BENZOTRIAZOLYLALKYLATION OF AROMATIC COMPOUNDS BY 1-BENZENESULPHONYLBENZOTRIAZOLE AND SYNTHESIS OF TRIARYLMETHANES

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Abstract - Mesitylene, 2-methoxynaphthalene, 1,3,5-trimethoxybenzene, xylene and anisole were all benzotriazolylalkylated by treatment with 1-(benzene-sulphonyl)benzotriazole and an aromatic aldehyde. Upon displacement of benzotriazole, the functionalized aromatic compounds were transformed into asymmetrically trisubstituted methanes and functionalized indoles.

INTRODUCTION

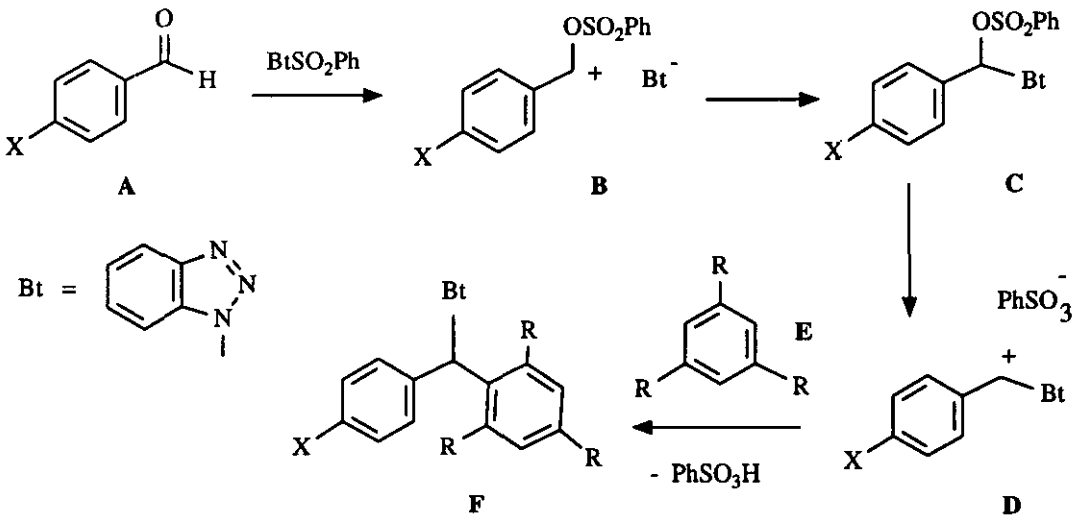
Benzotriazole has proven to be a useful moiety in the synthesis of a variety of heterocyclic compounds.[1] Benzotriazolylalkylation of aromatic compounds has led to the synthesis of different types of substituted aromatic compounds by a Mannich/Friedel-Crafts sequence. Most of our work on benzotriazolylalkylation has concentrated on the alkylation of activated compounds such as phenols and anilines. Phenols invariably undergo benzotriazolylalkylation[2] in the ortho position while anilines[3] and methoxybenzenes[4] were benzotriazolylalkylated exclusively in the para position using 1-hydroxymethylbenzotriazole. Some examples of the benzotriazolylalkylation of less activated aromatic compounds were reported using 1-chloromethylbenzotriazole as the electrophilic reagent.[5]

Symmetrical triarylmethanes have been used extensively as basic dyes for cotton using tannin as a mordant, or if they contain sulfonic acid groups, as acid dyes for wool and silk (e.g. malachite green and methyl violet).[6,7] We now wish to report a new method of benzotriazolylalkylation for the synthesis of aromatic compounds with a tertiary center next to the benzotriazole moiety using the combination of 1-benzenesulphonylbenzotriazole and an aromatic aldehyde. The tertiary center of the compounds so produced allows a general entry to asymmetric triarylmethanes and substituted indoles by displacement of the benzotriazole moiety under appropriate conditions. Indole derivatives such as these are used in the perfumery industry, as pharmaceuticals and also as colorants or fixatives.[8]

RESULTS AND DISCUSSION

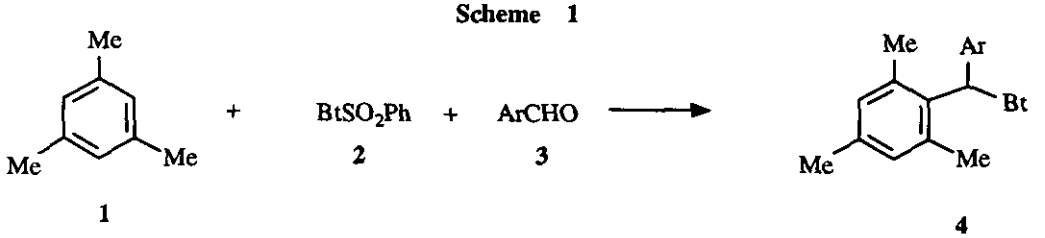
1-Benzenesulphonylbenzotriazole has been used to activate carboxylic acids in cases where the corresponding acid chlorides were not available or difficult to obtain.[9] Here, 1-benzenesulphonylbenzotriazole is used as an activating moiety for the benzotriazolylalkylation of aromatic compounds.

Mechanism



1-Benzenesulphonylbenzotriazole is thought to achieve this by virtue of its ability to supply initially the Lewis acid properties required for the activation of the aldehyde, and then subsequently render the benzotriazolate anion necessary for the displacement of the sulphonate residue. Hence, the reaction can be considered to proceed in different stages. Initially 1-benzenesulphonylbenzotriazole is presumed to behave as a Lewis acid, reacting with the aromatic aldehyde to form the benzyl stabilized carbocationic species **B** with the liberation of the benzotriazolate anion. Intermediate **B** is believed to then dissociate into **D**, via intermediate adduct **C**, and react in a Friedel-Crafts type reaction with the aromatic nucleus to afford the product **F**. The one-pot reaction was evaluated using different types of aromatic compounds (**E**) (e.g. with varying degrees of activation) in combination with a selection of aromatic aldehydes and 1-benzenesulphonylbenzotriazole. In the cases where **E** was a liquid, it was used as a solvent as well as a reagent, alternatively chlorobenzene was found to be the solvent of choice.

Scheme 1



3a and **4a** : Ar = C_6H_5 **3c** and **4c** : Ar = *p*-$MeOC_6H_4$

3b and **4b** : Ar = *p*-ClC_6H_4 **3d** and **4d** : Ar = *p*-$OHCC_6H_4$

At reflux temperatures in a sealed vessel, mesitylene reacted with aromatic aldehydes **3** to afford the alkylated products **4**. (Scheme 1). After decanting the reaction mixtures from the polar residue formed in the course of the reaction, the functionalized mesitylenes **4** were then purified by column chromatography in 32-60% yield. Although polymer formation accounted for significant product losses, larger yields were obtained from those aromatic aldehydes bearing electron donating groups in the para-position (Table 1) and thus stabilizing the carbocation **D** necessary for the Friedel-Crafts reaction. The electron donating methoxy substituent in compound **3c** allowed the isolation of **4c** in 60% yield while the yield dropped to 32% with the electron withdrawing formyl substituent present in **3d**.

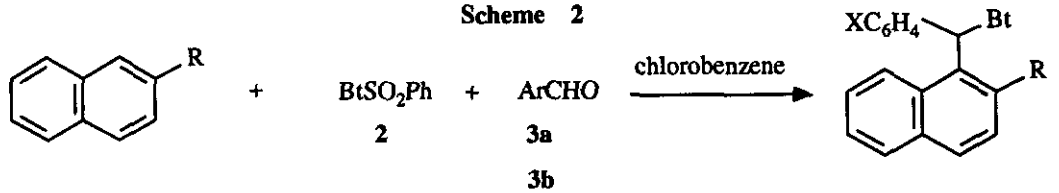
Table 1 : Preparation of Benzotriazolyl - substituted Aromatic Compounds.

Compound No	Ar	Yield %	mp °C	Molecular formula					
				Calcd			Found		
				C	H	N	C	H	N
4a	C_6H_5	48	53-55	80.70	6.46	12.83	80.89	6.48	12.99
4b	p-ClC_6H_4	56	54-56	73.02	5.57	11.61	73.01	5.67	11.46
4c	p-$MeOC_6H_4$	60	118-120	70.92	5.96	10.79	70.95	6.06	10.44
4d	p-$OHCC_6H_4$	32	159-161	77.72	5.96	11.82	77.42	5.94	11.62
6	C_6H_5	30	55-57	82.35	5.11	12.53	82.31	5.13	12.36
9	p-ClC_6H_4	55	52-54	64.47	4.92	10.25	64.43	4.91	10.11
11	p-ClC_6H_4	52	65-68	72.16	4.55	10.53	72.07	4.77	10.06
13	p-ClC_6H_4	25	135-137	72.51	5.22	12.08	72.48	5.19	11.97
15	p-ClC_6H_4	15	-	68.67	4.61	12.01		a	

[a] HRMS was in accordance with the proposed structure

In order to study the generality of the reaction and broaden its scope the reaction was extended to include naphthalene (**5**) as an aromatic substrate. However, the functionalized naphthalene (**6**) could only be isolated in 30%, presumably it suffers an increased tendency to polymerize in the presence of the benzenesulphonic acid formed in the reaction (Scheme 2).

Scheme 2



5 : R = H

10 : R = OMe

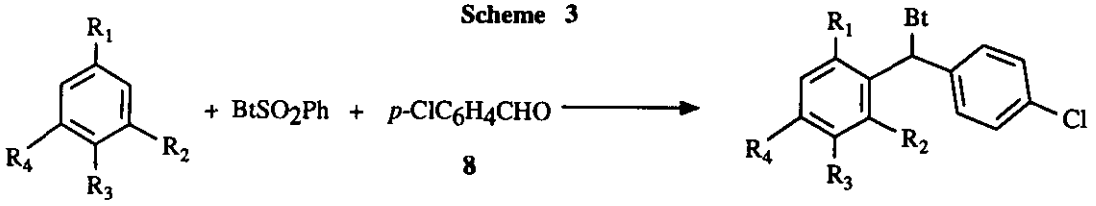
6 : R = H, X = H

11 : R = OMe , X = *p* - Cl

With 2-methoxynaphthalene (**10**) the benzotriazolylalkylation is invariably directed to the 1-position. This result is in accordance with the benzotriazolylalkylation of methoxynaphthalenes using 1-hydroxymethylbenzotriazole.[4] If the position para to a methoxy group in methoxynaphthalenes is substituted, alkylation occurs at the position ortho to the methoxy group; thus for 2-methoxynaphthalene, reaction occured at the 1-position.

The yield of the one-pot reaction is not only dependent upon the activation of the aldehyde, but also upon that of the aromatic compound, for the Friedel-Crafts reaction. This was illustrated by the reactivity of 1,3,5-trimethoxybenzene (**7**) (Scheme 3) in comparison with 1,4-dimethylbenzene (**12**) (Table 1). Using the activated 1,3,5-trimethoxybenzene, **9** could be isolated in 55% yield while **13** was afforded in only 25% yield.

Scheme 3



7 : R_1, R_2, R_4 = OMe ; R_3 = H

12 : R_1, R_3 = Me ; R_2, R_4 = H

14 : R_1 = OMe ; R_2, R_3, R_4 = H

9 : R_1, R_2, R_4 = OMe ; R_3 = H

13 : R_1, R_3 = Me ; R_2, R_4 = H

15 b : R_1 = OMe ; R_2, R_3, R_4 = H

15 a : R_1, R_2, R_3 = H ; R_4 = OMe

Using anisole (**14**) however, the yield of the reaction was surprisingly low (15%) and the reaction led to a mixture of the ortho- and para-substituted derivatives in a 40:60 ratio. The reactivity difference between the ortho- and the para-position is too small to direct the reaction to one center. Both isomers, however, could be separated by column chromatography and were characterized by the usual spectroscopic methods. The characterizations were based on the ^{13}C-nmr spectra which distinguished the two additional carbon signals for the ortho-isomer (Table 2). The ^{1}H-nmr spectrum of the ortho-isomer (Table 3) reveals a singlet at 7.62 ppm for the methine proton (CHBt), as where the signal for the para-isomer overlaps with the aromatic protons at 7.32 ppm. Two-dimensional nmr spectroscopy was in agreement with the proposed characterizations.

Table 2 : ^{13}C-Nmr Spectral shifts of substituted Aromatic Compounds.

Compound No	Benzotriazole ring						CHBt	Aryl	CH_3
	3a	4	5	6	7	7a			
4a	145.8	119.9	123.7	127.1	109.9	133.5	62.6	138.0, 137.5, 137.0,131.1, 130.5, 128.6, 127.9	21.0 20.7
4b	145.9	120.1	124.0	127.4	109.7	133.4	62.1	138.4, 137.4, 135.4, 134.0, 130.7, 130.5, 129.5, 129.0	21.0 20.8
4c	145.8	119.8	123.6	127.0	110.0	133.4	62.6	159.2, 137.8, 137.0, 131.3, 130.5, 129.7, 127.8, 113.9	55.1 20.7 20.7
4d[1]	146.2	120.5	124.5	128.0	109.9	133.8	62.6	144.8, 139.1, 138.1, 136.1, 131.1, 130.6, 130.3, 128.7	21.6 21.2
6	146.3	120 1	123.8	127 4	110.4	133.2	64.3	137.5, 133.7, 133.1, 131.0, 129.5, 128.9, 128.8, 128.4, 128.2, 127.0, 126.7, 126.0, 125.0, 122.7	-
9	145.6	119.3	123.0	126.1	111.6	133.2	57.6	161.7, 159.0, 136.0, 133.0, 129.3, 128.0, 106.3, 91.0	55.0 55.4
11	145.7	119.8	123.7	127.0	110 4	133.8	58.1	155.5, 136.1, 133.5, 132.2, 131.8, 129.6, 129.3, 128.6, 127.0, 124.5, 123.8, 117.3, 113.0	56.5
13	146.1	120.1	123.9	127.5	110.1	133.0	63.7	135.9, 135.9, 135.2, 134.2, 133.2, 130.9, 129.6, 129.4, 128.9, 128.5	21.1 18.8
15a	146.2	120.2	123.9	127.4	110.3	132.8	66.0	159.7, 136.6, 134.3, 129.6, 129.4, 129.2, 128.9, 114.2	55.3
15b	145.9	120.0	123.8	127.2	110.1	133.2	60.1	156.7, 136.3, 134.0, 130.0, 129.4, 129.1, 128.8, 125.8, 120.7, 110.7	55.5
4d[1] : 191.9 (CHO)									

All the newly synthesized benzotriazolylalkylated aromatic compounds exhibited a singlet in the region 7.41 - 8.27 ppm for the methine proton (CHBt) in the ^{1}H-nmr spectra (Table 3) and a signal at 58.1 - 66.0 ppm in the ^{13}C-nmr spectra (Table 2). The assignment of the methoxy signals and the methine carbons in compounds (**9**) and (**11**) was therefore based on the results from the HETCOR experiments. For compound (**9**), the signals at 55.0 and 55.4 ppm correspond to the methoxy carbons and the resonance at 57.6 ppm to the methine carbon. Similarly, the signal at 58.1 ppm for compound (**11**) was assigned to the methine carbon, while the methoxy carbon signal was observed at 56.5 ppm.

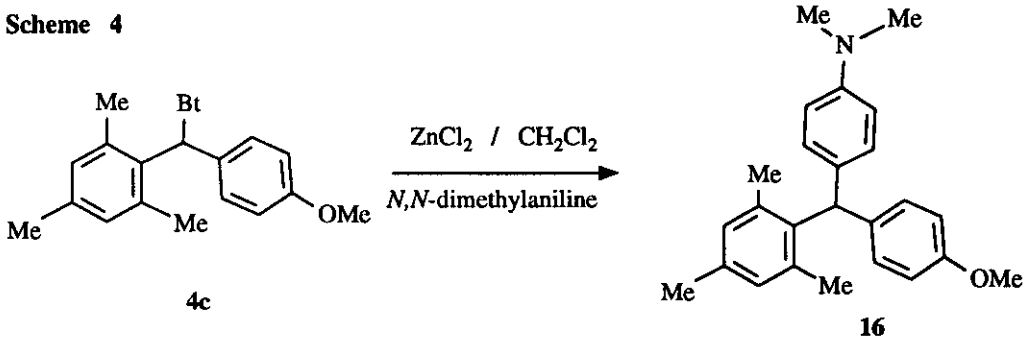
Table 3 : ^{1}H - Nmr Spectral shifts of substituted Aromatic Compounds.

No	Benzotriazole ring										Aryl				CHBt		CH_3		
	δ	m	J	δ	m	J	δ	m	J	δ	m			δ	m	δ	m	I
	H - 4			H - 5			H - 6			H - 7								
4a	8.07	m	-	7.30	m	-	7.30	m	-	7.30	m	-	7.30	m	2	-	7.50	s	2.26	s	3
													7.02	m	3	-			2.03	s	6
													6.87	s	2	-					
4b	8.09	m	-	7.35	m	-	7.35	m	-	7.07	m	-	7.35	m	2	-	7.42	s	2.28	s	3
													6.98	d	2	9			2.02	s	6
													6.88	s	2	-					
4c	8.05	m	-	7.29	m	-	7.29	m	-	6.93	m	-	7.02	m	2	-	7.42	s	3.77	s	3
													6.86	m	4	-			2.26	s	3
																			1.98	s	6
4d[1]	8.11	m	-	7.38	m	-	7.38	m	-	7.17	m	-	7.83	d	2	8.2	7.54	s	2.29	s	3
													7.17	m	2	-			2.06	s	6
													6.91	s	2	-					
6	8.06	m	-	7.85	m	-	7.85	m	-	7.85	m	-	7.30	m	10	-	8.14	s	-	-	-
													7.05	d	1	7.2					
													6.97	m	1	-					
9	8.00	m	-	7.24	m	-	7.24	m	-	6.93	m	-	7.24	m	2	-	7.82	s	3.74	s	3
													7.11	d	2	8.7			3.54	s	6
													6.13	s	2	-					
11	8.11	d	8.1	8.03	m	-	7.87	d	9.3	7.74	m	-	7.28	m	8	-	8.27	s	3.77	s	3
													7.06	d	2	8.7					
13	8.08	m	-	7.37	m	-	7.37	m	-	7.01	m	-	7.37	m	2	-	7.41	s	2.19	s	3
													7.07	m	4	-			2.11	s	3
													6.69	s	1	-					
15a	8.08	m	-	7.32	m	-	7.32	m	-	7.13	m	-	7.32	m	2	-	7.32	m	3.79	s	3
													7.13	m	4	-					
													6.87	m	2	-					
15b	8.07	m	-	7.32	m	-	7.32	m	-	7.20	m	-	7.32	m	3	-	7.62	s	3.70	s	3
													7.10	d	2	9					
													7.01	m	1	-					
													6.90	m	2	-					

4d[1] 9.99 (s, 1, CHO)

The substituted aromatic compounds prepared in this manner are well suited for the synthesis of non-symmetrical triarylmethanes. A variety of synthetic routes lead to symmetrical triarylmethanes, e.g., a. treatment of an aromatic aldehyde with an aromatic hydrocarbon in the presence of a Lewis acid;[10] b. treatment of a diarylmethanol with a hydrocarbon in acid medium;[11] c. reaction of an aromatic aldehyde with 2 equivalents of an aromatic Grignard reagent.[12] However, references to the corresponding asymmetrical analogues are scarce. Generally the known methods for the synthesis of symmetrical triarylmethanes suffer the limitation of mixed triaryl methane products. The previously reported methods using 1-arylmethylbenzotriazole followed by alkylation and displacement of benzotriazole[4,13] can not be used for the synthesis of asymmetrical triarylmethanes since halobenzenes are inappropriate electrophiles for the subsequent alkylations.

Scheme 4



4c **16**

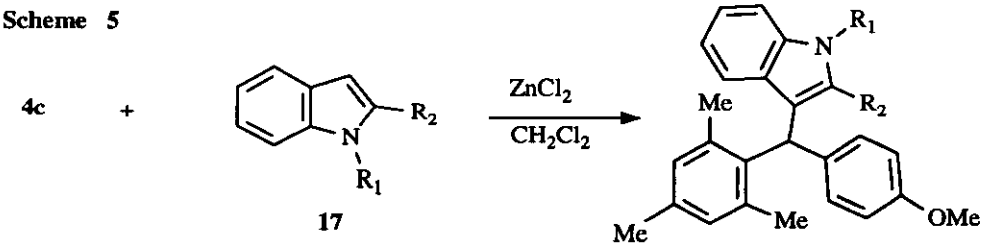
The utility of the generated products was evaluated using compound (**4c**) which was readily available from the condensation reaction after column chromatography. Treatment of **4c** with *N,N*-dimethylaniline in the presence of zinc dichloride led to the ionization of the starting compound forming a carbonium ion which was then reacted with *N,N*-dimethylaniline (Scheme 4). The asymmetric compound (**16**) was isolated as a bright pink oil as is often the case with symmetrical triaryl methanes. This example illustrates the feasibility of this method as a route to asymmetric triaryl methanes as potential leuco dyes. More attention, however, was paid to the indole displacement of benzotriazole in order to synthesize 3-substituted indoles (Table 4). The displacement of benzotriazole was accelerated by the use of zinc dichloride as a Lewis acid to promote the formation of the carbocation which was subsequently quenched by reaction with the 3-position of the indole nucleus.

3-(1-Alkyl-1-arylmethyl)indoles were synthesized previously in good yield by the alkylation of 4-benzotriazol-1-ylmethylanilines followed by displacement of benzotriazole by indole.[13] This method is, however, inappropriate for the synthesis of 3-(diarylmethyl)indoles since halobenzenes can not be used as electrophiles. The present method circumvents this problem by synthesizing first the diarylmethylbenzotriazole followed by displacement of benzotriazole.

Table 4 : Preparation of Trisubstituted Methanes.

Compound No	Yield %	mp °C	Molecular Formula					
			Calcd			Found		
			C	H	N	C	H	N
16	55	oil	83.51	8.14	3.90	83.67	8.43	3.61
18a	57	72	84.27	7.09	3.94	84.15	7.04	3.96
18b	70	78	84.51	7.37	3.79	84.51	7.77	3.48
18c	85	65	84.51	7.37	3.79	84.15	7.28	3.75

Scheme 5



17a and **18a** $R_1 = H$, $R_2 = H$

17b and **18b** $R_1 = H$, $R_2 = Me$

17c and **18c** $R_1 = Me$, $R_2 = H$

The indole substituted compounds were purified by column chromatography although some crude compounds were obtained in almost a pure state. In the case of **18c**, the product decomposed during purification by column chromatography although the crude solid gave adequate analyses. The spectrometric data is summarized in Tables 5 and 6.

Table 5: ^{13}C-Nmr Spectral Shifts for Trisubstituted Methanes.

Compound	Aromatic Carbons	CH	Me (mesityl)	OMe	Me
16	112.8, 113.5, 120.6, 129.9, 130.0,130.1 135.4, 137.5, 137.8, 148.4, 148.6, 157.6	49.4	20.7, 21.9	55.2	40.9
18a	111 0, 113.4, 119.3, 120.0, 122.0, 123.7 127.8, 129.8, 130.1, 135.3, 135.5, 136.7 137.2, 137.7, 139.5, 157.4	42.2	20.8, 21.5	55.2	-
18b	109.9, 113.0, 113.6, 119.1, 119.5, 120.6 129.3, 130.1, 130.2, 131.9, 134.7, 135.1 135.4, 137.2, 137.4, 157.9	43.4	20.7, 21.6	55.2	12.5
18c	109.0, 113.3, 115.4, 118.7, 119.5, 121 5 128.2, 128.4, 129.7, 130.0, 135.4, 135.5 137.1, 137.3, 138.0, 157.4	42.0	20.8, 21.6	55.1	32.6

In conclusion, a new procedure for benzotriazolylalkylation using 1-benzenesulphonylbenzotriazole has been developed for the synthesis of substituted aromatic compounds. The readily benzotriazolylated intermediates were then transformed, by displacement of the benzotriazole residue, into new asymmetric triarylmethanes and novel 3-substituted diarylmethyl indoles. The advantage of the present method lays in the use of a one-pot procedure to prepare precursors of the triarylmethanes and the 3-diarylmethyl indoles.

EXPERIMENTAL SECTION

Melting points were determined with a Kofler hot stage apparatus without correction. ^{1}H- and ^{13}C-nmr spectra were taken at 300 and 75 MHz, respectively, using a Varian XL 300 spectrometer. Tetramethylsilane was used as the internal standard for the ^{1}H-nmr spectra, and the central line of deuterated chloroform (δ=77.0 ppm) was referenced in the ^{13}C-nmr spectra. Elemental analyses were caried out at the University of Florida. 1-Benzenesulfonylbenzotriazole (**2**) was prepared using the literature procedure.[9]

General procedure for the benzotriazolylalkylation of unactivated aromatic compounds.

A mixture of 1-benzenesulphonylbenzotriazole (**2**) (1.30 g, 5 mmol), the aldehyde (5 mmol) and the appropriate aromatic compound (5 mmol) was heated in a closed vessel, at the reflux temperature of the

Table 6 : ^{1}H-Nmr Spectral Shifts of Trisubstituted Methanes.

Compound	Aromatic Protons				NH	CH	Methyl Groups			
	δ	m	I	J (Hz)			δ	m	I	Assign.
16	7.01	d	2	8.80		5.85	3.78	s	3	OMe
	6.95	d	2	8.79			2.92	s	6	NMe_2
	6.83	s	2	-			2.28	s	3	Me
	6.79	d	2	8.69			2.01	s	6	Me
	6.67	d	2	8.59						
18a	7.35	d	2	7.12	7.95	6.04	3.77	s	3	OMe
	7.27	d	2	7.13			2.27	s	3	Me
	7.18	t	1	8.04			2.06	s	6	Me
	7.04	t	1	8.04						
	7.00	d	2	7.27						
	6.83	s	2	-						
	6.75	d	2	8.73						
	6.60	dd	1	1.14; 2 27						
18b	7.20	d	2	8.63	7.63	6.03	3.78	s	3	OMe
	7.05	m	3	-			2.26	s	3	Me
	6.82	m	3	-			2.03	s	6	Me
	6.80	s	2	-			1.83	s	3	Me
	6.68	d	1	7.99						
18c	7.33	d	2	8.11		6.04	3.78	s	3	OMe
	7.24	t	1	6.93			3.68	s	3	Me
	7.06	d	2	8.10			2.29	s	3	Me
	7.03	t	1	6.87			2.08	s	6	Me
	6.86	s	2	-						
	6.77	d	2	8.75						
	6.47	d	1	0.99						

aromatic compound for up to 15 h (8 h for the case of naphthalene). In the cases where the aromatic compound was a solid, chlorobenzene was used as solvent. After the reaction, chloroform (20 ml) was added to the reaction mixture and the organic layer was washed with water (20ml). After drying ($MgSO_4$),

the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using chloroform/hexanes (25/75) as eluant to give the pure product. Data is summarized in Tables 1-3.

General Procedure for the Displacement of Benzotriazole from Compound 4c.

To a solution of 0.56 mmol of **4c** in 20 ml of dichloromethane was added 2 equivalents of zinc dichloride and 1 equivalent of nucleophile (*N,N*-dimethylaniline or indole **17**) and the mixture was refluxed for 24 h. After filtration, the reaction mixture was poured into an aqueous solution of sodium hydroxide (10%) (20 ml) and extracted three times with dichloromethane (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude products (an oil in the case of N,N-dimethylaniline; solids in the cases of an indole substituent) were purified by column chromatography using chloroform/hexanes (60:40) as eluant.

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