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Benzotriazole: A Novel Synthetic Auxiliary

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Abstract: *Benzotriazole and aldehydes react reversibly to give addition products: in the presence of amines and other NH-compounds water can be eliminated to form products of type Bt-CHR-NR'R''. The latter are versatile intermediates for the preparation of primary, secondary, and tertiary amines and in the alkylation of hydroxylamines, hydrazines, amides, thioamides, and sulfonamides. Polyfunctional amines and other polyfunctional compounds can also be prepared, and they enable significant extending of Mannich reaction.*

Similar oxygen compounds Bt-CRR'-OR'' enable new syntheses of ethers and esters. Reactions in which benzotriazole is eliminated rather than substituted open up new pathways to enamines, enol ethers, and nitrones. The methodology is capable of extension to a variety of vinylogous systems including benzenoid and heteroaromatic derivatives. In addition to acting as a versatile leaving group, benzotriazolyl residues activate neighboring CH bonds to proton loss and a variety of such applications is described.

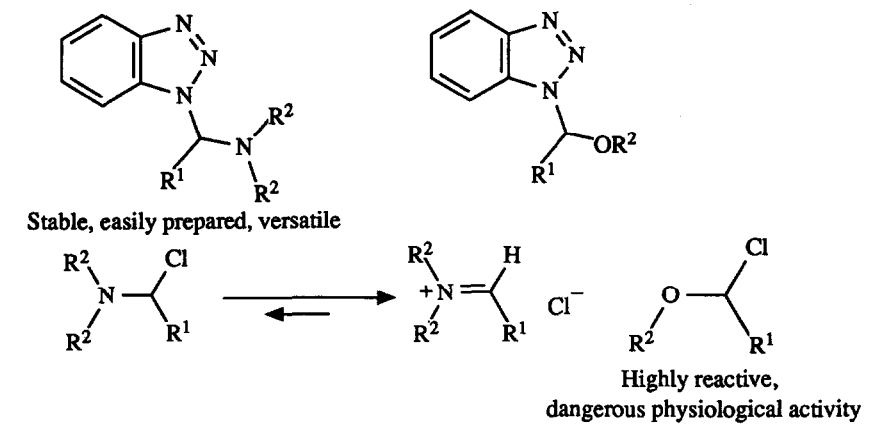
CONTENTS

INTRODUCTION

The subject of this review is the use of benzotriazole as a synthetic auxiliary. Because the benzotriazolate anion is a good leaving group, it may be used in place of a halogen substituent in many reactions. The benzotriazolyl group has the advantage, however, that the derivatives are frequently much more stable than their chloro or bromo anologues. For example, α-benzotriazolylalkyl amines and α-benzotriazolylalkyl ethers are stable, easily prepared compounds, whereas the corresponding α-chloroalkyl analogues are highly reactive and, in some cases, physiologically dangerous. This review will show that compounds of this type are of considerable synthetic importance in aminoalkylation and alkoxyalkylation reactions (cf Scheme 1).

No previous review of the present work has appeared with the exception of a short account published in "Il Farmaco".[1] 1-Hydroxybenzotriazole has been used for many years as a synthetic auxiliary in the synthesis of peptides,[2] but this work lies outside the scope of the present review.

Scheme 1. Benzotriazole -- A Tame Halogen Substitute

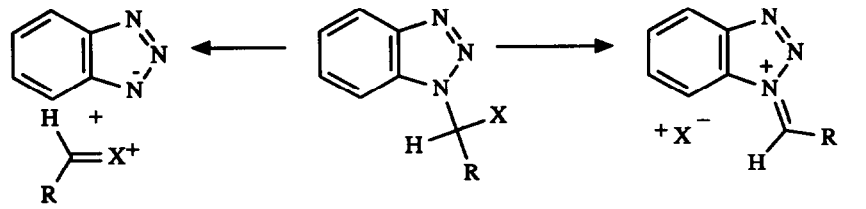


Scheme 2 illustrates the alternative ways in which benzotriazole derivatives can ionize. When X is an electron-donor group, in particular a nitrogen-linked substituent, ionization occurs to form the benzotriazolate anion. When X is itself a leaving group, for example, a halogen, then the benzotriazole nitrogen atom can assist the ionization of X as an anion, leaving the benzotriazole as part of the cationic species. It has been amply demonstrated that ionizations of both types occur with many benzotriazole derivatives.

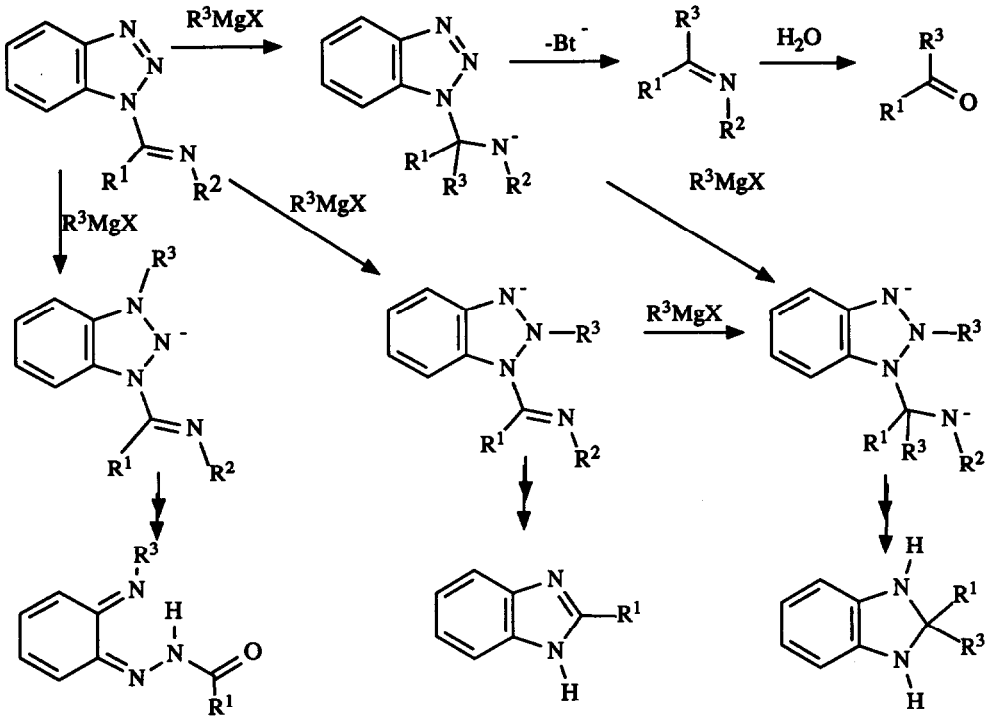
Benzotriazole methodology has already come a long way, but it is clear that it has still further to go. We believe that in the years to come benzotriazole will take its place as one of the most useful synthetic auxiliary groups available to the preparative chemist.

The benzotriazole ring is extremely stable and few examples are encountered of it being cleaved during a reaction. An exception to this was found in the reactions of 1-imidoylbenzotriazoles with Grignard reagents which afford a variety of products in which the triazole ring has been opened or modified (Scheme 3).[3]

Scheme 2. Ionization and Activation in Benzotriazole Derivatives



Scheme 3. Reaction of 1-Imidoylbenzotriazoles with Grignard Reagents.

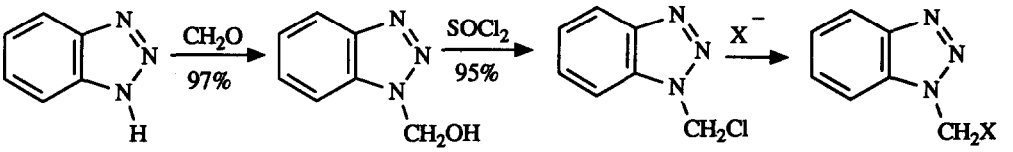


At high temperatures, pyrolysis of benzotriazoles has been observed to cause ring opening. Thus, N-vinylbenzotriazoles can afford indoles.[4]

REACTIONS WITH ALDEHYDES AND RELATED EQUILIBRIA

It has long been known that benzotriazole reacts with formaldehyde to give 1-hydroxymethylbenzotriazole in high yield, and that this compound can be converted into 1-chloromethylbenzotriazole. Some substitution reactions of this chlorine atom are reported in the literature and we have carried out many more (Scheme 4).[5] For example, we have shown that benzotriazol-1-ylmethylammonium salts can be prepared in quantitative yields by the reaction of 1-chloromethylbenzotriazole with tertiary amines.[6]

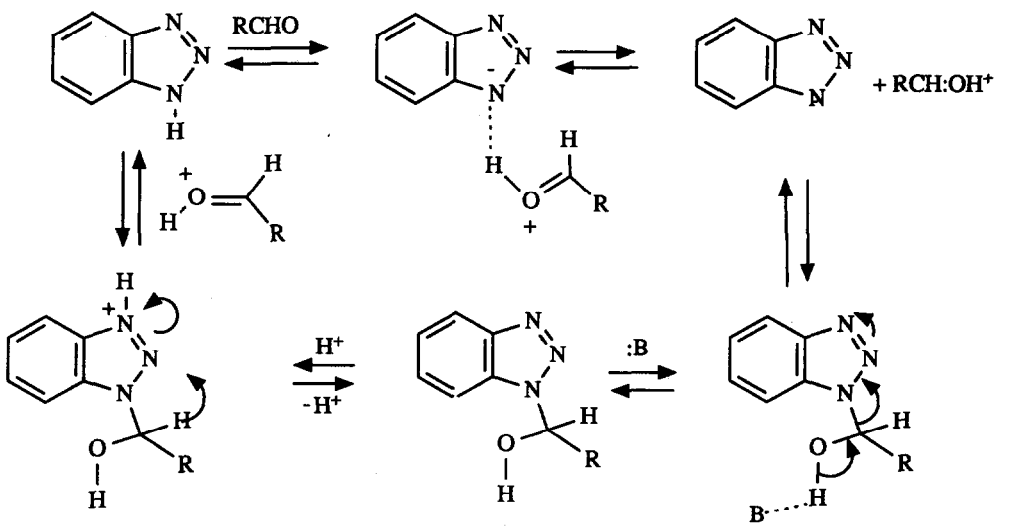
Scheme 4. Preparation of 1-Substituted Benzotriazoles



X = OEt	X = SO_2Ph	X = Pyrrolidinyl	X = SP(O)(OEt)SPr
= OPh	= Benzotriazolyl	= N_3	X = $DMAP^+ Cl^-$
= SPh	= Morpholinyl	= CN	X = CH_3
= SCH_2Ph	= Pyr^+Cl^-	= Ph	X = $PPH_3^+ Cl^-$

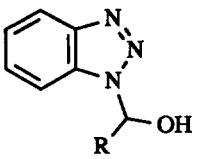
Excluding the reaction with formaldehyde discussed above, the reactions of benzotriazole with other aldehydes had not previously been studied. As shown in Scheme 5, benzotriazole reacts with a whole range of aliphatic and aromatic aldehydes to yield the corresponding adducts usually as crystalline solids.[7] These reactions occur simply on mixing the components together at room temperature. Some of the products are described in Scheme 6. All of these adducts show a strong O-H stretching band in the infrared, and the characteristic aldehyde proton resonance at around 9 ppm in the proton NMR spectrum has gone, being replaced by a peak usually between 6 and 7 ppm.

Scheme 5. Reactions of Benzotriazole with Aldehydes



crystalline solids

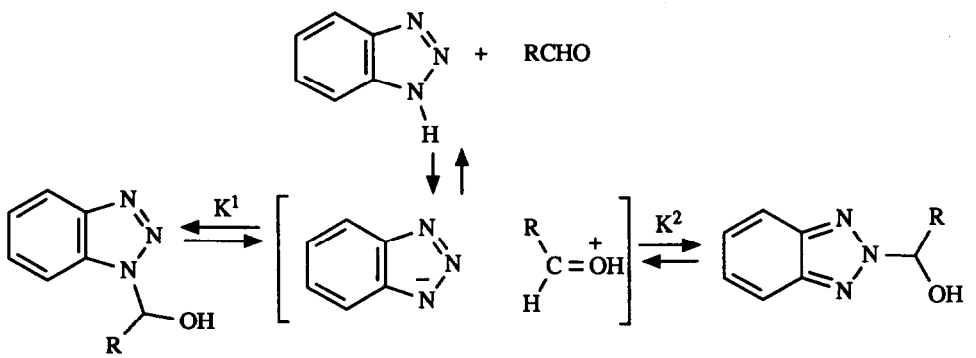
Scheme 6 Reaction Products of Benzotriazole and Aldehydes



R	M.p. (°C)	ν_{OH} (cm^{-1})	δ (CH-O) (p.p.m)
H	135-137	3182	6.12 (s)
CH_3	74-75	3140	6.55 (q)
CH_2CH_3	63-65	3148	6.54 (t)
$(CH_2)_2CH_3$	61-63	3162	6.61 (t)
$CH(CH_3)_2$	58-61	3187	6.25 (d)
$(CH_2)_3CH_3$	40-41	3184	6.61 (t)
$C(CH_3)_3$	54-56	3189	6.48 (s)
$(CH_2)_5CH_3$	53-54	3183	6.62 (t)
$(CH_2)_7CH_3$	54-55	3182	6.67 (t)
4-pyridyl	103-104	2589	7.5 (s)

We have studied quantitatively the equilibrium between free aldehyde and benzotriazole. These compounds are in dynamic equilibrium with the two products that can be formed by addition at either the 1- or 2-position (Scheme 7).[8] Ketones yield far less of the addition products.

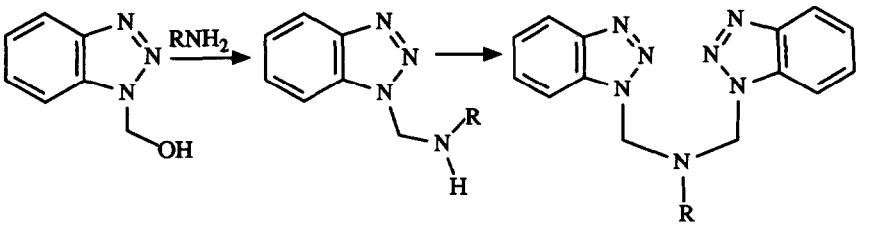
Scheme 7 Equilibria in Solutions of Benzotriazole and an Aldehyde in Hexadeuteriobenzene at 23°C



Carbonyl compound	K^1/M^{-1}	K^2/M^{-1}	ΔG_1° kcal/mol	ΔG_2° kcal/mol
CH_3CHO	22.3	1.87	-1.83	-0.368
CH_3CH_2CHO	18.6	1.40	-1.72	-0.198
$(CH_3)_2CHCHO$	14.7	1.16	-1.58	-0.087
$(CH_3)_3CCHO$	1.28	0.114	-0.145	1.28
2-C_5H_4NCHO	2.62	0.200	-0.567	0.947
4-$CH_3C_6H_5CHO$	< 0.001	< 0.001		
Cyclohexanone	0.100	0.034	1.35	1.99
CH_3COCO_2Et	0.110	0.018	1.30	2.36
Acetone	< 0.001	< 0.001		

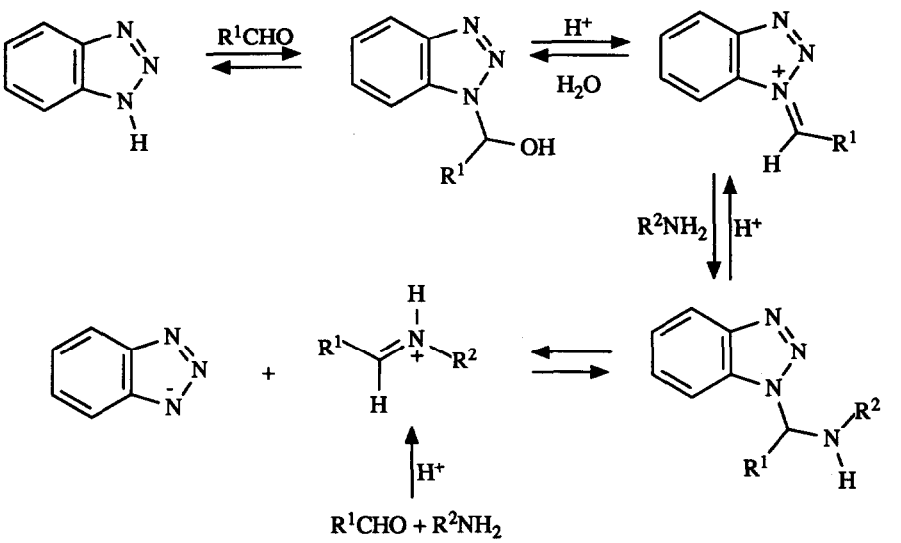
It has been known for some time that primary amines react with 1-(hydroxymethyl)benzotriazole. There are many examples of this type of addition reaction described in the literature in which one or both of the hydrogens of the primary amine are replaced (Scheme 8).

Scheme 8 Reaction of Primary Amines with 1-Hydroxymethylbenzotriazole



We have found that this reaction is general for a wide range of aldehydes.[9] Thus, benzotriazole, an aldehyde, and an aromatic primary amine react together to form product bases in high yield (Scheme 9).

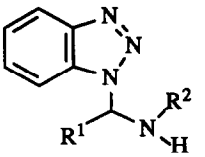
Scheme 9 Reaction of Primary Amines, Aldehydes, and Benzotriazole



Scheme 10 lists a few of the compounds that have been prepared in this way.[9] The yields are very high. In one particular case, the yield was optimized on the request of one of our sponsors to reach 99.8%.

Scheme 10 Reactions of Amines, Aldehydes and Benzotriazole:

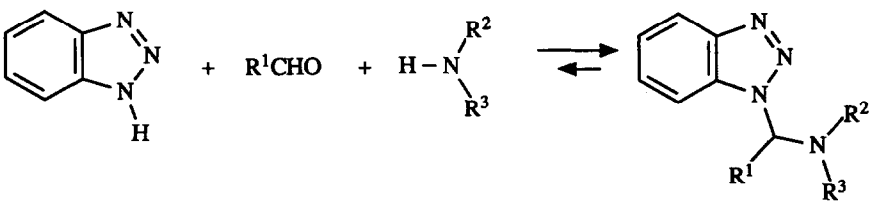
Compounds Prepared



R^1 of R^1CHO	R^2 of R^2NH_2	m.p. (°C)	Yield (%)
Pr	$C_6H_3Cl_2$-3,5	113-114	82
Me	2-Pyridyl	126-128	98
Et	2-Pyridyl	118-120	87
Bu^t	2-Pyridyl	189-190	85
4-C_6H_4Cl	2-Pyridyl	132-134	85
Pr	2-Pyrimidinyl	73-74	86

Reactions between lower aliphatic aldehydes, amines and benzotriazole can often be advantageously carried out in aqueous solution. For details see Scheme 11.[10]

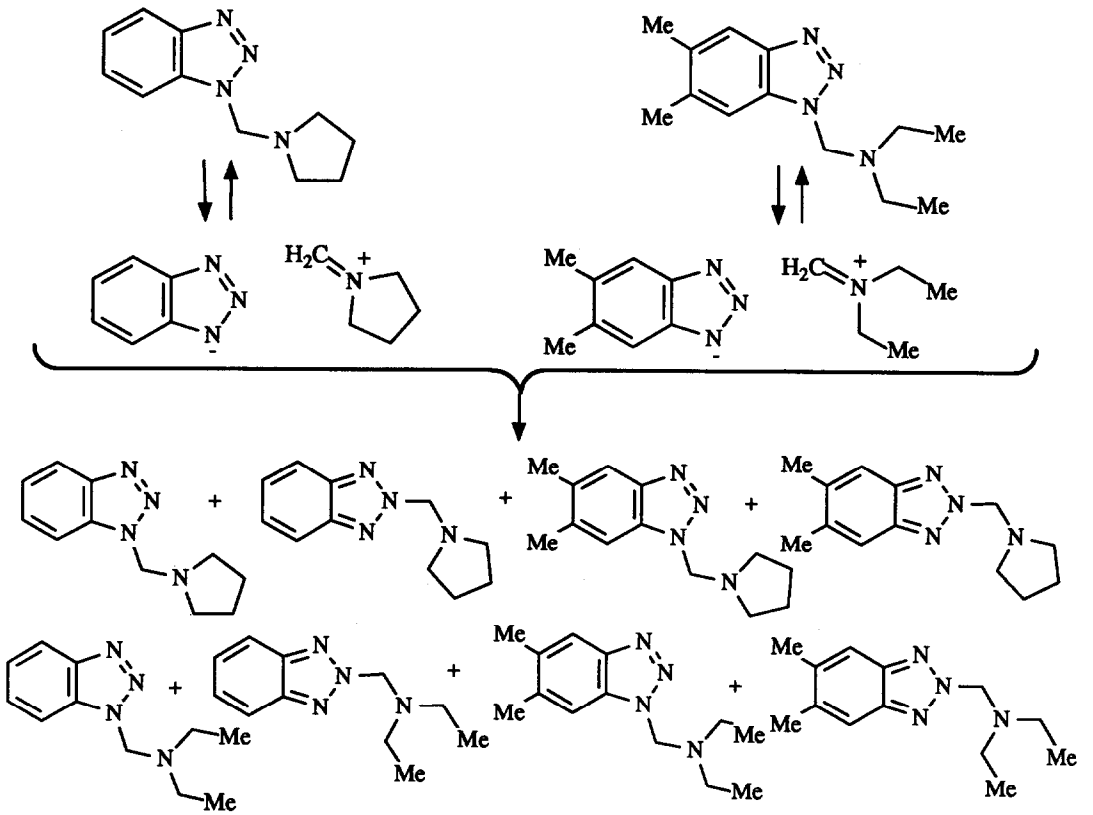
Scheme 11 Preparation of 1-(α-Aminoalkyl)benzotriazole in Aqueous Solution.



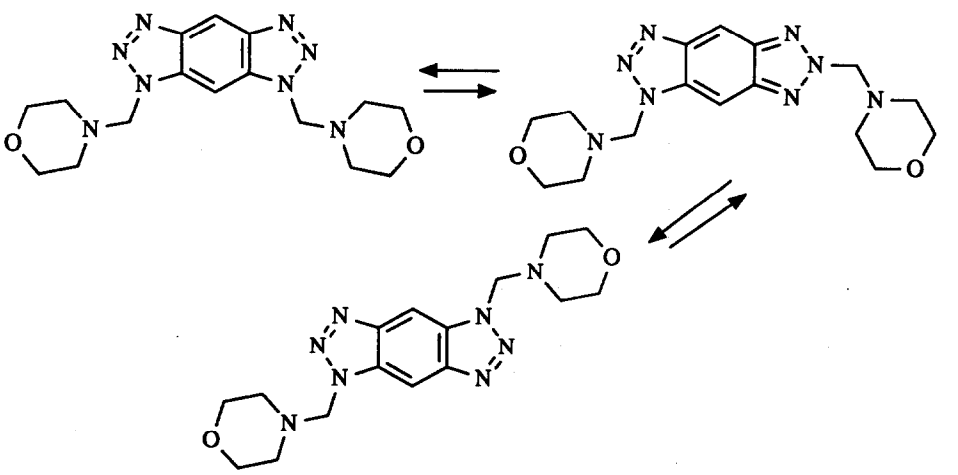
R^1	R^2	R^3	Yield (%)
H	H	Ph	90
H	CH_3	Ph	91
H	H	3-$O_2NC_6H_4$	97
H	H	4-BuC_6H_4	97
H	-$(CH_2)_4$-		92
H	-$(CH_2)_2$-O-$(CH_2)_2$-		91
CH_3	H	Ph	87
CH_3	H	4-BuC_6H_4	99
CH_3	H	2-Pyridyl	89
COOEt	H	4-$MeOC_6H_4$	93

In comparison with 1-(α-hydroxyalkyl)benzotriazoles, for the products from the reaction of an aldehyde, benzotriazole and an amine, the equilibrium lies very much farther to the condensation product. However, here also a dynamic equilibrium exists between the 1-substituted and the 2-substituted derivative (Scheme 7). By the cross-over method, this has been shown to take place by an intermolecular mechanism (Scheme 12).[11] Further studies of this reaction have shown that the free energy of activation for the 1- to 2-benzotriazolyl rearrangement is greatly dependent on the degree of stabilization provided to the cationic intermediate: the greater the stabilization the lower the energy barrier.[12] Compounds formed from other heterocycles, for example triazole and tetrazole, show similar equilibria (e.g. Scheme 13).[13]

Scheme 12 Cross-over Experiment.



Scheme 13 Equilibrium in Solution of 1,5-di(morpholinomethyl)bistriazolo[4,5-a][5,4-d]benzene.



THE PREPARATION OF AMINES

It is in the preparation of amines from the reaction of benzotriazolylmethylamines with carbanions in which we have discovered a wide variety of new synthetic methods (Scheme 14). Versatile routes have been developed for the synthesis of primary, secondary, and tertiary amines and, in general, higher yields are obtained than from existing methods for the preparation of such compounds.

Scheme 14 Preparation of Amines Using Carbanions (RMgBr, RLi) or $NaBH_4$

Aliphatic Amines:

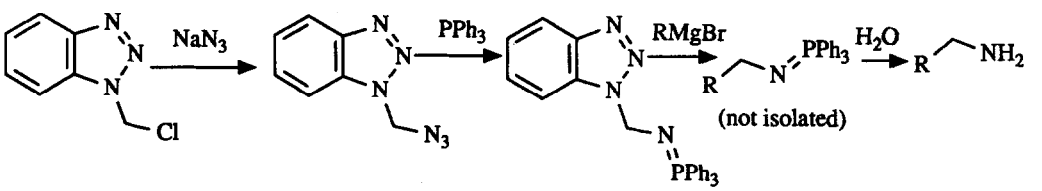
Primary	R^-	+ $BtCH_2N{:}PPh_3$	⟶	RCH_2NH_2
Symmetrical Secondary	$2R^-$	+ $(BtCH_2)_2NH$	⟶	$(RCH_2)_2NH$
Symmetrical Tertiary	$3R^-$	+ $(BtCH_2)_3N$	⟶	$(RCH_2)_3N$
Partly Symmetrical Tertiary	$2R^-$	+ $(BtCH_2)_2NR^1$	⟶	$(RCH_2)_2NR^1$
Unsymmetrical Tertiary	R^-	+ $BtCH_2NR^1R^2$	⟶	$RCH_2NR^1R^2$
Unsymmetrical Secondary	R^-	+ $BtCH_2NHR^1$	⟶	RCH_2NHR^1

Aromatic Amines

Secondary	R^-	+ $BtCHR^1NHAr$	⟶	$ArNHCHRR^1$
Symmetrical Tertiary	R^-	+ $(BtCH_2)_2NAr$	⟶	$ArN(CH_2R)_2$
Unsymmetrical Tertiary	R^-	+ $ArNR^1CH_2Bt$	⟶	$ArNR^1CH_2R$

Primary amines have previously been prepared using [N,N-bis(trimethylsilyl)amino]methoxymethane. However, our method using the readily available benzotriazolylphosphinamine $BtCH_2N{:}PPh_3$ affords a general route to primary amines using more convenient starting materials (Scheme 15).[14]

Scheme 15. Preparation of Primary Amines

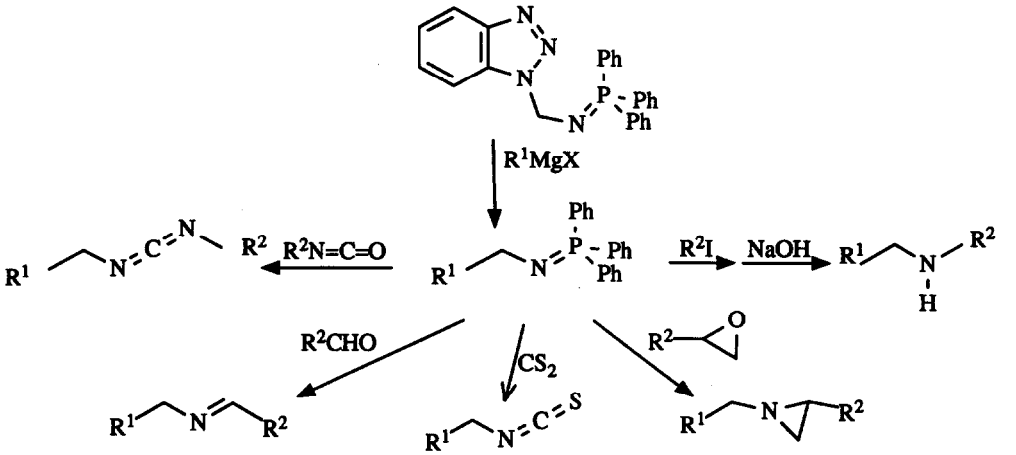


R =	PhC≡C	c-C_6H_{11}	Ph	2-Thienyl	2-Naphthyl
Yield (%) =	86	77	82	84	93
Yield (%)* =	61	52	75	67	52

*Previous work[14] using: $MeO\text{-}CH_2\text{-}Cl + HN(SiMe_3)_2 \longrightarrow MeO\text{-}CH_2\text{-}N(SiMe_3)_2$

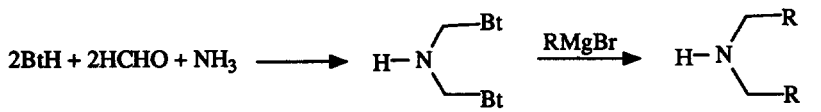
1-(Benzotriazol-1-yl)-N-triphenylphosphonilidenemethylamine has been shown to be a particularly versatile reagent and allows a wide variety of carbodiimides, imines, isothiocyanates, aziridines and secondary amines to be synthesized. The initial product from the reaction of the phosphonilidene with Grignard reagents need not be isolated prior to further manipulation[15] (Scheme 16).

Scheme 16. 1-(Benzotriazol-1-yl)-N-triphenylphosphonilidenemethylamine in Organic Synthesis



The synthesis of symmetrical secondary amines is achieved in high yield from the reaction of $(BtCH_2)_2NH$ with Grignard reagents (Scheme 17). Bis(benzotriazolylmethyl)amine is readily obtained from the reaction of benzotriazole, formaldehyde and ammonia. The symmetrical secondary amines are obtained as the sole products from the reaction, and, therefore, the purification problems usually experienced with alkylation procedures are absent. For a wide range of compounds of this type, this is the preferred method of preparation.

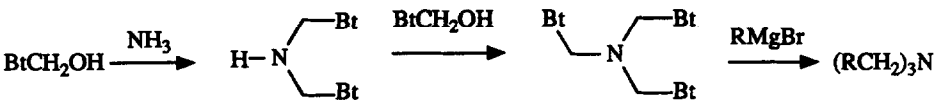
Scheme 17. Preparation of Symmetrical Secondary Amines



R =	Ph	$PhCH_2$	C_4H_9
Yield (%) =	75	95	65

The rapid synthetic construction of symmetrical secondary amines using $(BtCH_2)_2NH$ is described in Scheme 17.[16] Under more forcing conditions, benzotriazole, formaldehyde, and ammonia can be made to react to convert $(BtCH_2)_2NH$ into $(BtCH_2)_3N$. This compound reacts with Grignard reagents to give the symmetrical tertiary amine products in good yields (Scheme 18). As with the benzotriazole mediated synthesis of symmetrical secondary amines, no difficult isolation procedures are necessary to obtain the tertiary amine.

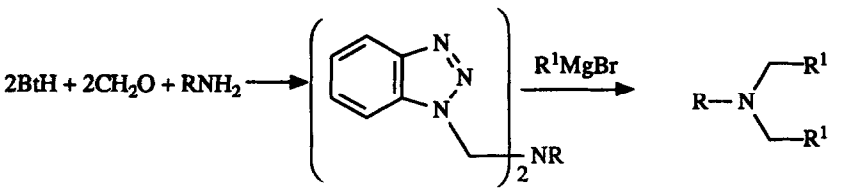
Scheme 18. Preparation of Symmetrical Tertiary Amines



Compound	Yield (%)	Compound	Yield (%)
$(PhCH_2)_3N$	74	$(Bu)_3N$	75
$(4\text{-}MeC_6H_4CH_2)_3N$	51	$(C_5H_{11})_3N$	40
$(1\text{-}Naphthyl\text{-}CH_2)_3N$	55	$(cyclo\text{-}C_6H_{11}CH_2)_3N$	66

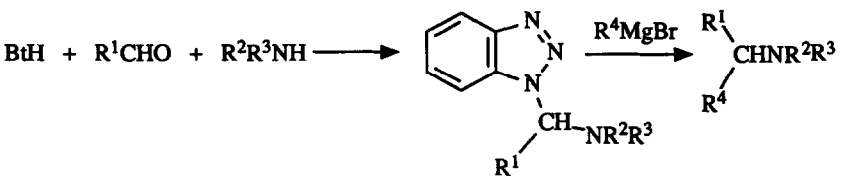
Analogous methods for the conversion of primary and secondary aliphatic amines to unsymmetrical tertiary amines are given in Schemes 19 and 20. Once again excellent yields are obtained.[16]

Scheme 19. Preparation of Partly Symmetrical Tertiary Amines



$R = Me, R^1 = Ph$: 91% $R = R^1 = C_8H_{17}$: 99%

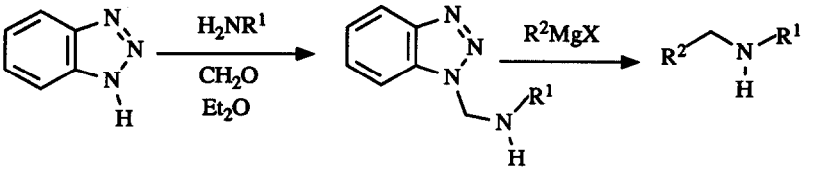
Scheme 20. Preparation of Unsymmetrical Tertiary Amines



R^1	R^2,R^3	R^4	Yield (%)
Pr^i	$-(CH_2)_4-$	$PhCH_2$	76
Pr^i	$-CH_2)_4-$	Ph	64
Pr^i	$PhCH_2$, $PhCH_2$	Me	76
Pr	$-(CH_2)_2O(CH_2)_2$	Ph	79
Ph	$-(CH_2)_2O(CH_2)_2$	Bu	82
Ph	$(CH_2)_5$	Pr^i	59

Under suitable conditions, the reaction of primary amines, benzotriazole and formaldehyde can be controlled to enable the conversion of primary aliphatic into secondary aliphatic amines.[17] The intermediate benzotriazolylmethylamine need not be isolated prior to reaction with the Grignard reagent (Scheme 21). We have also found that primary aliphatic amines can be converted into secondary amines *via* the reaction of the Strecker adducts formed by the reaction of the primary amine with formaldehyde and HCN.

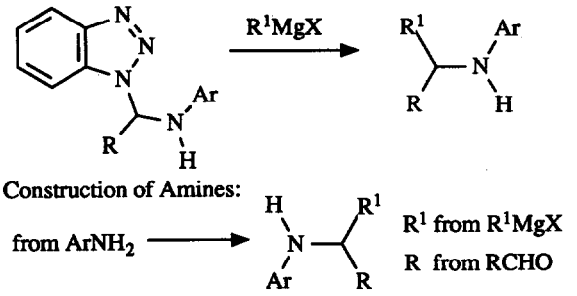
Scheme 21. Preparation of Unsymmetrical Secondary Aliphatic Amines



R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
cyclohexyl	Ph	50	octyl	Ph	49
cyclohexyl	$PhCH_2$	64	$(CH_3)_3C$	$PhCH_2$	51
$(CH_3)_3CCH_2$	$PhCH_2$	62	$(CH_3)_3C$	Ph	49

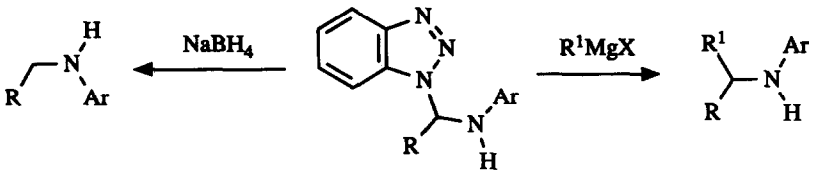
In addition to high-yielding reductions with sodium borohydride, the Mannich adducts from benzotriazole, an aldehyde, and an aromatic amine react readily with Grignard reagents to give secondary amines in excellent yields (Scheme 22).[18,19,20] Complex amines may be constructed from a combination of simple starting reagents (i.e., the original primary amine, the aldehyde and the Grignard reagent).

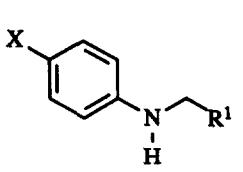
Scheme 22. Preparation of Secondary Aromatic Amines

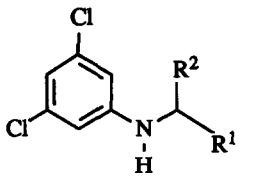


Examples of the application of these reactions to the N-alkylation of anilines are given in Scheme 23. These represent only a few examples of the many reactions we have carried out. This type of procedure is extremely useful for the N-methylation of various anilines and full details have been published for the preparation from 2-toluidine of 2-methyl-N-methylaniline.[19]

Scheme 23. Selective Monoalkylation of Aromatic Amines





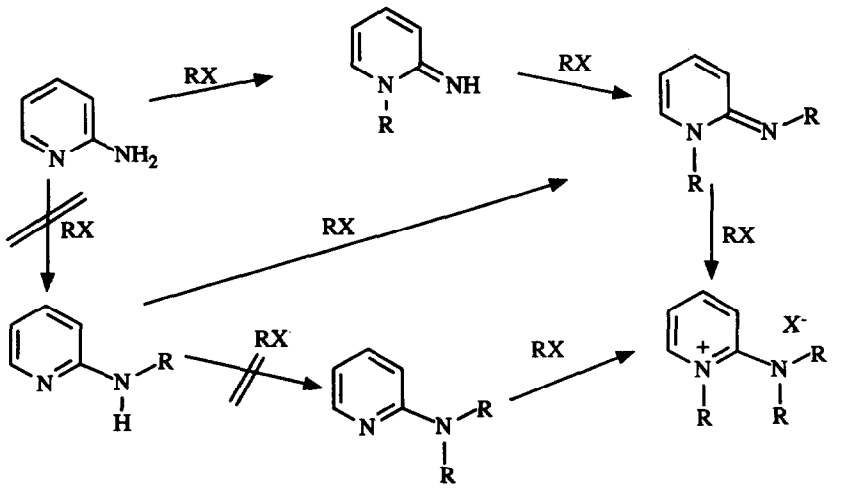


Reagent	X	R^1	Yield(%)
$NaBH_4$	Cl	H	80
$PhCH_2MgCl$	Cl	CH_2Ph	85
$NaBH_4$	CO_2H	H	91
PrMgBr	CO_2H	Pr	85
$NaBH_4$	NO_2	H	89

Reagent	R^1	R^2	Yield(%)
$NaBH_4$	Pr	H	68
MeMgI	Pr	Me	82

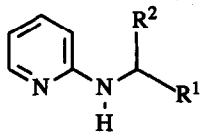
These methods for the conversion of anilines into mono- and di-N-substituted anilines are superior to previously reported methods. Moreover, their application can be extended to their heterocyclic analogues. For example, N-alkylation at the amino group of 2-aminopyridine is very difficult to achieve due to preferential reaction at the pyridine nitrogen atom to give a quaternary salt. 2-(Alkylamino)pyridines also react with alkylating agents at the pyridine nitrogen atom. Classically, alkylation of the amino group requires conversion of the aminopyridines to their anions prior to reaction with the alkylating agent. This procedure necessitates strongly basic conditions, and, furthermore, mixtures are often still obtained (Scheme 24).

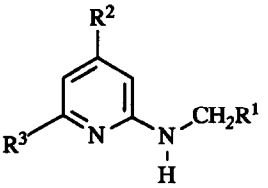
Scheme 24. Classical N-Alkylation of Aminopyridines



By contrast, the application of our new method allows the alkylation of compounds, such as 2-aminopyridine, specifically at the amino group (Scheme 25).[18]

Scheme 25. Compounds Prepared from 2-Aminopyridine





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

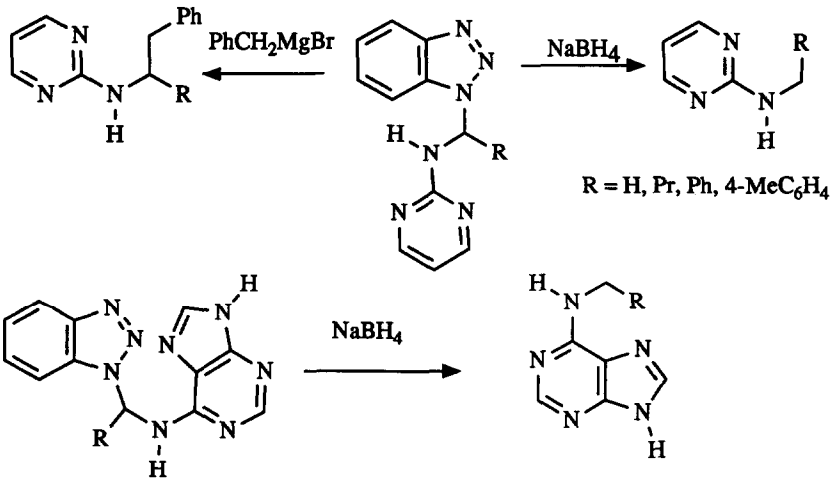
R^1 = H, Me, or Benzyl

R^2 = H or Me

R^3 = H or Me

Moreover, the methods can be generalized to heterocyclic amines of many different types. Thus in Scheme 26, examples are given of the preparation of alkylaminopyrimidines and alkylaminopurines.[18]

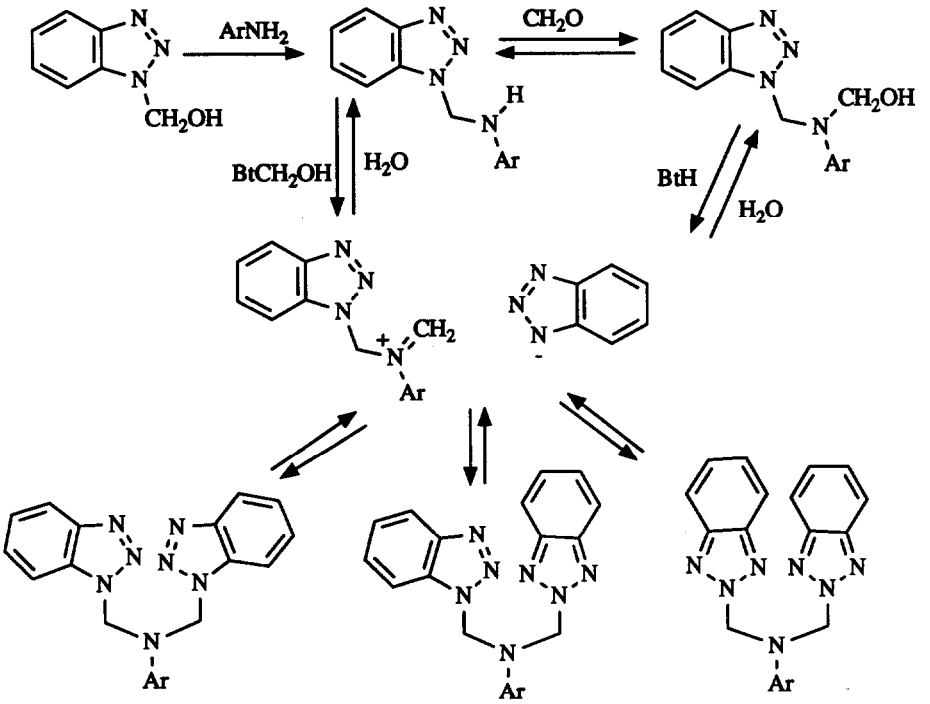
Scheme 26. Preparation of Alkylamino-pyrimidines and -purines



R = H, Pr, Ph, 4-MeC_6H_4

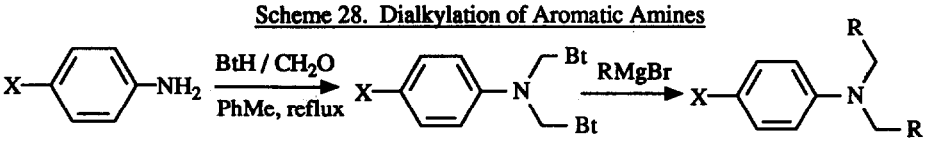
Under more forcing conditions, primary aryl amines will react with two moles of benzotriazole and two moles of formaldehyde to give the corresponding bis-derivative[21] (Scheme 27).

Scheme 27. Bisbenzotriazolylmethylation of Arylamines



These bis-derivatives can also be converted into aromatic tertiary amines by reaction with Grignard reagents (Scheme 28).[22]

Scheme 28. Dialkylation of Aromatic Amines

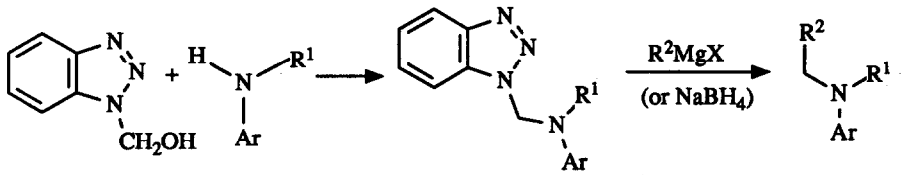


Examples:

X	R	Yield(%)	X	R	Yield(%)
H	Pr^i	87	OMe	Pr^i	68
Me	$PhCH_2$	85	H	allyl	99
Bu	$PhCH_2$	76			

Benzotriazolylmethylation of secondary aryl-alkyl amines and subsequent reduction or Grignard reaction provides a general method for the preparation of unsymmetrical N,N-dialkylarylamines as illustrated in Scheme 29.[22]

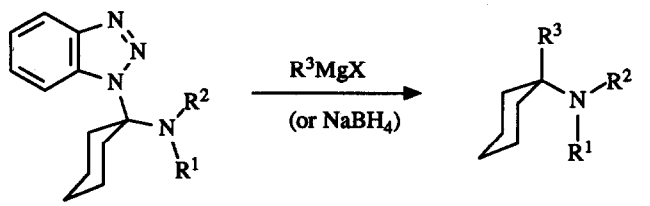
Scheme 29. Dialkylarylamines Possessing Different Alkyl Groups



Ar	R^1	R^2	Yield (%)
Ph	Me	$PhCH_2$	99
Ph	Et	$PhCH_2$	97
Ph	Me	H	77

The reaction of benzotriazole and amines with aldehydes cannot in general be extended to ketones, many of which give no product or poor yields. However, cyclohexanone has been condensed with a number of amines as shown in Scheme 30.[23]

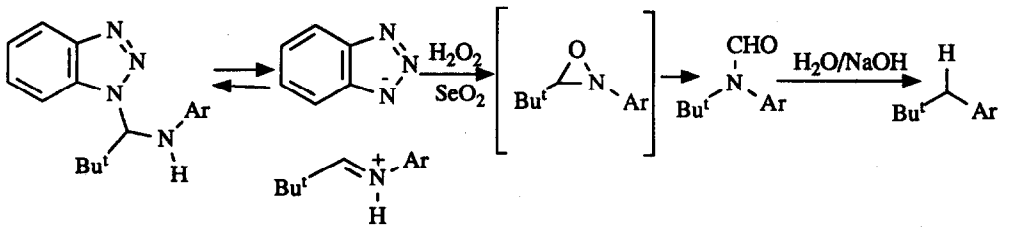
Scheme 30. Cyclohexylamines from Benzotriazole-cyclohexanone Adducts



R^1, R^2	R^3	Yield (%)	R^1, R^2	R^3	Yield (%)
$-CH_2CH_2OCH_2CH_2-$	H	82	$-CH_2CH_2OCH_2CH_2-$	$4\text{-}MeC_6H_4$	84
$-(CH_2)_4-$	Ph	73	$-CH_2CH_2OCH_2CH_2-$	$4\text{-}ClC_6H_4$	86
$-CH_2CH_2OCH_2CH_2-$	Ph	74	$-CH_2CH_2OCH_2CH_2-$	$PhCH_2$	65

A novel method for the N-tertiary butylation of aromatic and, in particular, heteroaromatic amines has been described (Scheme 31).[24] Selenium dioxide oxidation of the intermediate iminium ion is believed to result in formation of an azaepoxide, rapid rearrangement of which furnishes the formamide. Hydrolysis of this formamide results in formation of the corresponding amine.

Scheme 31. Mono-N-t-Butylation of Aromatic Amines

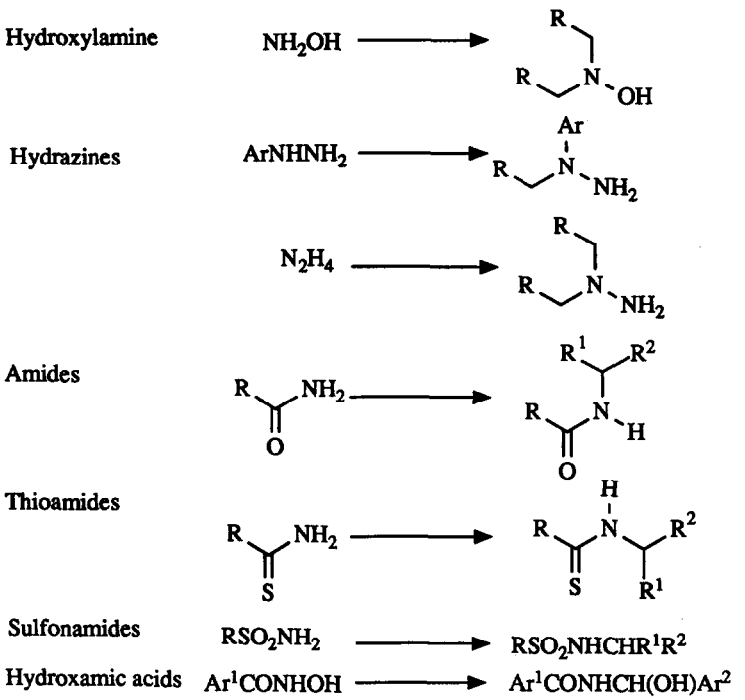


Ar	Yield	Ar	Yield
2-pyridyl	29 %	3-chlorophenyl	34 %
3-pyridyl	34 %	3-nitrophenyl	29 %
5-chloro-2-pyridyl	39 %		

ALKYLATION OF HYDROXYLAMINE, HYDRAZINES AND AMIDES

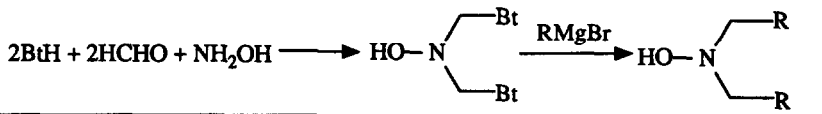
In addition to the NH groups of primary and secondary amines many other NH containing compounds can also be alkylated using this benzotriazole methodology. Such reactions for hydroxylamines, hydrazines, amides, and thioamides are shown schematically in the overview in Scheme 32.

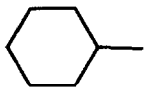
Scheme 32. Alkylation of Other NH Compounds



Symmetrical N,N-disubstituted hydroxylamines may be prepared in high yield from the reaction of bis(benzotriazolylmethyl)hydroxylamine with 2 equivalents of a Grignard reagent (Scheme 33). Once again, $(BtCH_2)_2NOH$ is readily available from the condensation reaction of benzotriazole, hydroxylamine and formaldehyde.[16]

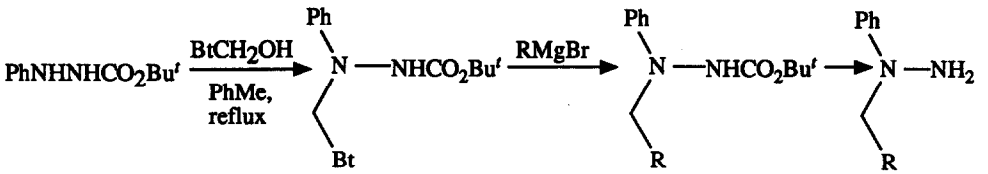
Scheme 33. Preparation of Symmetrical N,N-Disubstituted Hydroxylamines



R	Yield (%)	R	Yield (%)
PhC≡C–	87	C_8H_{17}	92
	86	C_4H_9	89
		Me_2CH	73
		Ph	94

The alkylation of hydrazines is described in Schemes 34 and 35. A mono-substituted hydrazine can be converted into a 1,1-disubstituted hydrazine by first protecting the free amino group (Scheme 34).[25] Subsequent reaction with hydroxymethylbenzotriazole, followed by reaction with a Grignard reagent, and, finally, removal of the protecting group results in the formation of the required products.

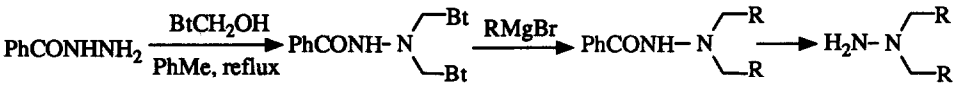
Scheme 34. Mono-Alkylation of Hydrazines



Compounds Prepared: R = Ph (92%), $PhCH_2$ (85%), PhC≡C (96%).

The preparation of symmetrical 1,1-dialkylhydrazines is achieved from the reaction of an acyl hydrazide with two moles of hydroxymethylbenzotriazole, followed by replacement of both the benzotriazolo groups with a Grignard reagent (Scheme 35).[25]

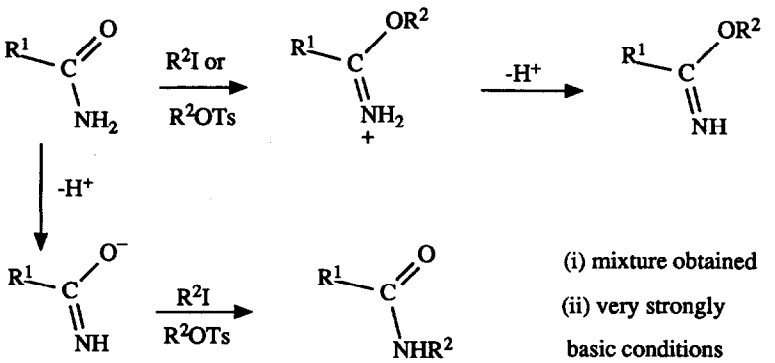
Scheme 35. Di-Alkylation of Hydrazines



R = $PhCH_2$ (80%), PhC≡C (92%)

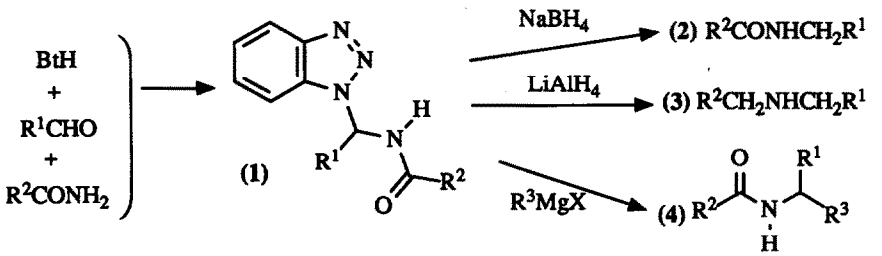
Classical methods for the alkylation of amides are described in Scheme 36. To avoid the formation of iminoethers resulting from alkylation at the oxygen atom, it is necessary to first deprotonate the amide so that alkylation occurs on the corresponding anion. This procedure has the disadvantage that it requires the use of strongly basic conditions and often results in the formation of product mixtures.

Scheme 36. Alkylation of Amides: Classical Methods



By contrast, the alkylation of amides using the benzotriazole method occurs specifically at the N-atom and in high yield.[26] The formation of the adducts is shown schematically in Scheme 37. Subsequent reduction with sodium borohydride or reaction with Grignard reagents results in the formation of N-alkylated secondary amides. Reduction with lithium aluminum hydride yields unsymmetrical secondary amines.[27]

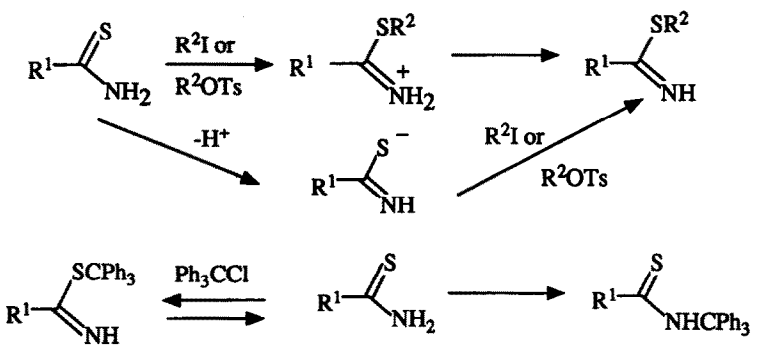
Scheme 37. Alkylation of Amides: Reaction Scheme



			Yield of compound (%)			
R^1	R^2	R^3	(1)	(2)	(3)	(4)
H	Ph		78	96	76	—
i-Propyl	Ph	$PhCH_2$	52	96	75	95
Propyl	Ph	Ph	59	96	58	92
Octyl	Ph		74	99	64	—
Ph	Ph	Butyl	60	94	65	85
Ph	Me		45	98	83	—

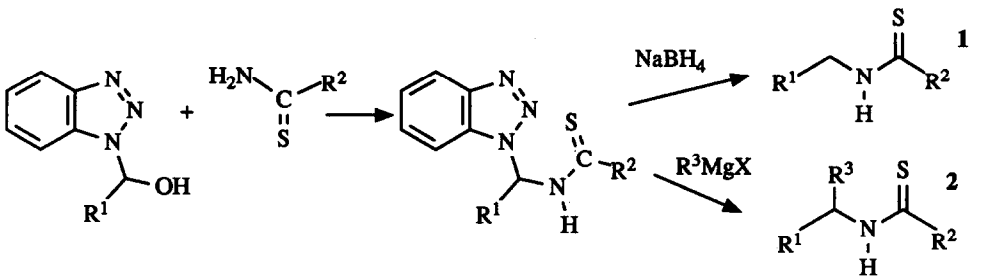
Until recently, the N-alkylation of thioamides had not been possible due to the preferential reaction at the highly nucleophilic sulphur atom. Formation of the thioamide anion does not result in alkylation at the nitrogen (Scheme 38). In the literature, nitrogen alkylation is only observed in the reaction of certain thioamides with trityl chloride. However, in this case, alkylation also occurs preferentially at the sulfur, but because the reaction is reversible, the S-tritylated product is gradually converted into the N-tritylated derivative.

Scheme 38. Alkylation of Thioamides: Classical Methods



Benzotriazole-mediated alkylation reactions invariably give the thermodynamically more stable products. Thus, it is no surprise that thioamides can also be alkylated at the nitrogen atom using this technique[27,28] (Scheme 39). Once again, the benzotriazolylmethylthioamide intermediate product need not be isolated prior to reaction with $NaBH_4$ or Grignard reagents.

Scheme 39. N-Alkylation of Thioamides via Benzotriazolylmethylthioamide Intermediates

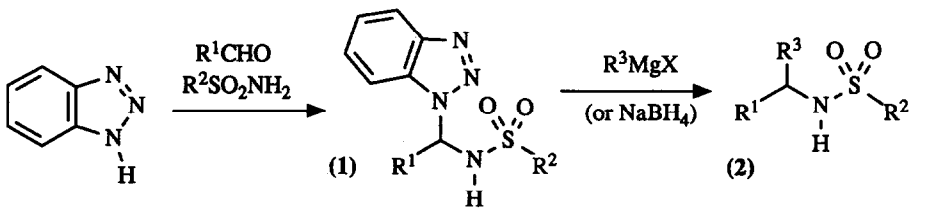


1:	R^1	R^2	Yield (%)
	H	Ph	98
	i-Pr	Ph	99
	C_5H_{11}	Ph	92
	C_7H_{15}	Ph	95
	i-Pr	NH_2	60

2:	R^1	R^2	R^3	Yield (%)
	i-Pr	Ph	$PhCH_2$	87
	Pr	Ph	Bu	89
	C_5H_{11}	Ph	Ph	88
	$C_{11}H_{23}$	Ph	$PhCH_2$	81
	H	Ph	$PhCH_2$	84

In a similar manner to thioamides, sulfonamides can be readily converted to N-alkyl sulfonamides (Scheme 40).[29] The N-(benzotriazolylmethyl)sulfonamides are prepared in high yields by the condensation of benzotriazole, an appropriate aldehyde and a primary sulfonamide.

Scheme 40. N-Alkylation of Sulfonamides

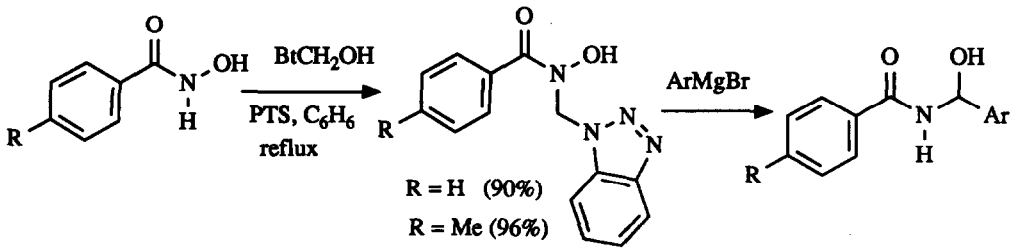


R^1	R^2	(1), Yield (%)	R^3	(2), Yield (%)
H	Ph	94	H	97
i-Pr	Ph	84	H	71
2-pyridyl	Ph	80	H	96
H	Ph	94	Ph	94
i-Pr	Ph	84	Ph	96
Ph	Ph	52	Ph	88
Ph	4-MeC_6H_4	61	H	75

Aryl hydroxamic acids react with hydroxymethylbenzotriazole to give N-(benzotriazol-1-yl)methylated derivatives. On reaction with aryl Grignard reagents, however, these compounds undergo a rearrangement to furnish acyclic N-(α-hydroxybenzyl)benzamides (Scheme 41).[30] Although α-hydroxylactams may be readily prepared, and are important synthetic intermediates, there are very few reports of the preparation of

their acyclic conterparts. Excluding those derived from formaldehyde, the equilibrium for formation of α-hydroxyamides generally lies well to the side of the amide and aldehyde.

Scheme 41. Synthesis of Acyclic N-(α-Hydroxybenzyl)benzamides

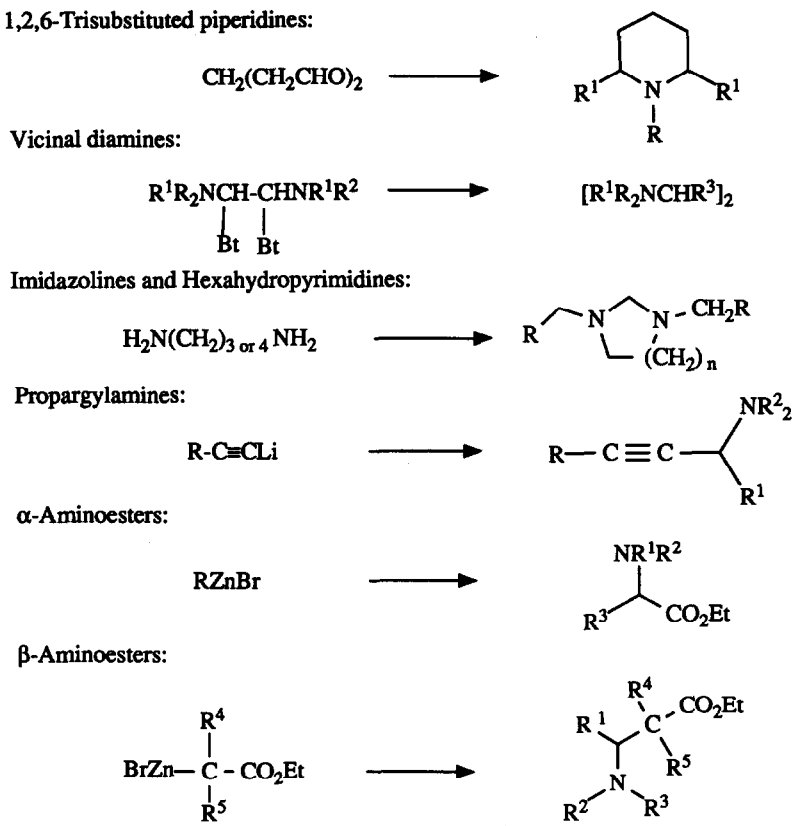


R	Ar	Amide Yield (%)
H	Ph	40
	4-$MeOC_6H_4$	35
	4-ClC_6H_4	60
Me	Ph	32
	4-ClC_6H_4	50
	1-naphthyl	52

THE SYNTHESIS OF POLYFUNCTIONAL AMINO COMPOUNDS

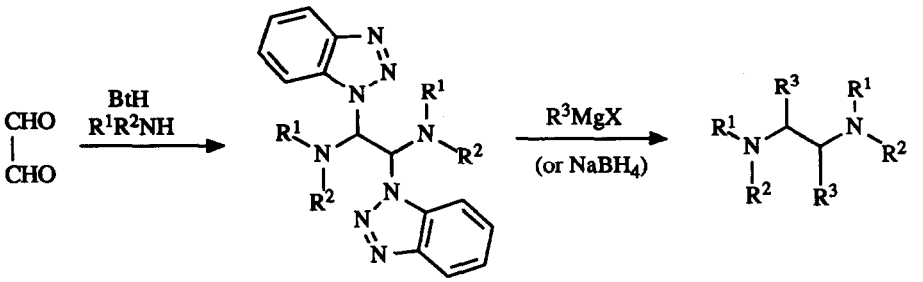
The use of benzotriazole as a synthetic auxiliary allows the efficient synthesis of many other types of polyfunctional amines. A selection of such applications is outlined in Scheme 42.

Scheme 42. Preparation of Polyfunctional Amines



The reaction of glyoxal with 2 equivalents of both benzotriazole and a primary or secondary amine results in both aldehyde functions undergoing the condensation reaction. Subsequent displacement of the benzotriazolo groups with sodium borohydride or Grignard reagents results in high yields of vicinal diamines (Scheme 43).[31]

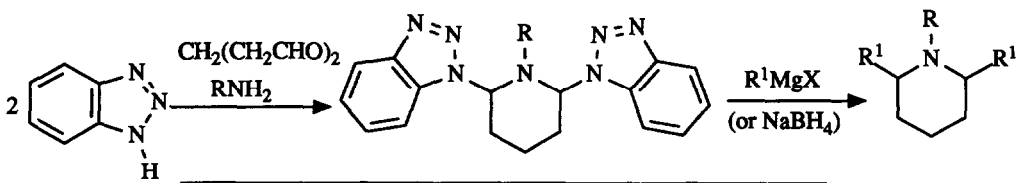
Scheme 43. Vicinal Diamines



R^1	R^2	R^3	Yield (%)
-$(CH_2)_5$-		H	79
-$CH_2CH_2OCH_2CH_2$-		H	76
$PhCH_2$	$PhCH_2$	H	87
Ph	H	H	90
4-MeC_6H_5	H	H	93
-$(CH_2)_5$-		Ph	78
-$(CH_2)_5$-		$PhCH_2$	77
-$(CH_2)_5$-		Me	70
-$(CH_2)_5$-		Bu	62
$PhCH_2$	$PhCH_2$	Ph	81
$PhCH_2$	$PhCH_2$	Me	83
Ph	H	$PhCH_2$	69

Symmetrical 2,6-disubstituted piperidines can be prepared by the reaction of Grignard reagents with 1-substituted 2,6-dibenzotriazolylpiperidine (Scheme 44). This latter compound is readily obtained from the reaction of two equivalents of benzotriazole with pentanedial and a primary amine.[32]

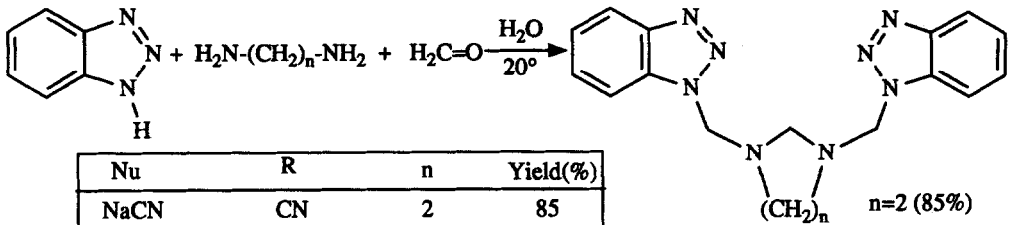
Scheme 44. Synthesis of 1,2,6-Trisubstituted Piperidines



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

The reaction of diamines with benzotriazole and formaldehyde frequently results in the formation of azapyrrolidines. Nucleophilic displacement of benzotriazolo groups from such compounds readily occurs (Scheme 45).[33]

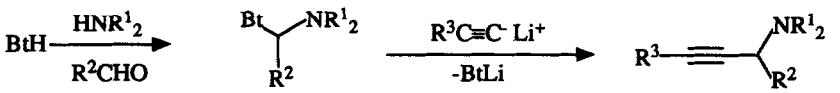
Scheme 45. Reaction of Benzotriazole with Formaldehyde and Primary Diamines

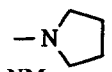
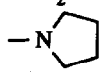
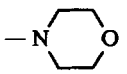
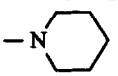
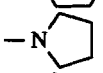
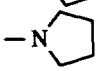


Nu	R	n	Yield(%)
NaCN	CN	2	85
NaCN	CN	3	87
EtMgBr	Et	2	72
EtMgBr	Et	3	77
BuMgBr	Bu	2	68
OctylMgBr	Octyl	2	75

The preparation of propargylamines by the reaction of benzotriazolylmethylamines with lithiated terminal alkynes (Scheme 46) [34] is far superior to all other reported methods. This benzotriazole mediated route is experimentally convenient, general, and high yielding. Propargylamines have been of interest recently because of their physiological properties.

Scheme 46. Preparation of Propargylamines



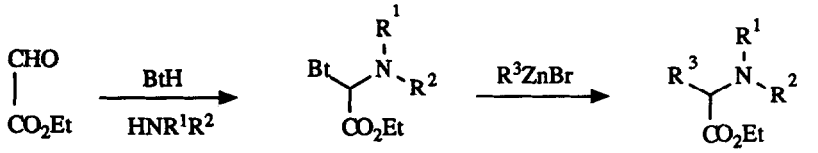
-NR^1_2	R^2	R^3	Yield (%)
-$N(CH_2Ph)_2$	H	Ph	70
	H	Ph	76
-NMe_2	H	Ph	71
	-$CHMe_2$	Ph	67
-$N(CH_2Ph)_2$	-$CHMe_2$	Ph	95
	Ph	Ph	32.5
-$N(CH_2Ph)_2$	-$CHMe_2$	C_6H_{13}	96
	Ph	Ph	73*
	-$CHMe_2$	C_6H_{13}	71*
	-$CHMe_2$	C_4H_9	75*

*overall yield, intermediate N-(benzotriazolylmethyl)amine not isolated

Ethyl glyoxylate condenses with benzotriazole and an amine in an analogous manner to other aldehydes. Substitution of benzotriazolate anion from these adducts using alkylzinc halides furnishes a facile route to α-aminoesters (Scheme 47).[35]

Replacing the glyoxylate ester in this condensation reaction with the diethoxymonoacetal of glyoxal, followed by Grignard reaction and hydrolysis, results in a simple route to α-aminoaldehydes.[36]

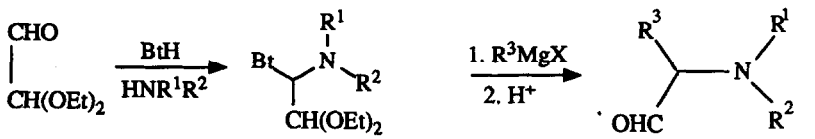
Scheme 47. α-Amino Esters



(not isolated)

R^1, R^2	R^3	Yield	R^1, R^2	R^3	Yield
Et, Et	Ph	75	$(CH_2)_5$	$PhCH_2$	75
$(CH_2)_4$	Ph	75	$(CH_2)_5$	4-MeC_6H_4	69
$(CH_2)_5$	Me	55			

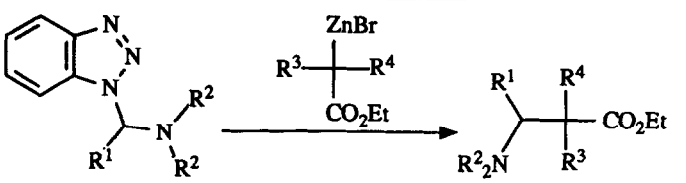
Scheme 48. α-Amino Aldehydes



R^1, R^2 = - $CH_2CH_2OCH_2CH_2$ - $R^3 = CH_3CH_2$ Yield = 70%

In a similar manner, β-aminoesters have been prepared from benzotriazolylmethylamines by their reaction with Reformatsky reagents (Scheme 49).[37] A wide range of β-amino and β-alkoxycarbonylamino esters have been synthesized in this manner.

Scheme 49. β-Amino Esters



(not isolated)

R^1	NR^2_2	R^3	R^4	Yield %
$(CH_3)_2CH$	Morpholinyl	H	Me	82
Ph	Piperidinyl	Me	Me	73
$CH_3CH_2CH_2$	Pyrrolidinyl	H	H	51
H	Dibenzylamino	Me	Me	76
$(CH_3)_2CHCH_2$	$NHCO_2CH_2Ph$	H	H	57
Ph	$NHCO_2CH_2Ph$	H	H	55

PREPARATION OF OTHER POLYFUNCTIONAL COMPOUNDS

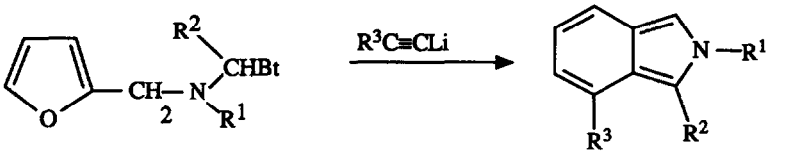
Benzotriazole methodology can be used in the preparation of many other classes of polyfunctional compounds. Some of these methods are summarized in Scheme 50.

Scheme 50. Preparation of Other Polyfunctional Compounds

Unsymmetrical Formamidines:

$$BtCH_2NC \longrightarrow BtCH_2N{:}CHNR'_2 \longrightarrow R''CH_2N{:}CHNR'_2$$

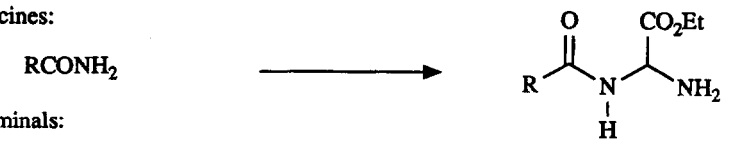
Isoindoles:



Isoimidazoles:

Formaminals:

α-Aminoglycines:

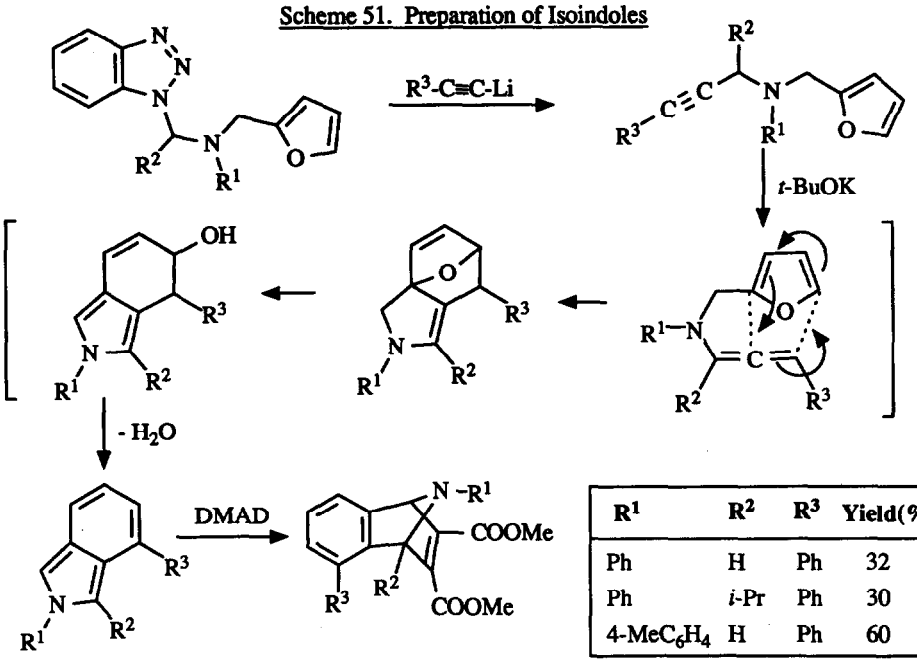


monoacyl aminals:

Bt - assisted synthesis of peptides

This method for the preparation of propargylamines already described has been extended to a synthesis of bridged iso-indoles (Scheme 51).[38] Treatment of an N-furfurylmethylpropargylamine with potassium t-butoxide results in intramolecular Diels-Alder reaction of the intermediate allene. The diene that results undergoes further Diels-Alder reaction with dimethyl acetylenedicarboxylate to give the bridged isoindole product.

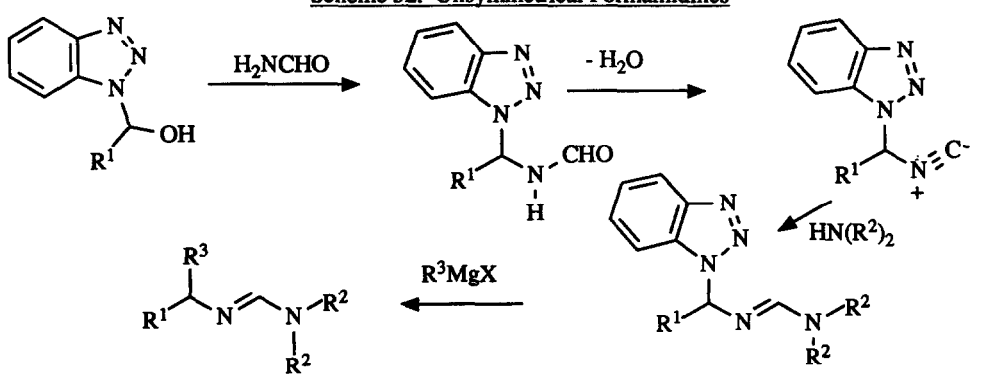
Scheme 51. Preparation of Isoindoles



R^1	R^2	R^3	Yield(%)
Ph	H	Ph	32
Ph	*i*-Pr	Ph	30
4-MeC_6H_4	H	Ph	60

The synthesis of formamidines can be accomplished by treatment of the isonitriles formed by dehydration of N-(benzotriazolylmethyl)formamides with secondary amines. Subsequent reaction with Grignard reagents results in displacement of the benzotriazole residue (Scheme 52).[39]

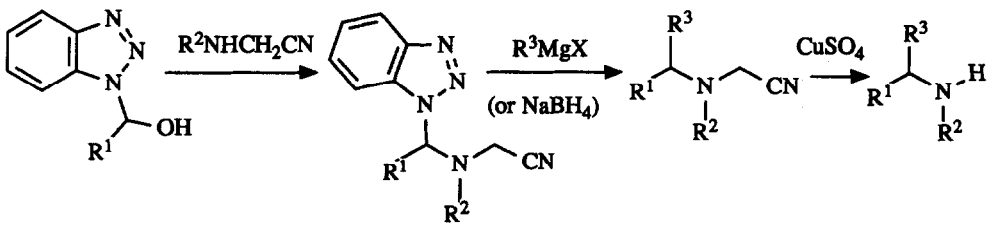
Scheme 52. Unsymmetrical Formamidines



R^1	R^2	R^3	Yield (%)
H	-$(CH_2)_5$-	Ph	80
H	-$CH_2CH_2OCH_2CH_2$-	Ph	82
H	-$(CH_2)_4$	Ph	79
H	-$(CH_2)_5$	4-MeC_6H_4	62
H	-$(CH_2)_5$	CH_2=CH	76
i-Pr	-$(CH_2)_5$	Ph	53

α-Aminonitriles may be polyfunctionalized by using these compounds in place of amines in the condensation reaction with benzotriazole and aldehydes. After displacement of benzotriazolate anion with an organometallic reagent, demethylcyanation can be accomplished by treatment with $CuSO_4$ (Scheme 53), thus affording a route to unsymmetrical secondary amines.

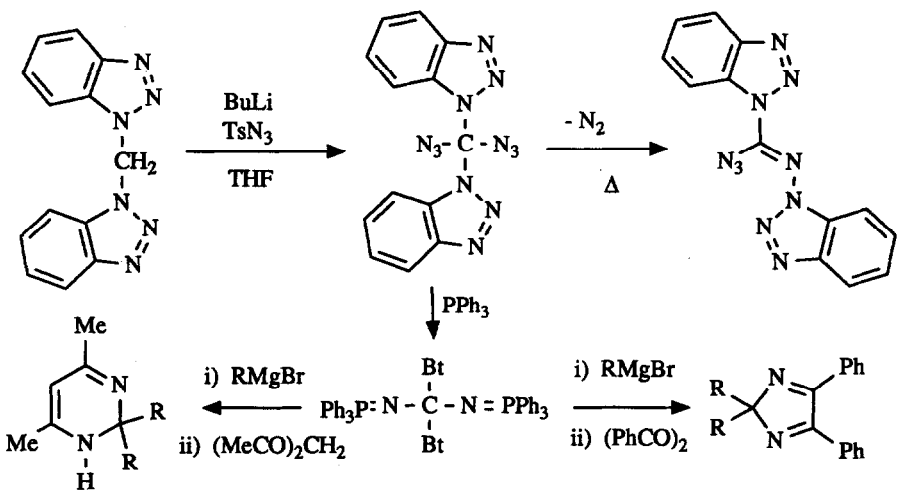
Scheme 53. Polyfunctional α-Aminonitriles



R^1	R^2	R^3	Acetonitrile (%)	Amine (%)
octyl	H	H	66	90
octyl	Pr	H	70	87
octyl	Ph	H	77	95
octyl	*i*-Pr	H	73	97
octyl	H	$PhCH_2$	65	99
cyclohexyl	H	$PhCH_2$	63	93

Other geminal diamino derivatives may be synthesized using the diazide shown in Scheme 54. This compound is prepared by the reaction of tosyl azide with dibenzotriazolylmethane.[40]

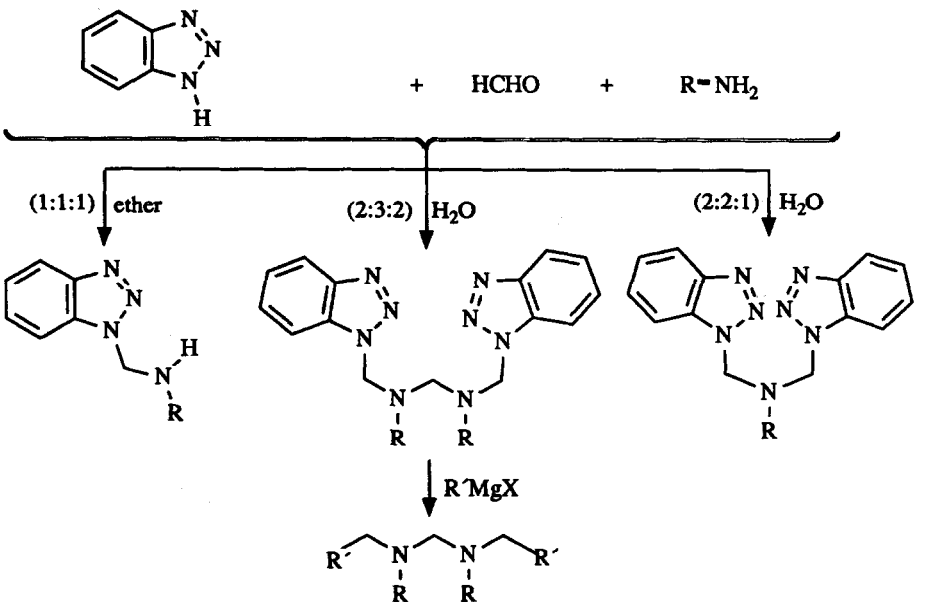
Scheme 54. Diazides and Derivatives of 1,1-Diamines



As already described, the reaction of a primary aromatic amine with benzotriazole and an aldehyde is easy to stop at the mono-adduct stage. With primary aliphatic amines, the situation is more complex. The reactions of primary aliphatic amines with benzotriazole and formaldehyde are outlined in Scheme 55. In

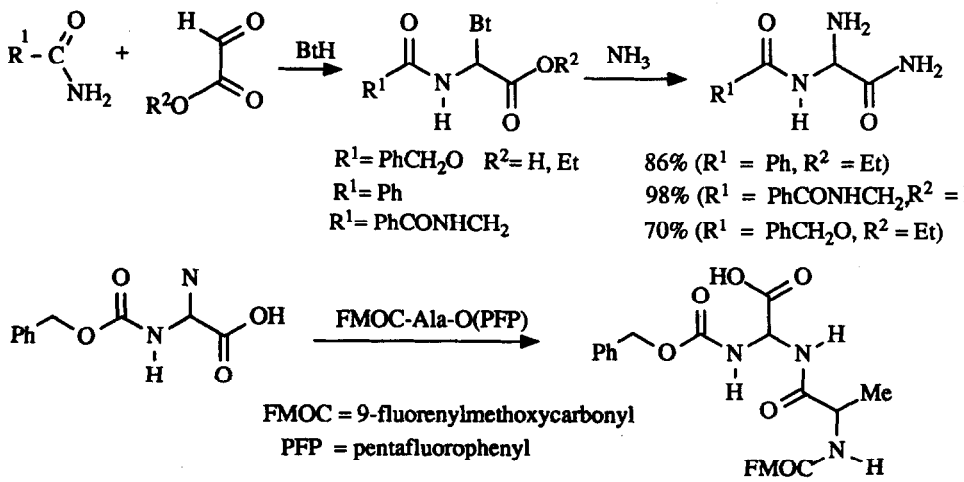
addition to the bis-product which is formed when R is unhindered,[33] we have isolated several examples of the mono-substituted derivatives from more hindered primary amines. Furthermore, by using an excess of formaldehyde and less benzotriazole, products derived from two molecules of amine, three of formaldehyde and two of benzotriazole, have been isolated.[33]

Scheme 55. Benzotriazolylmethylation of Primary Aliphatic Amines



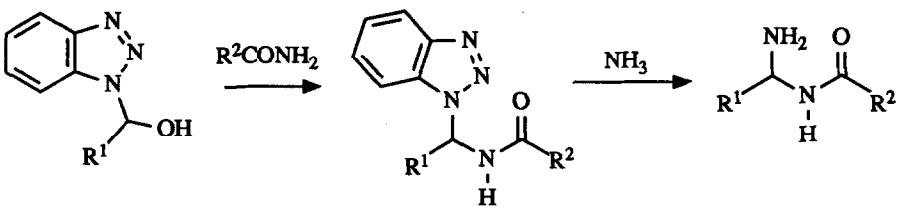
We have also found that it is possible to replace the benzotriazole residue in amide adducts using ammonia. This has led to efficient syntheses of mono-acyl-α-aminoglycines and of the corresponding "reversed" peptides, as shown in Scheme 56.[41]

Scheme 56. Benzotriazole-assisted Synthesis of Monoacyl α-Aminoglycines



Recently, this method has been extended to the preparation of a variety of other aminals[42] (Scheme 57). Thus, treatment of benzotriazolylmethylamides with ammonia results in formation of monoacyl aminals in high yield.

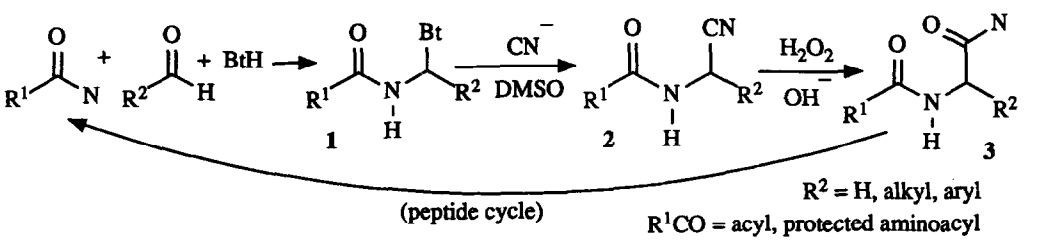
Scheme 57. Monoacyl Aminals



R^1	R^2	Adduct (%)	Aminal (%)	R^1	R^2	Adduct (%)	Aminal (%)
H	$PhCH_2O$	80	77	Ph	$PhCH_2O$	87	63
Pr	$PhCH_2O$	90	74	COOEt	Me	72	91
i-Pr	$PhCH_2O$	75	66	COOEt	Ph	74	86
i-Bu	$PhCH_2O$	85	77	COOEt	$PhCH_2O$	70	37

Substitution of the benzotriazole residue with CN^- followed by mild hydrolysis of the nitrile, allows a novel method for the elongation of peptides (Scheme 58).[43]

Scheme 58. Benzotriazole-Assisted Synthesis of Amino Acids and Peptides: The CN^- Method



(peptide cycle)

R^2 = H, alkyl, aryl

R^1CO = acyl, protected aminoacyl

	R^1	R^2	Yields 1[a]	2	3
(a) simple amides	$PhCH_2O$	H	80	80	-
	"	Pr^n	90	85	-
	"	Pr^i	75	80	-
	"	Bu^i	85	90	-
	"	Ph	70	90	99
	Bu^tO	Pr^i	70	90	-
(b) protected amino acid amides	$BzNHCH_2$	Pr^i	74	73	-
	ZNHCH(Bzl)	Pr^i	73/62	95	93
	ZNHCH(Bu^s)	Pr^i	60	86	-
	ZNHCH(Ph)	Bu^i	88/20	87	95
	ZNHCH(Pr^i)-L	Bu^i	50/55	85	-
	ZNHCH(Pr^i)	Bu^i	80	85	-
	ZPheNHCH(Pr^i)	Bu^i	84	94	85

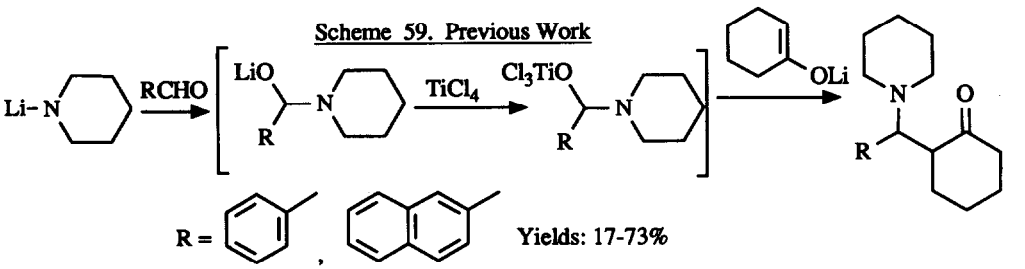
[a] crude/diastereo homogeneous

Z = $PhCH_2OCO$, Phe = Phenylamine

GENERALIZED MANNICH REACTION OF KETONES AND NITRO COMPOUNDS

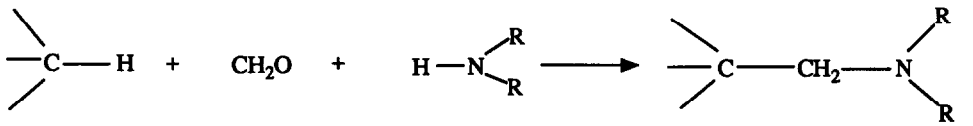
In general, the aminoalkylation of ketones (Mannich reaction) has been limited to the synthesis of derivatives in which the nitrogen atom is linked by a CH_2 group. An exception to this has been the work of Seebach (Scheme 59).[44]

Scheme 59. Previous Work



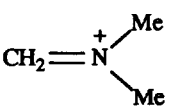
α-Benzotriazolylalkylamines possess considerable synthetic importance because they allow serious limitations of the Mannich reaction to be surmounted. The Mannich reaction involves the condensation reaction of an active hydrogen compound, formaldehyde, and a compound containing an NH or NH_2 group (Scheme 60). The two main limitations of this reaction are (i) that it is, with few exceptions, limited to formaldehyde (i.e. few Mannich reactions involving other aldehydes are known), and (ii) that it is difficult to prevent multiple reactions. Eschenmoser introduced the so-called,"Eschenmoser Salts", as Mannich components which has overcome the second limitation.[45,46,47] Because of the ability of the benzotriazolyl adducts to ionize, they may behave as Eschenmoser Salts, and thus the potential arises to extend the Mannich reaction to aldehydes in a general manner.

Scheme 60. Limitation of Mannich Reaction

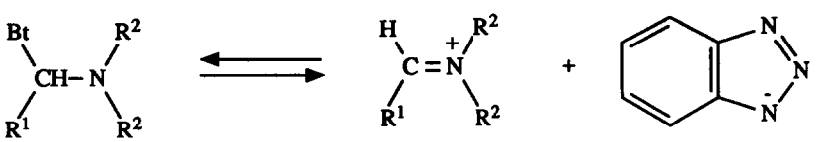


(active C-H)

(i) limited to formaldehyde
(ii) difficult to prevent multiple reactions

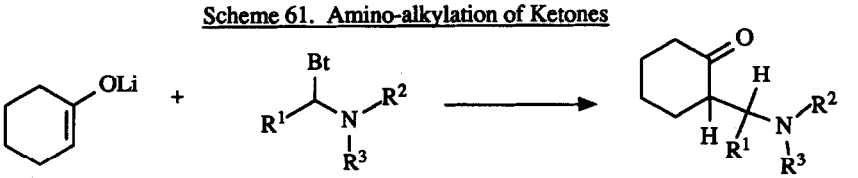
Eschenmoser's salts : e.g.,  as Mannich components

Benzotriazole compounds as generalized Eschenmosers's salts allow the extension of the Mannich Reaction to most aldehydes



We have shown that the benzotriazolylmethylamine derivatives react with lithium enolates to give good yields of aminoalkylated ketones. Secondary or primary amines, amides, or sulfonamides may be used to form the nitrogen adduct (Scheme 61).[48]

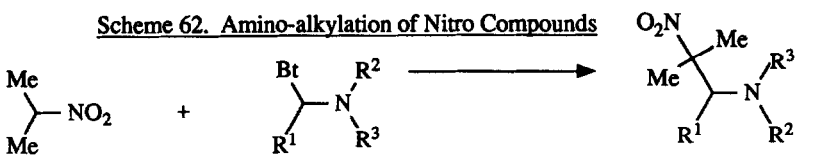
Scheme 61. Amino-alkylation of Ketones



R^1	R^2	R^3	Yield (%)	Anti/Syn	Previous Work
CH_3	(morpholino)		50	1:1	none
Ph	(piperidino)		48	4:1	84HCA1593 (%)
H	Ph	H	85	---	8 CA(99)5287c (%)
H	COPh	H	85	---	none
Pr^i	(piperidino)		52	1:1	none
H	(piperidino)		67	---	27AP598 (%)

The aminoalkylation of aliphatic nitro compounds has also been limited in previous reports. The benzotriazole methodology may also be successfully applied to this class of compounds (Scheme 62).[49]

Scheme 62. Amino-alkylation of Nitro Compounds



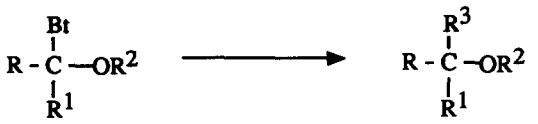
R^1	R^2	R^3	Yield (%)	Previous Preparations
Me	2-Py	H	64	none
2-Py	2-Py	H	61	none
Ph	PhCO	H	90	none
Me	Ph	H	63	none
H	$CH_2CH_2OCH_2CH_2$		68	46JA12

SYNTHESIS OF ETHERS AND ESTERS

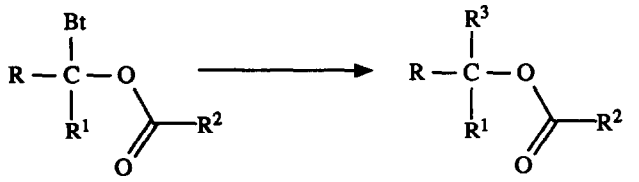
So far we have discussed the use of benzotriazole in the synthesis of nitrogen containing compounds. However, this is only one of the fields of application. Recently we have extended the utility of benzotriazole (as a synthetic auxiliary) to the preparation of oxygen compounds such as ethers and esters (Scheme 63).

Scheme 63. Synthesis of Oxygen Compounds

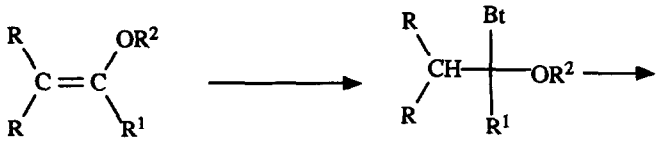
Ethers:



Esters:

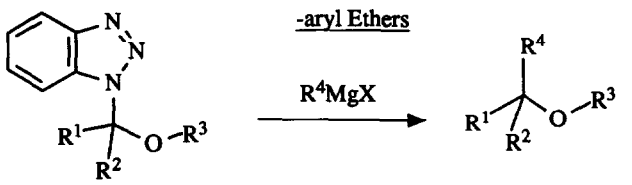


Use of Unsaturated Ethers:

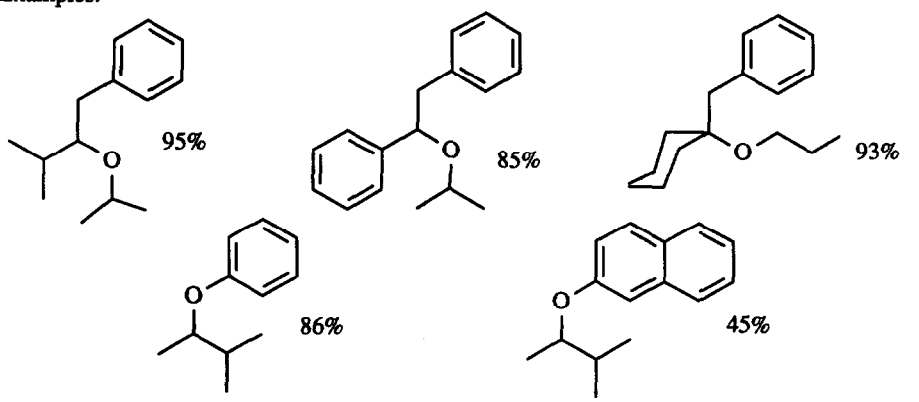


Examples of some new ethers prepared by this method are shown in Scheme 64.[50] These compounds would be extremely difficult to make, for example, by the classical Williamson ether synthesis due to the occurrence of facile elimination in such reactions.

Scheme 64. Synthesis of Ethers: Grignard Reactions on α-Benzotriazolyl-alkyl and -aryl Ethers



Examples:

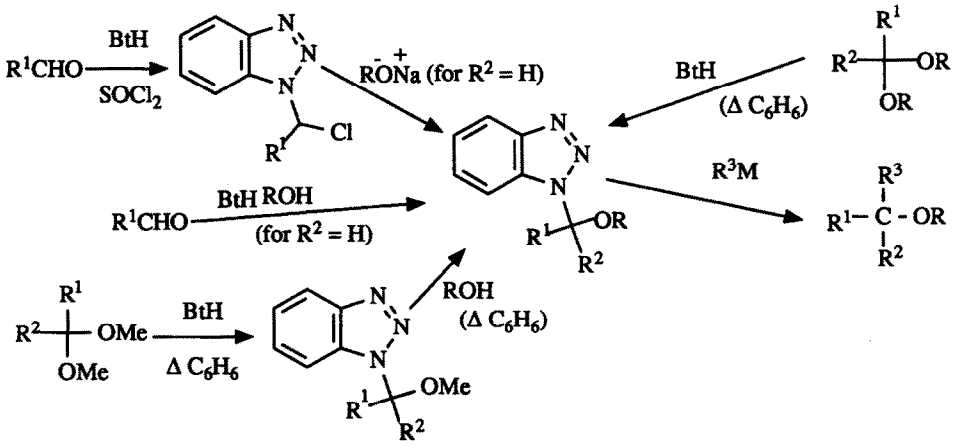


The starting materials for this ether synthesis are α-(alkoxyalkyl)benzotriazoles and these can be obtained by four different routes (Scheme 65). Each of these methods provides a simple entry to these

compounds, however, that using 1-(α-chloroalkyl)benzotriazoles easily prepared,[51] is particularly suitable for the synthesis of aryl-alkyl ethers.

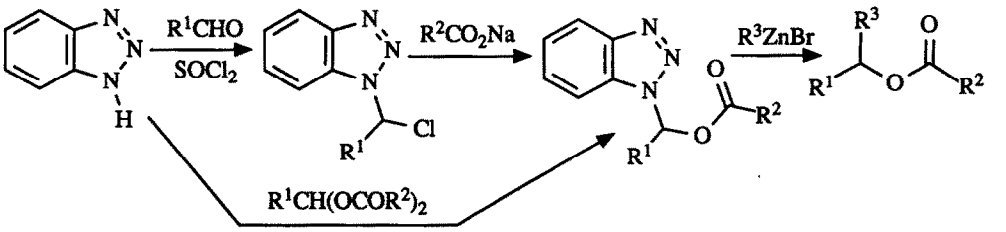
The reaction of Grignard reagents with the α-(alkoxyalkyl)benzotriazoles gives access to a wide range of ethers.[50]

Scheme 65. Preparation of Ether Starting Materials



This type of reaction has been further extended to the preparation of carboxylic esters as shown in Scheme 66.[52]

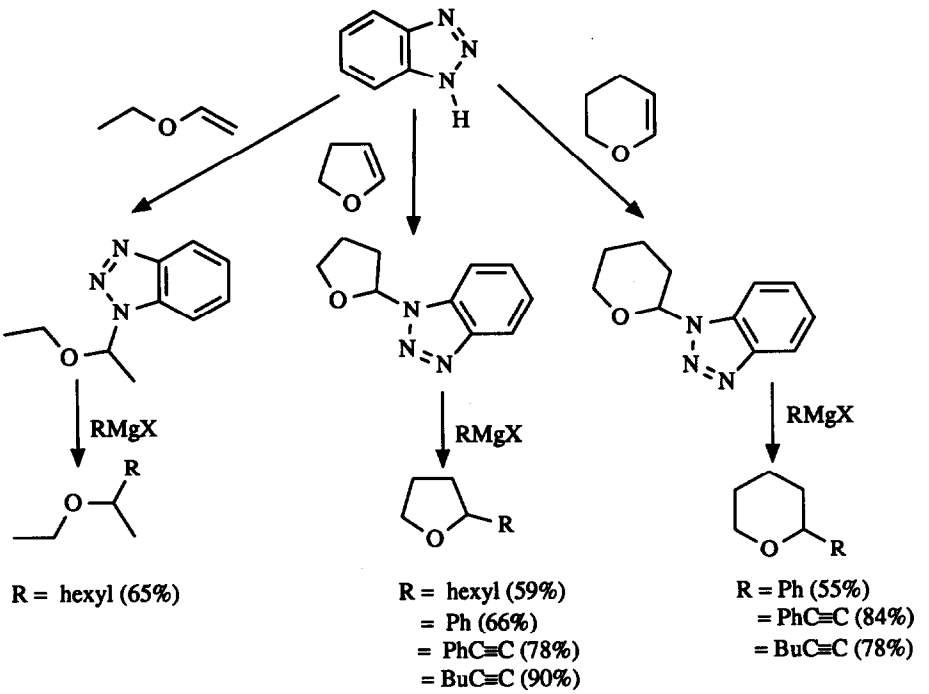
Scheme 66. Preparation of Carboxylic Acid Esters



R¹	R²	R³	Yield (%)
H	Ph	$PhCH_2$	64
H	Ph	$BuC{\equiv}C$	85
Pr	Me	Ph	74
Pr	Me	$PhCH_2$	94
Pr	Me	$PhC{\equiv}C$	87
Pr	C_5H_{11}	$PhCH_2$	95
Ph	Me	Bu	96
Ph	Me	$PhCH_2$	98

This ether synthesis has also been extended to allow modification of a wide range of cyclic ethers. Vinyl ethers readily add benzotriazole, and these adducts react with a wide variety of Grignard reagents to form the expected α-alkylated saturated ethers (Scheme 67).[53]

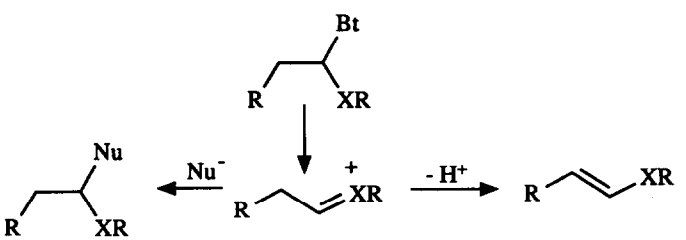
Scheme 67. Preparation of α-Alkylated Saturated Ethers from Unsaturated Ethers



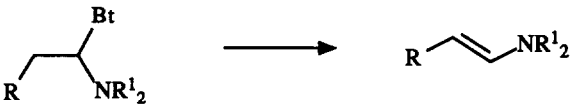
SYNTHETIC METHODS DEPENDING ON THE ELIMINATION OF BENZOTRIAZOLE

Many of the reactions that have been discussed depend on the ionization of an N-(α-aminoalkyl)benzotriazole to an imonium cation and the benzotriazole anion or of an N-(α-alkoxyalkyl)benzotriazole to an oxonium cation, with subsequent reaction of the cation with a nucleophile. However, another fundamentally different route is available in which, instead of reacting with a nucleophile, the imonium or oxonium cation loses a proton (Scheme 68), allowing synthetic routes to enamines, enol ethers and nitrones.

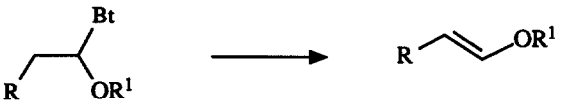
Scheme 68. Reaction Pathways of N-(α-Heteroatom-alkyl)benzotriazoles



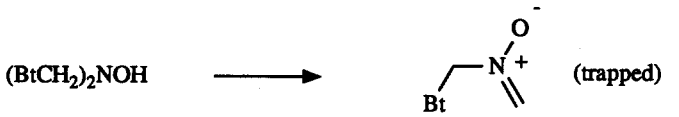
Enamines:



Enol ethers:

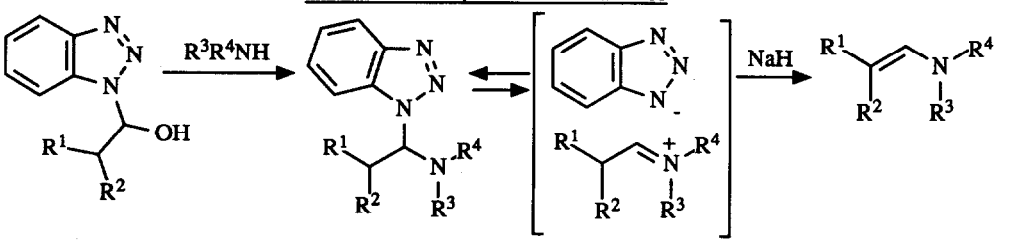


Nitrones:



In this way, a synthesis of enamines has been developed[54] (Scheme 69). Many enamine syntheses are available but in all of them an excess of the amine component is used and the yield is calculated based on the carbonyl component. Using benzotriazole as a synthetic auxiliary in this new method gives good yields calculated on the amino component.

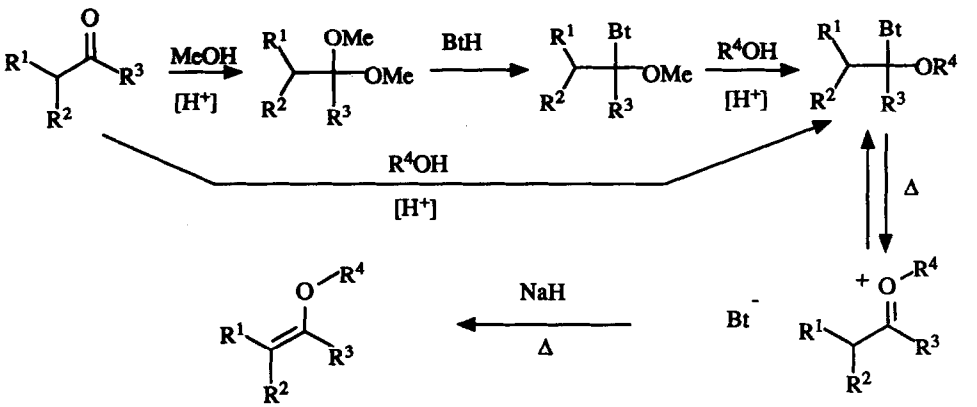
Scheme 69. Preparation of Enamines



R^1	R^2	R^3	R^4	Yield (%)
Me	H	$-CH_2CH_2OCH_2CH_2-$		95
Et	H	$-CH_2CH_2OCH_2CH_2-$		87
H	H	$-CH_2CH_2OCH_2CH_2-$		88
Me	Me	$-CH_2CH_2OCH_2CH_2-$		95
Pr	H	$-CH_2CH_2OCH_2CH_2-$		81
Bu	H	$-CH_2CH_2OCH_2CH_2-$		93

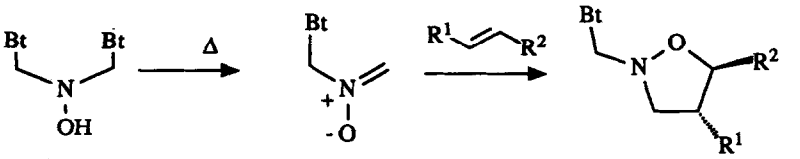
An analogous procedure to that for the synthesis of enamines can be used to make enol ethers (Scheme 70).[55]

Scheme 70. Synthesis of Enol Ethers



Benzotriazole derivatives have also been shown to be useful as components in cycloaddition reactions. Thus, bis(benzotriazolylmethyl)hydroxylamine acts as a nitrone synthon and undergoes 1,3-dipolar cycloaddition with a wide range of 1,3-dipolarophiles (Scheme 71).[56] This elimination reaction is clearly related to those just described.

Scheme 71. Isoxazolidines

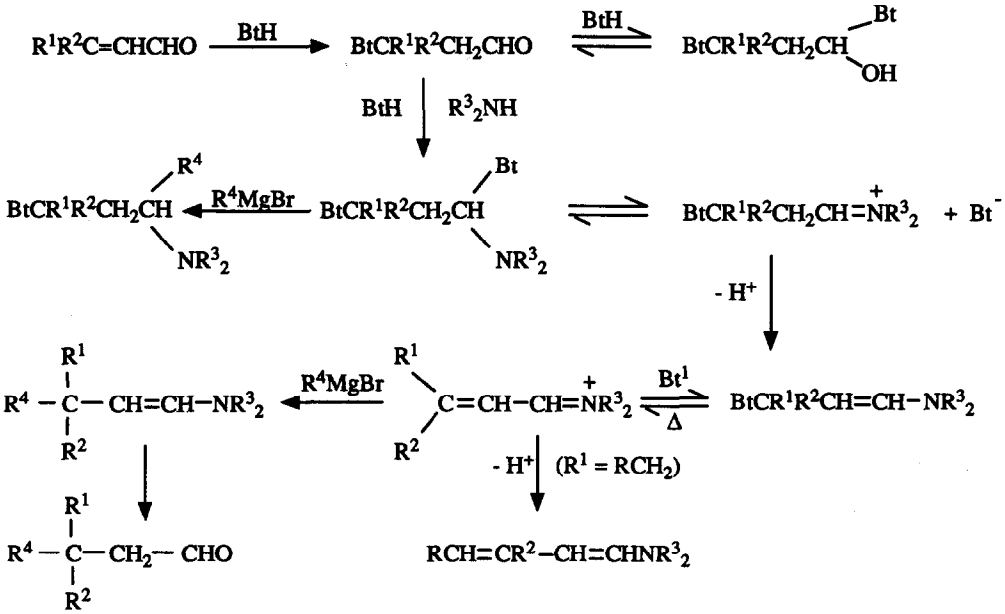


R^1	R^2	Yield (%)
H	COOMe	100
H	2-pyridyl	83
H	4-pyridyl	81
H	CN	88
COOMe	COOMe	91

WORK WITH VINYLOGOUS AND RELATED SYSTEMS

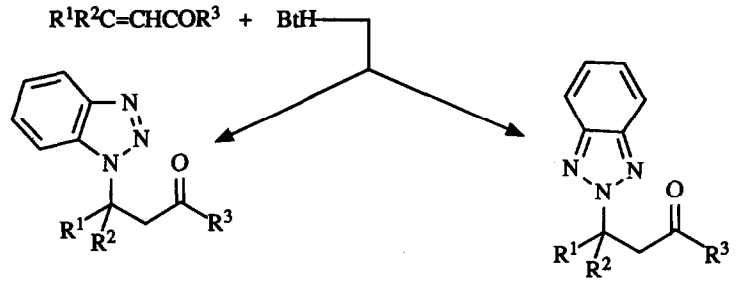
Some of the products which can be derived from reactions of benzotriazole and amines with αβ-unsaturated aldehydes are shown in the overview of Scheme 72.

Scheme 72. Benzotriazole - Mediated Reactions of αβ-Unsaturated Aldehydes



Benzotriazole undergoes addition to α,β-unsaturated aldehydes and ketones to form the corresponding β-benzotriazolyl-aldehydes and -ketones (usually as mixtures of Bt-1 and Bt-2 isomers) in high yields (Scheme 73).[57]

Scheme 73. Addition of Benzotriazole to α, β-Unsaturated Aldehydes and Ketones

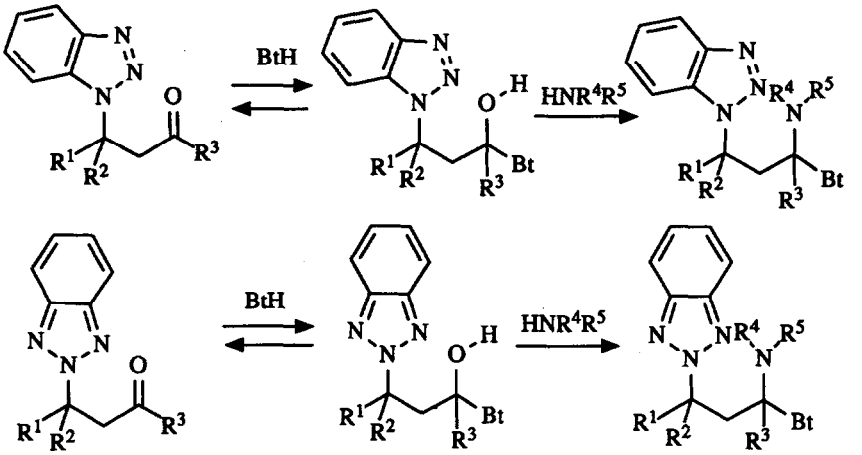


R^1	R^2	R^3	Yield (%) (mixture of isomers)
H	H	H	85
Me	H	H	54
H	H	Me	80
Ph	H	Me	80
PhCO	H	Ph	80
Me	Me	Me	76

αβ-Unsaturated aldehydes will react with a further molar equivalent of benzotriazole to give 1,3-bis(benzotriazolyl)alcohols. These adducts are usually rather unstable, although careful recrystallization

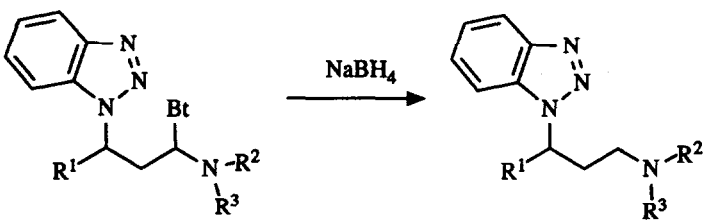
can sometimes give analytically pure compounds. When an amine is added to the reaction mixture, 1,3-bis(benzotriazolylalkyl)amines are formed as stable crystalline products (Scheme 74).[57]

Scheme 74. Addition of Benzotriazole and an Amine to α, β-Unsaturated Aldehydes



The benzotriazolyl substituent in the 1-position of 1,3-di(benzotriazolyl)alkylamines is labile (as are derivatives of this type derived from saturated aliphatic aldehydes). For example, it can be easily removed by reduction with sodium borohydride to give 3-benzotriazolylalkylamines in high yields (Scheme 75).[57]

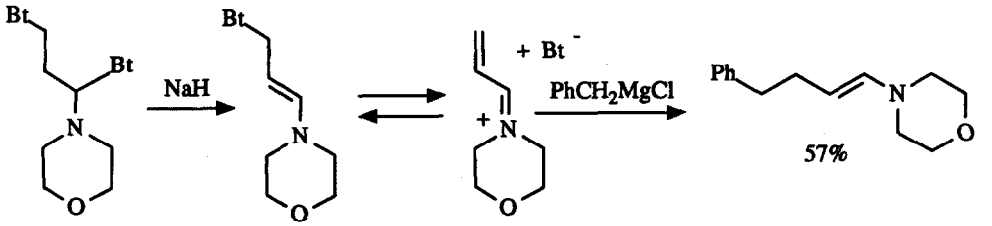
Scheme 75. 3-(Benzotriazol-1-yl)alkylamines



R^1	R^2	R^3	Yield (%)
Me	Ph	H	95
Me	4-MeC_6H_4	H	93
Me	4-ClC_6H_4	H	90
H	4-MeC_6H_4	H	76
H	-$CH_2CH_2OCH_2CH_2$-		84
Ph	-$CH_2CH_2OCH_2CH_2$-		83

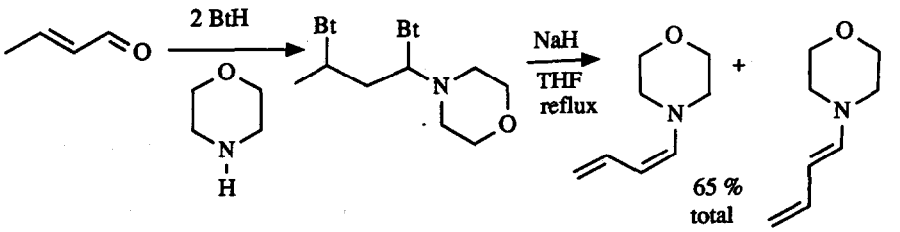
The benzotriazolyl substituent of position 1 can also be eliminated by treatment of 1,3-di(benzotriazolyl)alkylamines with sodium hydride in refluxing THF. The 3-benzotriazolyl-enamines thus formed still possess the ability to ionize to the benzotriazolyl anion and eniminium cation: the amine electron donor influence being transmitted via the C=C bond. The eniminium cation can be trapped by an organometallic reagent providing a new synthesis of complex enamines (Scheme 76).[58]

Scheme 76. 3-(Benzotriazol-1-yl)enamines and Their Use in Synthesis



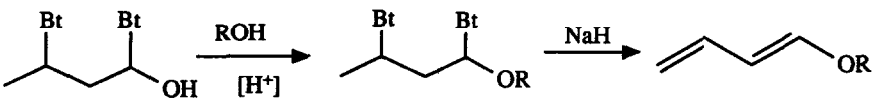
Alternatively, both benzotriazolyl residues can be removed by excess NaH to afford dienamines (Scheme 77).[59]

Scheme 77. Preparation of Dienamines



In an exactly analogous manner, dienyl ethers can be obtained as illustrated in Scheme 78.[59]

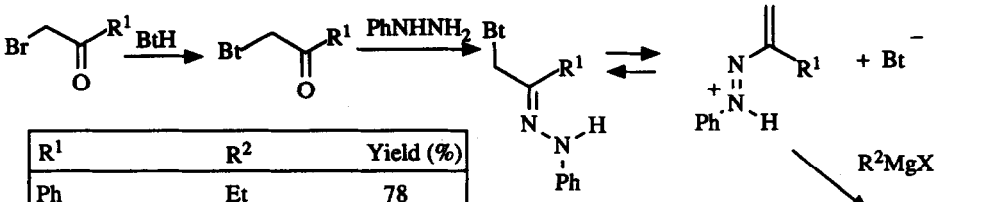
Scheme 78. Preparation of Dienyl Ethers



R = Me, CH_2Ph

Benzotriazolylmethyl ketones are readily obtained from the reactions of benzotriazole with α-bromoketones. The hydrazones of these ketones also tend to undergo ionization to the 2-aza-analogues of the cations discussed above. Reaction of these cations with Grignard reagents, and subsequent hydrolysis, provides a new synthetic route to ketones (Scheme 79).[60]

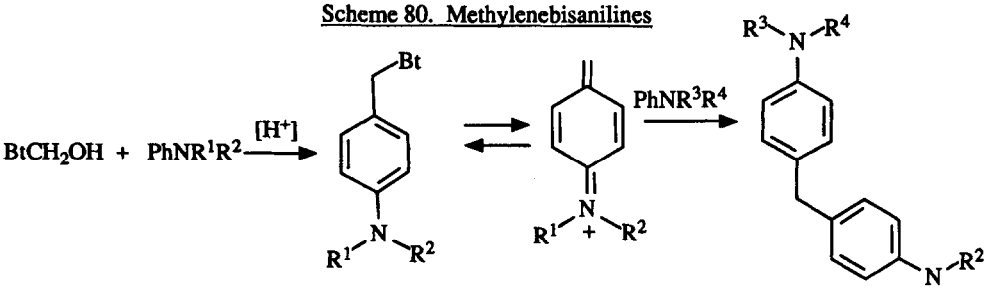
Scheme 79. The Synthesis of Ketones from Hydrazones



R^1	R^2	Yield (%)
Ph	Et	78
Ph	heptyl	72
Ph	octyl	75
Ph	Ph	72
2-naphthyl	Ph	76
biphenyl-4-yl	Et	67
biphenyl-4-yl	i-Pr	62

Under acidic conditions, aromatic amines are benzotriazolylmethylated exclusively at the para position. The 4-(benzotriazol-1-ylmethyl)anilines obtained can also ionize to the benzotriazolyl anion and a quinonoid type cation. The electron donating influence of the amino group is transmitted via the aromatic ring to the methylene cabon atom in the para position. Treatment of the 4-(benzotriazol-1-ylmethyl)arylamines with aniline and N-substituted anilines leads to formation of methylenebisanilines in high yield. Asymmetrical substituted methylenebisanilines are conveniently produced in this way (Scheme 80).[61]

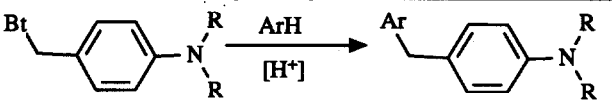
Scheme 80. Methylenebisanilines



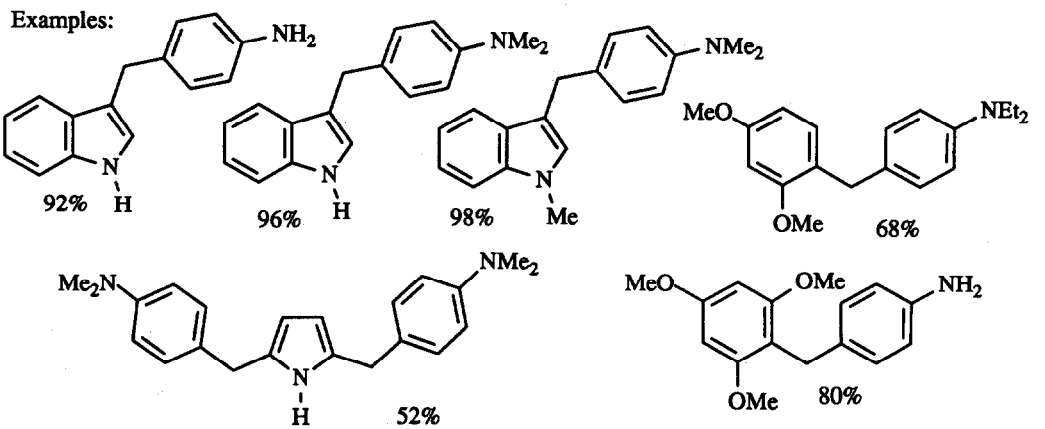
R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	58
H	H	Me	Me	70
H	H	Me	H	66
Me	Me	Me	Me	97
Et	Et	Et	Et	95
Me	Me	Me	Et	96
Et	Et	Et	Me	96

The cation which is formed from 4-(benzotriazol-1-ylmethyl)anilines can also attack other electron rich aromatic systems, giving substitution of the aromatic proton with a 4-aminobenzyl group.[62] Examples of such reactions are given in Scheme 81.

Scheme 81. Reaction of 4-(Benzotriazol-1-yl-methyl)anilines with Other Reactive Aromatic Systems

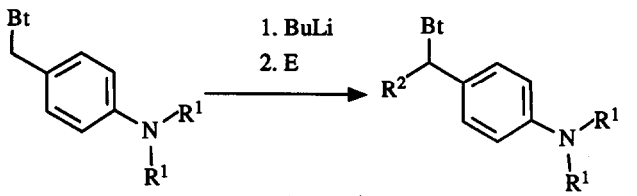


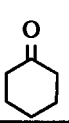
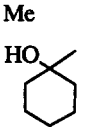
Examples:



The methylene protons of 4-(benzotriazol-1-ylmethyl)anilines are sufficiently activated to be abstracted by butyllithium (see following section). The anion can then react with alkyl halides to give the corresponding 4-[α-(benzotriazol-1-yl)alkyl]anilines. When aldehydes are used as electrophiles in this reaction, the corresponding α-(benzotriazol-1-yl)-β-hydroxy derivatives are formed, while esters give α-(benzotriazol-1-yl)-4-aminophenylmethyl ketones (Scheme 82).[62]

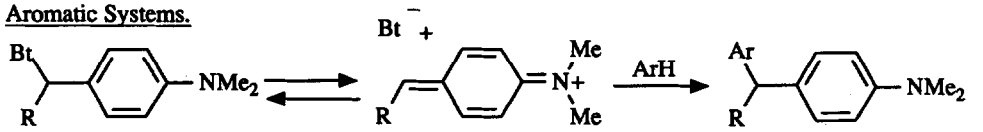
Scheme 82. 4-(Benzotriazol-1-ylmethyl)anilines: Electrophilic Substitution of the Methylene Protons



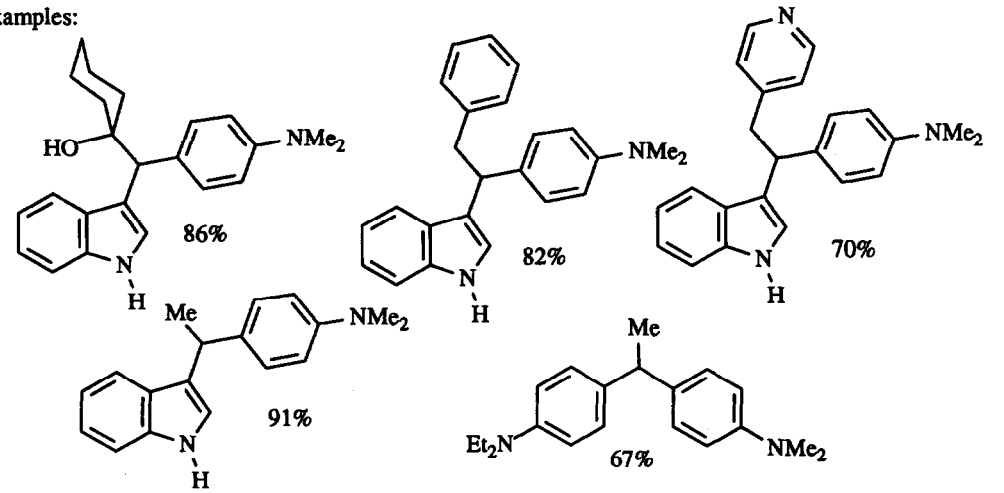
R^1	E	R^2	Yield (%)
Me	MeI	Me	99
Me	$PhCH_2Br$	$PhCH_2$	90
Me	$4\text{-}CH_3C_6H_4CHO$	$4\text{-}CH_3C_6H_4CHOH$	79
Me	$Ph_2C{=}O$	PhCOH	77
Me	$4\text{-}CH_3C_6H_4COOEt$	$4\text{-}CH_3C_6H_4CO$	62
Et	MeI	Me	72
Et			69

Derivatives bearing a substituent on the carbon atom binding the benzotriazole system with the amine aryl ring undergo similar electrophilic aromatic substitution with electron rich aromatic molecules as do the simple 4-(benzoriazol-1-ylmethyl)anilines discussed above. This allows the substitution at C-3 of indole with complex substituents and the preparation of 1,1-bis(4-aminophenyl) alkanes with asymmetrically substituted amino groups (Scheme 83).[62]

Scheme 83. Reactions of 4-(α-Benzotriazol-1-ylalkyl)-N,N-dimethylaniline with Electron Rich Aromatic Systems.



Examples:

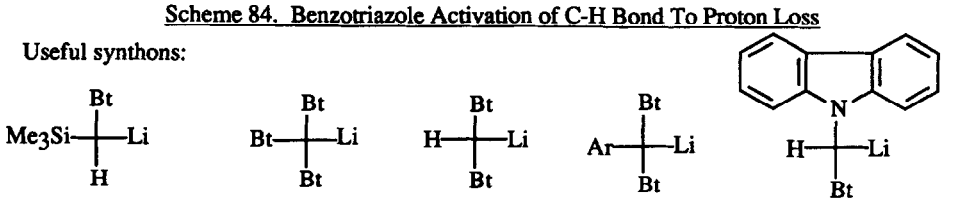


ACTIVATION OF CH TO PROTON LOSS BY BENZOTRIAZOLYL GROUPS

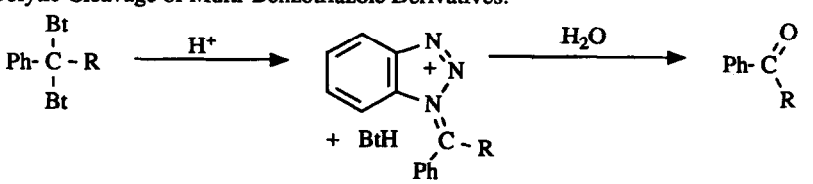
An N-benzotriazolyl substituent stabilizes the formation of an α-carbanion to approximately the same degree as a phenyl group, and several useful synthons have been derived (Scheme 84).

Scheme 84. Benzotriazole Activation of C-H Bond To Proton Loss

Useful synthons:

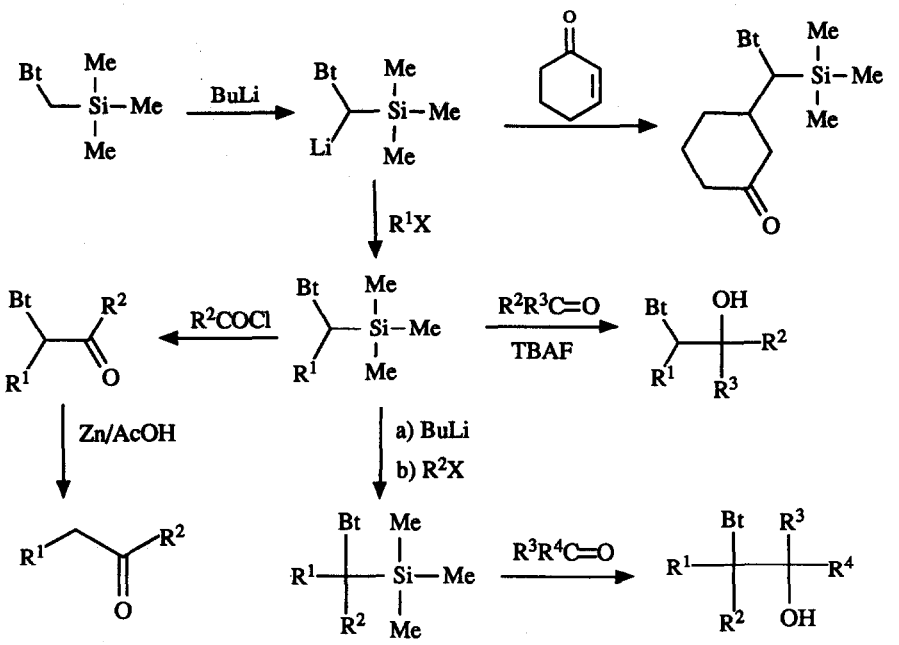


Hydrolytic Cleavage of Multi-Benzotriazole Derivatives:



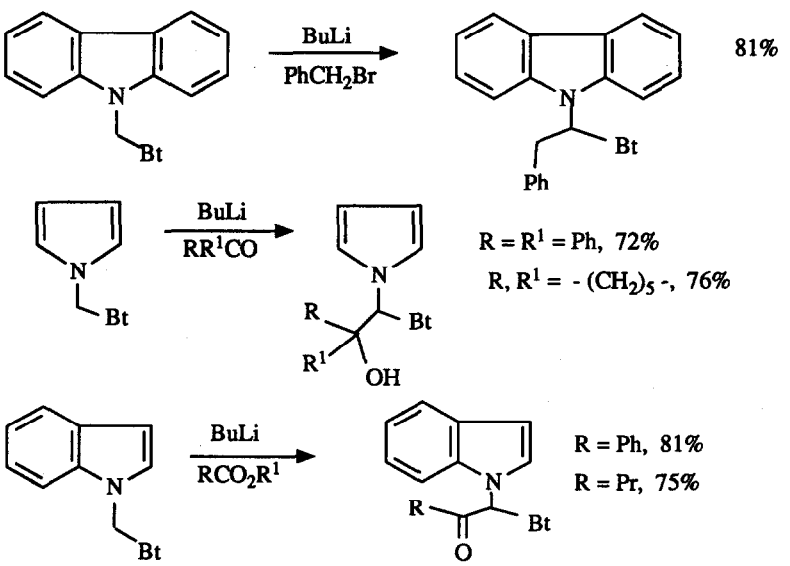
1-(Trimethylsilylmethyl)benzotriazole can be deprotonated at the methylene group and the anion undergoes further reactions as shown in Scheme 85.[63]

Scheme 85. Reactions of the 1-(Trimethylsilylmethyl)benzotriazolate Anion



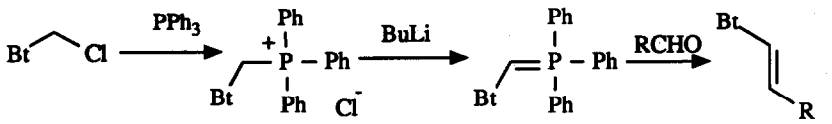
Similarly, many benzotriazolylmethyl-N-heterocycles undergo deprotonation and these anions also undergo reaction with a variety of electrophiles.[64]

Scheme 86. Reaction of Benzotriazolylmethyl-N-heterocycles with Electrophiles



As expected, Wittig reagents are easily formed as shown in Scheme 87.[65]

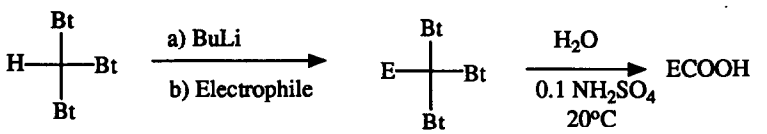
Scheme 87. Synthesis of 1-(1-Alkenyl)benzotriazoles



R	Yield (%)
Pr	30
Ph	50
4-$O_2NC_6H_4$	40
4-$Me_2NC_6H_4$	98
PhCH=CH	56

Another application of this same type is the use of tribenzotriazolylmethide as a carboxylate anion synthon, some applications of which are shown in Scheme 88.[66] The very mild hydrolytic conditions are noteworthy.

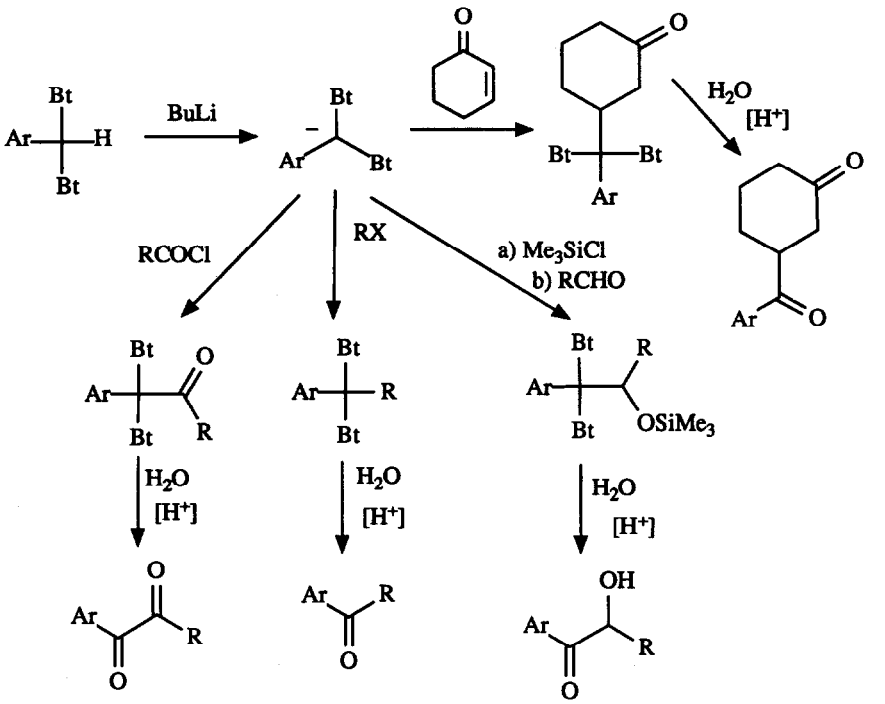
Scheme 88. A Carboxylate Anion Synthon



Acids Prepared	Yield (%)
$PhCH_2COOH$	92
$PhCH=CHCH_2COOH$	73
PhCOCOOH	81
4-$MeC_6H_4COCOOH$	83
PhCH(OH)COOH	78
4-$MeC_6H_4CH(OH)COOH$	76
BuCOOH	79
PhNHCSCOOH	82
1-$C_{10}H_7NHCSCOOH$	87
$PhCH_2NHCSCOOH$	74

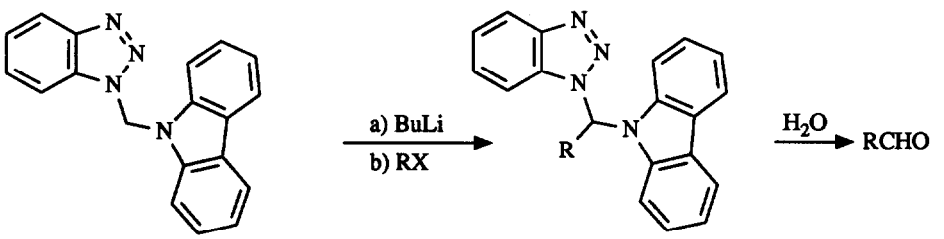
When two N-benzotriazolyl substituents and a phenyl group are attached to the same carbon atom, hydrolysis of the two benzotriazolyl groups is easy. Overall an efficient synthesis of arylketones is thus achieved. It has been extended to α-hydroxyketones and α-diketones[67] (Scheme 89).

Scheme 89. Preparation of Aryl Ketones



This reaction sequence cannot be extended to aldehydes or ketones in general because the hydrolysis is less easy. However, we have found that when one benzotriazole group and one carbazole group are attached to the same methylene, then the compound functions as an excellent formyl anion synthon (Scheme 90).[68]

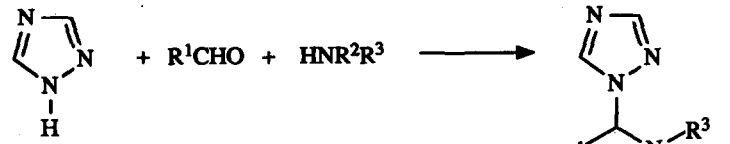
Scheme 90. A Formyl Anion Synthon



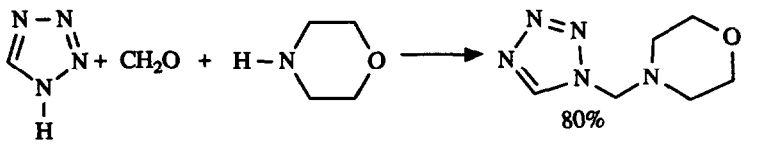
COMPARISON WITH OTHER AZOLES

Benzotriazole cannot be considered unique in its ability to stabilize reaction intermediates, and then to behave as a good leaving group in a later step of the synthetic program. Other azoles such as 1,2,4-triazole and tetrazole behave in a similar manner, and give stable condensation products with aldehydes and amines analogous to the benzotriazole derivatives (Scheme 91).[69]

Scheme 91. 1-(α-Aminoalkyl) Derivatives of 1,2,4-Triazole and Tetrazole

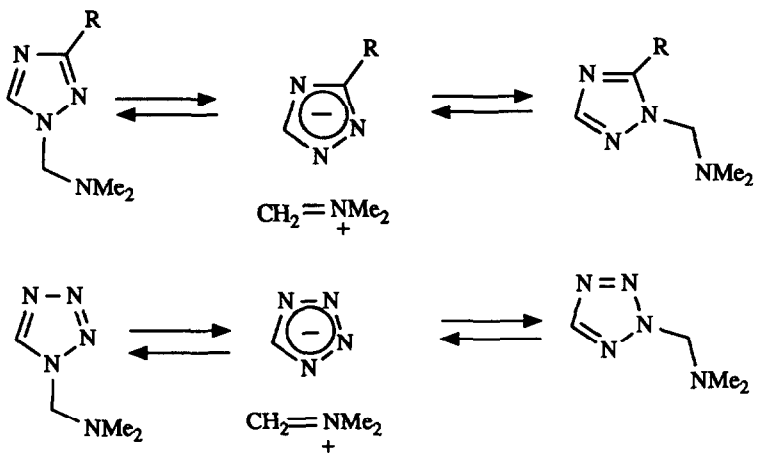


R^1	NR^2R^3	Yield (%)
H	$N(CH_2CH_2)_2O$	83
H	NHCOPh	80
Ph	$N(CH_2CH_2)_2O$	29



1-(Aminomethyl)-1,2,4-triazoles and 1-(aminomethyl)tetrazoles also undergo ionization and rearrangement to the N-2 isomers in solution (Scheme 92).[69] This suggests 1,2,4-triazole and tetrazole may also be used as synthetic auxiliaries in organic reactions. However, differences in behaviour may arise because of the small size of these molecules, their greater polarity, and high solubility in water. From an economic standpoint, tetrazole is much more expensive than benzotriazole, but 1,2,4-triazole is cheaper in bulk, although more expensive as a laboratory chemical.

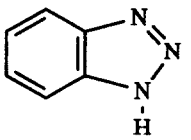
Scheme 92. Equilibria in Chloroform Solutions of Aminomethyl-(1,2,4-triazoles) and -tetrazoles



CONCLUSIONS AND OUTLOOK

The use of benzotriazole as a synthetic auxiliary has a number of significant advantages (Scheme 93). It is readily available and quite cheap. It can be converted to a wide range of N-substituted derivatives from which the benzotriazole residue can be removed by a variety of procedures. It is acidic with a pK_a of about 8, which enables easy separation and recovery. The benzotriazole ring can both donate and accept electrons, and it can help the loss of a proton attached to a 1-position carbon atom by stabilizing the resultant carbanion.

Scheme 93. Benzotriazole as a Synthetic Auxiliary



1. Readily available
2. N-substituted derivatives easy to prepare
3. Bt-residue can be cleaved by a variety of procedures
4. Acid of pK_a *ca* 8 enables easy separation and recovery
5. Ring can donate or accept electrons
6. Interesting reactivity patterns

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