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A Stepwise Synthesis of Hydroxylated Polyaryls

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Introduction

The oxidative coupling of phenols is an important synthetic method for the construction of hydroxylated bi- and polyaryls and may be accomplished by chemical, photochemical, and electrochemical means.[1] The application of this approach to biaryl synthesis has been amply described in various papers and reviews.[2] Usually the reaction produces mixtures of compounds from which hydroxylated biaryls and triaryls are isolated with efficient separative techniques.

Our recent studies have focused on the use of dichloroaluminum phenolates as reagents to promote highly selective coupling of phenolic substrates.[3] Thus compounds **2** were synthesized in good yields and excellent selectivities by reacting equimolecular mixtures of convenient phenols and $AlCl_3$ with $FeCl_3$ in CH_3NO_2 (Scheme 1).

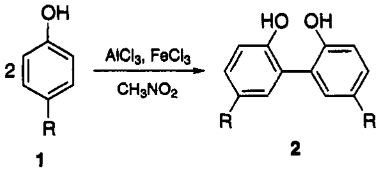
Moreover compounds **2** underwent further oxidative coupling giving tetraaryls **3** in moderate yields (Scheme 2).

Results and Discussion

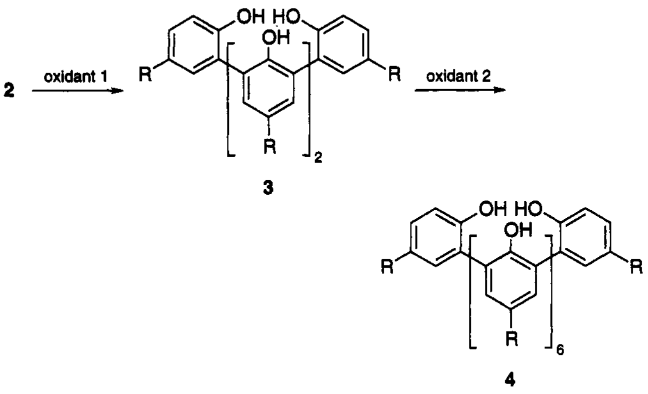
On the basis of these results, we became interested in the design of an iterative approach to linear and branched tetra- and octaaryls such as **3**, **4**, and **6** which represent important intermediates for the construction of spherands[4] and are subunits in the preparation of special polymers and materials related to molecular recognition and liquid crystals.[5]

Our first target was to achieve the optimum conditions for the synthesis of tetraaryl **3a** ($R = CH_3$) by oxidative coupling of **2a** selected as the model substrate.[3] After a number of trials with various oxidants and solvents, $FeCl_3$ in trichloroethylene at 50 °C was found to be the best promoter (49% yield). The reaction was successively extended to the biaryl **2c** ($R = OCH_3$), yielding the expected product **3c** in 17% yield. For the synthesis of the tetraaryl **3b** ($R = Bu^t$) from **2b**, DDQ in CS_2 in the presence of a stoichiometric amount of $Li(OH)H_2O$ (Table 1) was utilized as the oxidant (in order to avoid detertbutylation).

Scheme 1



Scheme 2[a]



[a] Oxidant 1 = $FeCl_3$ or DDQ; oxidant 2 = $Mn(OAc)_3{\cdot}2H_2O$ or DDQ.

Table 1. Synthesis of Some Tetraaryls 3

entry	2	R	oxidant	solvent	*T* (°C)	3	yield (%)
1	**2a**	CH_3	$FeCl_3$	$CHCl{=}CCl_2$	50	**3a**	49
2	**2b**	$(CH_3)_3C$	DDQ	CS_2	25	**3b**	71[a]
3	**2c**	OCH_3	$FeCl_3$	$CHCl{=}CCl_2$	50	**3c**	17

[a] The octaaryl **4b** was also recovered in 8% yield.

Table 2. Synthesis of Some Octaaryls 4 and 6

entry	3 or 5	R	oxidant	solvent	*T* (°C)	4 or 6	yield (%)
1	**3a**	CH_3	$Mn(OAc)_3{\cdot}2H_2O$	$CHCl{=}CCl_2$	50	**4a**	23
2	**3b**	$(CH_3)_3C$	DDQ	CS_2	25	**4b**	58
3	**5**	$4(OH)C_6H_4$	$Mn(OAc)_3{\cdot}2H_2O$	EtOH	50	**6**	50[a]

[a] Mixture of three isomers **6x**, **6y**, and **6z** in 18%, 21%, and 11% yield, respectively.

Following our program, we successively decided to study the possibility that the coupling products **3** would allow further couplings, producing the octameric compounds **4** (Scheme 2). Thus **3a** was subjected to oxidative dimerization by using $Mn(OAc)_3{\cdot}2H_2O$ as promoter with a redox potential higher than $FeCl_3$. The octaaryl **4a** was obtained in 23% yield after normal workup.

Unfortunately the tetraaryl **3c** ($R = OCH_3$) was found to produce intractable mixtures of products under these conditions.

With the tetraaryl **3b**, DDQ was utilized in CS_2 under conditions similar to those noted for **2b** and the expected octaaryl **4b** was obtained in 58% yield (Table 2).

The comparison of this result with that reported in Table 1 (entry 2) allowed us to suppose that the formation of **3b** in 71% yield accompained by a small amount of **4b** (8% yield) presumably arises from a very fast dimerization, which rapidly reduces the concentration of DDQ in the reaction medium and minimizes the further oxidative coupling. This was confirmed by carrying out the reaction in the presence of 2 equiv of DDQ; under these conditions

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[1] (a) Kovacic, P.; Jones, M. B. *Chem. Rev.* **1987**, *87*, 357. (b) Baumgartner, M. T.; Pierini, A. B.; Rossi, R. A. *Tetrahedron Lett.* **1992**, *33*, 2323. (c) Torii, S.; Inokuchi, T.; Dhimane, A. L.; Araki, Y.; Maki, T. *Electroorganic Synthesis*; M. Dekker Inc.: New York, 1991. (d) Kashiwagi, Y.; Ono, H.; Osa, T. *Chem. Lett.* **1993**, 81.

[2] (a) Musso, H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 723. (b) Taylor, W. I.; Battersby, A. R. *Oxidative Coupling of Phenols*; M. Dekker Inc.: New York, 1967. (c) Whiting, D. A. *Oxidative Coupling of Phenols and Phenol Ethers* in *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991, Vol. 3, pp 659–701.

[3] (a) Sartori, G.; Maggi, R.; Bigi, F.; Arienti, A.; Casnati. G.; Mori, G. *Tetrahedron* **1992**, *48*, 9483. (b) Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* **1993**, *58*, 7271.

[4] Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009.

[5] Unran, C. M.; Campbell, M. G.; Sniekus, V. *Tetrahedron Lett.* **1992**, *33*, 2773 and references therein.

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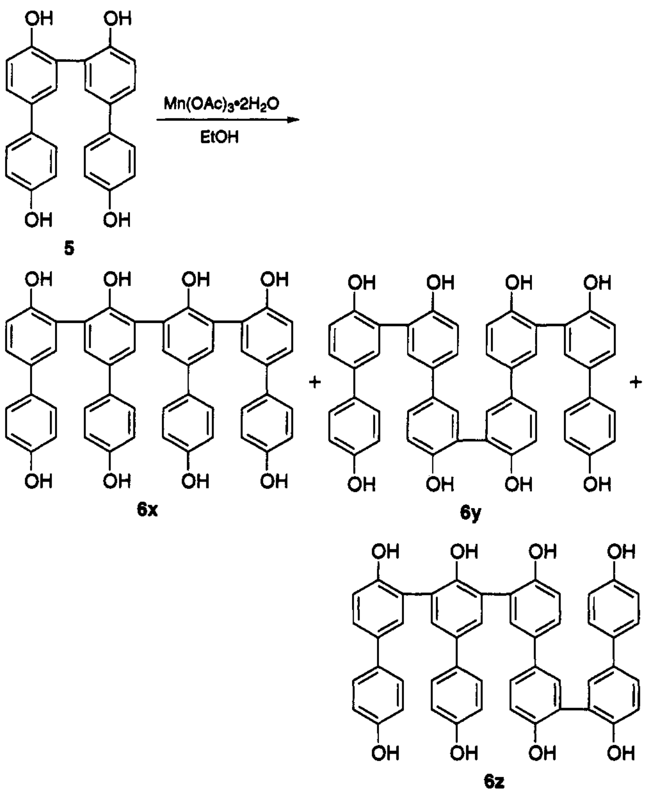
Scheme 3



the two products **3b** and **4b** were obtained in 40% and 38% yield, respectively.

Finally, as an extension of the present study, we decided to apply to the oxidative dimerization of the tetraaryl **5** with $Mn(OAc)_3 \cdot 2H_2O$ for the preparation of branched octaaryls (Scheme 3).

The reaction of **5** with 1 equiv of the oxidant in EtOH proceeded smoothly at 25 °C to give a mixture of all the three possible C—C coupled octaaryls **6x** (18% yield), **6y** (21% yield), and **6z** (11% yield). All of them have been separated and gave the same mass spectrum. Successively we examined their ^{1}H NMR spectra: the more symmetric compound **6x** shows a clear signals pattern that is in accordance with the structure depicted (all the ^{1}H NMR signals were assigned: see Experimental Section). The remaining two compounds have more complex spectra due to overlapping signals; the structure of isomer **6z** has been attributed on the basis of the presence in its ^{1}H NMR spectrum of six doublets, due to three para systems, possible only for this structure. The last isomer **6y** has been attributed by comparison of its ^{1}H NMR spectrum with those of the other two products. In this case the four doublets belonging to the two para systems present in the molecule overlap, so a complete attribution of each ^{1}H NMR signals is not possible.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz. Mass spectra were obtained in EI mode at 70 eV. Microanalyses were carried out by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy. TLC analyses were performed on Merck 60 PF_{254} silica gel plates using mixtures of hexane–ethyl acetate (30–100%). The solvents were dried on 4-Å molecular sieves. All the reagents were of commercial quality from freshly opened containers.

Synthesis of Products 3a and 3c. General Procedure. To a solution of the selected biaryl (0.005 mol) in dry trichloroethylene (15 mL) was added a solution of anhydrous $FeCl_3$ (0.81 g, 0.005 mol) in trichloroethylene (15 mL) under nitrogen. The mixture was heated at 50 °C for 3 h under stirring. After cooling, a solution of 2 N HCl (30 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried (Na_2SO_4), CH_2Cl_2 was distilled off, and the residue was chromatographed on silica gel plates with hexane–ethyl acetate mixtures (40–50%) to give the products.

Synthesis of Product 3b. General Procedure. To a solution of 2,2′-dihydroxy-5,5′-di-*tert*-butylbiphenyl (1.49 g, 0.005 mol) in CS_2 (30 mL) was added solid $Li(OH)H_2O$ (0.42 g, 0.01 mol). The mixture was stirred for 1 h at rt; then a solution of anhydrous DDQ (0.56 g, 0.0025 mol) in CS_2 (30 mL) was added and the reaction mixture was stirred out for 3 h. A solution of 2 N HCl (30 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried (Na_2SO_4), CH_2Cl_2 was distilled off, and the residue was chromatographed on silica gel plates with hexane–ethyl acetate mixture (20%) to give the product.

Synthesis of Products 4a, 6x, 6y, and 6z. General Procedure. To a solution of the selected tetraaryl (0.005 mol) in the selected solvent (50 mL) (see Table 2) was added a solution of $Mn(OAc)_3 \cdot 2H_2O$ (1.34 g, 0.005 mol) in the same solvent (50 mL) under stirring. The mixture was heated at 50 °C for 3 h. After cooling, a solution of 2 N HCl (30 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried (Na_2SO_4), CH_2Cl_2 was distilled off, and the residue was chromatographed on silica gel plates with hexane–ethyl acetate mixtures (30–100%) to give the products.

Synthesis of Product 4b. General Procedure. To a solution of the 2,2′,2″,2‴-tetrahydroxy-5,5′,5″,5‴-tetra-*tert*-butyl-1,1′:3′,1″:3″,1‴quaterphenyl (2.97 g, 0.005 mol) in CS_2 (50 mL) was added a solution of DDQ (0.56 g, 0.0025 mol) in CS_2 (50 mL), and the mixture was stirred for 3 h. A solution of 2 N HCl (30 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried (Na_2SO_4), CH_2Cl_2 was distilled off, and the residue was chromatographed on silica gel plates with hexane–ethyl acetate mixture (20%) to give the product.

2,2′,2″,2‴-Tetrahydroxy-5,5′,5″,5‴-tetramethyl-1,1′:3′,1″:3″,1‴-quaterphenyl (3a): yield 0.52 g (49%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6–MeOD) δ 7.14 (2 H, d, J = 1.9 Hz), 7.13 (2 H, d, J = 2.3 Hz), 7.11 (2 H, d, J = 2.3 Hz), 7.04 (2 H, d, J = 8.1 Hz), 6.95 (2 H, dd, J = 8.1, 1.9 Hz), 2.17 (6 H, s), 2.16 (6 H, s); IR (KBr) 3380 cm^{-1} (OH); MS m/z (M^+) (rel intensity) 426 (100), 297 (10), 285 (16), 257 (99). Anal. Calcd for $C_{28}H_{26}O_4$: C, 78.9; H, 6.1. Found: C, 78.9; H, 6.2.

2,2′,2″,2‴-Tetrahydroxy-5,5′,5″,5‴-tetra-*tert*-butyl-1,1′:3′,1″:3″,1‴-quaterphenyl (3b): yield 1.05 g (71%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.56 (2 H, d, J = 2.3 Hz), 7.52 (2 H, d, J = 2.3 Hz), 7.50 (2 H, d, J = 2.1 Hz), 7.10 (2 H, dd, J = 8.4, 2.1 Hz), 6.88 (2 H, d, J = 8.4 Hz), 1.24 (18 H, s), 1.23 (18 H, s); IR (KBr) 3367 cm^{-1} (OH); MS m/z (M^+) (rel intensity) 594 (100), 579 (33), 539 (22), 483 (43), 427 (30). Anal. Calcd for $C_{40}H_{50}O_4$: C, 80.8; H, 8.5. Found: C, 80.7; H, 8.4.

2,2′,2″,2‴-Tetrahydroxy-5,5′,5″,5‴-tetramethoxy-1,1′:3′,1″:3″,1‴-quaterphenyl (3c): yield 0.21 g (17%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6–MeOD) δ 6.99 (2 H, d, J = 8.8 Hz), 6.98 (2 H, d, J = 3.1 Hz), 6.96 (2 H, d, J = 3.1 Hz), 6.95 (2 H, d, J = 3.1 Hz), 6.82 (2 H, dd, J = 8.8, 3.1 Hz), 3.58 (12 H, s); IR (KBr) 3480 cm^{-1} (OH); MS m/z (M^+) (rel intensity) 490 (100), 247 (51). Anal. Calcd for $C_{28}H_{26}O_8$: C, 68.6; H, 5.3. Found: C, 68.7; H, 5.3.

2,2′,2″,2‴,2^{iv},2^{v},2^{vi},2^{vii}-Octahydroxy-5,5′,5″,5‴,5^{iv},5^{v},5^{vi},5^{vii}-octamethyl-1,1′:3′,1″:3″,1‴:3‴,1^{iv}:3^{iv},1^{v}:3^{v},1^{vi}:3^{vi},1^{vii}-octiphenyl (4a): yield 0.49 g (23%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.25 (2 H, d, J = 2.5 Hz), 7.28, 7.27, 7.25, 7.22, 7.20, and 7.19 (12 H, 6 d, J = 2.2 Hz), 7.10 (2 H, d, J = 8.1 Hz), 6.97 (2 H, dd, J = 8.1, 2.5 Hz), 4.7 (8 H, br s), 2.27 (18 H, s), 2.21 (6 H, s); IR (KBr) 3400 cm^{-1} (OH); MS m/z (M^+) (rel intensity) 850 (8), 614 (7), 455 (18), 427 (100). Anal. Calcd for $C_{56}H_{50}O_8$: C, 79.0; H, 5.9. Found: C, 78.9; H, 5.8.

2,2′,2″,2‴,2^{iv},2^{v},2^{vi},2^{vii}-Octahydroxy-5,5′,5″,5‴,5^{iv},5^{v},5^{vi},5^{vii}-octa-*tert*-butyl-1,1′:3′,1″:3″,1‴:3‴,1^{iv}:3^{iv},1^{v}:3^{v},1^{vi}:3^{vi},1^{vii}-octiphenyl (4b): yield 1.72 g (58%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 8.1–7.0 (23 H, m), 6.98 (2 H, br s), 6.60 (2 H, d, J = 8.5 Hz), 6.27 (2 H, br d, J = 8.5 Hz), 1.42 (9 H, s), 1.32 (9 H, s), 1.31 (9 H, s), 1.30 (9 H, s), 1.27

(9 H, s), 1.15 (9 H, s), 1.08 (18 H, s); IR (KBr) 3367 cm^{-1} (OH); MS *m/z* (M$^+$) (rel intensity) 1188 (100), 1172 (25), 890 (16). Anal. Calcd for $C_{80}H_{98}O_8$: C, 80.9; H, 8.3. Found: C, 81.0; H, 8.2.

4,4′,2″,2‴,2$^{\mathrm{iv}}$,4$^{\mathrm{v}}$-Hexahydroxy-5″,5‴-bis(4-hydroxyphenyl)-1,1′:3′,1″: 3″,1‴:3‴,1$^{\mathrm{iv}}$:5$^{\mathrm{iv}}$,1$^{\mathrm{v}}$-sexiphenyl (6x): yield 0.33 g (18%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.76 (2 H, d, $J = 2.3$ Hz), 7.75 (2 H, d, $J = 2.3$ Hz), 7.73 (2 H, d, $J = 2.3$ Hz), 7.49 (2 H, dd, $J = 8.4, 2.3$ Hz), 7.47 and 7.08 (8 H, 2 d, $J = 8.6$ Hz), 7.44 and 7.06 (8 H, 2 d, $J = 8.7$ Hz), 7.23 (2 H, d, $J = 8.4$ Hz), 4.6 (8 H, br s); IR (KBr) 3226 cm^{-1} (OH); MS *m/z* (M$^+$) (rel intensity) 738 (100). Anal. Calcd for $C_{48}H_{34}O_8$: C, 78.0; H, 4.6. Found: C, 77.9; H, 4.7.

4,4′,6″,4‴,6$^{\mathrm{iv}}$,4$^{\mathrm{v}}$,6$^{\mathrm{vi}}$,4$^{\mathrm{vii}}$-Octahydroxy-1,1′:3′,1″:3″,1‴:3‴,1$^{\mathrm{iv}}$: 3$^{\mathrm{iv}}$,1$^{\mathrm{v}}$:3$^{\mathrm{v}}$,1$^{\mathrm{vi}}$: 3$^{\mathrm{vi}}$,1$^{\mathrm{vii}}$-octiphenyl (6y): yield 0.39 g (21%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.9−6.9 (26 H, m), 4.4 (8 H, br s); IR (KBr) 3356 cm^{-1} (OH); MS *m/z* (M$^+$) (rel intensity) 738 (90), 555 (45). Anal. Calcd for $C_{48}H_{34}O_8$: C, 78.0; H, 4.6. Found: C, 77.9; H, 4.6.

4,4′,2″,6‴,4$^{\mathrm{iv}}$,6$^{\mathrm{v}}$,4$^{\mathrm{vi}}$-Heptahydroxy-5″-(4-hydroxyphenyl)-1,1′:3′,1″: 3″,1‴:3‴,1$^{\mathrm{iv}}$:3$^{\mathrm{iv}}$,1$^{\mathrm{v}}$:3$^{\mathrm{v}}$,1$^{\mathrm{vi}}$-septiphenyl (6z): yield 0.20 g (11%), pale yellow solid, dec before melting (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.8−7.2 (14 H, m), 7.46 and 7.09 (4 H, 2 d, $J = 8.6$ Hz), 7.42 and 7.05 (4 H, 2 d, $J = 8.7$ Hz), 7.41 and 7.04 (4 H, 2 d, $J = 8.7$ Hz), 4.7 (8 H, br s); IR (KBr) 3333 cm^{-1} (OH); MS *m/z* (M$^+$) (rel intensity) 738 (100). Anal. Calcd for $C_{48}H_{34}O_8$: C, 78.0; H, 4.6. Found: C, 78.1; H, 4.5.

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Supplementary Material Available: ^{1}H NMR data of all compounds with peak assignments included (2 pages). This material is contained in libraires on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.