Notes

Selective Synthesis of Unsymmetrical Hydroxylated and Methoxylated Biaryls

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Introduction

Unsymmetrically substituted hydroxylated and methoxylated biaryls are widespread in nature[1] and constitute the central building blocks of a large number of products with different biological activity.[2] The classical methods for biaryl synthesis, such as the Ullmann[3] and the Gomberg[4] reactions, are rarely applicable to them with satisfactory efficiency. Cross-coupling of phenanthrols, naphthols, and naphthylamines provides a convenient but limited method of preparing unsymmetrical naphthalene–phenanthrene diols and substituted binaphthyls,[5] but the chemoselective direct cross-coupling of different phenols still remains an open problem.

Additionally, the reaction of Grignard, organotin reagents, arylboronic acids, and specifically substituted haloarenes with the assistance of transition metal catalysts is alternatively utilized.[6] This approach requires that the starting reagents have a substituent group in a specific position which is lost during the coupling process and is limited to iodo- and bromoarenes, and cross-coupling with phenols is not reported.

In order to overcome such a limitation, direct phenol and methoxyarene cross-coupling was studied.

Results and Discussion

Recently we have reported the $FeCl_3$-promoted oxidative coupling of dichloroaluminum phenolates as a viable method for synthesizing variously substituted symmetrical 2,2′-dihydroxybiaryls in good yields and excellent selectivities.[7] In this paper we now communicate our preliminary results on the oxidative cross-coupling of different phenols and phenyl ethers. We selected *p*-methylphenol (**1a**) and *p*-methoxyphenol (**1b**) as the model substrates for our feasibility study. On the basis of our previous studies, all experiments were performed by using dichloroaluminum phenolates easily prepared by reacting $AlCl_3$ and the selected phenols as reported earlier in the literature.[8] First, several combinations of $AlCl_3$ and aromatic substrates as well as different orders of addition of the reagents were examined by carrying out the reaction for 1 h at room temperature.

Scheme I

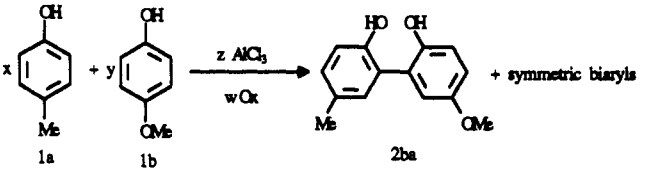

Table I. Reaction Time, Temperature, Reagents Ratio, and Oxidant Effect in the Oxidative Cross-Coupling of *p*-Methoxyphenol and *p*-Cresol in the Presence of $AlCl_3$

entry	*x*	*y*	*z*	*T* (°C)	*t* (h)	*w*Ox	**2ba** %, yield (% selectivity)[a]
a	1	1	1	25	1	$2FeCl_3$	27 (60)
b	2	1	1	25	1	$2FeCl_3$	26 (65)
c	1	2	1	25	1	$2FeCl_3$	13 (50)
d	1	1	2	25	1	$2FeCl_3$	45 (70)
e	1	1	2	50	1	$2FeCl_3$	48 (65)
f	1	1	2	80	1	$2FeCl_3$	42 (62)
g	1	1	2	25	2	$2FeCl_3$	46 (68)
h	1	1	2	25	5	$2FeCl_3$	44 (72)
i	1	1	2	25	1	$VOCl_3$	60 (83)
l	1	1	2	25	1	*p*-benzoquinone	32 (60)
m	1	1	2	25	1	$2CuBr_2$	15 (84)
n	1	1	2	25	1	DDQ	70 (85)

[a] Selectivity = yield of **2ba** (%)/reacted **1a** (%).

On the basis of these experiments it was found that the best yield of the cross-coupling product **2ba** was obtained when $AlCl_3$ was added to a solution of the two phenols in nitromethane followed by addition of $FeCl_3$ (molar ratio x/y/z/w = 1:1:2:2) (Table I, entry d). Next, the effect of reaction temperature and time was examined. Our results suggest that the optimum yield and selectivity is obtained by carrying out the reaction at 25 °C for 1 h, the complete process being unaffected by higher temperatures and longer reaction times (Table I, entries e–h). Finally, different coupling reagents were considered. After many experiments with mono- and bielectronic oxidants we found that the desired selective cross-coupling could be best achieved using DDQ in molar ratio x/y/z/w = 1:1:2:1 (Table I, entry n). In all experiments variable amounts of the two symmetrical biaryls derived from homocoupling of the substrates **1a** and **1b** were recovered as the sole byproducts. The highly selective synthesis of biaryls

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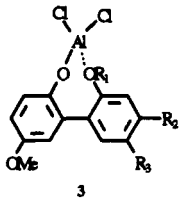

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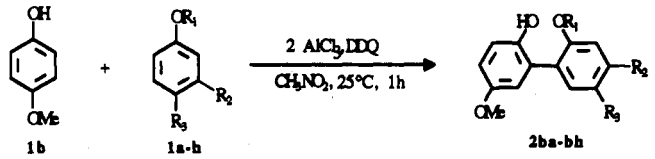
Figure 1.

Table II. Synthesis of Some Unsymmetrical Hydroxylated Biaryls *via* Oxidative Cross-Coupling of Phenols and Phenyl Ethers

compound	R_1	R_2	R_3	% yield (% selectivity)[a]
2ba	H	H	CH_3	70 (85)
2bc	H	H	$(CH_3)_3C$	66 (87)
2bd	H	$(CH_3)_3C$[b]	H	71 (82)
2be	H	OH	H	33 (77)
2bf	H	CH_3[b]	H	25 (78)
2bg	CH_3	H	OCH_3	60 (89)
2bh	CH_3	H	CH_3	50 (87)

[a] Selectivity = yield of **2ba–bh** (%)/reacted **1a,c–h** (%). [b] No ortho,para-coupling products were recovered.

Scheme II



1b 1a-h 2ba-bh

without the formation of tri- and polyaryl byproducts has been previously explained by the formation of an aluminum chelate **3** which stabilizes the biaryl *via* coordinative interactions.[7] Although we have not attempted to rigorously establish the mechanistic details, it is likely that the first electron transfer occurs more easily from the *p*-methoxyphenol, essentially depleting that reagent, which then couples with the other phenol. This hypothesis is in agreement with our previous mechanistic studies of the oxidative coupling of dichloroaluminum phenolates, indicating that the free phenoxy radical attacks the phenolate leading to a dimeric radical which is in turn oxidized further.[7,9] The specificity of the cross-coupling process constitutes the subject of intensive studies in our laboratories.

Our attempts to extend the reaction to a variety of phenols and phenyl ethers **1** under the optimum conditions of Table I gave the unsymmetrical biaryls **2** in satisfactory yields and with good selectivity (Table II).

All the reactions reported in the Table II are of considerable preparative value as they represent an easy and direct access to unsymmetrically substituted biaryls **2ba–bh**. Pure products are obtained after flash chromatography of the crude reaction mixture with hexane–ethyl acetate combinations.

When an alkyl group was introduced at the ortho-position of the phenol or phenyl ether **1**, cross-coupling was inhibited and only the homocoupling product **2bb** was obtained in moderate yield. A similar behavior was observed with phenols or phenyl ethers bearing electron-withdrawing groups such as $COCH_3$ and CN. These results clearly show that this process is sensitive to steric and electronic effect of the substituents R_2 and R_3, in agreement with similar reactions previously reported in the literature.[6]

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On the other hand alkyl and methoxy groups at meta- or para-positions resulted in activation of the reactive system.

Further applications of this cross-coupling reaction as well as detailed mechanistic studies will be reported at a later date.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were recorded at 200 MHz and 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 (15–40%). The solvents were dried on 4-Å molecular sieves. All the reagents were of commercial quality from freshly opened containers and $AlCl_3$ was sublimed.

Synthesis of Unsymmetrical Biaryls. General Procedure. To a solution of the selected aromatic compound (0.01 mol) and *p*-methoxyphenol (1.24 g, 0.01 mol) in dry nitromethane (25 mL) was added $AlCl_3$ (2.66 g, 0.02 mol) in dry nitromethane (25 mL) under nitrogen. After stirring the mixture for 15 min, DDQ (2.27 g, 0.01 mol) in dry nitromethane (50 mL) was added dropwise and the solution was stirred at rt for 1 h. A solution of 2 N HCl was added with stirring. The resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried (Na_2SO_4), the CH_2Cl_2 was distilled off, and the residue was chromatographed to give the products.

2,2′-Dihydroxy-5′-methyl-5-methoxybiphenyl (2ba): yield 1.61 g (70%), brown solid; mp 107–109 °C (Et_2O); ^1H NMR (400 MHz, C_6D_6–MeOD) δ 7.00 (1 H, d, *J* = 2.8 Hz, H-6′), 6.86 (1 H, dd, *J* = 8.1, 2.8 Hz, H-4′), 6.85 (1 H, d, *J* = 3.0 Hz, H-6), 6.80 (1 H, d, *J* = 8.8 Hz, H-3), 6.78 (1 H, d, *J* = 8.1 Hz, H-3′), 6.72 (1 H, dd, *J* = 8.8, 3.0 Hz, H-4), 5.7 (1 H, br s, OH), 5.6 (1 H, br s, OH), 3.28 (3 H, s, OCH_3), 2.07 (3 H, s, CH_3); IR (KBr) 3170 cm^{-1}; MS *m/z* (M^+) 230 (100%). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.9; H, 6.1.

2,2′-Dihydroxy-5′-*tert*-butyl-5-methoxybiphenyl (2bc): yield 1.80 g (66%), brown solid; mp 47–50 °C (benzene); ^1H NMR (200 MHz, C_6D_6) δ 7.38 (1 H, d, *J* = 2.5 Hz, H-6′ or H-6), 7.15 (1 H, dd, *J* = 8.5, 2.5 Hz, H-4′ or H-4), 6.92 (1 H, d, *J* = 2.9 Hz, H-6 or H-6′), 6.85 (1 H, d, *J* = 8.5 Hz, H-3′ or H-3), 6.82 (1 H, d, *J* = 8.8 Hz, H-3 or H-3′), 6.71 (1 H, dd, *J* = 8.8, 2.9 Hz, H-4 or H-4′), 5.75 (1 H, s, OH), 5.51 (1 H, s, OH), 3.29 (3 H, s, OCH_3), 1.19 (9 H, s, $(CH_3)_3C$); IR (KBr) 3311 cm^{-1}; MS *m/z* (M^+) 272 (85%), 257 (100%), 216 (32%). Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4. Found: C, 75.0; H, 7.5.

2,2′-Dihydroxy-4′-*tert*-butyl-5-methoxybiphenyl (2bd): yield 1.93 g (71%), yellow solid; mp 100.5–102 °C (benzene); ^1H NMR (400 MHz, C_6D_6) δ 7.22 (1 H, d, *J* = 8.0 Hz, H-6′ or H-3), 7.08 (1 H, dd, *J* = 8.0, 1.8 Hz, H-5′ or H-4), 7.05 (1 H, d, *J* = 1.8 Hz, H-3′ or H-6), 6.95 (1 H, d, *J* = 8.8 Hz, H-3 or H-6′), 6.86 (1 H, dd, *J* = 8.8, 3.0 Hz, H-4 or H-5′), 6.82 (1 H, d, *J* = 3.0 Hz, H-6 or H-3′), 5.9 (1 H, br s, OH), 5.6 (1 H, br s, OH), 3.78 (3 H, s, OCH_3), 1.34 (9 H, s, $(CH_3)_3C$); IR (KBr) 3279 cm^{-1}; MS *m/z* (M^+) 272 (15%), 115 (23%), 109 (100%). Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4. Found: C, 74.8; H, 7.3.

2,2′,4′-Trihydroxy-5-methoxybiphenyl (2be): yield 0.77 g (33%), brown oil; ^1H NMR (400 MHz, C_6D_6–MeOD) δ 7.23 (1 H, d, *J* = 8.4 Hz, H-3 or H-6′), 7.05 (1 H, d, *J* = 8.8 Hz, H-6′ or H-3), 6.97 (1 H, d, *J* = 3.1 Hz, H-3′ or H-6), 6.86 (1 H, d, *J* = 2.4 Hz, H-6 or H-3′), 6.76 (1 H, dd, *J* = 8.8, 3.1 Hz, H-5′ or H-4), 6.71 (1 H, dd, *J* = 8.4, 2.4 Hz, H-4 or H-5′), 3.41 (3 H, s, OCH_3); IR (NaCl) 3344 cm^{-1}; MS *m/z* (M^+) 232 (100%). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 67.3; H, 5.3.

2,2′-Dihydroxy-4′-methyl-5-methoxybiphenyl (2bf): yield 0.58 g (25%), brown solid; mp 87–90 °C (benzene); ^1H NMR (400 MHz, C_6D_6–MeOD) δ 7.12 (1 H, d, *J* = 7.7 Hz, H-6′), 6.86 (1 H, d, *J* = 3.0 Hz, H-6), 6.79 (1 H, d, *J* = 8.8 Hz, H-3), 6.71 (1 H, dd, *J* = 8.8, 3.0 Hz, H-4), 6.68 (1 H, br s, H-3′), 6.65 (1 H, br d, *J* = 7.7 Hz, H-5′), 5.9 (1 H, br s, OH), 5.6 (1 H, br s, OH), 3.29 (3 H, s, OCH_3), 2.08 (3 H, s, CH_3); IR (KBr) 3306 cm^{-1}; MS *m/z* (M^+) 230 (100%), 215 (4%). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 73.1; H, 6.2.

2-Hydroxy-2′,5,5′-trimethoxybiphenyl (2bg): yield 1.56 g (60%), brown solid; mp 91–93 °C (benzene); ^{1}H NMR (200 MHz, C_6D_6) δ 7.16 (1 H, d, J = 8.7 Hz, H-3 or H-3′), 6.97 (1 H, d, J = 3.1 Hz, H-6 or H-6′), 6.92 (1 H, d, J = 3.0 Hz, H-6′ or H-6), 6.77 (1 H, dd, J = 8.7, 3.1 Hz, H-4 or H-4′), 6.73 (1 H, dd, J = 8.8, 3.0 Hz, H-4′ or H-4), 6.48 (1 H, d, J = 8.8 Hz, H-3′ or H-3), 6.40 (1 H, s, OH), 3.34 (3 H, s, OCH_3), 3.29 (3 H, s, OCH_3), 3.10 (3 H, s, OCH_3); IR (KBr) 3466 cm^{-1}; MS m/z (M^+) 260 (100%), 245 (31%), 230 (15%), 213 (19%). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.4; H, 6.3.

2-Hydroxy-5′-methyl-2′,5-dimethoxybiphenyl (2bh): yield 1.22 g (50%), brown solid; mp 97–98.5 °C (Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.19 (1 H, d, J = 8.8 Hz, H-3), 7.08 (1 H, br s, H-6′), 6.98 (1 H, d, J = 3.1 Hz, H-6), 6.91 (1 H, br d, J = 8.3 Hz, H-4′), 6.79 (1 H, dd, J = 8.8, 3.1 Hz, H-4), 6.45 (1 H, d, J = 8.3 Hz, H-3′), 6.30 (1 H, s, OH), 3.35 (3 H, s, OCH_3), 3.07 (3 H, s, OCH_3), 2.09 (3 H, s, CH_3); IR (KBr) 3367 cm^{-1}; MS m/z (M^+) 244 (100%). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6. Found: C, 73.7; H, 6.5.

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