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REACTIVITY OF 3,6-DIMETHOXY-3,6-DIMETHYLCYCLOHEXA-1,4-DIENE (PART 2).[1] REGIOSELECTIVE ARYLATION OF ELECTRON-RICH AROMATIC COMPOUNDS

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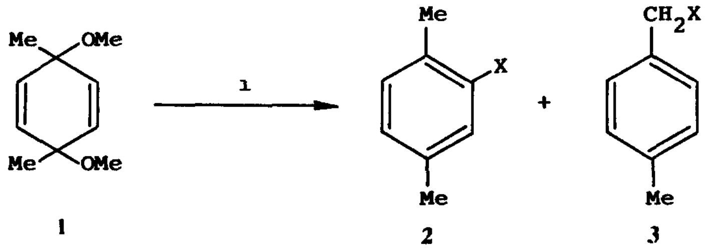
Summary: The reaction of 3,6-dimethoxy-3,6-dimethylcyclohexa-1,4-diene (**1**) with electron-rich heterocycles (furan, thiophene, pyrrole, 2-methylfuran, indole) and 1,3,5-trimethoxybenzene in the presence of catalytic amounts of zinc dichloride or concentrated sulfuric acid leads to the corresponding 2-aryl substituted *p*-xylenes **4** in good yields and in a regioselective manner

Introduction

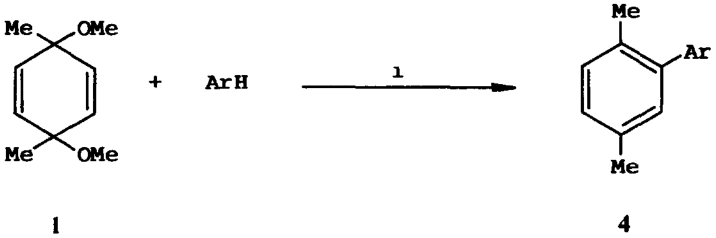
Aromatic arylation is in general a difficult process, which is seldom useful from a synthetic viewpoint[2] Almost the only electrophilic reaction of this type is the so called *Scholl reaction*,[3] which occurs at high temperatures and using strong-acid catalysts, so in many cases the reaction fails due to the decomposition of the substrates under these reaction conditions On the other hand, we have recently explored the reactivity of 3,6-dimethoxy-3,6-dimethylcyclohexa-1,4-diene (**1**) (easily prepared from *p*-xylene by electrochemical oxidation[4] in multigram scale[5]) toward nucleophilic reagents such as organolithium compounds, alcohols, thioethers, or hydrazoic acid[1] In this process a mixture of products **2** and **3** arising from a nuclear or a benzylic substitution, respectively, was generally obtained (Scheme 1) In this paper we studied the use of compound **1** in the arylation of electron-rich aromatic compounds under mild reaction conditions



Scheme 1 *Reagents*. i, Nu/X = RLi/R, ROH/RO, RSH/RS, HN_3/N_3.

Results and Discussion

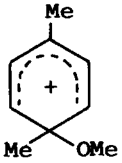
The reaction of a *cis/trans*-mixture of **1** (*ca* 1/1)[4,5] with different electron-rich heterocycles (furan, thiophene, pyrrole, 2-methylfuran, indole) or 1,3,5-trimethoxybenzene in the presence of a catalytic amount of zinc dichloride (or concentrated sulfuric acid in the case of using thiophene) led to the corresponding 2-substituted *p*-xylenes **4** as the only reaction product (Scheme 2 and Table 1)



Scheme 2 *Reagents* i, $ZnCl_2$ (cat) or H_2SO_4 (cat)

When other less activated aromatic compounds such as anisole, *N,N*-dimethylaniline, thioanisole or 1,4-dimethoxybenzene were used, the reaction failed, yielding 2,5-dimethylanisole from the decomposition of the starting material **1** under the acidic reaction conditions [1]

The mechanism of the process should involve the acid catalyzed formation of the delocalized carbocation **5** followed by electrophilic attack of this species to the aromatic compound ArH, and final aromatization to give **4** When the activation of the aromatic system is low, the intermediate **5** undergoes 1,2-migration of the methoxy group followed by aromatization yielding 2,5-dimethylanisole [1]



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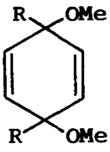

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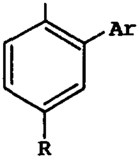

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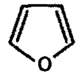
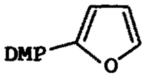
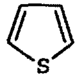
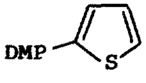
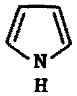
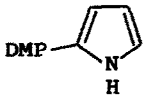
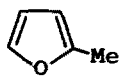
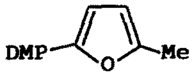
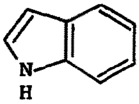
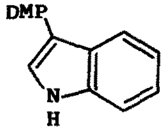
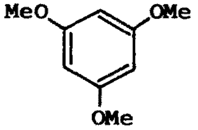
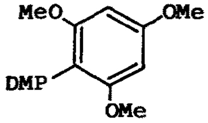
As compounds of the type **6** may generally be prepared (by anodic methoxylation of 1,4-dialkylbenzenes[6] and even chemically from quinones[7]), we conclude that the method described here represents an adequate regioselective route for products of the type **7**, in which the Ar group is an electron-rich aromatic system

Table 1 Preparation of Compounds 4

ArH	Reaction conditions			Product[a]		
	solvent	catalyst	time(h)	structure[b]	no	yield(%)[c]
	neat	$ZnCl_2$	0.5		4a	95
	neat	H_2SO_4 c	2		4b	71
	neat	$ZnCl_2$	1.5		4c	90
	neat	$ZnCl_2$	1.5		4d	95
	CH_2Cl_2	$ZnCl_2$	1.5		4e	95
	CH_2Cl_2	$ZnCl_2$	2		4f	80

[a] All products 4 were >95% pure (g.l c. and 300 MHz n.m r). [b] DMP 2,5-dimethylphenyl [c] Isolated yields after column chromatography based on the starting material 1

Experimental

General.- For general information see reference 1. ^{1}H and ^{13}C n m.r were recorded on a Bruker AC-300 spectrometer using $CDCl_3$ as solvent and $SiMe_4$ as internal standard. High resolution mass spectra were obtained with a VG-Micromass ZAB-2F spectrometer Hexane/ethyl acetate (95/5) was used as eluant in t.l.c. (unless otherwise stated) for R_f values All reagents were commercially available (Aldrich)

Preparation of Compounds **4.** *General Procedure.*- A solution of 3,6-dimethoxy-3,6-dimethylcyclohexa-1,4-diene (**1**) (1 mmol), the aromatic reagent (ArH) (4 ml) and zinc dichloride (0.04 mmol) was stirred for 0.5-2 h at room temperature (see Table 1). The resulting mixture was then hydrolyzed with water (1 ml), extracted with ether (2 x 3 ml), and the organic layer dried over sodium sulfate Solvents were evaporated (15 torr) and the residue was purified by column chromatography (silica gel; hexane/ethyl acetate: 98/2) In the case of using indole or 1,3,5-trimethoxybenzene (3 mmol) dichloromethane (4 ml) was used as solvent When thiophene was used as aromatic compound, concentrated sulfuric acid (0.01 mmol) was employed as catalyst instead of zinc dichloride.

2-(2,5-Dimethylphenyl)furan (**4a**) t_r = 12.95 min, R_f = 0.62, ν_{max} (film) 3100, 3010, 1605 (HC=C), and 1015 cm^{-1} (C-O), δ_H 2.33, 2.43 (6 H, 2 s, 2 x Me), 6.46-6.50 (2 H, m, H-3 and H-4), 7.00, 7.10 (2 H, 2 d, *J* = 7.7, H-3'and H-4'), 7.46 (1 H, d, *J* = 1.1, H-5), and 7.50 (1 H, s, H-6'), δ_C 20.9, 21.3 (2 x Me), 108.3, 111.2, 127.6, 128.2, 130.0, 131.0, 131.5, 135.5, 141.5, and 153.7 (aromatic C); *m/z* 173 (M^+ + 1, 52%), 172 (M^+, 98), 171 (25), 157 (59), 144 (42), 143 (94), 142 (24), 141 (62), 139 (16), 130 (27), 129 (89), 128 (100), 127 (75), 126 (14), 116 (17), 115 (77), 103 (21), 102 (31), 91 (29), 89 (32), 87 (14), 86 (18), 85 (14), 79 (10), 78 (25), 77 (54), 76 (16), 75 (21), 74 (19), 65 (13), and 63 (26).

2-(2,5-Dimethylphenyl)thiophene (**4b**) t_r = 14.48 min, R_f = 0.66, ν_{max} (film) 3100, 3060, and 1510 cm^{-1} (HC=C); δ_H 1.84 (6 H, s, 2 x Me), 6.84-6.90, and 7.11-7.14 (6 H, 2 m, aromatic H); δ_C 33.1 (2 x Me), 123.0, 123.4, 124.9, 126.3, 128.4, 129.2, and 155.4 (aromatic C), *m/z* 189 (M^+ + 1, 18%), 188 (M^+, 100), 187 (57), 174 (17), 173 (100), 172 (22), 171 (28), 155 (12), 141 (11), 129 (25), 128 (26), 115 (21), 97 (28), 89 (10), 77 (12), and 45 (11) (Found M^+, 188.0654 $C_{12}H_{12}S$ requires M, 188.0660)

2-(2,5-Dimethylphenyl)pyrrole (**4c**) t_r = 15.18 min, R_f = 0.28, ν_{max} (film) 3410 (NH), 3100, 3020, and 1610 cm^{-1} (HC=C), δ_H 2.33, 2.41 (6 H, 2 s, 2 x Me), 6.31-6.32 (2 H, m, H-3 and H-4), 6.85-6.87 (1 H, m, H-5), 6.99-7.01, 7.13-7.17 (3 H, 2 m, H-3', H-4', and H-6'), and 8.25 (1 H, br s, NH); δ_C 20.7, 20.9 (2 x Me), 108.6, 109.2, 117.8, 127.5, 128.6, 131.0, 132.0, 132.7, 135.4 (aromatic C), *m/z* 172 (M^+ + 1, 12%), 171 (M^+, 100), 170 (67), 156 (35), 155 (12), 154 (15), 144 (14), 143 (21), 141 (12), 129 (29), 128 (36), 127 (12), 115 (19), 77 (15), 63 (14), and 51 (16)

2-(2,5-Dimethylphenyl)-5-methylfuran (**4d**) t_r = 14.16 min, R_f = 0.62, ν_{max} (film) 3100, 3030, 3010, 1660, 1600 (HC=C), and 1020 cm^{-1} (C-O), δ_H 2.33, 2.42 (6 H, 2s, 2 x xylylic Me), 2.35 (3 H, s, furylic Me), 6.04-6.05 (1 H, m, H-4), 6.38 (1 H, d, *J* = 3.0, H-3), 6.95, 7.07 (2 H, 2 d, *J* = 7.7, H-3' and H-4'), and 7.49 (1 H, s, H-6'), δ_C 13.6 (furylic Me), 20.9, 21.4 (2 x xylylic Me), 107.3, 109.4, 127.1, 127.6, 130.2, 131.0, 135.2, 151.2, and 151.9 (aromatic C), *m/z* 187 (M^+ + 1, 13%), 186 (M^+, 100), 171 (18), 144 (12), 143 (93), 142 (15), 141 (27), 129 (15), 128 (87), 127 (16), 115 (35), 78 (10), 77 (21), 63 (13), 53 (11), 51 (21), and 43 (18) (Found M^+, 186.1051. $C_{13}H_{14}O$ requires M, 186.1045)

3-(2,5-Dimethylphenyl)indole (**4e**) t_r = 21.14 min, R_f = 0.60 (hexane/ethyl acetate. 7/3), ν_{max} (film) 3410 (NH), 3050, 3010, and 1610 cm^{-1} (HC=C), δ_H 2.27, 2.36 (6 H, 2 s, 2 x Me), 7.08-7.25 (6 H, m, H-2, H-5, H-6, H-3', H-4', and H-6'), 7.41, 7.52 (2 H, 2 d, *J* = 8.0, 7.8, H-4 and H-7), and 8.15 (1 H, br s, NH), δ_C 20.2, 20.9 (2 x Me), 111.1, 117.7, 119.9, 120.2, 122.1, 122.7, 127.2, 127.5, 130.2, 131.5, 133.7, 134.2, 135.0, and 135.9 (aromatic C), *m/z* 222 (M^+ + 1, 15%), 221 (M^+, 100), 220 (79), 206 (20), 205 (19), 204 (25), 178 (17), 102 (10), 89 (10), 77 (12), 63 (13), and 51 (16) (Found M^+, 221.1199. $C_{16}H_{15}N$ requires M, 221.1205)

2,4,6-Trimethoxy-2',5'-dimethylbiphenyl (**4f**) t_r = 19.86 min, R_f = 2.20, m p 125°C; ν_{max} (KBr) 3030, 1600, 1580 (HC=C), 1150, and 1130 cm^{-1} (C-O), δ_H 2.02, 2.31 (6 H, 2 s, 2 x Me), 3.68 (6 H, s, 2 x *o*-MeO), 3.85 (3 H, s, *p*-MeO), 6.22 (2 H, s, H-3 and H-5), 6.93 (1 H, s, H-6'), 7.03, and 7.14 (2 H, 2 d, *J* = 7.5, H-3' and H-4'), δ_C 19.2, 21.0 (2 x Me), 55.3, 55.8 (3 x MeO), 90.7, 112.0, 127.9, 129.3, 131.9, 133.8, 134.3, 134.6, 158.3, and 160.5 (aromatic C); *m/z* 273 (M^+ + 1, 18%), 272 (M^+, 100), 257 (17), 242 (14), 241 (54), 226 (18), 210 (112), 128 (11), and 115 (11) (Found M^+, 272.1415 $C_{17}H_{20}O_3$ requires M, 272.1413)[8]

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