Benzotriazole-mediated Arylalkylation and Heteroarylalkylation

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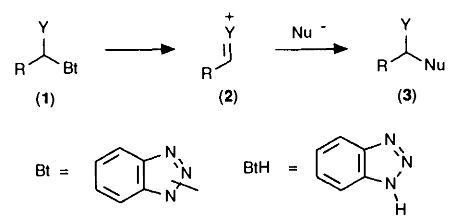
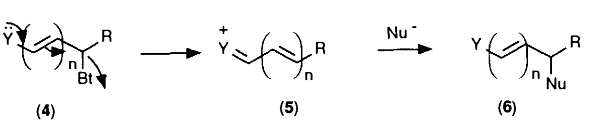
1 Introduction

A recent review discussed reactions important for the preparation of useful benzotriazolyl intermediates and the displacements by nucleophiles of the benzotriazole groups in such derivatives of (1).[1] We rationalized that these displacements of benzotriazole were assisted by the lone electron pair on the heteroatom substituents Y. Thus, initial ionization of (1) occurred to give the reactive intermediate iminiums (2), which then reacted with nucleophiles to give the final products (3) (Scheme 1).



Scheme 1

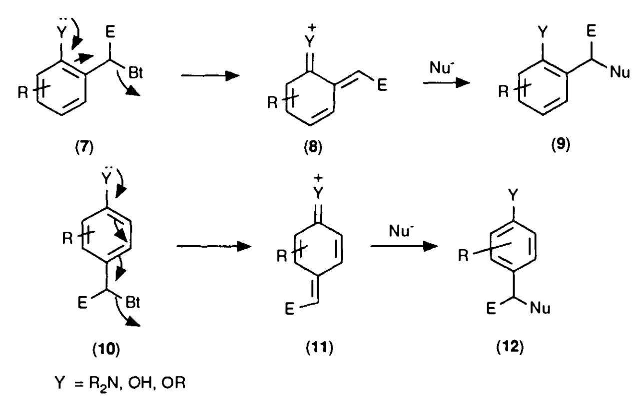
In reactions of this type, the benzotriazole group and the heteroatom are connected to the same carbon. In recent years it has been shown in our group that such assistance by an electron pair could also be effected through a conjugated system as shown in compounds of type (4). The displacement of benzotriazole by nucleophiles is thus realized through conjugation as shown in Scheme 2.



Scheme 2

In the present overview, we discuss such conjugated systems, specifically those involving benzene rings. Some work on the similar system with conjugation through a simple vinyl group was covered in a previous review.[2] We now describe displacements by nucleophiles, such as Grignard reagents, electron-rich aromatic and heteroaromatic compounds, active CH acids, alcohols, thiols, *etc.* of benzotriazole groups activated by conjugation through benzene rings to give substituted aromatic compounds. Furthermore, the electron-withdrawing ability of benzotriazole further activates the directly attached benzylic carbon and renders the *alpha* protons acidic. Such compounds can thus be lithiated and substituents introduced by subsequent reaction with electrophiles. The displacement of the benzotriazole group in the resulting derivatives will afford trisubstituted methanes.

The general scheme is represented in Scheme 3, where E = H corresponds to the parent benzotriazole derivatives, E ≠ H to derivatives obtained *via* lithiation. An electron pair on the heteroatom in substituent Y can render assistance from both the *ortho* and the *para* positions, as shown in Scheme 3. The heteroatom substituent Y can be an amino or substituted amino group as in the case of anilines, the hydroxy group of a phenol, or the alkoxy group of a phenol ether.



Scheme 3

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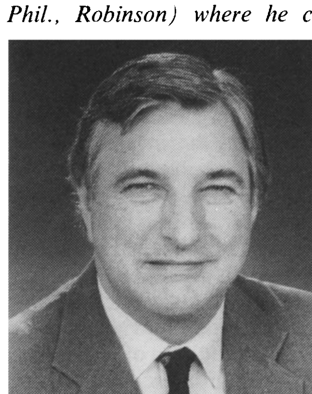
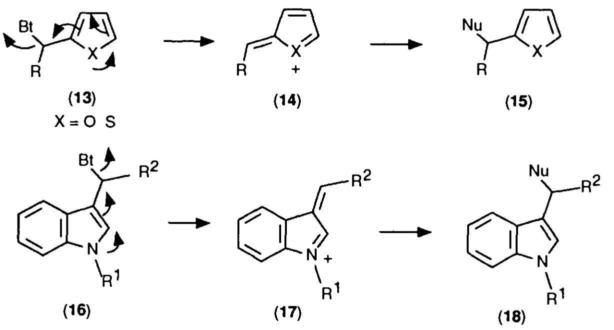


Alan Katritzky (b. 1928, London) was educated at Oxford (D. Phil., Robinson) where he carried out independent research from 1953. He moved to Cambridge in 1958 (Lecturer and Fellow of Churchill), then to East Anglia to found the School of Chemical Sciences, and finally to Florida in 1980 where he is Kenan Professor and Director of the Center for Heterocyclic Compounds. A light-hearted account of his life is published in J. Het. Chem., 1994, ***31****, pp. 569—602, and an overview of his scientific work in Heterocyles, 1994,* ***37****, pp. 3—130.*

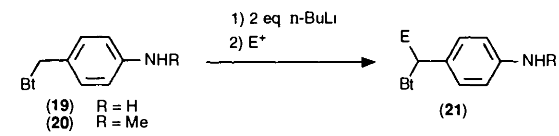
Similar reactions with heterocycles will be described in which the assistance comes from a free electron pair of the heteroatom incorporated in a heterocycle such as furan, thiophene, and indole, as shown in Scheme 4



Scheme 4

2 Elaboration of Benzotriazole Derivatives *via* Lithiation

Heteroatom assisted lithiations have attracted considerable attention in organic synthesis [3] 1- and 2-Benzylbenzotriazoles have been shown to undergo lithiation at the benzylic carbon atom[4] and similar reactions were demonstrated in reaction sequences leading to the preparation of aromatic ketones [5] 4-(Benzotriazol-1-ylmethyl)anilines likewise react with Bu^nLi and quenching the anions with a variety of electrophiles affords the expected substituted products in good yields Various electrophiles, including alkyl halides, aldehydes, and ketones, *etc* , were employed The lithiations of *N*,*N*-dialkylaniline derivatives were covered in a previous review [2] We have recently successfully extended such lithiations to (19) and (20), where the amino group is an NH_2 or an NHMe, by using two equivalents of Bu^nLi[6] (Table 1)

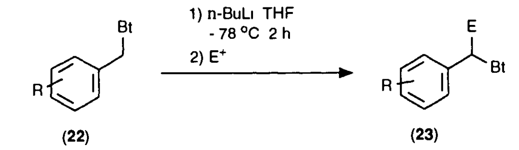


(21)	R	E+	E	Yield (%)
a	H	$PhCH_2Br$	$PhCH_2$	88
b	H	$4\text{-}MeC_6H_4CHO$	$4\text{-}MeC_6H_4CH(OH)$	71
c	Me	$PhCH_2Br$	$PhCH_2$	81
d	Me	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4CH(OH)$	53

Table 1 Lithiation of 4-(benzotriazol-1-ylmethyl)aniline (19) and 4-(benzotriazol-1-ylmethyl)-*N*-methylaniline (20)

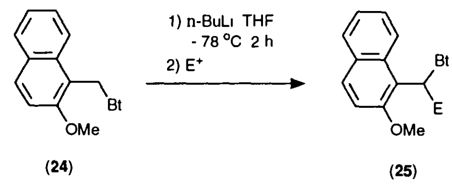
Lithiation also occurred smoothly in 1-[(methoxyphenyl)-methyl]benzotriazole (22) good to excellent yields were obtained with a variety of electrophiles [7] This lithiation sequence also succeeds for the naphthalene system (24) (Tables 2, 3)

The phenolic hydroxy group required a modification to the lithiation procedure due to two factors the initially formed phenoxide possessed less acidic methylene protons and the system formed a less soluble dilithiated product [8—11] Treatment with Bu^nLi or Bu^tLi in THF of *o*-(benzotriazol-1-ylmethyl)phenols of type (26) gave satisfactory results only when the phenolic hydroxy group was protected by trimethylsilylation A one-pot process was developed by treatment of the substrate (26) with one equivalent of Bu^nLi, followed by one equivalent of trimethylsilyl chloride to give (27) Further addition of one equivalent of Bu^nLi and subsequent treatment with one equivalent of the electrophile gave (28) The protecting group was easily removed by stirring (28) in an acidic ethanolic solution Good



(23)	R	E+	E	Yield (%)
a	4-MeO	MeI	Me	80
b	4 MeO	$PhCH_2Br$	$PhCH_2$	85
c	4-MeO	$Ph_2C{=}O$	$Ph_2C(OH)$	80
d	4-MeO	CO_2	CO_2H	78
e	2-MeO-3-Me	MeI	Me	90
f	2-MeO-3 Me	$PhCH_2Br$	$PhCH_2$	70
g	2-MeO-3-Me	$4\text{-}MeC_6H_4CHO$	$4\text{-}MeC_6H_4CH(OH)$	87
h	2-MeO-3-Me	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	80
i	2-MeO 3-Me	$Ph_2C{=}O$	$Ph_2C(OH)$	75
j	2-MeO 3-Me	$PhCO_2Et$	PhC=O	76
k	2 4 6-$(MeO)_3$	MeI	Me	85
l	2 4 6-$(MeO)_3$	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	72

Table 2 Lithiation of 1-[(methoxyphenyl)methyl]benzotriazole (22)



(25)	E+	E	Yield (%)
a	MeI	Me	98
b	$4\text{-}MeC_6H_4CHO$	$4\text{-}MeC_6H_4CH(OH)$	60

Table 3 Lithiation of 1-(benzotriazol-1-ylmethyl)-2-methoxynaphthalene (24)

overall yields of the desired products (29) were obtained A variety of electrophiles including alkyl halides, aldehydes, ketones, and carbon dioxide were employed (Table 4)

1-Methyl-3-(benzotriazol-1-ylmethyl)indole (30) underwent smooth lithiation at the methylene carbon and the anion reacted with methyl iodide, benzophenone, phenyl isocyanate, and diphenyl disulfide to give the desired derivatives (31) in good yields (Table 5) [12]

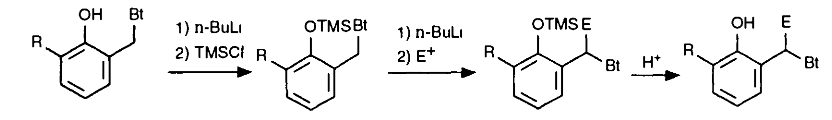
Similarly, we found recently[13] that 2-(benzotriazol-1-ylmethyl)indole (32) reacted with two equivalents of n-butyllithium to give a dianion (33) The dianion was quenched with one equivalent of an alkyl halide to give alkylated indole (35) and with three equivalents of methyl iodide to afford the dialkylated compound (34) in both cases in excellent yields (Table 6)

3 Displacement of Benzotriazole by Grignard Reagents and Hydride

We have found that treatment with RMgBr or $LiAlH_4$ of the parent products $Y\text{-}C_6H_4\text{-}CH_2\text{-}Bt$, as well as the $Y\text{-}C_6H_4\text{-}CHR\text{-}Bt$ derivatives obtained *via* lithiation, gave the expected alkyl aromatic compounds $Y\text{-}C_6H_4\text{-}CHR\text{-}R'$

3.1 Preparation of 4-Alkylanilines

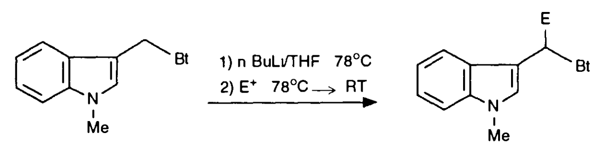
4-(Benzotriazol-1-ylmethyl)anilines, and their derivatives (36) obtained *via* lithiation, reacted with an excess of Grignard reagents in refluxing benzene or toluene to give the desired 4-alkylanilines (38)[6] (Table 7) Presumably cations (37) are the reactive intermediates A hydroxy functional group was readily



(26) (27) (28) (29)

(29)	R	E+	E	Yield (%)
a	H	PhCHO	PhCH(OH)	68
b	Me	MeI	Me	71
c	Me	n BuI	n Bu	50
d	Me	CO_2	CO_2H	71
e	Me	Ph_2CO	$Ph_2C(OH)$	62

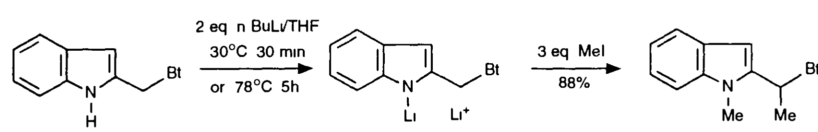
Table 4 Lithiation of *o*-(benzotriazol-1-ylmethyl)phenols (26)



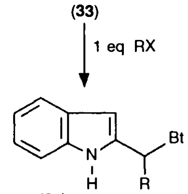
(30) (31)

(31)	E+	E	Yield (%)
a	MeI	Me	83
b	$Ph_2C{=}O$	$Ph_2C(OH)$	95
c	PhN=C=O	PhNHC=O	90
d	PhSSPh	PhS	58

Table 5 Lithiation of 1-methyl-3-(benzotriazol-1-ylmethyl)indole (30)



(32) (33) (34)



(35)

(35)	RX	R	Yield (%)
a	n C_4H_9I	n C_4H_9	98
b	MeI	Me	86
c	$PhCH_2Br$	$PhCH_2$	81

Table 6 Lithiation of 2-(benzotriazol-1-ylmethyl)indole (32)

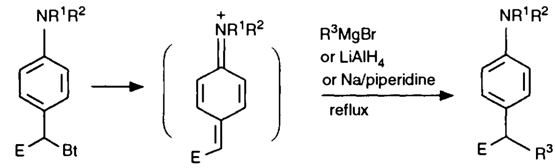
introduced in the alkyl substituent as shown by the examples of (38 l,m) Noteworthy is the stability of the initially formed alkoxide under such vigorous conditions In such a manner, an R^3CHE group is introduced at the *para* position of the anilines where E evolves from the electrophile and R^3 from the Grignard reagent Good to excellent yields of (38) were usually obtained Such 4-alkylanilines are generally not easily available by other methods For example, 4-benzyl- and 4-pentyl-*N*,*N*-dimethylaniline were previously prepared by acidic reduction[14 15] from the appropriate ketone and alcohol, but such methods obviously suffer from the unavailability of the starting materials Classical Friedel–Crafts reactions are not generally applicable to the preparation of 4-alkylanilines owing to the deactivation effect of nitrogen on the Lewis acid catalysts Thus our method offers considerable advantages of easily available starting materials, high yields, and generality Also, a hydroxy functional group could easily be introduced

Under similar reaction conditions, the benzotriazole group in derivatives of type (36) was replaced by hydride by the action of $LiAlH_4$[6] or sodium in piperidine [16]

3.2 Preparation of *ortho*-Alkylsubstituted Phenols

Just as for the (4-benzotriazolylalkyl)anilines described above, *o*-(benzotriazolylalkyl)phenols (39) reacted with Grignard reagents or $LiAlH_4$ to give *ortho*-alkylsubstituted phenols (41)[17] (Table 8) Similarly, the naphthol derivatives (42) under such conditions afforded the corresponding 1-alkyl-2-naphthols (44) (Table 9) The net effect of these transformations is the replacement of an *ortho*-ring hydrogen by an RECH group, where E evolves from the electrophile (in the case of phenol, but alternatively from the aldehyde in the case of naphthol), and R from the Grignard reagent or from $LiAlH_4$ In this way, normal as well as branched chain alkyl groups are easily introduced in moderate to excellent yields into the position *ortho* to a phenolic OH-group

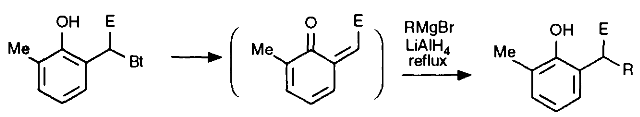
In support of our proposal[17] that these reactions involve the *o*-quinone methides (40) and (43) as intermediates, such heterodienes were successfully trapped by the dienophiles ethyl vinyl ether and 1-vinyl-2-pyrrolidinone to give chroman derivatives (47) and (49) in excellent yields[18] (Tables 10, 11)



(36) (37) (38)

(38)	R^1	R^2	E	Reagent	R^3	Solvent	Time (h)	Yield (%)
a	H	H	H	PhMgBr	Ph	benzene	48	48
b	H	H	H	n-BuMgBr	n-Bu	benzene	48	50
c	H	Me	H	PhMgBr	Ph	toluene	12	36
d	H	Me	H	n-BuMgBr	n-Bu	benzene	24	30
e	H	H	$PhCH_2$	PhMgBr	Ph	benzene	17	68
f	Me	Me	H	PhMgBr	Ph	benzene	24	97
g	Et	Et	H	PhMgBr	Ph	benzene	24	92
h	Me	Me	H	n-BuMgBr	n-Bu	benzene	25	52
i	Et	Et	H	n-BuMgBr	n-Bu	benzene	17	78
j	Me	Me	Me	PhMgBr	Ph	benzene	10	82
k	Me	Me	$PhCH_2$	PhMgBr	Ph	benzene	10	91
l	Me	Me	$(CH_2)_5C(OH)$	PhMgBr	Ph	toluene	18	81
m	Me	Me	PhCH(OH)	PhMgBr	Ph	toluene	18	69
n	Me	Me	$PhCH_2$	$LiAlH_4$	H	benzene	4	78
o	Et	Et	Me	$LiAlH_4$	H	toluene	13	77
p	Me	Me	Et	Na	H	piperidine	24	45

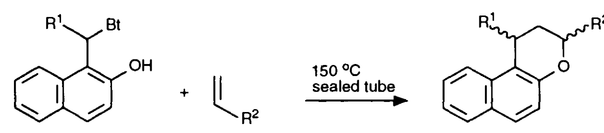
Table 7 Displacement of benzotriazole in 4-(benzotriazol-1-ylalkyl)anilines (36) by Grignard reagents or $LiAlH_4$ or Na/piperidine



(39) (40) (41)

(41)	E	R	Reagent	Solvent	Time (h)	Yield (%)
a	H	Ph	PhMgBr	toluene	72	45
b	H	n-Bu	n-BuMgBr	toluene	24	29
c	H	H	$LiAlH_4$	toluene	48	50
d	Me	Ph	PhMgBr	THF	17	50
e	Me	$PhCH_2$	$PhCH_2MgBr$	THF	12	80
f	Me	H	$LiAlH_4$	THF	48	66
g	n-Bu	H	$LiAlH_4$	THF	48	62

Table 8 Displacement of benzotriazole in *o*-(benzotriazol-1-ylalkyl)phenols (39) by Grignard reagents or $LiAlH_4$



(45) (46) (47)

(47)	R^1	R^2	Time (h)	Yield (%)
a	H	OEt	36	95
b	Ph	OEt	5	92
c	Ph	pyrr	3	82
d	$4\text{-}Me_2NC_6H_4$	OEt	5	92
e	$4\text{-}Me_2NC_6H_4$	pyrr	3	87

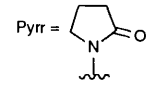
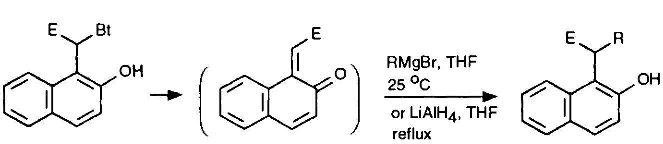


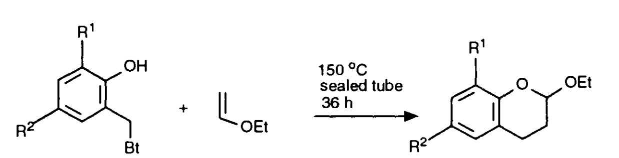
Table 10 Preparation of chroman derivatives (47)



(42) (43) (44)

(44)	E	Reagent	R	Time (h)	Yield (%)
a	Ph	PhMgBr	Ph	22	66
b	Ph	$PhCH_2MgBr$	$PhCH_2$	3	86
c	Ph	$LiAlH_4$	H	22	90
d	$4\text{-}Me_2NC_6H_4$	PhMgBr	Ph	12	68
e	$4\text{-}Me_2NC_6H_4$	$PhCH_2MgBr$	$PhCH_2$	2	90
f	$4\text{-}Me_2NC_6H_4$	$LiAlH_4$	H	3	94

Table 9 Displacement of benzotriazole in 1-(α-benzotriazol-1-ylalkyl)-2-naphthols (42) by Grignard reagents or $LiAlH_4$



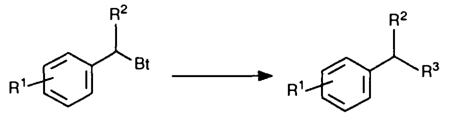
(48) (49)

(49)	R^1	R^2	Yield (%)
a	Me	H	92
b	t-Bu	H	91
c	t-Bu	Me	93

Table 11 Preparation of chroman derivatives (49)

3.3 Preparation of Alkyl-substituted Aryl Ethers

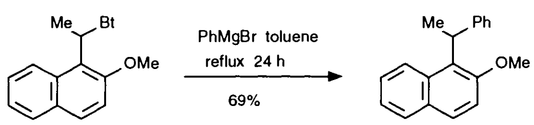
The benzotriazole group in 1-[(methoxyphenyl)alkyl]benzotriazoles (50) was displaced by Grignard reagents or organozinc reagents to give the alkyl-substituted aryl ethers (51) [7] Sodium in piperidine also caused reduction of the benzotriazole group[16] (Table 12) 1-(1-Benzotriazol-1-ylethyl)-2-methoxynaphthalene (52) reacted with PhMgBr to give compound (53) in 69% yield (Scheme 5)



(50) (51)

(51)	R¹	R²	Reagent	Solvent	Condition (°C h)	Yield (%)
a	2 MeO 3 Me	Me	PhZnBr	toluene	reflux (72)	75
b	2 4 6 (MeO)$_3$	H	PhMgBr	toluene	reflux (8)	56
c	3 4 (MeO)$_2$	Et	Na	piperidine	100 (24)	54

Table 12 Preparation of alkyl substituted aryl ethers (45)

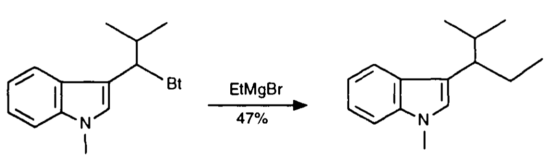


(52) (53)

Scheme 5

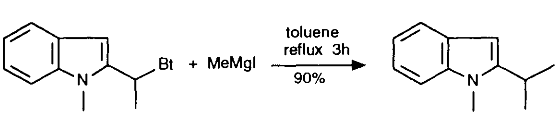
3.4 Preparation of Substituted Indoles

The benzotriazole moiety in compound (54) was displaced with ethyl magnesium bromide to give compound (55) in 47% yield (Scheme 6) [12] Similarly, compound (56) reacted with methyl magnesium iodide in toluene to afford compound (57) in 90% yield (Scheme 7) [13]



(54) (55)

Scheme 6



(56) (57)

Scheme 7

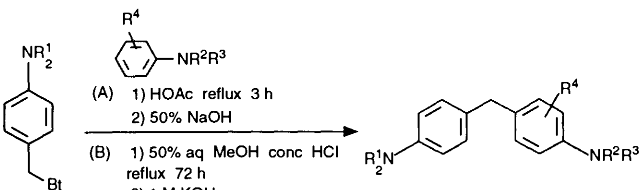
4 Displacement of Benzotriazole by Electron-rich Aromatic and Heteroaromatic Compounds

4.1 With 4-(Benzotriazol-1-ylalkyl)aniline Derivatives

4 1 1 Methylenebisanilines

Methylenebisanilines are well known compounds A large number of papers and patents exist dealing with the preparation and extensive applications of such compounds [19–22] Thus they are used as curing agents for epoxy resins and urethane elastomers, as intermediates in the preparation of polyurethanes, in the synthesis of polyamides, in the preparation of azo and other dyes, in the production of recording materials, as antioxidants for lubricating oils, as curing agents of epoxy resins, and as electrically insulating composite materials

Methylenebisanilines have been prepared by the reaction of an arylamine with formaldehyde in the presence of concentrated hydrochloric acid[23–25] and by the reaction of *N*-(alkoxymethyl)arylamines under acidic conditions [26] These two methods work only for symmetrical analogues Organomercury(II) compounds were reported as intermediates for the preparation of both symmetrical and unsymmetrical analogues,[27,28] organomercurials, however, are toxic and difficult to use industrially 4-(Hydroxymethyl)-*N N*-dialkylanilines can provide unsymmetrical methylenebisanilines,[29–31] but are reportedly rather unstable No other general methods are available However, we have found that the stable and easily accessible 4-(benzotriazol-1-ylmethyl)anilines (58) react with anilines bearing an NH_2, an NHR, or an NR_2 group, with or without other ring substituents to give both symmetrical and unsymmetrical methylenebisanilines (59) in excellent yields[32] (Table 13)



(58) (59)

(59)	R¹	R²	R³	R⁴	Condition	Yield (%)
a	H	H	H	H	A	80
b	H	H	H	2 Me	A	78
c	H	H	H	2 Cl	A	72
d	H	H	Me	H	A	66
e	H	Me	Me	H	A	70
f	Me	H	H	H	A	83
g	Me	Me	Me	H	B	97
h	Me	Me	Et	H	B	96
i	Me	Et	Et	H	B	99
j	Et	Et	Et	H	B	90
k	Et	Me	Me	H	B	100
l	Et	Me	Et	H	B	99

Table 13 Preparation of methylenebisanilines (59)

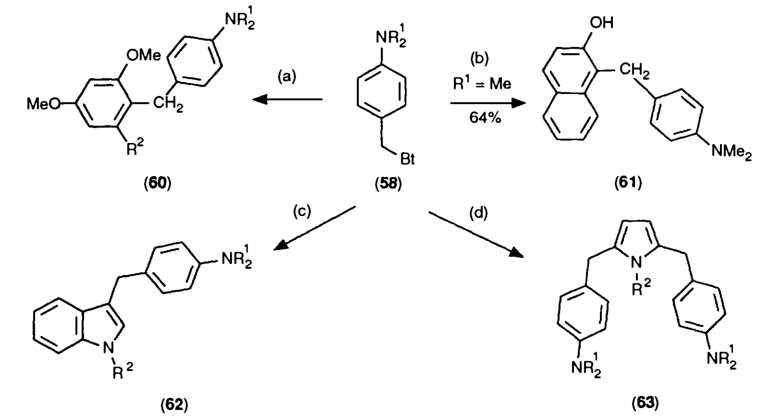
4 1 2 Diarylmethanes and their Hetero Analogues

Such displacements were also successful with other electron-rich aromatic compounds such as 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene, and 2-naphthol to give diaryl methanes (60) and (61) Similar reactions with electron-rich heterocycles such as indole, *N*-methylindole, pyrrole, and *N*-methylpyrrole, afforded the hetero analogues (62) and (63), respectively[33] (Table 14)

4 1 3 Substituted Diarylmethanes

Di- and triarylmethanes containing electron-donating groups in the *ortho* or *para* positions are of considerable importance as they are leuco dyes which, on hydride abstraction by oxidizing agents, give coloured cations of the type of Michler's hydrol (64), Crystal Violet (65), and Malachite Green (66) [34]

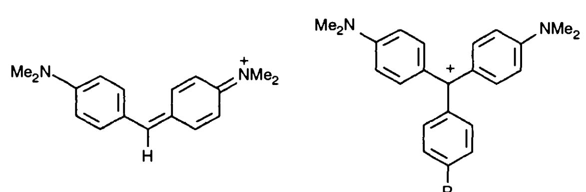
The derivatives (68) (obtained *via* lithiation) react with aniline and indole to give the substituted diarylmethanes (67) and the heteroaryl analogues (69) in good yields [33] It is noteworthy that under the acidic conditions, the hydroxyl group is stable as shown in cases of (69c—e) (Table 15) For the derivative from benzophenone, a mixture of four products (72)—(75) was obtained This strengthens our belief that in such reactions, benzotriazole leaves initially forming a relatively stable benzylic cation which can then be trapped by various nucleophiles Thus, the initially formed cation (71) can be trapped by indole to give



Reaction conditions: (1) 50% aq. MeOH, conc. HCl, reflux; (2) 1 M KOH.
(**a**) 1,3-Dimethoxy- or 1,3,5-trimethoxybenzene; (**b**) 2-Naphthol; (**c**) Indole or N-methylindole; (**d**) Pyrrole or N-methylpyrrole.

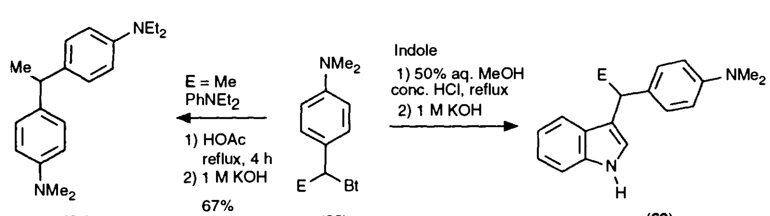
			Yield (Time, h)		
	R^1	R^2	(**60**)	(**62**)	(**63**)
a	H	H	53% (72)	92% (48)	29% (55)
b	Me	H	50% (72)	96% (7)	52% (21)
c	Et	H	68% (72)	95% (72)	41% (120)
d	H	OMe	80% (57)		
e	Me	OMe	73% (27)		
f	Et	OMe	72% (72)		
g	H	Me		85% (72)	
h	Me	Me		98% (20)	45% (24)
i	Et	Me		82% (44)	

Table 14 Preparation of diarylmethanes (60) and (61) and their hetero analogues (62) and (63)



(**64**) Michler's Hydrol

(**65**) R = NMe_2 Crystal Violet
(**66**) R = H Malachite Green



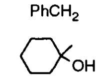
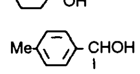
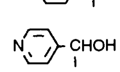
(**69**)	E	Time (h)	Yield (%)
a	Me	18	91
b	$PhCH_2$	40	82
c		17	86
d		72	38
e		20	70

Table 15 Preparation of substituted diarylmethanes (67) and heteroaryl analogues (69)

the regular product (72), or by MeOH to give (73) Dehydration of (72) afforded (75) and migration of a phenyl group gave (74) (Scheme 8)

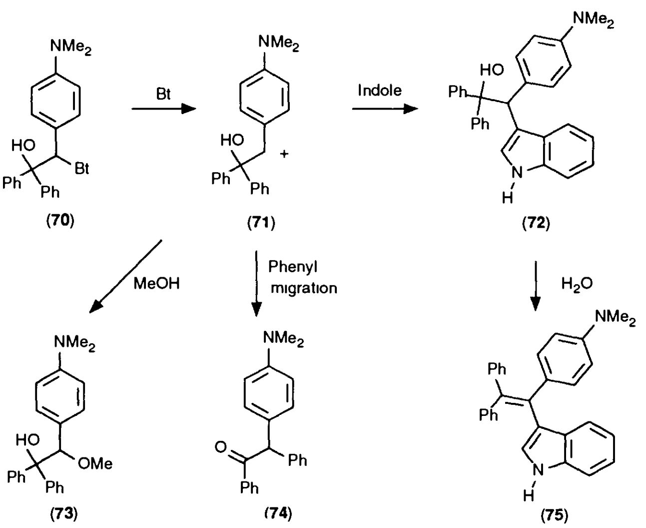
4.2 With *o*-(Benzotriazol-1-ylalkyl)phenol Derivatives

4 2 1 o o'-Methylenebisphenols

Symmetrical *o o'*-methylenebisphenols are well known, but unsymmetrical analogues are far less investigated Part of the reason can be attributed to the difficulty of their preparation [35] The methylenebisphenols are important precursors to calix[*n*]arenes which act as molecular receptors or enzyme mimics [36–38]

Two papers[35,39] have described a general procedure for the preparation of both symmetrical and unsymmetrical *o o'*-alkylidenebisphenols by using the magnesium salt of benzylic alcohols However, the procedure started with a limited number of uncommon substituted *o*-hydroxybenzaldehydes as starting materials

We found that displacement of the benzotriazole group in the *o*-(benzotriazol-1-ylmethyl)phenols (76) could be effected by phenols in the presence of sodium isopropoxide to afford symmetrical as well as unsymmetrical *o o'*-methylenebisphenols (78) in moderate to good yields[40] (Table 16) Similar displacement with derivatives bearing a substituent at the methylene carbon (obtained *via* lithiation) is still under investigation



Reaction condition (1) 50% aq MeOH conc HCl (2) 1 M KOH

Product	(72)	(73)	(74)	(75)
Yield (%)	26	9	5	10

Scheme 8

4 2 2 Diarylmethanes

The benzotriazole group was also displaced by 1,3-dimethoxybenzene and indole to give the desired diarylmethanes (79) and (80), respectively[40] (Scheme 9)

4.3 With 1-[(Methoxyaryl)alkyl]benzotriazoles

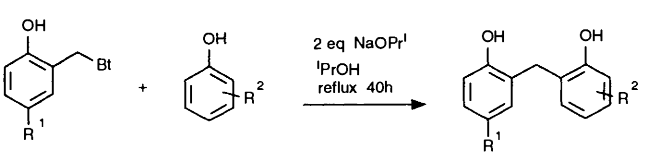
4 3 1 Diarylmethanes

Similar to the aniline and phenol derivatives, 1-[(methoxyaryl)-alkyl]benzotriazoles react with electron-rich aromatic compounds such as *N N*-dimethylaniline, 1,3,5-trimethoxybenzene, and 1,3-dimethoxybenzene to give the expected products such as (82) and (83) [7] In the case of 1,3-dimethoxybenzene, in addition to the simple product (84), disubstituted product (85) is also formed (Scheme 10) 1-(1-Benzotriazol-1-ylalkyl)-2-methoxynaphthalene (86) reacts similarly with 2-methoxynaphthalene, *N N*-dimethylaniline, and indole to give (87), (88), and (89), respectively (Scheme 11)

4.4 With 1-(Diarylalkyl)benzotriazoles

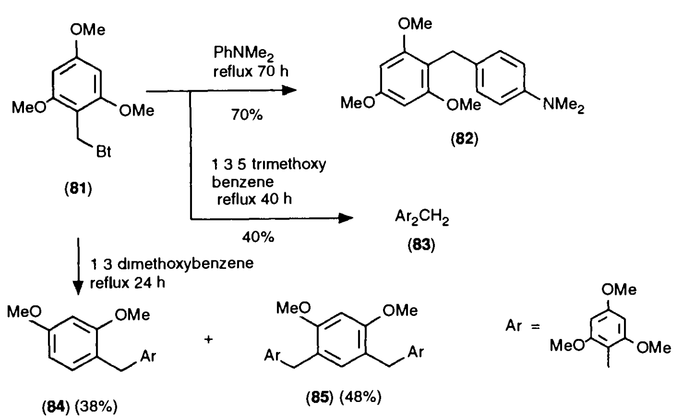
4 4 1 Asymmetric Triarylmethanes

We recently found[41] that 1-(diarylalkyl)benzotriazoles can be obtained from the reactions of an aromatic compound with 1-(benzenesulfonyl)benzotriazole and an aromatic aldehyde The derivatives thus obtained can then react with an electron-rich



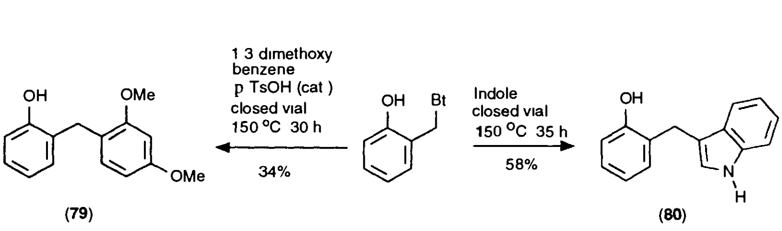
(78)	R¹	R²	Yield (%)
a	H	H	28
b	H	4 Me	57
c	H	4 t Bu	39
d	H	3 5 di Me	55
e	H	4 Ph	28
f	t Bu	4 Me	62

Table 16 Preparation of *o o* methylenebisphenols (78)

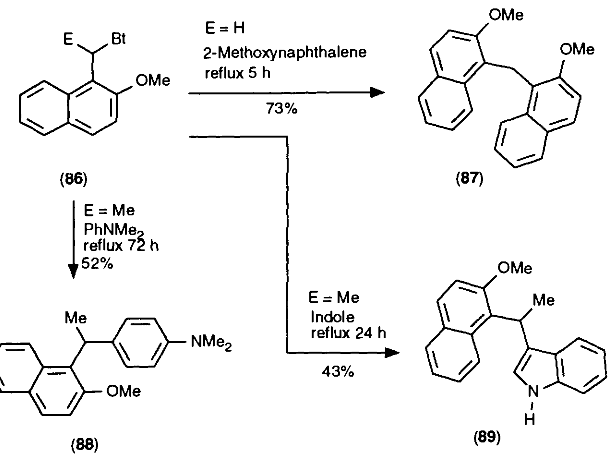


Reaction condition (1) 50% aq MeOH conc HCl reflux (2) 1 M KOH

Scheme 10



Scheme 9



Reaction condition (1) 50% aq MeOH, conc HCl, reflux, (2) 1 M KOH

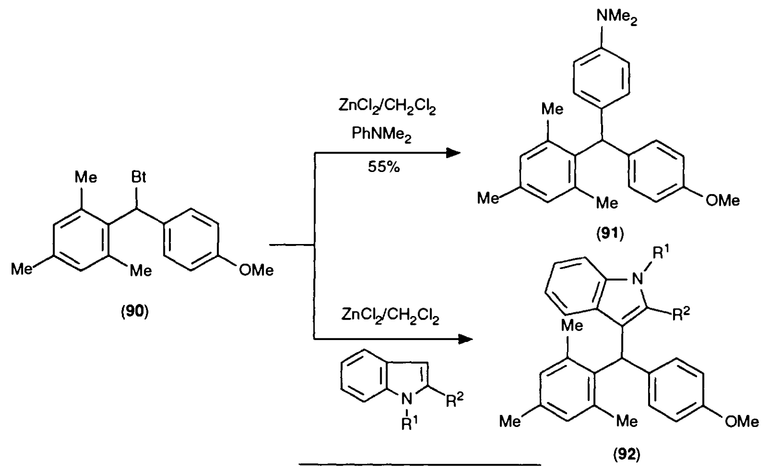
Scheme 11

aromatic or heteroaromatic compound to give asymmetrical triarylmethanes. Thus, compound (90) was treated with *N,N*-dimethylaniline and indoles in CH_2Cl_2 in the presence of zinc chloride to give compounds (91) and (92) in good yields (Table 17).

4.5 With (α-Benzotriazolylalkyl)-substituted Heterocycles

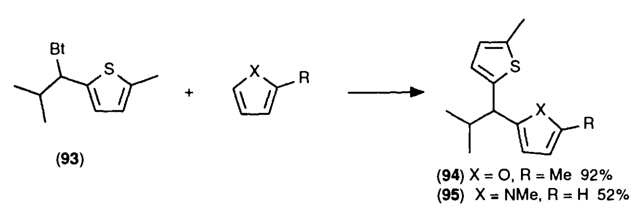
4.5.1 1,1-Bis(heteroaryl)alkanes

(α-Benzotriazolylalkyl)-substituted heterocycles (93) and (96) react with 2-methylfuran, 2-methylthiophene, *N*-methylpyrrole, *N*-methylaniline, and *N,N*-dimethylaniline to give 1,1-bis (heteroaryl)alkanes (94)—(95), (97—(98) and diarylmethanes (99)—(100) in good to excellent yields[12,42] (Schemes 12, 13). The derivatives obtained *via* lithiation of 1-methyl-3-(benzotriazol-1-ylmethyl)indole also reacted with *N*-methylaniline, and a Grignard reagent to afford compounds (102)—(104) (Scheme 14).[12]

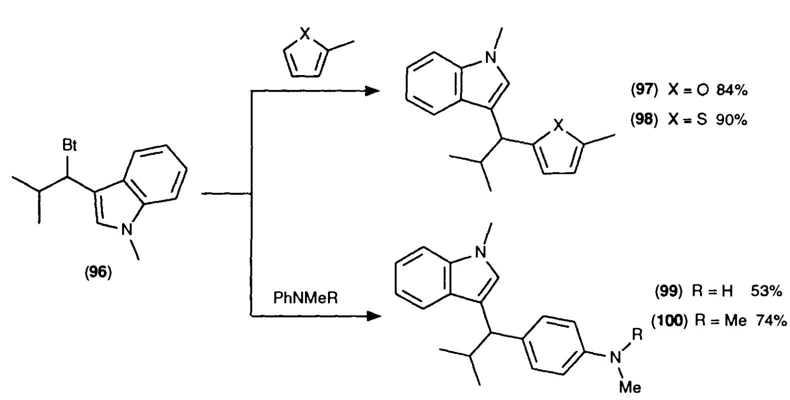


(92)	R^1	R^2	Yield (%)
a	H	H	57
c	H	Me	70
b	Me	H	85

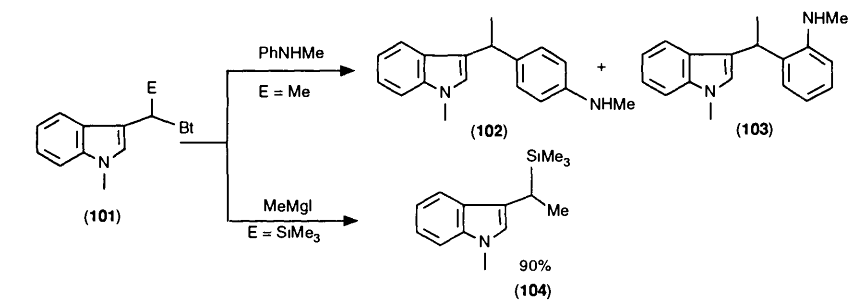
Table 17 Preparation of asymmetrical triarylmethanes (91) and (92)



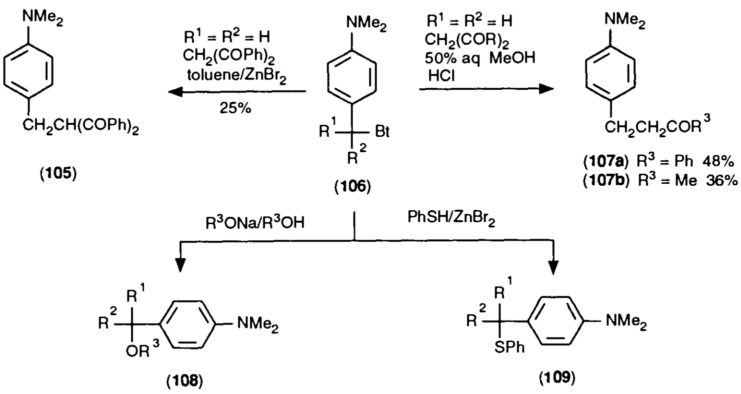
Scheme 12



Scheme 13



Scheme 14



R^1	Et	Et	Et	Et
R^2	Et	H	Et	H
R^3	Et	Bu^n	_	_
(108)	43%	48%	_	_
(109)	_	_	44%	71%

Table 18 Displacement of benzotriazole in 4-(benzotriazol-1-ylaklyl)- anilines by active methylene compounds, alcohols, and thiols

5 Displacement of Benzotriazole by Other Nucleophiles

5.1 From 4-(Benzotriazol-1-ylalkyl)anilines

4-(Benzotriazol-1-ylalkyl)anilines (106) react with other nucleophiles Active methylene compounds,[33] alcohols, and thiophenol[16] each give the corresponding *para*-substituted products (105), (107)—(109) The active methylene compounds yield different products depending on the reaction medium used Thus, in anhydrous/aprotic conditions, with $ZnBr_2$ as the catalyst, compound (105) was obtained While in aqueous acid, one of the acyl groups was removed by hydrolysis to give simple ketones (107) (Table 18)

5.2 From *o*-(Benzotriazol-1-ylmethyl)phenols

As we have shown earlier in the present account, reactions of *o*-(benzotriazol-1-ylmethyl)phenols involve *o*-quinone methides as the reactive intermediates, which are trapped by dienophiles *via* [2 + 4] cycloaddition [18] We have further demonstrated that such *o*-quinone methides are Michael acceptors [43,44] thus, *o*-(benzotriazol-1-ylmethyl)phenols (111) react with thiols, alcohols, amines, and active methylene compounds to give the substituted phenols (110), (112)—(114) [45] With diethyl methylmalonate, ester exchange was observed in isopropoxide to give product (114) in 53% yield (Table 19)

5.3 From 1-[(Methoxyphenyl)alkyl]benzotriazoles

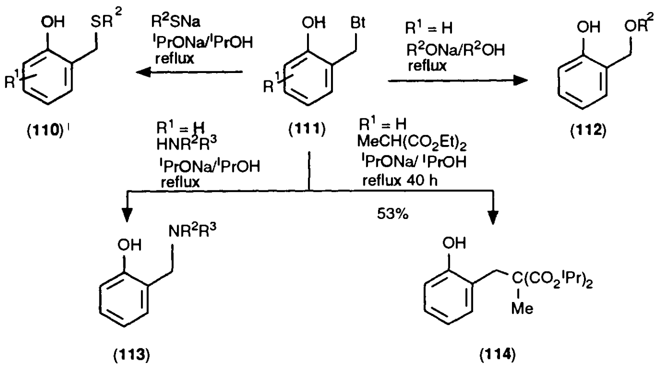
Similar to the aniline and phenol derivatives, 1-[(methoxyphenyl)alkyl]benzotriazoles (115) also reacted with phenol and thiophenol to give substituted phenyl ethers and sulfides (116)[16] (Table 20)

5.4 From (Benzotriazolylalkyl)indoles

The benzotriazole moiety in (benzotriazolylalkyl)indoles (117) was also displaced by a thiophenol group to give substituted indole (118)[12] (Scheme 15)

6 Summary

N-(Arylmethyl)benzotriazoles, containing in the aryl ring an *ortho* or *para* electron-donating group such as amino, hydroxy, or methoxy, undergo lithiation at the methylene carbons to give anions which react with a variety of electrophiles The benzotriazole groups in the parent derivatives as well as those obtained *via* lithiation, have been displaced by Grignard reagents and reductively removed with $LiAlH_4$ or Na/piperidine, to give alkyl-substituted aromatic compounds These *N*-(arylmethyl)- and *N*-(arylalkyl)benzotriazoles are also efficient arylalkylating reagents for electron-rich aromatic and heteroaromatic compounds, alcohols, thiols, amines, and active methylene compounds This general methodology has also been extended to heteroaryl analogues in which the ring heteroatom acts as the electron-donating group In general, the reactions proceed in good to excellent yields and isolation and purification of the products was simple In many instances this new methodology represents the method of choice for the preparation of whole classes of compounds

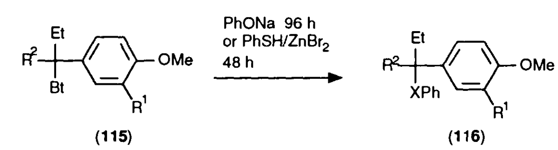


(110)	R^1	R^2	Time (h)	Yield (%)
a	H	Ph	40	55
b	H	n-C_8H_{17}	40	69
c	2-^{t}Bu	n-C_8H_{17}	2 5	74
d	2-Me	n-C_8H_{17}	30	74

(112)	R^1	R^2	Time (h)	Yield (%)
a	H	Et	40	26
b	H	^{i}Pr	40	60

(113)	R^1	NR^2R^3	Time (h)	Yield (%)
a	H	$N(CH_2CH_2)_2O$	40	66
b	H	NMePh	24	33

Table 19 Displacement of benzotriazole in *o*-(benzotriazol-1-ylmethyl)-phenols (111) by thiols, alcohols, active methylene compounds, and amines



(116)	R^1	R^2	X	Solvent	Temp (°C)	Yield (%)
a	H	Et	O	PhOH	180	33
b	H	H	O	PhOH	180	35
c	OMe	H	O	PhOH	180	27
d	H	Et	S	toluene	80	45
e	OMe	H	S	toluene	80	48
f	H	H	S	toluene	40	56

Table 20 Displacement of benzotriazole in 1-(methoxyphenylalkyl)benzotriazoles (115) by phenol and thiophenol

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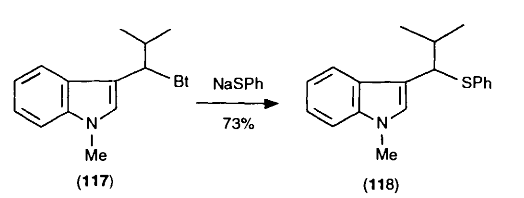

Scheme 15

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