thien-2-yl	H	H	$PhCH_2CH_2$	76[393]
5-methyl-thien-2-yl	H	Ph	Me	90[393]
5-methyl-thien-2-yl	H	$-(CH_2)_5-$		66[393]
5-methyl-thien-2-yl	H	$-(CH_2)_3CH(Me)-$		67[393]
5-methyl-thien-2-yl	H	$-(CH_2)_4CH(Me)-$		82[a,393]
1-methyl-indol-3-yl	H	H	4-ClC_6H_4	70[393]
1-methyl-indol-3-yl	H	*t*-Bu	Me	87[391]
1-methyl-indol-3-yl	H	$-(CH_2)_5-$		76[393]
1-methyl-indol-3-yl	H	$-(CH_2)_3CH(Me)-$		85[393]
1-methyl-indol-3-yl	H	$-(CH_2)_4CH(Me)-$		84[a,393]
carbazol-9-yl	H	H	Ph	70[392]
carbazol-9-yl	H	H	4-ClC_6H_4	73[392]
carbazol-9-yl	H	Ph	Me	36[392]
carbazol-9-yl	Me	H	Ph	56[392]

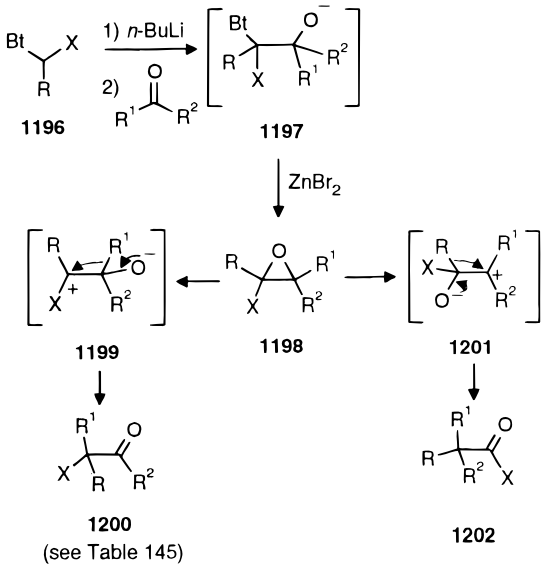
[a] Obtained as a mixture of regioisomers.

Chart 6. Selected Examples of Carbon Insertion into Aldehydes and Ketones

Carbonyl Compound	Bt-reagent **1196**	Product **1200**	Yield %
			67
			87
			88
			60
			47
$PhCH_2CH_2CHO$	$BtCH_2OPh$	$Ph(CH_2)_2COCH_2OMe$	50
			91
			51
	$BtCH_2SPh$		86
$PhC(O)Me$	$BtCH_2SPh$	$PhCH(SPh)COMe$	65

group: substrates with R = aryl or alkyl, which provide better stabilization of the ionic intermediate, rearrange in refluxing THF, whereas for compounds with R = H the reflux in 1,1,2,2-tetrachloroethane is required.[392] The reaction with cyclic ketones leads to the formation of ring expansion products (for example, see Chart 6). Interestingly, when **1196** (X = MeO, R = H) reacts with 1-indanone or cinnamaldehyde, no expected methoxymethylene insertion products were obtained, but the corresponding one carbon homologated esters **1202** were isolated in moderate yields. The formation of these esters can be accounted for abnormal direction of the ring opening of the intermediate oxirane **1198** with subsequent migration of the R group (Scheme 373). The initial formation of **1198** was confirmed by isolation

Scheme 373. Carbon Insertion into Aldehydes and Ketones

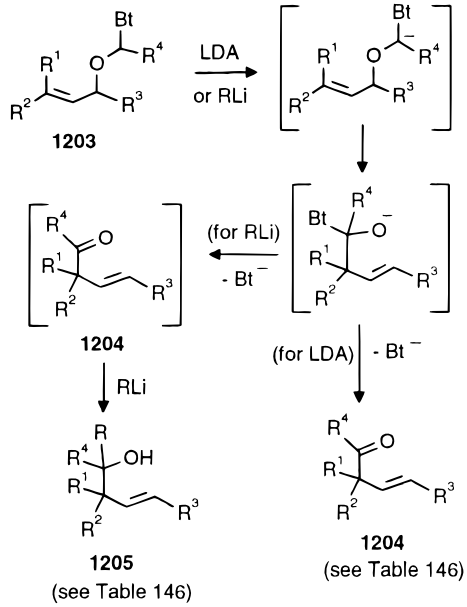


of the corresponding epoxides in the reactions of cyclohexanone with **1196** (X = OMe, OPh).[392]

H. [2,3]-Wittig Rearrangement Followed by Elimination

Readily accessible allyl 1-(benzotriazol-1-yl)alkyl ethers **1203** (for preparation, see sections II.B.1.b and III.B.2) upon treatment with 2.5 equiv of alkyl- or aryllithium reagents give in excellent yields secondary and tertiary homoallyl alcohols **1205**, exclusively

Scheme 374. Preparation of Homoallyl Alcohols and β,γ-Unsaturated Ketones



in the *E* configuration (Scheme 374, Table 146).[93] The mechanism involves deprotonation followed by [2,3]-Wittig rearrangement, elimination of the benzotriazolyl group, and then nucleophilic addition of organolithium to the carbonyl compound formed. Treatment of allyl ethers **1203** with nonnucleophilic LDA results in formation of β,γ-unsaturated ketones **1204**.

Table 146. Preparation of β,γ-Unsaturated Ketones 1204 and Homoallyl Alcohols 1205

compound	R^1	R^2	R^3	R^4	R	yield %
1204	H	H	Et	4-MeC_6H_4		89
	H	H	*n*-C_5H_{11}	Ph		92
	Me	Me	H	Ph		91
	Me	Me	H	4-MeC_6H_4		86
1205	H	H	Et	H	Ph	85
	H	H	*n*-C_5H_{11}	H	Me	86
	H	H	*n*-C_5H_{11}	H	*n*-Bu	84
	H	H	*n*-C_5H_{11}	H	Ph	84
	H	H	*n*-C_5H_{11}	Ph	Ph	86
	H	Ph	H	H	Me	81
	H	Ph	H	Ph	*n*-Bu	83
	Me	Me	H	H	*n*-Bu	87
	Me	Me	H	Ph	Ph	72
	Me	Me	H	4-MeC_6H_4	*n*-Bu	89

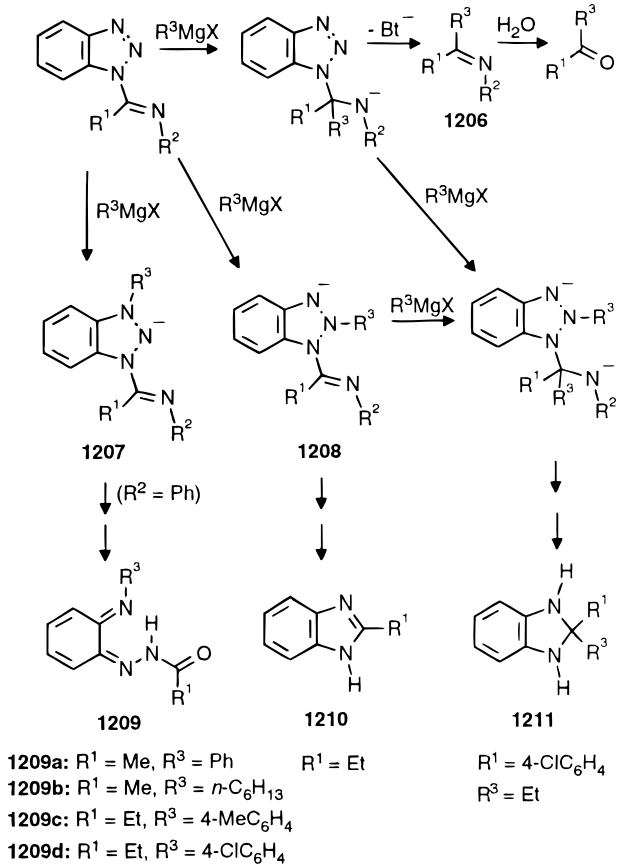
V. Reactions Involving Cleavage of the Bt Ring

In nearly all the reactions of *N*-substituted benzotriazoles, the benzotriazole ring emerges unchanged at the end of the reaction sequence. However, exceptions to this generalization have been found and they are sometimes of preparative significance.

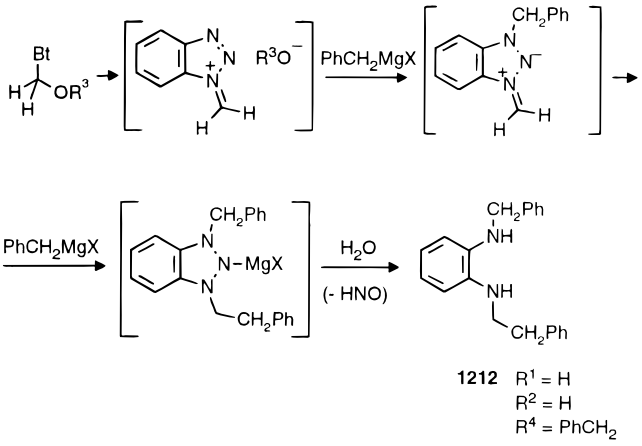
A. Ring Attack by Organometallic Reagents

In reactions of 1-imidoylbenzotriazoles with Grignard reagents, as shown in Scheme 375, the benzotriazole derivatives are attacked not only at the expected imidoyl carbon atom leading to the formation of imines **1206**, but also at both the N-3 (to give **1207**) and N-2 positions (to give **1208**) of the benzotriazole ring leading, eventually, to the products **1209**−**1211**.[73] Similar examples of Grignard attack

Scheme 375. Reactions of Imidoylbenzotriazoles with Grignard Reagents



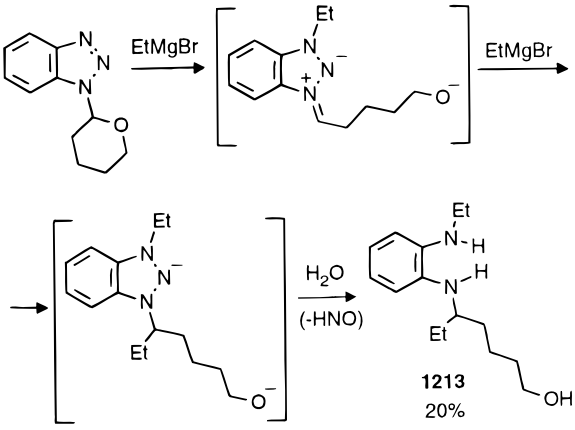
Scheme 376. Attack on Benzotriazole Ring in *N*-(Alkoxyalkyl)benzotriazoles by a Grignard Reagent



on the N-3 are observed in reactions with 1-(α-alkoxyalkyl)benzotriazoles[75] (Scheme 376).

On treatment with Grignard reagents or lithium aluminum hydride, cyclic α-benzotriazolyl-substituted ethers undergo benzotriazole ring opening along with ether ring opening to give the corresponding alcohols (Scheme 377).[154,269] The ratio of Grignard

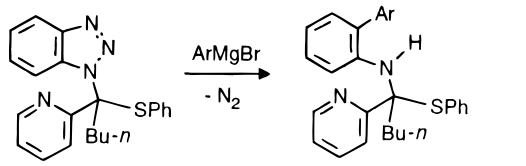
Scheme 377. Benzotriazole Ring Opening in a Cyclic α-Benzotriazolyl Ether



substitution product to ring-opening product depends strongly on both the ring size of the ether and nucleophilicity of the Grignard reagent. For example, tetrahydropyran derivatives are more susceptible to ring opening than their five-membered ring analogues, while less reactive Grignard reagents, such as arylmagnesium bromide or alkynylmagnesium bromide, favor the benzotriazole substitution with cyclic substrate structure retained.[154]

Reaction of 2-(1-benzotriazol-1-ylbutyl)pyridine (**1214**) with arylmagnesium bromides gives instead of the normal Grignard substitution product (see section IV.B.9.f), unexpectedly, aniline derivatives **1215a**,**b** in moderate yields (Scheme 378).[359] The mechanism probably involves the initial coordination of the Grignard magnesium atom with the pyridinyl nitrogen, which allows the unusual previously unprecedented nucleophilic attack of the Grignard reagent on C-3a atom of benzotriazole followed by the ring cleavage and extrusion of a molecule of nitrogen.

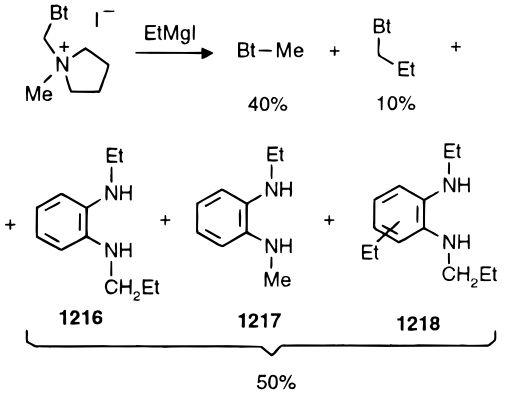
Scheme 378. Benzotriazole Ring Opening in 2-[1-(Phenylthio)-1-benzotriazol-1-ylalkyl]pyridines



1215a: Ar = Ph, 52%
1215b: Ar = 4-MeC_6H_4, 47%

Cleavage of the benzotriazole ring is also observed in the reaction of *N*-(benzotriazol-1-ylmethyl)-*N*-methylpyrrolidinium iodide with ethylmagnesium iodide[105] (Scheme 379) with the formation of products **1216**−**1218**.

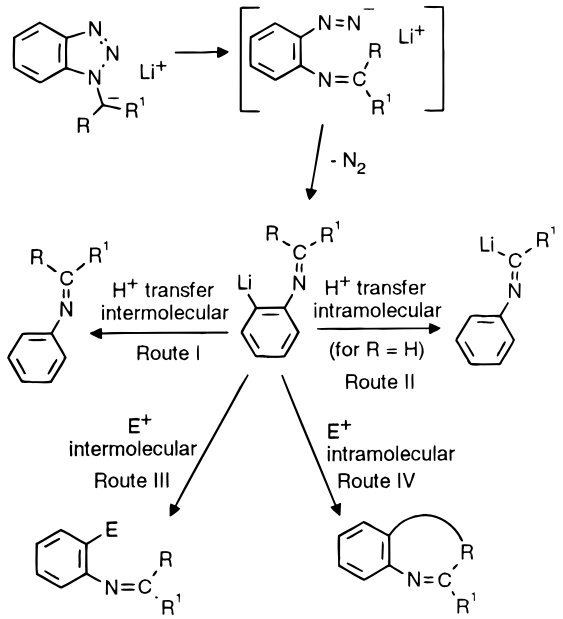
Scheme 379. Reactions of (Benzotriazolylmethyl)-ammonium Salts with Grignard Reagents



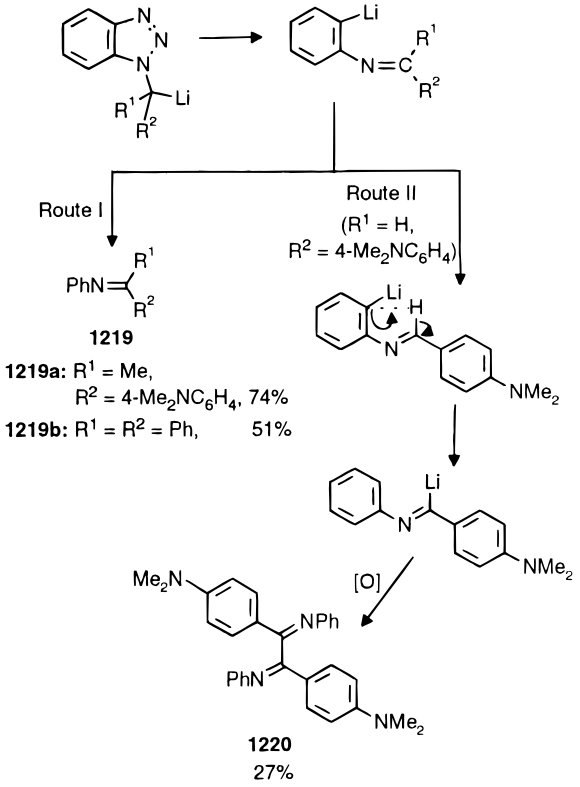
B. Ring Opening of α-Carbanions and Related Reactions

On standing, many α-lithium derivatives of 1-substituted benzotriazoles eliminate nitrogen with transfer of the lithium atom to the *ortho* position of the ring.[394] As shown in Scheme 380, four different

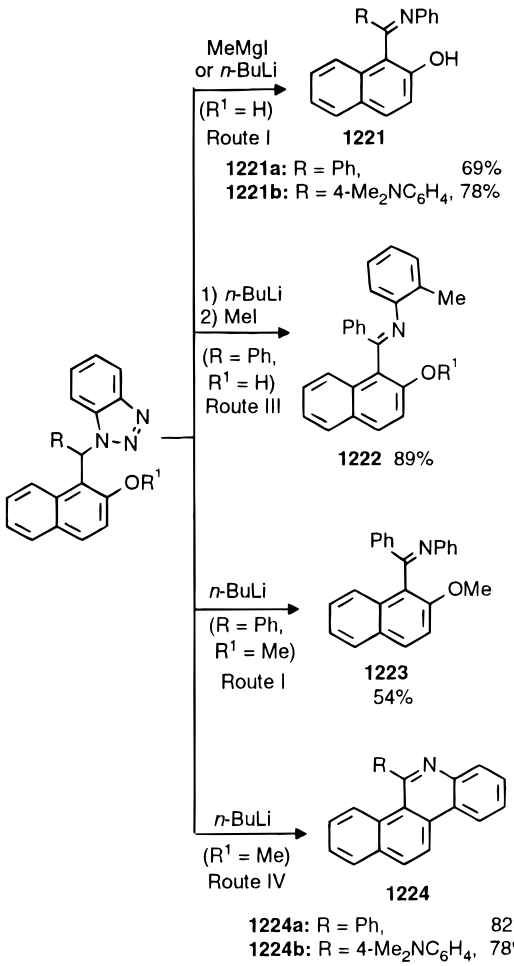
Scheme 380. Ring Opening of Benzotriazole α Carbanions and Subsequent Reactions



Scheme 381. Formation of Imines by Ring Opening of α Carbanions



Scheme 382. Ring Opening Followed by Electrophilic Attack at *Ortho* Position

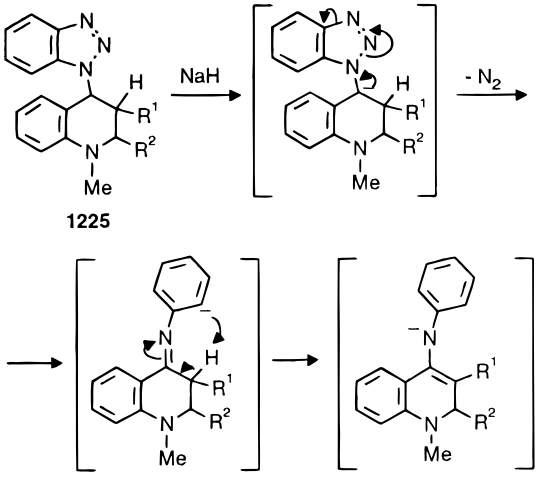


processes can then occur. The lithium atom can be replaced by a proton, via either intermolecular (route I) or intramolecular (route II) hydrogen transfer, or by other electrophiles, again in either an inter- (route III) or intramolecular (route IV) manner.

Examples of routes I and II, i.e., hydrogen transfer, are shown by the formation of products **1219** and **1220** (Scheme 381) and **1221** and **1223** (Scheme 382). Routes III and IV with attacks by other electrophiles are exemplified by the formation of **1222** and **1224** (Scheme 382). In most cases the products are obtained in high yields.

α-Carbanions generated from 4-benzotriazolyl-1,2,3,4-tetrahydroquinolines **1225** behave slightly differently. After loss of molecular nitrogen, the resulting carbanion **1226** abstracts the hydrogen α to the C=N double bond to yield nitrogen anion **1227**, which gives either enamine **1228** upon quenching with water, or imine **1229** upon quenching with acetic acid (Scheme 383).[270] Enamines **1228** are

Scheme 383. Base-Catalyzed Ring Opening in 4-Benzotriazolyl-1,2,3,4-tetrahydroquinolines

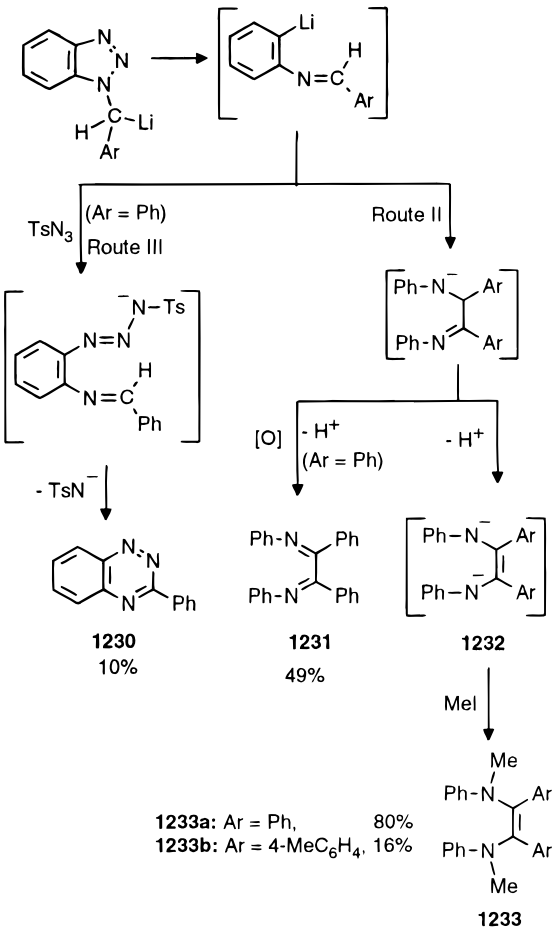


		yield (%)	
R^1	R^2	**1228**	**1229**
Me	H	72	88
n-Pr	H	65	72
Ph	H	-	28
Ph	$PhCH_2$	-	57
$PhCH_2$	H	75	57

isomerized to imines **1229** by treatment with acetic acid. The similar benzotriazole ring cleavage is observed for tricyclic julolidines.[101]

N-Benzylbenzotriazolyl anion also undergoes ring opening (Scheme 384): when tosyl azide is used as

Scheme 384. Ring-Opening Reactions of *N*-Benzyl Anions



an electrophile, 3-phenyl-1,2,4-benzotriazine (**1230**) is obtained from route III along with product **1231** from route II. 1,2-Bis(*N*-methylanilino)-1,2-diarylethenes **1233** are obtained by quenching the dianion **1232** with MeI.[190]

Similar ring opening is observed in 1-(2-aminoalken-1-yl)benzotriazoles **1234**.[200] The lone electron

Scheme 385. Formation of Quinazolines

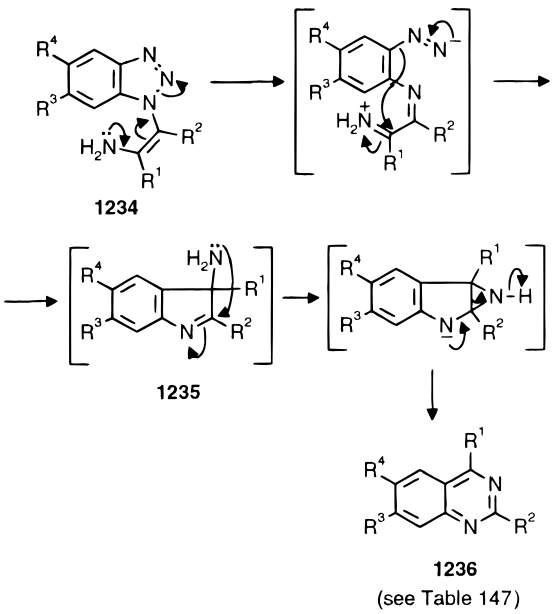


Table 147. Preparation of 2,4-Disubstituted Quinazolines 1236

R^1	R^2	R^3	R^4	yield %
Ph	Ph	H	H	64
Ph	Ph	Me	Me	57
Ph	4-MeC_6H_4	H	H	61
Ph	4-$MeOC_6H_4$	H	H	67
4-BrC_6H_4	Ph	H	H	73
4-MeC_6H_4	Ph	H	H	74
4-$MeOC_6H_4$	Ph	H	H	30

pair on the amino nitrogen facilitates the ring opening of the triazole ring through the vinyl conjugation (Scheme 385). Loss of a molecule of nitrogen is followed by cyclization to an indoline **1235**. Subsequent formation of an aziridine ring followed by ring expansion leads to the formation of 2,4-disubstituted quinazoline **1236** (Table 147).

The ring opening of *N*-(α-alkoxybenzyl)benzotriazole anions **1237** (Scheme 386) deserves special

Scheme 386. Ring Opening of Lithiated 1-(α-Alkoxyarylmethyl)benzotriazoles and Subsequent Reactions with Electrophiles

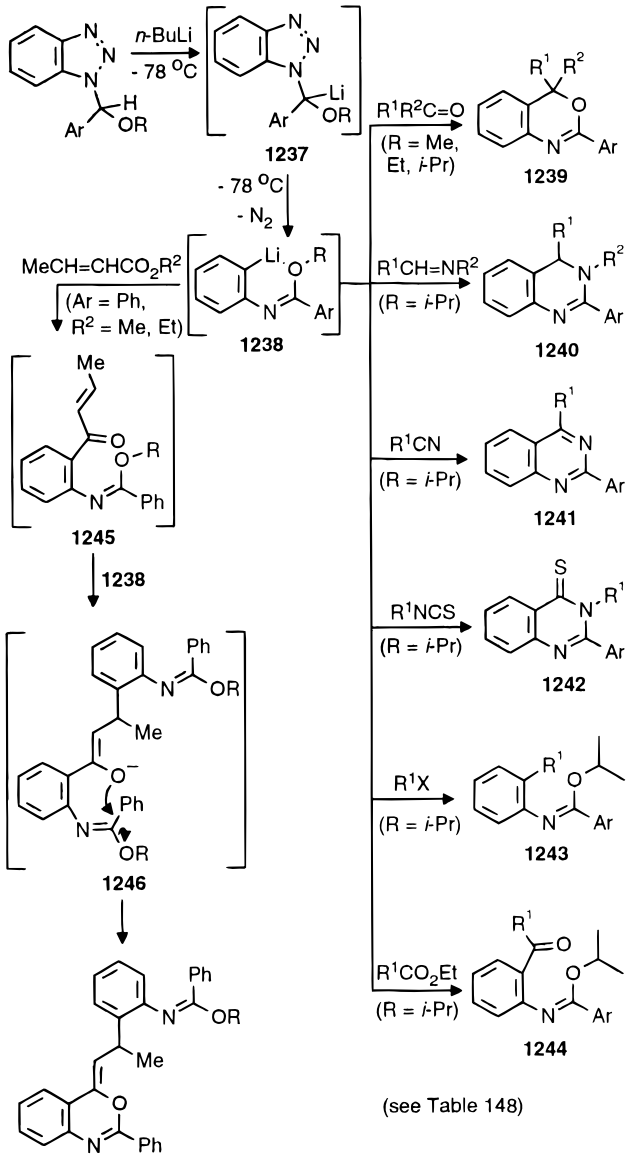


Table 148. Ring Opening of (α-Alkoxybenzyl)benzotriazole Anions 1237 and Subsequent Reactions with Electrophiles

compound	Ar	R^1	R^2	yield %
1239	Ph	$-(CH_2)_5-$		53
	Ph	Ph	H	57
	Ph	Ph	Me	60
	Ph	Ph	Ph	70
	Ph	4-MeC_6H_4	H	55
1240	Ph	Ph	Ph	83
	Ph	4-MeC_6H_4	4-MeC_6H_4	80
	1-naphthyl	4-MeC_6H_4	4-MeC_6H_4	79
1241	Ph	Ph		81
	Ph	4-MeC_6H_4		47
1242	4-MeC_6H_4	Ph		67
	1-naphthyl	Ph		74
1243	Ph	Me		77
	Ph	*n*-Bu		88
1244	Ph	Me		17
	Ph	Ph		57

attention. The alkoxy group has two important functions: (i) it facilitates the ring opening via the chelation between its oxygen atom and the *o*-lithium in the resulting anions **1238**, and (ii) it can serve as a leaving group thus making anions **1238** potential 1,4-bifunctional species useful for the synthesis of various heterocycles. Such applications include the synthesis of 4*H*-3,1-benzoxazines **1239** from aldehydes and ketones, 3,4-dihydroquinazolines **1240** from imines, quinazolines **1241** from nitriles, and 3*H*-quinazoline-4-thiones **1242** from isothiocyanates (Scheme 386, Table 148).[92] Interestingly, when anions **1238** (e.g., Ar = Ph) are treated with ethyl or methyl crotonate, 4*H*-3,1-benzoxazines **1247** are obtained as the final products, formed via 1,4-addition of the second molecule of **1238** to the intermediates **1245**. Anions **1238** can also be trapped with other electrophiles: alkyl halides and carboxylate esters afford the adducts **1243** and **1244**, respectively.

When diarylbenzotriazol-1-ylmethyl anions **1248** are treated with copper(I) iodide in THF, 6-arylphenanthridine derivatives **1249** are obtained (Scheme 387, Table 149).[19] The mechanism is believed to

Scheme 387. Preparation of 6-Arylphenanthridines from 1-(Diarylmethyl)benzotriazoles

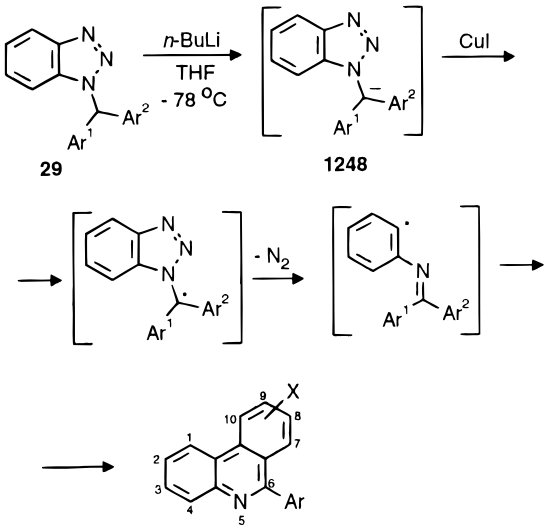


Table 149. Preparation of 6-Arylphenanthridines 1249 from 1-(Diarylmethyl)benzotriazoles 2a

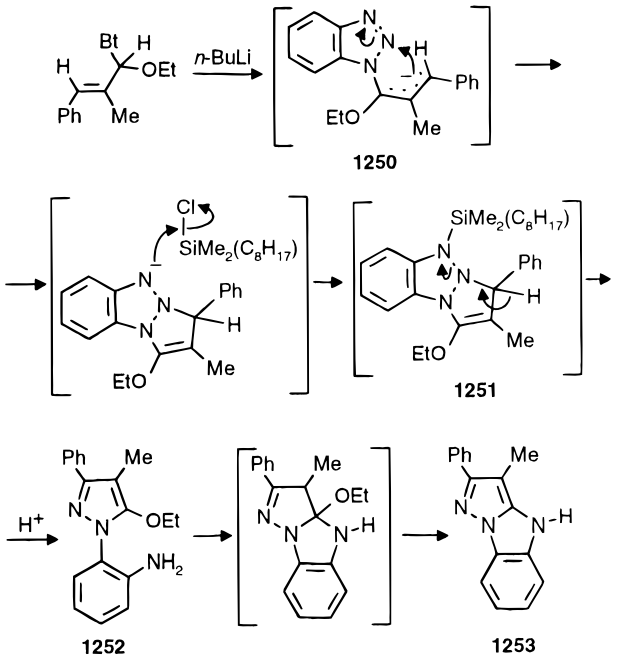
Ar^1	Ar^2	Ar	X	yield %
Ph	Ph	Ph	H	55
4-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4	9-Cl	57
4-FC_6H_4	4-FC_6H_4	4-FC_6H_4	9-F	36
4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	9-Me	48
dibenzosuberanediyl		dibenzosubereandiyl		39
4-$Me_2NC_6H_4$	Ph	4-$Me_2NC_6H_4$	H	7
4-ClC_6H_4[a]	Ph	Ph	9-Cl	20
		4-ClC_6H_4	H	25
4-MeC_6H_4[a]	Ph	Ph	9-Me	50
		4-MeC_6H_4	H	40

[a] Cyclization gives a mixture of isomeric products in comparable amounts.

involve a radical promoted ring opening of the benzotriazolyl group with subsequent cyclization. The regioselectivity of this reaction depends on the magnitude of the electron density of the aromatic ring. When Ar^1 and Ar^2 are different but of a similar electronic nature, the isomers are formed in comparable amounts. When Ar^1 and Ar^2 are of significantly different electron densities, ring closure takes place preferentially on the ring with lower electron density, resulting in the formation of only one product.

As shown in section III.A.7 1-(α-ethoxyallyl)benzotriazoles **398** undergo deprotonation with organolithiums and subsequent reactions with electrophiles provide a wide variety of substituted alkenyl ketones. Treatment of lithiated **398** with trimethylchlorosilane gives the expected product **399d** (see Scheme 129).[188] However, the reaction of lithiated 1-(1-ethoxy-2-methyl-3-phenylprop-2-enyl)benzotriazole of **1250** with more sterically hindered dimethyloctylchlorosilane by contrast gives only two pyrazole derivatives **1252** and **1253** in 70% and 12% yields, respectively (Scheme 388).[395] The mechanism for the formation of these compounds probably involves the intramolecular cyclization of allylic anion **1250**, (assisted by chlorosilane), to give intermediate **1251**, which undergoes ring opening with loss of the trialkylsilyl group to produce the pyrazole **1252**. The intermediacy of **1252** in the formation of **1253** is supported by acid treatment of previously isolated **1252**, to give **1253** in 50% yield.

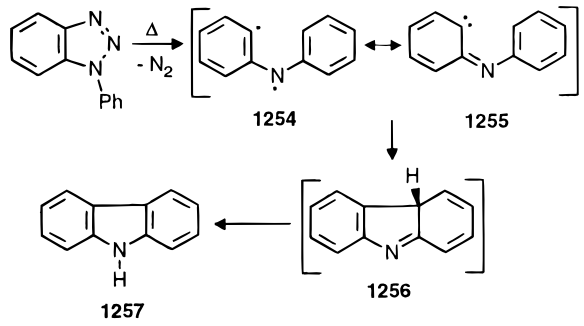
Scheme 388. Formation of Pyrazole Derivatives from 1-(α-Ethoxyalken-2-yl)benzotriazoles



C. Thermolysis (Graebe–Ullmann Reaction) and Photolysis: Loss of N_2

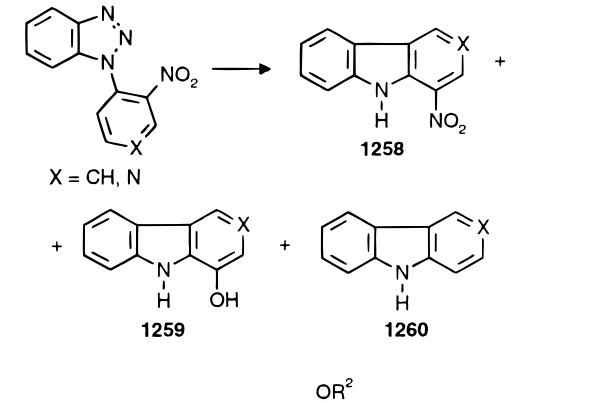
The Graebe−Ullmann synthesis of carbazole **1257** from 1-phenylbenzotriazole is well-known.[396] The reaction mechanism has been shown to involve the cyclization of a diradical **1254** or iminocarbene **1255** intermediate to 4a*H*-carbazole **1256**, which, isomerizes to carbazole via a hydrogen shift (Scheme 389).

Scheme 389. Proposed Mechanism of Ring Opening in 1-Phenylbenzotriazole



The position and nature of a substituent in the aryl group significantly affect the composition and ratio of the resulting products. Thus, flash-vacuum pyrolysis of *N*-aryl- or *N*-heteroarylbenzotriazoles, bearing a nitro group in the *ortho* position to benzotriazolyl group leads to the formation, along with expected 1-nitrocarbazoles **1258**, of the corresponding 1-hydroxycarbazoles **1259** and unsubstituted carbazoles **1260** (Scheme 390).[397] A similar substituent

Scheme 390. Flash-Vacuum Pyrolysis of *N*-Aryl- or *N*-Heteroarylbenzotriazoles

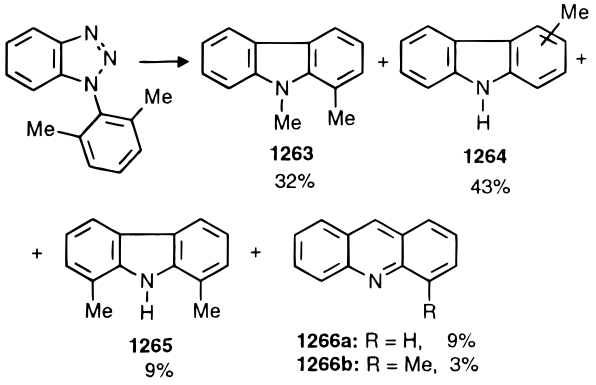


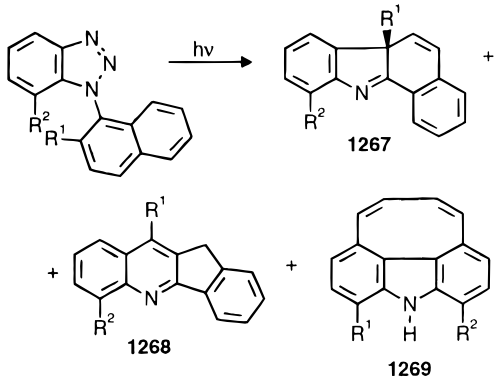
X	Y	R^1	R^2	yield (%) 1261	1262
N	CH	*i*-Pr	Me	84	9
CH	N	Me	*i*-Pr	30	15

elimination is observed also in *N*-arylbenzotriazoles with an alkoxy group in the *ortho* position to the benzotriazolyl group[398] (Scheme 390). Increase in the size of the *ortho* substituent leads to an increased amount of **1261**.

Benzotriazoles, bearing an 1-aryl substituent in which both *ortho* positions are blocked by methyl groups, on thermolysis, flash-vacuum pyrolysis, or irradiation in acetonitrile give complex mixtures, containing isomeric *N*-methylcarbazoles, and *N*-unsubstituted carbazoles and acridines (Scheme 391).[399]

Scheme 391. Flash-Vacuum Pyrolysis or Photolysis of *N*-(*ortho*-Substituted aryl)benzotriazoles





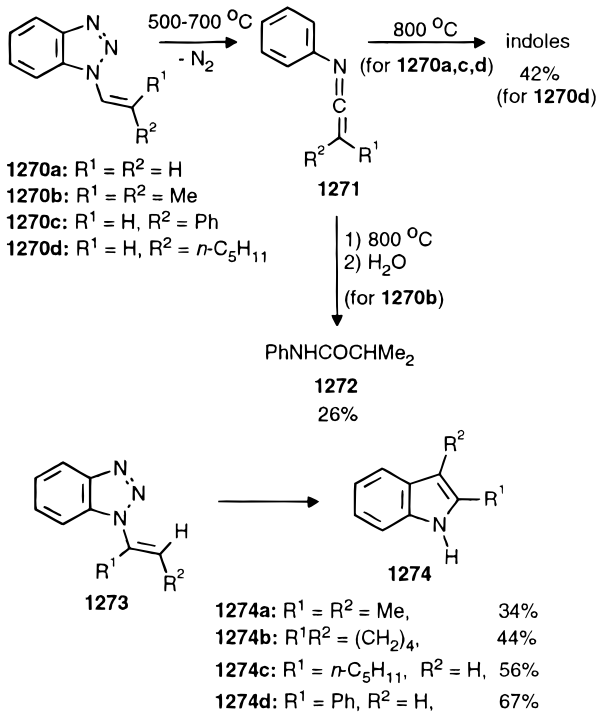
yield (%)

R^1	R^2	1267	1268	1269
H	H	10	-	5
Me	H	24	32	30
Me	Me	25	42	20
OMe	H	26	-	-
$SiMe_3$	H	-	-	47

Although the pyrolysis of 1-(benzotriazol-1-yl)naphthalene gives also a complex mixture, irradiation of its acetonitrile solution leads to rather interesting results: a number of cycloocta[*def*]carbazoles **1269** are obtained together with 6a*H*-benzo[*a*]carbazoles **1267** and indenoquinolines **1268**.[400−402] The formation of cyclooctacarbazoles **1269** is favored in the presence of bulky naphthyl substituents R^1.

Mass spectroscopy studies of flash-vacuum pyrolysis of *β*-substituted 1-vinylbenzotriazoles **1270** (Scheme 392) suggest that the compounds, initially formed at 500−700 °C, are the corresponding *N*-phenylketenimines **1271**, which under more drastic conditions (~800 °C) isomerize into indoles.[403] Pyrolysis of **1270c** at 800 °C gives 2- and 3-phenylindole[403] while of **1270d** affords only 3-pentylindole.[404] Amide **1272**

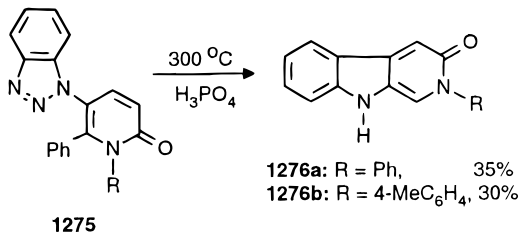
Scheme 392. Flash Pyrolysis of 1-Alkenylbenzotriazoles



is obtained as the only product in the flash-vacuum pyrolysis of **1270b**, which supports the formation of a ketenimine in the pyrolysis of 1-vinylbenzotriazoles with an α-vinyl hydrogen. However, the flash-vacuum pyrolysis of the α-substituted 1-vinylbenzotriazoles **1273** also affords the corresponding indoles **1274** in moderate yields[404] and this cannot be explained by the mechanism discussed above because α-vinyl hydrogens are not available in these cases. A reasonable mechanism for pyrolytic conversion of **1273** into an indole probably involves the direct collapse of the initially formed diradical (Scheme 389).

Pyrolysis of 5-(benzotriazol-1-yl)pyrid-2-ones **1275** catalyzed by 85% phosphoric acid gives the corresponding *β*-carbolines **1276a**,**b** in moderate yields (Scheme 393).[26]

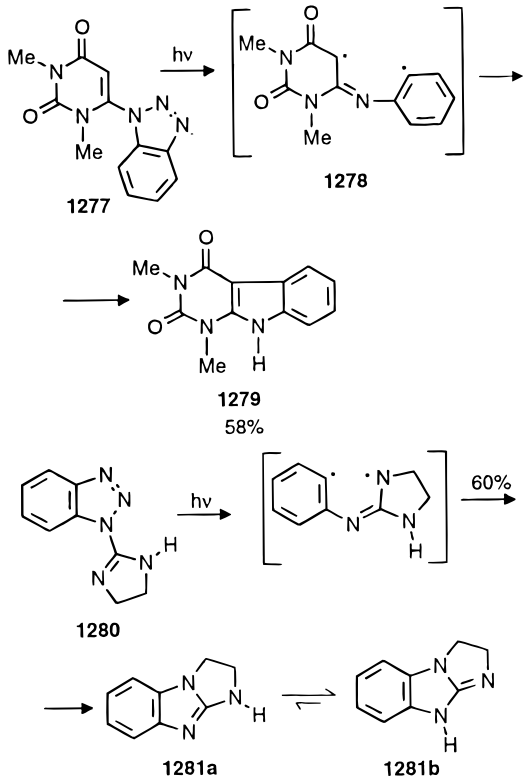
Scheme 393. Pyrolysis of 5-Benzotriazolylpyrid-2-ones



The analogous elimination of nitrogen under photolytic conditions with the formation of a biradical is observed on the irradiation of 6-benzotriazol-1-yluracil **1277**, a cyclic analogue of the vinylbenzotriazoles described above. Subsequent recombination of diradical **1278** affords the corresponding pyrrolo[2,3-

d]pyrimidine **1279** in respectable yield (Scheme 394).[405] A similar reaction occurs with benzotriazole-

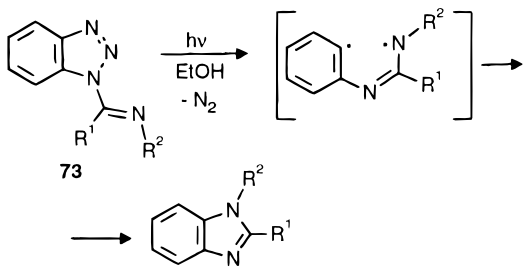
Scheme 394. Photolysis of 6-Benzotriazol-1-yluracil and *N*-(4,5-Dihydro-1*H*-imidazol-2-yl)benzotriazole



substituted cyclic imines as demonstrated by the photolysis of 1-(4,5-dihydro-1*H*-imidazol-2-yl)benzotriazole (**1280**, Scheme 394),[406] which in acetonitrile gives the expected tricyclic product **1281** in 60% yield.

Irradiation of ethanolic solutions of acyclic 1-imidoylbenzotriazoles **73** (for preparation, see section II.A.3) induces radical ring opening with nitrogen extrusion (Scheme 395) by the same mechanism as

Scheme 395. Photolysis of Imidoylbenzotriazoles

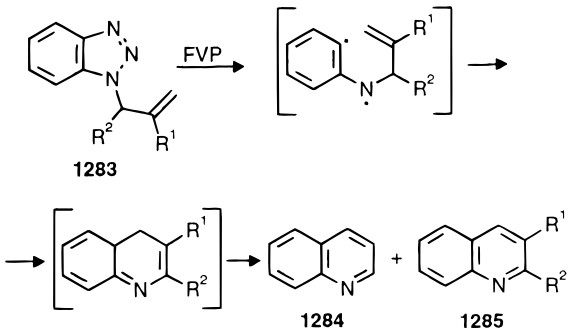


1282a: R^1 = Me, R^2 = Ph, 67%
1282b: R^1 = Me, R^2 = 4-BrC_6H_4, 61%
1282c: R^1 = Me, R^2 = 4-MeC_6H_4, 23%
1282d: R^1 = Me, R^2 = 2-MeCOC_6H_4, 79%
1282e: R^1 = R^2 = Ph, 87%
1282f: R^1 = Ph, R^2 = 4-ClC_6H_4, 53%
1282g: R^1 = Ph, R^2 = 4-(*i*-Pr)C_6H_4, 51%

discussed above.[72] The 1,2-disubstituted benzimidazoles products **1282** are sensitive to prolonged irradiation and slowly decompose under the reaction conditions.

Flash-vacuum pyrolysis of 1-allylbenzotriazoles **1283** also provides the corresponding diradicals which, after electrocyclization followed by rapid intramolecular 1,5-H shift, afford quinolines (Scheme 396). Unfortunately, the synthetic utility of this

Scheme 396. Flash-Vacuum Pyrolysis of 1-Allylbenzotriazoles

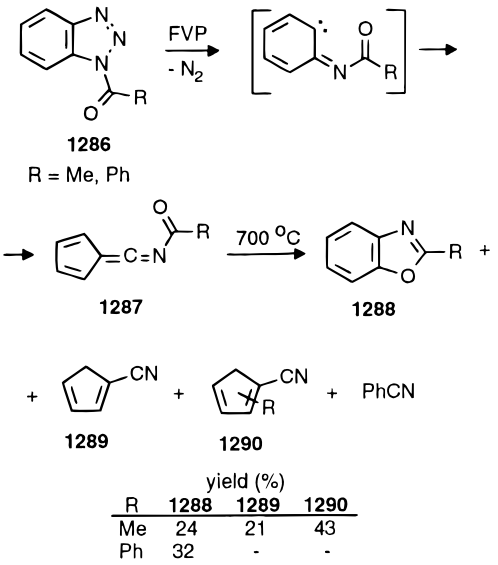


		yield (%)	
R^1	R^2	**1284**	**1285**
H	H	46	-
H	Me	34	6
Me	H	54	10

reaction is limited, because of the predominant formation of unsubstituted quinoline **1284** even when substituted allylbenzotriazoles are used.[407]

Flash-vacuum pyrolysis of 1-acetyl- and 1-benzoylbenzotriazole in the temperature range 500−600 °C affords *N*-acetyl- and *N*-benzoylcyclopenta-2,4-dienylidenemethaneimines **1287**, respectively (Scheme 397).[408] At higher temperatures (700 °C), 1-acetyl-

Scheme 397. Flash-Vacuum Pyrolysis of *N*-Acetyl- and *N*-benzoylbenzotriazole



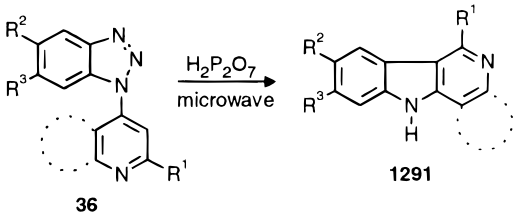
	yield (%)		
R	**1288**	**1289**	**1290**
Me	24	21	43
Ph	32	-	-

benzotriazole gives 2-methylbenzoxazole **1288** (R = Me), cyanocyclopentadiene **1289**, isomeric methylcyanocyclopentadienes **1290** (R = Me), benzonitrile, and ketene. On the other hand, in the photolysis of 1-acetylbenzotriazole, *N*-acyl fission predominates over nitrogen extrusion leading to the formation of benzotriazolyl radical.[409]

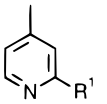
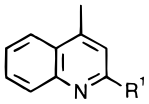
A one-pot Graebe−Ullmann synthesis of 3-azacarbazoles under microwave irradiation conditions has

been reported recently.[28] The reaction occurs in the presence of pyrophosphoric acid to give **1291** in moderate to good yields (Scheme 398).

Scheme 398. Preparation of 3-Azacarbazoles under Microwave Irradiation



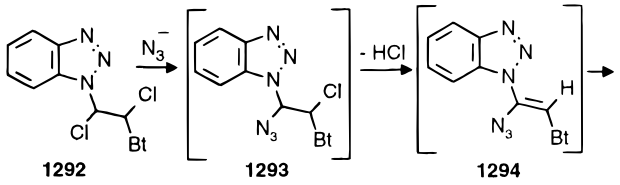
36 1291

azine moiety	R^1	R^2	R^3	yield %
	H	H	H	60%
	H	Me	Me	71%
	H	H	H	76%
	H	Me	Me	81%
	Me	H	H	32%
	Me	Me	Me	48%

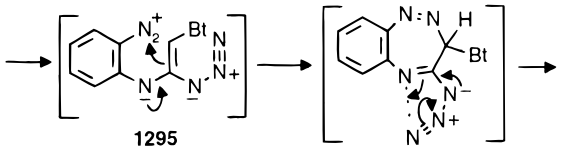
D. Miscellaneous Ring Openings

A novel benzotriazole ring opening is observed in the reaction of 1,2-dibenzotriazol-1-yl-1,2-dichloroethane (**1292**) with sodium azide. Instead of the 1,2-diazido derivative, a new heterocyclic compound, 4-benzotriazol-1-yl-6*H*-benzo[*o*]tetraazolo[1,5-*e*][1,2,5]-triazepine **1297** is obtained[410] (Scheme 399). The key

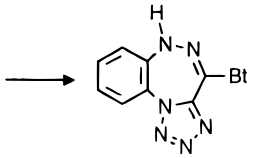
Scheme 399. Formation of Tetraazolotriazepines



1292 1293 1294



1295 1296

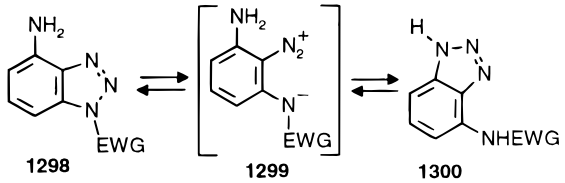


1297
64%

step in the reaction sequence is believed to be the ring opening of **1294** to **1295**.

The Dimroth rearrangement involving 1*H*-1,2,3-triazoles has long been known.[411] However, no similar rearrangements of 4-amino- or 4-imino-substituted 1*H*-benzotriazoles had been reported until we found that such a rearrangement occurs when there is a strongly electron-withdrawing group at the N-1 position which weakens the N-1−N-2 bond.[412] Ring opening leading to diazo intermediate **1299** takes place without the extrusion of nitrogen due to the presence of 4-amino group (Scheme 400).

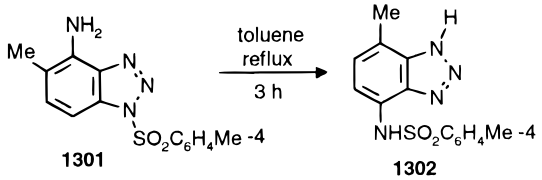
Scheme 400. Dimroth-Type Rearrangement of 4-Aminobenzotriazoles



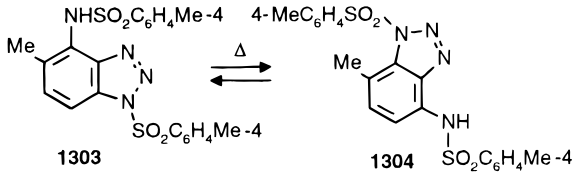
1298 1299 1300

The details of such rearrangement are given in Scheme 401. When compound **1301** is refluxed in

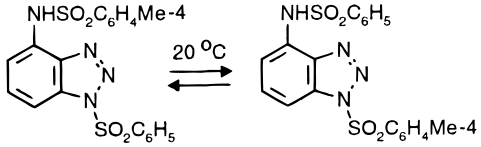
Scheme 401. Examples of Dimroth-Type Rearrangements of 4-Aminobenzotriazoles



1301 1302
97%



1303 1304

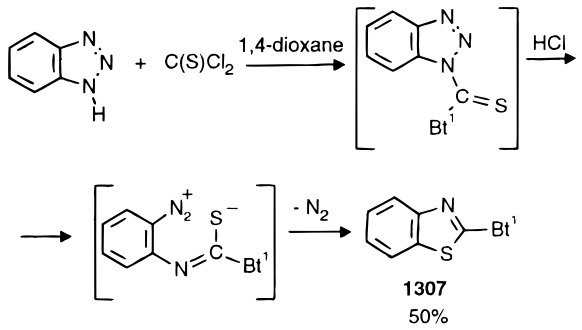


1305 1306

toluene for 3 h, complete rearrangement into **1302** is observed. Efforts to convert **1302** back to **1301** were unsuccessful, indicating the influence of the electron-withdrawing group at the N-1 nitrogen. While compound **1305** exists in solution in equilibrium with **1306** at room temperature, the rearrangement of **1303** into **1304** requires heating and a polar solvent such as DMSO; no rearrangement is observed in chloroform. This solvent effect suggests the formation of a polar intermediate or transition state. Cross-over experiments indicate an intramolecular mechanism. The rearrangement is supported by separation and characterization of the products, NOE experiments, variable-temperature NMR studies, and X-ray crystal structure determination.

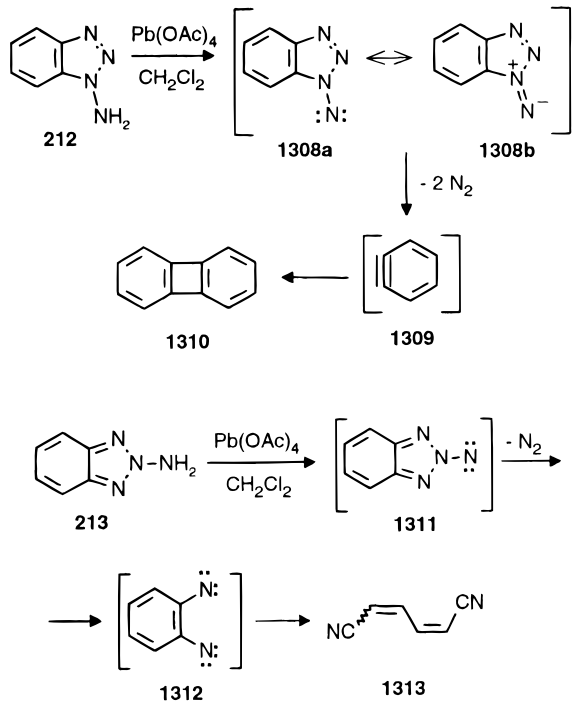
Reaction of benzotriazole with thiophosgene in stoichiometic amounts in the absence of an acid scavenger results in formation of the abnormal product, 1-benzothiazol-2-ylbenzotriazole (**1307**)[63] (Scheme 402). The suggested mechanism involves acid-catalyzed ring opening in the manner described above for the Dimroth-type rearrangements, with subsequent nitrogen extrusion.

Scheme 402. Reaction of Benzotriazole with Thiophosgene

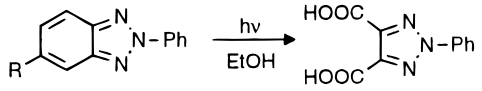


Oxidative removal of the amino hydrogens from 1-aminobenzotriazole **212** by treatment with lead tetraacetate yields nitrene species **1308**, which undergoes fragmentation to benzyne **1309** and two molecules of nitrogen[164] (Scheme 403). In the absence of a trapping agent, the benzyne dimerizes to biphenylene **1310** in yields of up to 83%. The initial formation of benzyne was confirmed by the similar oxidations of 5- and 7-methyl-1-aminobenzotriazoles, which gave two isomeric biphenylenes in each case.[164] Later it was found that the oxidative ring-opening reaction can also be effected using NBS.[341b] However, the oxidation of analogous 2-aminobenzotriazole **213** with lead tetraacetate resulted in no formation of benzyne species instead a mixture of *cis*,*cis*- and *cis*,*trans*-muconononitriles **1313** was obtained in moderate yield. It is suggested that initially formed nitrene **1311** eliminates one molecule of nitrogen to generate "dinitrene" intermediates **1312**, which subsequently undergo aromatic ring opening to give **1313**. The oxidation of 2-aminobenzotriazole with iodobenzene diacetate gives exclusively *cis*,*cis*-muconononitrile in quantitative yield.[164]

Scheme 403. Oxidative Ring Opening of *N*-Aminobenzotriazoles



Scheme 404. Photolysis of 2-Arylbenzotriazoles



1314a: R = H
1314b: R = Me

1315 93% (from **1314a**)
47% (from **1314b**)

Ultraviolet irradiation of dilute ethanolic solutions of 2-arylbenzotriazoles **1314** under aerobic conditions effects the ring opening and degradation of the benzene ring, yielding 2-aryl-1,2,3-triazole-4,5-dicarboxylic acids **1315** (Scheme 404).[413] The presence of a methyl group in the 6 position of the benzotriazole ring does not affect the course of the reaction.

The ring expansion via intramolecular attack in benzotriazolium ylides is considered in section III.A.5.a (see formation of compound **340** in Scheme 111).

VI. Acknowledgments

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