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An easy access to unsymmetric trisubstituted methane derivatives (TRSMs)☆

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Abstract—A new series of unsymmetric trisubstituted methane derivatives (TRSMs) has been synthesized through Friedel–Crafts alkylation of aromatic nucleophiles using acid-sensitive heteroaryl carbinols.

Trisubstituted methane derivatives (TRSMs) represent an important class of biologically active molecules. Substituted triarylmethanes (TRAMs), a class of TRSMs is of considerable interest as dyes, photochromic agents and materials for theoretical studies.[1] Examples of TRSMs include the potent and selective non-steroidal aromatase inhibitors[2] (NSAIs) letrozole[3] **1** (Ciba Geigy) and vorozole[4] **2** (Janssen). Recently, the antiproliferative activity of the nonimidazole part of clotrimazole analogues such as **3** was also reported,[5] Figure 1.

TRAMs have also served as suitable building blocks for generating dendrimers.[6] Dendrimers with appropriate peripheral functionalities have been used in bioconjugation,[7] cross-linking,[8] mass spectrometry,[9] fluorescence[10] and optics.[10] Triphenylmethyl (trityl) derivatives, are widely used as protecting groups in organic synthesis to block various functional moieties. These applications are well documented and have been the subject of a number of reviews.[11]

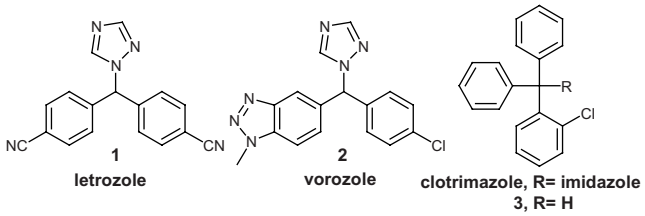

Figure 1.

Recently, we reported a new series of substituted triarylmethane derivatives (TRAMs) having antitubercular activity.[12] In continuation of our earlier work, we became interested in synthesizing some heteroaryldiarylmethane derivatives where one of the aryl rings is replaced by a heterocycle. Two well-established methods are known for the synthesis of TRAMs.[13] One is the Bayer condensation in which an aromatic or heterocyclic aldehyde is condensed with another aromatic or heterocyclic ring. A second method involved Friedel–Crafts alkylation of aromatic compounds using diaryl carbinols as alkylating agents. Surprisingly, to the best of our knowledge, the synthesis of unsymmetric triarylmethanes is less developed. One method involves displacement of a benzotriazole moiety in (benzotriazol-1-yl)-diarylmethanes either by an electron rich arene or by [4-(*N*,*N*-dimethylamino)phenyl]magnesium bromide.[1] Furthermore, the synthesis of heteroaryldiarylmethanes is not well established using acid catalyzed Friedel–Crafts alkylation chemistry. This could be due to the fact that the heterocyclic ring of heteroaryl carbinols, especially acid sensitive rings, for example, furan and pyridine, are easily attacked by the protic or Lewis acid catalysts used in Friedel–Crafts alkylation reactions. Isomerization of 2-furylcarbinols to cyclopentenones in the presence of acids has also been described.[14] Another disadvantage is that the synthesis of unsymmetric heteroaryldiarylmethanes is not possible using the Bayer condensation as it leads to symmetric heteroaryldiaryl or aryldiheteroarylmethanes. Thus, we

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0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
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have undertaken the synthesis of unsymmetric heteroaryldiarylmethanes, a class of trisubstituted methanes (TRSMs) by way of a Friedel–Crafts alkylation strategy using thienyl, pyridyl and (5-methyl)-furyl carbinols.

4-Methoxyphenyl magnesium bromide **4** was reacted with thiophene-2-carbaldehyde **5**, pyridine-3-carbaldehyde **6** and 5-methylfurfural **7** at room temperature to furnish the carbinols **8**, **9** and **10**, respectively (Table 1). It is important to mention that the carbinol **10** was not stable and got decomposed at room temperature. The isolation of the carbinol **10** was achieved through column chromatography (basic alumina) and was stored at 0 °C.

To begin with, carbinol **8** was used as a building block for the synthesis of various unsymmetric heteroaryldiarylmethane derivatives. Towards this objective, **8** was treated with the various nucleophiles such as phenol, anisole, *N*,*N*-dimethylaniline, *N*-ethylaniline, thiophenol and 3-thiocresol in the presence of concd H_2SO_4 to furnish TRSMs **11**, **12**, **13**, **14**, **15** and **16** as the arylated products.[15] Nucleophilic attack of phenol occurred through the *o*- and *p*-carbon atoms of the benzene ring to give **11b** as the major product and **11a** as the minor one. The singlet methine proton appeared at δ 5.55 ppm in the ^{1}H NMR of **11b** whereas the same proton appeared at δ 5.86 ppm in **11a** due to the increased −I effect of the *o*-hydroxyl in **11a** than the *p*-hydroxyl in **11b**, Table 2. We did not isolate any *o*-substituted product in the cases of anisole and *N*,*N*-dimethylaniline. However, reaction with *N*-ethylaniline, contrary to our expectation, furnished **13** through attack of the *p*-carbon of the *N*-ethylaniline. It was interesting to note that nucleophilic attack occurred through sulfur when thiophenol and 3-thiocresol were used as the nucleophiles. This is possibly due to the higher nucleophilicity of sulfur than the carbon atoms of the benzene ring. We did not isolate any *O*-alkylated product when phenol was used as the nucleophile.

We next used carbinol **9** as the alkylating agent in the Friedel–Crafts (FC) reaction. During FC alkylation using protic or Lewis acids, the N atom of the pyridine ring is protonated or complexed with metals and thus the heterocycle separates out from the reaction mixture giving no FC alkylated product. Under our reaction conditions, treatment of carbinol **9** with various aromatic nucleophiles in the presence of anhydrous $AlCl_3$ furnished heteroaryldiarylmethane derivatives **17**–**23**.[15] As indicated in Table 2, nucleophilic attack occurred through the sulfur of thiophenol and 3-thiocresol onto the carbinol carbon atom of **9** giving rise to **21** and **22**, respectively.

After the successful demonstration of the FC reaction with thiophenes and pyridines, we wanted to explore our synthetic strategy with acid sensitive furans. Furyl carbinols are well known for their isomerization to cyclopentenones in the presence of protic and Lewis acids.[14] However, treatment of furyl carbinol **10** with *N*,*N*-dimethylaniline, *N*-ethylaniline, thiophenol, 2-thiocresol and 3-thiocresol in the presence of anhydrous $AlCl_3$ gave the corresponding alkylated products **24**, **25**, **26**, **27** and **28**, respectively, in good yields and purity.[15]

In conclusion, we have developed a very short and easy synthetic route for the preparation of unsymmetric trisubstituted methane derivatives. A new series of TRSMs **15**, **16**, **21**, **22**, **26**, **27** and **28** containing a

Table 1. Synthesis of carbinols **8**, **9** and **10**

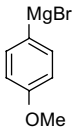
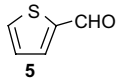
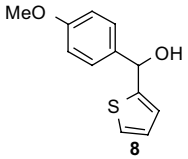
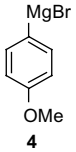
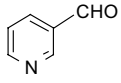
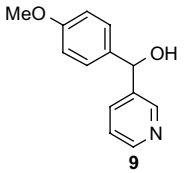
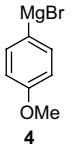
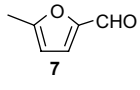
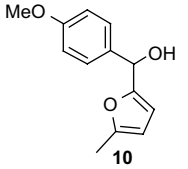
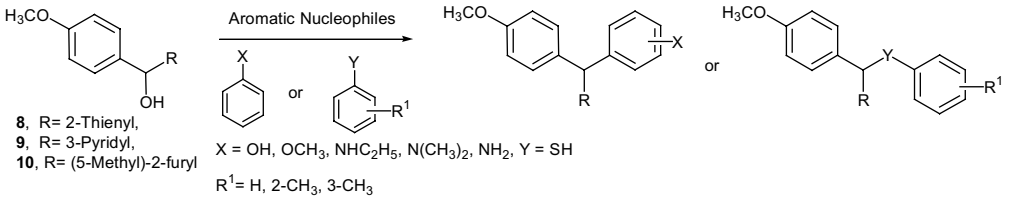
Entry	Grignard reagent	RCHO	Carbinol	Conditions and yield
1	 **4**	 **5**	 **8** (yellow oil)	rt, THF, 1 h, 68%
2	 **4**	 **6**	 **9** pale yellow solid, m.p. 105°C	rt, THF, 2 h, 68%
3	 **4**	 **7**	 **10** yellow oil	rt, THF, 1 h, 65%

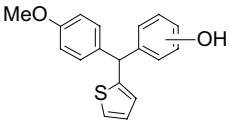
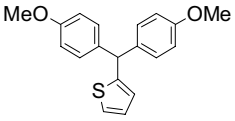
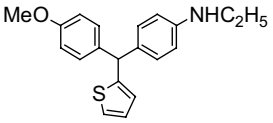
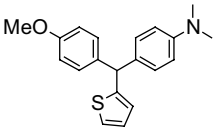
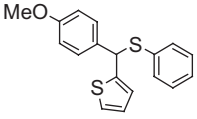
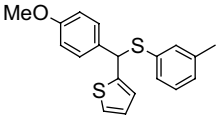
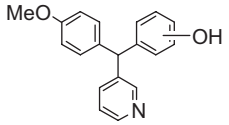
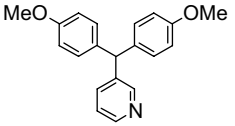
Table 2. Synthesis of unsymmetric methane derivatives **11**–**28** from the carbinols **8**, **9** and **10**



8, R= 2-Thienyl,
9, R= 3-Pyridyl,
10, R= (5-Methyl)-2-furyl

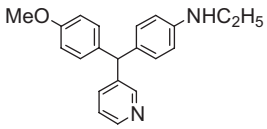
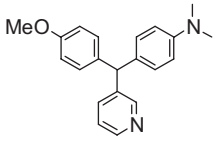
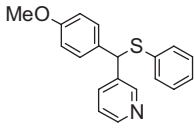
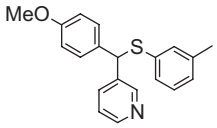
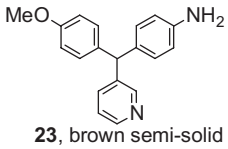
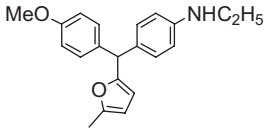
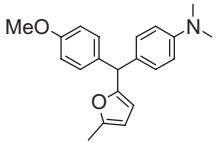
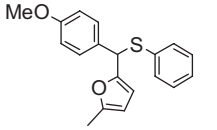
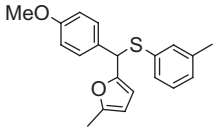
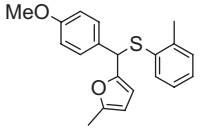
X = OH, OCH_3, NHC_2H_5, $N(CH_3)_2$, NH_2, Y = SH

R^1= H, 2-CH_3, 3-CH_3

Entry	Carbinol (1 equiv)	Nucleophile (1.5 equiv)	Product[a]	Reaction conditions[b,c]	Yield[d]
1	**8**	Phenol	 *ortho*-OH, **11a**, brown semi-solid *para*-OH, **11b**, brown semi-solid	Benzene, concd H_2SO_4, 60 °C, 2 h	**11a** (10%) **11b** (60%)
2	**8**	Anisole	 **12,** pale yellow solid, m.p. 90°C	Benzene, concd H_2SO_4, 60 °C, 2 h	63%
3	**8**	*N*-Ethylaniline	 **13**, black semi-solid	Benzene, concd H_2SO_4, 60 °C, 45 min	76%
4	**8**	*N*,*N*-Dimethylaniline	 **14**, black semi-solid	Benzene, concd H_2SO_4, 60 °C, 45 min	73%
5	**8**	Thiophenol	 **15,** white solid, m.p. 76°C	Benzene, concd H_2SO_4, 60 °C, 30 min	80%
6	**8**	3-Thiocresol	 **16**, yellow oil	Benzene, concd H_2SO_4, 60 °C, 30 min	70%
7	**9**	Phenol	 *ortho*-OH, **17a**, colourless semi-solid *para*-OH, **17b,** colourless semi-solid	Benzene, anhyd $AlCl_3$, 70 °C, 2 h	**17a** (5%) **17b** (55%)
8	**9**	Anisole	 **18**, light yellow semi-solid	Benzene, anhyd $AlCl_3$, 70 °C, 2 h	67%

(*continued on next page*)

Table 2 (*continued*)

Entry	Carbinol (1 equiv)	Nucleophile (1.5 equiv)	Product[a]	Reaction conditions[b,c]	Yield[d]
9	**9**	*N*-Ethylaniline	 **19,** light yellow semi-solid	Benzene, anhyd $AlCl_3$, 70 °C, 1 h	65%
10	**9**	*N*,*N*-dimethylaniline	 **20,** light yellow semi-solid	Benzene, anhyd $AlCl_3$, 70 °C, 45 min	70%
11	**9**	Thiophenol	 **21**, light yellow solid, m.p. 84°C	Benzene, anhyd $AlCl_3$, 70 °C, 30 min	72%
12	**9**	3-Thiocresol	 **22,** yellow semi-solid	Benzene, anhyd $AlCl_3$, 70 °C, 30 min	64%
13	**9**	Aniline	 **23**, brown semi-solid	Benzene, anhyd $AlCl_3$, 70 °C, 2 h	50%
14	**10**	*N*-Ethylaniline	 **24**, pale yellow oil	Benzene, anhyd $AlCl_3$, rt, 30 min	63%
15	**10**	*N*,*N*-Dimethylaniline	 **25**, yellow oil	Benzene, anhyd $AlCl_3$, rt, 45 min	61%
16	**10**	Thiophenol	 **26**, light yellow semi-solid	Benzene, anhyd $AlCl_3$, rt, 30 min	60%
17	**10**	3-Thiocresol	 **27,** yellow oil	Benzene, anhyd $AlCl_3$, rt, 30 min	78%
18	**10**	2-Thiocresol	 **28**, yellow oil	Benzene, anhyd $AlCl_3$, rt, 30 min	75%

[a] Although all the Friedel–Crafts alkylated products were unsymmetric except for **12** and **18**, they were isolated as racemic mixtures.
[b] Concd H_2SO_4 was used in catalytic amounts.
[c] One equivalent of anhydrous $AlCl_3$ was used.
[d] Isolated yield after silica gel column chromatography.

thioether group has been synthesized in only two steps, that is, the Grignard reaction and Friedel–Crafts alkylation. These thioethers cannot be synthesized using previously reported methodology.[1] We have shown that carbinols containing acid-sensitive heterocycles can be used as alkylating agents in FC reactions.

Acknowledgements

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15. Friedel–Crafts Alkylation: (i) To a solution of carbinol **8** {0.18 g, 0.818 mmol (1 equiv)} and nucleophile (1.5 equiv) in dry benzene (10 mL) was added a catalytic amount of H_2SO_4 and the mixture was refluxed at 60 °C until completion of the reaction. Extraction with ethyl acetate and column chromatography of the crude product over silica gel (ethyl acetate/hexane) furnished compounds **11a–b**, **12**, **13**, **14**, **15** and **16**.
(ii) To a solution of carbinol **9** {0.18 g, 0.83 mmol (1 equiv)} and nucleophile (1.5 equiv) in dry benzene (15 mL), anhydrous $AlCl_3$ (1.0 equiv) was added and the mixture was refluxed at 70 °C. After usual work-up, column chromatography over silica gel (ethyl acetate/hexane) furnished **17a–b**, **18**, **19**, **20**, **21**, **22** and **23**. (iii) To a solution of carbinol **10** {0.18 g, 0.82 mmol (1 equiv)} and nucleophile (1.5 equiv) in dry benzene (15 mL), anhydrous $AlCl_3$ (1.0 equiv) was added and the mixture was stirred at rt. After usual work-up, column chromatography over silica gel (ethyl acetate/hexane) furnished **24**, **25**, **26**, **27** and **28**.
Selected Spectral Data: 2-[(4-Methoxyphenyl)phenylsulfanylmethyl]thiophene **15**: IR (KBr): 1603, 1511, 1352, 1251, 1177, 695 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 7.33 (d, 2H, $J = 6.8$ Hz), 7.31–7.29 (m, 2H), 7.18–7.14 (m, 4H), 6.86 (d, 2H, $J = 8.6$ Hz), 6.81 (d, 2H, $J = 8.6$ Hz), 5.64 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.4, 146.3, 135.9, 133.6, 131.9, 129.7, 129.2, 127.5, 127.0, 126.4, 125.6, 114.3, 55.6, 53.0; MS (FAB): 312 (M^+), Anal. $C_{18}H_{16}OS_2$; calcd: C, 69.19; H, 5.16. Found: C, 69.29; H, 5.25.
4-[(4-Methoxyphenyl)pyridin-3-ylmethyl]phenol **17b**: IR (KBr): 3428, 1611, 1510, 1458, 1249, 757 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 8.43 (d, 1H, $J = 7.0$ Hz), 8.37 (s, 1H), 7.44 (d, 1H, $J = 7.8$ Hz), 7.26 (m, 1H), 6.98 (d, 2H, $J = 8.6$ Hz), 6.87 (d, 2H, $J = 8.6$ Hz), 6.81 (d, 2H, $J = 8.6$ Hz), 6.75 (d, 2H, $J = 8.6$ Hz), 5.41 (s, 1H), 3.76 (s, 3H), ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.7, 156.3, 150.1, 146.8, 141.5, 138.0, 135.4, 134.1, 130.5, 124.0, 116.1, 114.3, 55.6, 53.1; MS (FAB): 292 (M^++H), Anal. $C_{19}H_{17}NO_2$; calcd: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.43; H, 5.90; N, 4.83.
{4-[(4-Methoxyphenyl)pyridin-3-ylmethyl]phenyl} dimethylamine 20: IR (neat): 1612, 1515, 1249, 757 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 8.33 (m, 2H), 7.67 (d, 1H, $J = 7.8$ Hz), 7.27 (m, 1H), 6.91 (d, 2H, $J = 8.6$ Hz), 6.84 (d, 2H, $J = 8.6$ Hz), 6.71 (d, 2H, $J = 8.6$ Hz), 6.55 (d, 2H, $J = 8.6$ Hz), 5.30 (s, 1H), 3.64 (s, 3H), 2.79 (s, 6H), ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.5, 151.2, 149.7, 147.8, 140.9, 137.0, 136.1, 131.3, 130.5, 130.2, 123.5, 114.2, 113.0, 55.6, 53.1, 41.0, 30.1 MS (FAB): 318 (M^+), Anal. $C_{21}H_{22}N_2O$: Calcd: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.25; H, 6.99; N, 8.90.
{4-[(4-Methoxyphenyl)-(5-methyl-furan-2-yl)methyl]phenyl}dimethylamine **25**: IR (neat): 2951, 1612, 1516, 1448, 1349, 1220, 1033, 759 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 7.07 (d, 2H, $J = 8.6$ Hz), 7.01 (d, 2H, $J = 8.6$ Hz), 6.79 (d, 2H, $J = 8.8$ Hz), 6.64 (d, 2H, $J = 8.8$ Hz), 5.83 (d, 1H, $J = 2.0$ Hz), 5.71 (d, 1H, $J = 2.0$ Hz), 5.24 (s, 1H), 3.72 (s, 3H), 2.87 (s, 6H), 2.21 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.6, 156.5, 151.5, 149.8, 135.5, 131.0, 130.1, 129.7, 114.1, 113.1, 109.0, 106.3, 55.6, 49.7, 41.1, 14.1; MS (FAB): 321 (M^+), Anal. $C_{21}H_{23}NO_2$: Calcd: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.50; H, 7.25; N, 4.40.
2-[(4-Methoxyphenyl)phenylsulfanylmethyl]-5-methylfuran **26**: IR (neat): 1602, 1510, 1352, 1250, 760 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 7.32 (d, 2H, $J = 6.8$ Hz), 7.32–7.16 (m, 5H), 6.82 (d, 2H, $J = 8.8$ Hz), 6.01 (d, 1H,

J = 3.0 Hz), 5.84 (d, 1H, J = 3.0 Hz), 5.35 (s, 1H), 3.77 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.4, 152.4, 152.1, 135.7, 132.5, 131.7, 129.9, 129.0, 127.6, 114.3, 109.5, 106.7, 55.6, 51.3, 14.0; MS (FAB): 201 ($M^+ - SC_6H_5$), Anal. $C_{19}H_{18}O_2S$: Calcd: C, 73.52; H, 5.84. Found: C, 73.40; H, 5.90.