A NOVEL AND CONVENIENT ROUTE TO (1*H*-1,2,4-TRIAZOL-1-YLMETHYL)PHENOLS, ANILINES, *N*-ALKYLANILINES AND *N,N*-DIALKYLANILINES

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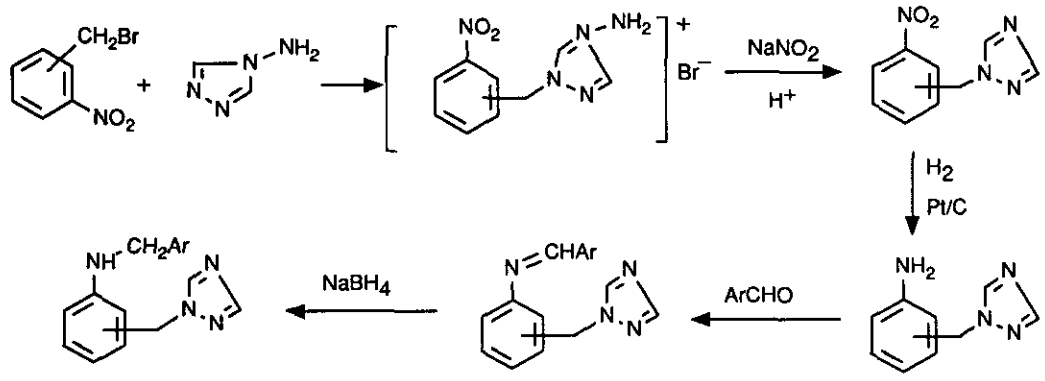
Abstract- Phenols, naphthols, anilines, *N*-alkylanilines and *N,N*-dialkylanilines are readily alkylated by 1-hydroxymethyl-1,2,4-triazole to afford the corresponding triazole derivatives in good yields.

1,2,4-Triazoles constitute an important class of nitrogen heterocycles: representatives possess diverse types of biological activity and include herbicides, defoliants, growth regulators, fungicides and insecticides.[1] Specifically, 3-amino-1,2,4-triazole has been widely used as the neutral herbicide and defoliant of cotton, and in low concentration it may promote growth.[1] Recently, the antimycotic activity of some (1*H*-1,2,4-triazol-1-ylmethyl)aniline derivatives has also been investigated.[2] However, preparations of triazolylmethyl substituted phenols and anilines are far less documented. 2-(3,5-Dimethyl-1*H*-1,2,4-triazol-1-ylmethyl)-4-nitrophenol was previously prepared by reaction of 2-hydroxy-5-nitrobenzyl chloride with the 3,5-dimethyltriazole in EtOH in the presence of EtONa.[3] Another triazolylmethylphenol derivative, 2,4-dichloro-6-(1*H*-1,2,4-triazolylmethyl)phenol, was reported in a patent.[4] Scalzo *et al.* have recently reported a multi-step sequence for the preparation of triazolylmethyl substituted anilines and *N*-alkylanilines,[2] as shown in Scheme 1. Obviously, development of simple and efficient methods for the preparation of these types of compounds is desirable.

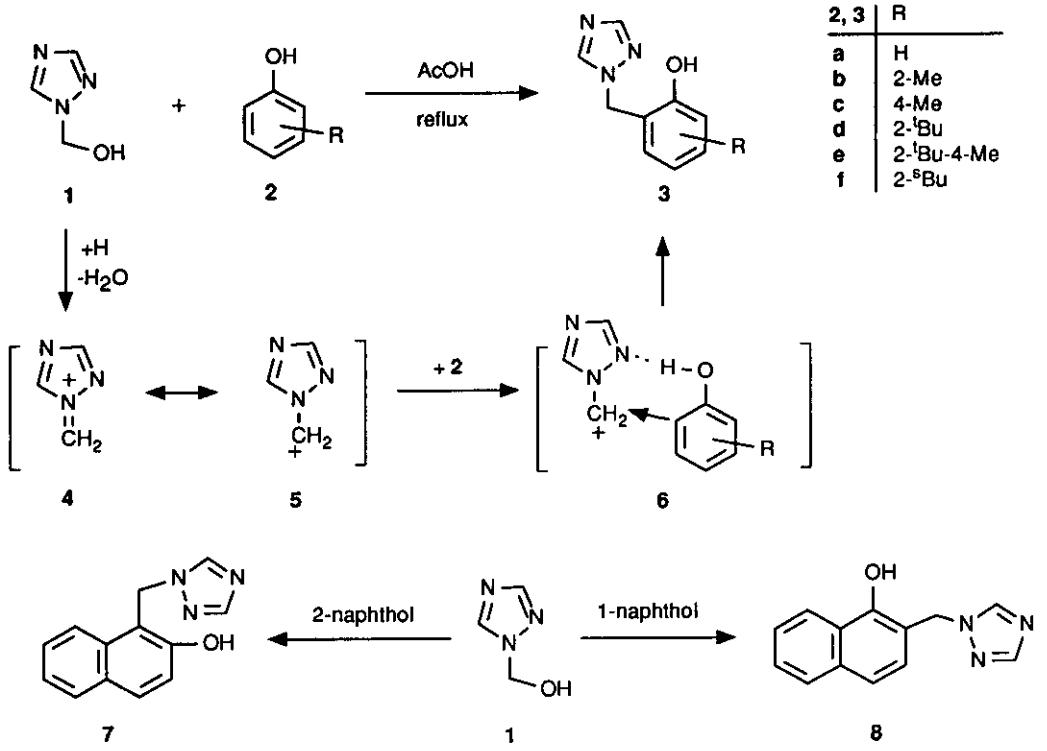
Scheme 1



Recent achievements in the chemistry of benzotriazole[5] *in our group have provided a firm scientific basis for* further researches in this area. Specifically, the benzotriazolylalkylation strategy (i.e. the introduction of benzotriazolylalkyl groups into the appropriate substrate) has been elaborated and successfully applied to new and efficient preparations of benzotriazole and other organic derivatives.[5] A variety of substituted phenols[6,7] and anilines[8,9] has been prepared by this methodology. In this paper, we wish to report the successful preparation of the (1*H*-1,2,4-triazol-1-ylmethyl) substituted phenols, anilines, *N*-alkylanilines and *N,N*-dialkylanilines by reaction of the corresponding phenols or anilines with 1-hydroxymethyl-1,2,4-triazole or in some case by direct reaction of a phenol with formaldehyde and 1,2,4-triazole.

Reactions of Phenols and Naphthols with 1-Hydroxymethyl-1,2,4-triazole 1.-1-Hydroxymethyltriazole (**1**) is readily obtained by stirring a mixture of 1,2,4-triazole with formalin in water at room temperature for 5 h,[10] or better by refluxing 1,2,4-triazole with paraformaldehyde in ethanol in the presence of a catalytic amount of triethylamine.[11] In the latter case, an almost quantitative yield (98%) was achieved. Reaction of phenols (**2**) with 1-hydroxymethyl-1,2,4-triazole (**1**) in acetic acid gave the corresponding *ortho*-substituted products (**3**) in good yields. Thus, heating a mixture of **2a** and 1 equivalent of 1-hydroxymethyltriazole under reflux for 12 h yielded the desired **3a** in 65% yield. Compounds (**3b-f**) were similarly obtained in 66 -73% yields (see Table 1). It was found that naphthols could also undergo a similar triazolylalkylation reaction to give the corresponding triazole derivatives. *O*-(1*H*-1,2,4-triazol-1-ylmethyl) substituted 1-naphthol (**8**) and 2-naphthol (**7**) were prepared in this way in 68% and 70% yields, respectively.

Scheme 2

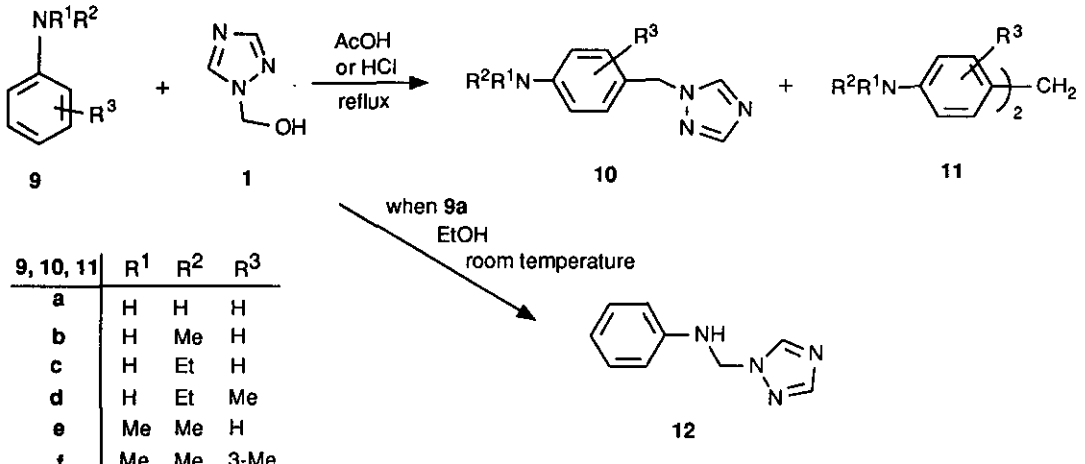


2, 3	R
a	H
b	2-Me
c	4-Me
d	2-^{t}Bu
e	2-^{t}Bu-4-Me
f	2-^{s}Bu

The present reaction can be considered as a type of Mannich reaction. The Mannich reaction has long been of great important in synthetic organic chemistry. In its most general representation, formaldehyde (rarely other aldehydes) is condensed with a primary or secondary amine and a compound containing an active hydrogen atom (CH-).[12-14] Important extensions of the Mannich reaction in which amides, imides, ureas, thioureas etc. replace the amine component are well documented.[15a-e] We now extend the Mannich reaction to triazole, employing hydroxymethyltriazole to replace the amine and aldehyde components. Phenols have widely been employed as the active CH- compounds in Mannich condensations.[15a-e] In the present cases, under acidic conditions, protonation of the oxygen in **1**, followed by loss of water, would give rise to reactive cations (**4** or **5**). Hydrogen bonding between the phenolic hydrogen and the basic nitrogen of the triazole ring then leads to *ortho*-substitution. Zaugg[16] attributed the high *ortho*- to *para*-preference to the assistance of the phenolic hydroxy group. Burckhalter *et al.*[17,18] assumed that the preference of *ortho*-substitution was attributed to a quasi six-membered chelate ring. In the present case, seven-membered ring intermediates (**6**) are more likely due to the chelation of phenolic hydroxy with the 2-position nitrogen of triazole ring as shown in Scheme 2.

Reactions of Anilines, *N*-Alkylanilines and *N,N*-Dialkylanilines with 1-Hydroxymethyl-1,2,4-triazole.-Previous work in our group has demonstrated that aniline, *N*-methylaniline and *N,N*-dialkylanilines could be benzotriazolylalkylated in acetic acid in the presence of a strong acid (HCl or H_2SO_4), or better by direct reaction of their hydrochloride salts with 1-hydroxymethylbenzotriazole.[8-9] Thesing *et al.* reported the preparation of 4-(indol-3-ylmethyl)-*N,N*-dimethylaniline by reacting *N,N*-dimethylaniline with 3-hydroxymethylindole in acetic acid.[19] The *N*-methyl analog has been prepared by direct reaction of *N*-methylaniline with formaldehyde and indole.[19] Lau *et al.* prepared 4-(4′-chlorophenyl)thiomethyl-*N*-methylaniline from the condensation of 4-chlorophenylthiol, formaldehyde and *N*-methylaniline in acetic acid under reflux.[20] In all the afore-mentioned reactions, *para*- substituted products were obtained exclusively due to the steric effect.

Scheme 3



9, 10, 11	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	H	Et	H
d	H	Et	Me
e	Me	Me	H
f	Me	Me	3-Me

In the present work, reaction of *N*-methylaniline chloride with 1-hydroxymethyl-1,2,4-triazole (**1**) in acetic acid under reflux for 5 minutes gave **10a** in 59% yield. Compounds (**10b, c, d**) were obtained in better yields and with fewer by-products by refluxing the corresponding **9b, 9c** or **9d** with **1** in concentrated hydrochloric acid for 7 h; although these compounds could also be prepared under similar conditions as **10a** (refluxing in acetic acid). Similarly, **10e** and **10f** were prepared in 61% and 65% yields respectively, by initial treatment of the corresponding **9e** and **9f** with concentrated HCl to form the chlorides, then reaction with 1-hydroxymethyltriazole.

Table 1 Preparation of Triazole Derivatives (3a-f, 7, 8, and 10a-f).

Compd.	React. time	Yield (%)	mp (°C)	Molecular formula	Calcd/Found		
					C	H	N
3a	12	65	140-41	$C_9H_9N_3O$	61.70/61.76	5.18/5.25	23.99/23.91
3b	12	66	110-12	$C_{10}H_{11}N_3O$		-[a]	
3c	12	68	160-61	$C_{10}H_{11}N_3O$	63.48/63.78	5.85/5.94	22.21/22.02
3d	12	70	oil	$C_{13}H_{17}N_3O$	67.57/67.51	7.41/7.49	18.17/17.89
3e	12	73	124-25	$C_{14}H_{19}N_3O$	68.59/68.69	7.81/8.04	17.13/17.20
3f	12	68	56-57	$C_{13}H_{17}N_3O$	67.49/67.07	7.41/7.50	18.17/17.79
7	4	70	226-27	$C_{13}H_{11}N_3O$	69.32/69.57	4.92/4.93	18.65/18.23
8	2	68	122-23	$C_{13}H_{11}N_3O$		-[b]	
10a	0.1	59	122-23[c]	$C_9H_{10}N_4$	62.05/61.71	5.79/5.80	32.16/32.45
10b	7	62	99-100	$C_{10}H_{12}N_4$	63.81/63.91	6.43/6.46	29.76/29.89
10c	5	72	94-95	$C_{11}H_{14}N_4$	65.32/64.98	6.98/6.97	27.70/27.56
10d	8	63	59-60	$C_{12}H_{16}N_4$		-[d]	
10e	11	61	97-98	$C_{11}H_{14}N_4$	65.32/65.63	6.98/7.08	27.70/28.00
10f	10	65	79-80	$C_{12}H_{16}N_4$	66.64/66.66	7.46/7.53	25.90/26.02

[a] $C_{10}H_{11}N_3O$ requires MW= 189.0902, found MW= 189.0935. [b] $C_{13}H_{11}N_3O$ requires MW= 225.0902, found MW=225.0903. [c] Lit., mp 121 °C [2]. [d] $C_{12}H_{16}N_4$ requires MW=216.1375, found MW=216.1357.

Use of the chloride salts, or alternatively, the free aniline or analogs in the presence of a strong acid, is very important for the triazolylalkylation reaction. This is especially the case where an active hydrogen (N-H) exists in the molecules, because this active hydrogen would react more easily with 1-hydroxymethyltriazole than the aromatic CH-. The *N*-triazolylmethyl substituted aniline (**12**) has easily been prepared by direct reaction of the aniline with **1** in EtOH. Thus, stirring a mixtute of **9a** with 1-hydroxymethyltriazole in ethanol at room temperature for 2 h afforded **12** in 70% yield.

In each of above cases, the symmetrical methylenebisaniline or its *N*-substituted and *N,N*-disubstituted analogs (**11**) was formed as a by-product. The triazole derivatives (**10**) formed evidently undergo displacement of the

Table 2 ^{1}H Nmr Spectral Data of Compounds (3a-f, 7, 8 and 10a-f)

Compd.	OH or NR^1R^2	R	$ArCH_2N$-	Other groups
3a	9.43(s, 1H)	-	5.34	6.83(t, 1H, J=7.5), 6.91(d, J=7.9), 7.15(t, 1H, J=7.6), 7.18(d, 1H, J=7.8), 7.89(s, 1H), 8.20(s, 1H)
3b	6.00(br s, 1H)	2.18(s, 3H)	5.43	6.75(t, 1H, J=7.6), 6.93(d, 1H, J=7.6),7.07 (d, 1H, J=7.7), 8.30(s, 1H), 9.01(s, 1H)
3c	9.95(br s, 1H)	2.15(s, 3H)	5.26	6.76(d, 1H, J=8.3), 6.82(s, 1H), 6.91(d, 1H, J=8.3), 7.93(s, 1H), 8.48(s, 1H)
3d	9.06(s, 1H)	1.44(s, 9H)	5.27	6.85(t, 1H, J=7.6), 7.07(dd, 1H, J=7.3, 1.6), 7.30(dd, 1H, J=7.9, 1.6), 7.97(s, 1H), 8.16 (s, 1H)
3e	8.76(s, 1H)	1.42(s, 9H) 2.26(s, 3H)	5.24	6.90(s, 1H), 7.11(s, 1H), 7.97(s, 1H), 8.16 (s, 1H)
3f	8.15(br s, 1H)	0.85(t, 3H, J=7.2), 1.19 (d, 3H, J=7.0), 1.60(m, 2H), 3.10(m, 1H)	5.30	6.89(td, 1H, J=7.6, 2.4), 7.07(dd, 1H, J=7.6, 1.5), 7.18(dd, 1H, J=7.6, 1.3), 7.97(s, 1H), 8.18(s, 1H)
7	10.30(s, 1H)	-	5.77	7.24(d, 1H, J=8.8), 7.32(t, 1H, J=7.6), 7.50 (t, 1H, J=7.3), 7.81(d, 2H, J=8.8), 7.89(s, 1H), 8.09(d, 1H, J=8.7), 8.42(s, 1H)
8	9.82(br s, 1H)	-	5.39	7.27(d, 1H, J=8.4), 7.3-7.5(m, 3H), 7.74(m, 1H), 7.94(s, 1H), 8.13(s, 1H), 8.36(m, 1H)
10a	4.33(br s, 2H)	-	5.18	6.65(d, 2H, J=8.5), 7.04(d, 2H, J=8.1), 7.89 (s, 1H), 8.10(s, 1H)
10b	2.83(s, 3H) 3.88(br s, 1H)	-	5.20	6.60(d, 2H, J=8.5), 7.13(d, 2H, J=8.5), 7.95 (s, 1H), 7.97(s, 1H)
10c	1.22(t, 3H, J=7.2) 3.13(q, 2H, J=7.2) 4.05(br s, 1H)	-	5.20	6.57(d, 2H, J=8.5), 7.10(d, 2H, J=8.5), 7.92 (s, 1H), 8.02(s, 1H)
10d	1.23(t, 3H, J=7.1) 3.12(q, 2H, J=7.1) 3.70(br s, 1H)	2.17(s, 3H)	5.19	6.41(d, 1H, J=6.6), 6.43(s, 1H), 7.02(d, 1H, J=9.0), 7.82(s, 1H), 7.93(s, 1H)
10e	2.95(s, 6H)	-	5.21	6.68(d, 2H, J=8.0), 7.17(d, 2H, J=7.9), 7.93 (s, 1H), 7.95(s, 1H)
10f	2.96(s, 6H)	2.23(s, 3H)	5.24	6.55(m, 2H), 7.10(d,1H, J=9.1), 7.82(s, 1H), 7.94(s, 1H)

triazole group by a second mole of aniline or an *N*-substituted or *N,N*-disubstituted analog to produce the symmetrical methylenebisaniline compounds. Previous work[8] in our group has reported a similar observation when 1-hydroxymethylbenzotriazole was reacted with aniline and *N,N*-dialkylanilines. We isolated the symmetrical methylenebisaniline by-products (**11a-c**) from the reaction mixture in 8 - 10% yields which were then identified by their ^{1}H nmr and ^{13}C nmr spectra.

Table 3 ^{13}C **Nmr Spectral Data of Compounds 3a-f, 7, 8 and 10a-f**

Compd.	NR^1R^2	R	$ArCH_2N$-	Other groups
3a	-	-	48.5	115.3, 119.1, 120.8, 129.5, 129.9, 143.0, 150.7, 155.1
3b	-	16.6	49.1	119.6, 122.4, 125.2, 127.7, 131.1, 143.4, 148.9, 153.1
3c	-	20.1	47.8	115.2, 121.8, 127.2, 129.7, 130.1, 144.2, 151.2, 153.0
3d	-	29.6, 34.9	50.9	120.3, 123.0, 128.2, 128.3, 139.7, 142.6, 151.5, 154.7
3e	-	20.6, 29.7 34.8	50.9	122.9, 128.5, 129.0, 129.4, 139.5, 142.5, 151.5, 152.1
3f	-	12.1, 20.4 29.8, 33.6	50.7	120.7, 121.8, 127.6, 128.2, 136.7, 142.7, 151.3, 153.0
7	-	-	43.0	112.3, 118.0, 122.4, 122.7, 126.9, 128.0, 128.4, 130.4 133.1, 143.6, 151.0, 154.1
8	-	-	47.9	116.9, 119.5, 122.2, 125.2, 126.3, 127.4, 127.6, 128.3 134.1, 144.1, 150.5, 151.4
10a	-	-	52.3	113.9, 122.2, 128.6, 141.9, 146.9, 150.7
10b	30.5	-	53.6	112.5, 122.2, 129.7, 142.5, 149.6, 151.8
10c	14.3, 37.8	-	53.1	112.3, 121.6, 129.3, 142.3, 148.4, 151.3
10d	14.7, 38.1	19.1	51.7	110.2, 114.7, 120.1, 131.3, 138.0, 142.4, 149.0, 151.6
10e	40.3	-	53.5	112.4, 121.3, 129.5, 142.6, 150.6, 151.8
10f	40.3	19.4	51.7	110.1, 114.4, 119.4, 131.2, 137.7, 142.5, 150.9, 151.7

The structures of the triazole derivatives (**3**) and (**10**) were confirmed by their nmr spectral data and elemental analyses. The methylene signals of the derivatives in both ^1H and ^{13}C spectra were shifted upfield (^1H, 5.20 - 5.41ppm; ^{13}C, 47.4 - 53.6 ppm) compared to the signal of methylene in 1-hydroxymethyl-1,2,4-triazole (^1H, 5.47 ppm; ^{13}C, 71.2 ppm) due to the loss of the electron-withdrawing -OH group. In the cases of **10a-c,e** , the ^1H spectra show two symmetrical aromatic signals, and only 4 aromatic (excluding the triazole ring) carbon peaks appear in the ^{13}C nmr spectra. This indicates that *para*- substituted products were obtained. As for the unsubstituted triazolylmethylphenol (**3a**), its ^{13}C spectrum clearly gives six benzene ring peaks, indicating no formation of the *para*-product. The data for known compounds are in agreement with those reported in the literature (see Tables 2, 3).

Conclusions: The presently reported method provides a novel and efficient route for the preparation of (1*H*-1,2,4-triazol-1-ylmethyl) substituted phenols, naphthols, aniline, *N*-alkylanilines and *N,N*-dialkylanilines. Compared with previous methods, our route has the advantages of readily available starting materials, high yields, short reaction times, and is attractive and potentially useful for the synthesis of biologically active compounds containing these functionalities.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus without correction. ^{1}H Nmr and ^{13}C nmr spectra were recorded on a Varian 300 MHz spectrometer using TMS as an internal reference for ^{1}H spectra and solvent $CDCl_3$ or DMSO for ^{13}C spectra. Elemental analyses were performed on a Carlo Erba-1106 instrument, and high resolution mass measurements were performed on an AEL MS-30 mass spectrometer. Column chromatography was carried out on MCB silca gel (230-400 mesh).

1-Hydroxymethyl-1,2,4-triazole 1 was prepared according to a literature procedure.[11]

Preparation of *o*-(1*H*-1,2,4-Triazol-1-ylmethyl)phenols (3a-f, 7, 8). General procedure: A mixture of 1-hydroxymethyltriazole (**1**) (2.47 g, 25 mmol) and the appropriate phenol (**2**) (25 mmol) was heated in acetic acid (25 ml) under reflux for the appropriate time. The solvent was then removed under reduced pressure, and to the residue was added $NaHCO_3$ solution (10 N, 30 ml). The solution was extracted with ether (3 × 100 ml), washed with water and dried with $MgSO_4$. Evaporation of the solvent gave a residue which was purified by column chromatography using hexane and ethyl acetate (5:1) as eluent. The preparative details and the nmr spectral data of the products are given in Tables 1-3.

Preparation of *p*-(1*H*-1,2,4-Triazol-1-ylmethyl)aniline (10a). A mixture of aniline hydrochloride (3.21 g, 25 mmol), and 1-hydroxymethyl-1,2,4-triazole (1) (2.47 g, 25 mmol) was heated in acetic acid (25 ml) under reflux for 7 h. The solution was then poured onto ice-water (200 ml), rendered alkaline with NaOH (2 N, 20 ml), extracted with ethyl acetate (3 × 150 ml)and dried with $MgSO_4$. The extracts were removed in vacuo, and the residue was chromatographed with hexane and ethyl acetate (5:1). The preparative details and the nmr spectral data of the product are given in Tables 1-3.

Preparation of *p*-(1*H*-1,2,4-Triazol-1-ylmethyl)-N-methylaniline (10b-d). A mixture of *N*-methylaniline (**9b**) (or **9c**, **9d**, 25 mmol) and 1-hydroxymethyl-1,2,4-triazole (**1**) (2.47 g, 25 mmol) was heated in concentrated hydrochloric acid (25 ml) under reflux for 7 h. The resulting solution was rendered basic with sodium hydroxide (2 N, 30 ml), extracted with ethyl acetate (3×150 ml) and dried with $MgSO_4$. The extracts were then removed in vacuo, and the residue was chromatographed with hexane and ethyl acetate (5:1). The preparative details and the nmr spectral data of the products are given in Tables 1-3.

Preparation of *p*-(1*H*-1,2,4-Triazol-1-ylmethyl)-*N*,*N*-dialkylanilines (10e-f). A mixture of **9e** (or **9f**) (25 mmol) and concentrated HCl (25 ml) was heated under refux for 1 h. Then the 1-hydroxymethyl-1,2,4-triazole (2.47 g, 25 mmol) was added, and the whole was refluxed for another 11 h. The resulting solution was rendered basic with NaOH (5 N, 30 ml), extracted with ethyl acetate (3 × 150 ml) and dried with $MgSO_4$. Evaporation of the solvent gave a crude product which was chromatographed with hexane and ethyl acetate (5:1). The preparative details and the nmr spectral data of the products are shown in Tables 1-3.

Bis(4-aminophenyl)methane (11a). Obtained as a by-product in the preparation of **10a**. Yield: 10%. mp 90 - 92 °C (lit.,[8] 90 -92 °C). ^{1}H Nmr δ 3.45 (br s, 4 H), 3.75 (s, 2 H), 6.62 (d, 4 H, J = 8.4 Hz), 6.92 (d, 4 H, J = 8.4 Hz). ^{13}C Nmr δ 40.1, 115.2, 129.6, 131.9, 144.2.

Bis(4-(*N*-methyl)aminophenyl)methane (11b). Obtained as a by-product in the preparation of **10b**. Yield: 8%. mp 53 - 54 °C. (Lit.,[21] mp 56 °C; Found: C, 79.43; H, 8.16; N, 12.06. $C_{15}H_{18}N_2$ requires C, 79.61; H, 8.02; N, 12.38). ^{1}H Nmr δ 2.78 (s, 6 H), 3.50 (br s, 2 H), 3.77 (s, 2 H), 6.53 (d, 4 H, J = 8.5 Hz), 7.01 (d, 4 H, J = 8.5 Hz). ^{13}C Nmr δ 30.9, 40.0, 112.5, 129.5, 130.8, 147.4.

Bis(4-(*N*-ethyl)aminophenyl)methane (11c). Obtained as an oil in the preparation of **10c**. Yield: 8%. (Lit.,[21] bp 255 °C/10mm).^{1}H Nmr δ 1.19 (t, 6 H, J = 7.2 Hz), 3.07 (q, 4 H, J = 7.1 Hz), 3.36 (br s, 2 H), 3.74 (s, 2 H), 6.51 (d, 4 H, J = 6.6 Hz), 6.95 (d, 4 H, J = 7.3 Hz). ^{13}C Nmr δ 14.8, 38.6, 40.0, 112.7, 129.4, 130.7, 146.4.

***N*-(1*H*-1,2,4-Triazol-1-ylmethyl)aniline (12).** A mixture of 1-hydroxymethyltriazole (94.14 g, 60 mmol) and aniline (5.58 g, 60 mmol) in aqueous EtOH (80 ml, 25%) was stirred at room temperature for 2 h, and kept at 5 °C overnight. The resultant white precipitate was filtered off. The yellow oil was separated from the aqueous media by decantation and dried in vacuo to yield the desired product (7.3 g, 70%). (HRms found: 174.0903; $C_9H_{10}N_4O$ requires 174.0905). ^{1}H Nmr δ 5.47 (d, 2 H, J = 7.4 Hz), 5.68 (t, 1 H, J = 7.4 Hz), 6.65 (dd, 2 H, J = 7.7, 1.0 Hz), 6.77 (t, 1 H, J = 7.4 Hz), 7.14 (dt, 2 H, J = 7.4, 1.2 Hz), 7.93 (s, 1 H), 8.18 (s, 1 H). ^{13}C Nmr δ 58.5, 113.0, 119.2, 129.1, 142.1, 144.3, 151.3.

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Received, 15th March, 1994