Oxidative Coupling of Quinones and Aromatic Compounds by Palladium(II) Acetate

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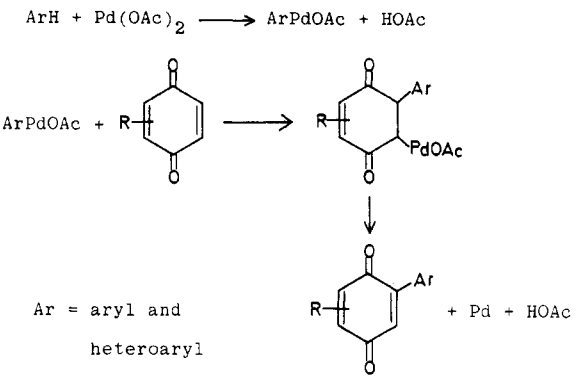
The oxidation of 1,4-benzoquinone, 2-phenyl-1,4-benzoquinone, 1,4-naphthoquinone, and 1,2-naphthoquinone by palladium(II) acetate in acetic acid containing arenes gave the corresponding aryl-substituted quinones. Treatment of 1,4-naphthoquinone with aromatic heterocycles such as furfural, 2-acetylfuran, methyl 2-furoate, 2-acetylthiophene, 1-(phenylsulfonyl)pyrrole, 1-(phenylsulfonyl)indole, 4-pyrone, and 1-methyl-2-pyridone in the presence of palladium acetate gave the corresponding 2-heteroaryl-substituted 1,4-naphthoquinones.

The quinone moiety is found commonly in nature. Quinones play an important role in electron-transport processes. Compounds containing the quinone group have been shown to have chemotherapeutic value as antitumor, antifungal, and antibacterial drugs. Model quinone-containing derivatives have been used extensively to study bioenergetic pathways.[1] Furthermore, aryl-substituted quinones are of interest in connection with existence of naturally occurring compounds such as volucrisporin.[2] Aryl-substituted quinones have been synthesized by the reaction of quinones with aryldiazonium salts,[3] but no report of oxidative coupling of quinones and arenes has been published except for the γ-radiolysis of 1,4-quinones in benzene.[4] On the other hand, oxidative coupling of olefins and aromatic compounds by palladium(II) salts has been studied as an effective method for the preparation of aryl-substituted olefins.[5] However, little attention has been paid to oxidative coupling of quinones and aromatic compounds,[6] although the use of quinones as reoxidants for the palladium(II) salts catalyzed reactions is now well-known.[7] This paper outlines the preparation of aryl- and heteroarylquinone derivatives by oxidative coupling of palladium acetate.

Results and Discussions

Treatment of 1,4-benzoquinone (1) with palladium acetate in acetic acid that contained arenes such as benzene, *p*-xylene, and *p*-dichlorobenzene at reflux temperature under nitrogen gave the corresponding 2-aryl-, 2,5-diaryl-, and 2,6-diaryl-1,4-benzoquinones. The arylation of 2-phenyl-1,4-benzoquinone (**2a**) with *p*-dichlorobenzene gave 1,4-benzoquinones that bear two different aryl substituents. Treatment of 1,4-naphthoquinone (**5**) with palladium acetate in acetic acid containing arenes also gave the corresponding 2-aryl-1,4-naphthoquinones in good yields. The reaction of 1,2-naphthoquinone (**7**) with benzene gave 4-phenyl-1,2-naphthoquinone (**8a**),[8] but 3-phenyl-1,2-naphthoquinone[9] was not detected. Furthermore, the product isolated from the reaction of **7** and *p*-dichlorobenzene was assigned to 4-(2,5-dichlorophenyl)-1,2-naphthoquinone (**8c**) on the basis of the ^{1}H NMR data compared with that of **8a**. These results are summarized in Table I.

Scheme I



We previously reported that the treatment of methyl acrylate and polymethylbenzene such as mesitylene and pentamethylbenzene with palladium acetate did not give the expected coupling products because of the steric effects,[10] although Watanabe et al.[11] reported the oxidative coupling of styrene and mesitylene. On the other hand, the arylation of **5** with mesitylene and 1,2,3,4-tetramethylbenzene gave the expected coupling products **6e** and **6f**, respectively. However, the reaction of **5** with durene and with pentamethylbenzene gave complex reaction mixtures.

Coupling reactions of olefins and aromatic heterocycles are an effective method for the preparation of important precursors of biologically and physiologically active compounds. Therefore, the oxidative coupling of olefins and aromatic heterocycles such as furans,[12-15] thiophene,[12-14] pyrroles,[10,12] pyrazoles,[10] indoles,[14,16,17] and 1-methyl-2-pyridone[15] by palladium(II) salts has been reported. The oxidative coupling of **5** and aromatic heterocycles by

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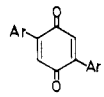
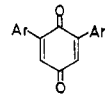
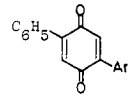
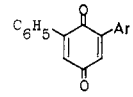
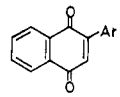
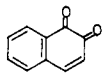
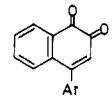
(2) Chandra, P.; Read, G.; Vining, L. C. *Can. J. Chem.* **1966**, *44*, 403.
(3) Finley, K. T. "The Chemistry of the Quinonoid Compounds"; Patai, S., Ed.; Wiley: London, 1974; Part 2, pp 1043-1047.
(4) Wilson, J. G.; Sweeting, J. W. *Aust. J. Chem.* **1972**, *25*, 1877.
(5) For a review, see: Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524.
(6) Preliminary communication: Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, 859.
(7) Moiseev, I. I.; Vorgaftik, M. N.; Syrkin, Y. K. *Dokl. Akad. Nauk. SSSR*, **1963**, *130*, 820. Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241.
(8) Cassebaum, H.; Langenbeck, W. *Chem. Ber.* **1957**, *90*, 339.
(9) Fieser, L. F.; Bader, A. R. *J. Am. Chem. Soc.* **1951**, *73*, 681.
(10) Itahara, T.; Kawasaki, K.; Ouseto, F. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3488.
(11) Watanabe, M.; Yamamura, M.; Moritani, I.; Fujiwara, Y.; Sonoda, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 663.
(12) Asano, R.; Moritani, I.; Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 663.
(13) Kozhevnikov, I. V. *React. Kinet. Catal. Lett.* **1976**, *5*, 439.
(14) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851.
(15) Itahara, T.; Ouseto, F. *Synthesis* **1984**, 488.
(16) Itahara, T.; Kawasaki, K.; Ouseto, F. *Synthesis* **1984**, 236.
(17) Itahara, T.; Ikeda, M.; Sakakibara, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1361.

0022-3263/85/1950-5546$01.50/0

Table I. Arylation of Quinones with Arenes and Palladium Acetate[a]

quinone (mmol)	ArH, Ar	$Pd(OAc)_2$, mmol	AcOH, mL	reacn time, h	conv,[b] %	products (yield,[c,d] %)		
								
1 (4.0)	C_6H_5 (100 mL)	4.0	100	14	78	**2a** (41)	**3a** (12)	**4a** (6)
1 (4.0)	2,5-$Me_2C_6H_3$ (100 mL)	4.0	100	14	80	**2b** (25)	**3b** (13)	**4b** (8)
1 (4.0)	2,5-$Cl_2C_6H_3$ (30 g)	4.0	120	14	70	**2c** (50)	**3c** (3)	**4c** (2)
								
2a (4.0)	2,5-Cl_2CH_3 (30 g)	4.0	120	14	88	**3d** (36)	**4d** (19)	
								
5 (2.0)	C_6H_5 (50 mL)	2.0	50	14	100	**6a** (85)		
5 (2.0)	2,5-$Me_2C_6H_3$ (50 mL)	2.0	50	14	100	**6b** (78)		
5 (2.0)	2,5-$Cl_2C_6H_3$ (15 g)	2.0	60	14	100	**6c** (70)		
5 (2.0)	2,5-$F_2C_6H_3$ (5 g)	2.0	25	7	40	**6d** (76)		
5 (2.0)	2,4,6-$Me_3C_6H_2$ (40 mL)	2.0	40	7	37	**6e** (69)		
5 (2.0)	2,3,4,5-Me_4C_6H (15 mL)	2.0	35	7	89	**6f** (86)		
								
7 (2.0)	C_6H_5 (50 mL)	2.0	50	14	100	**8a** (30)		
7 (2.0)	2,5-$Cl_2C_6H_3$ (15 g)	2.0	60	14	100	**8c** (27)		

[a] All reactions were performed at reflux temperature under nitrogen. [b] Conversion of quinones. [c] Yields based on quinones consumed. [d] Isolated.

palladium acetate was further investigated.

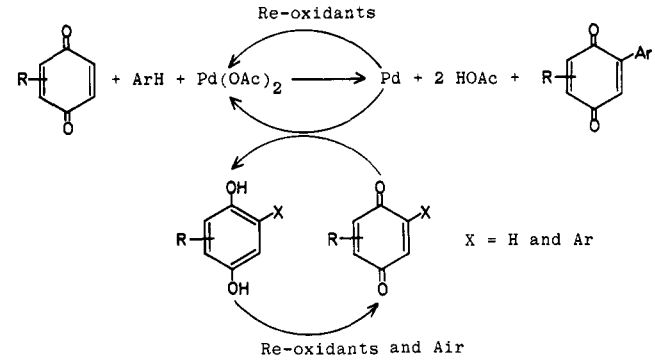
Although the attempted oxidative coupling of **5** and simple aromatic heterocycles such as furan and thiophene was unsuccessful under our conditions, the reaction of **5** with aromatic heterocycles with attached functional groups such as formyl, acetyl, and ester groups gave the expected products. In palladium-catalyzed reactions,[18] increasing interest is being shown in the compatibility of functional groups.[19] Oxidative coupling of **5** and furfural, 2-acetylfuran, methyl 2-furoate, and 2-acetylthiophene is of interest from the view point of the compatibility of functional groups. These results are summarized in Table II.

The use of the phenylsulfonyl group as a nitrogen-protecting group of indoles[20] and pyrroles[21] has been reported. 1-(Phenylsulfonyl)pyrrole and 1-(phenylsulfonyl)indole also reacted with **5** and palladium acetate to give **13** and **14**, respectively. Furthermore, the reaction of **5** with 4-pyrone gave **15** and **16** and with 1-methyl-2-pyridone gave **17** and **18**.

In view of the known reports on the oxidative coupling of arenes and olefins[5] and our present results, it seemed reasonable to assume that the coupling of quinones and aromatic compounds proceeded via aryl- or heteroarylpalladium(II) intermediates, as shown in Scheme I.

Palladium acetate catalyzed oxidative coupling of **5** and benzene were carried out in air using several reoxidants which are listed in Table III. Among the reoxidants, peroxodisulfate salts were found to be particularly effective for the palladium acetate catalyzed reactions,[22] although

Scheme II



potassium peroxodisulfate was already used in the acetoxylation of arenes.[23] Palladium acetate catalyzed arylation of **5** with *p*-xylene and of **1** with benzene in the presence of sodium peroxodisulfate were further investigated. These results are summarized in Table III. The proposed mechanism of the palladium acetate catalyzed arylation of quinones in the presence of reoxidants is shown in Scheme II.

Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a JEOL PMX60A spectrometer using tetramethylsilane as an internal standard, and the chemical shifts are reported in δ values. Infrared spectra were measured with a JASCO IRA-1 spectrometer. The elemental analyses were performed by the Analytical Center of Kyoto University. Column chromatography was performed with Wako silica gel C-200,

(18) For a review of palladium-catalyzed reactions of organic halides with olefins, see: Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
(19) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833 and references therein.
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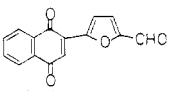
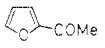
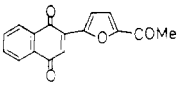
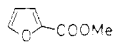
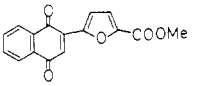
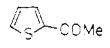
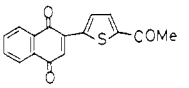
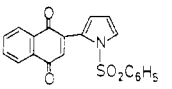
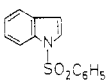
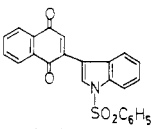
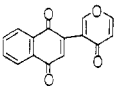
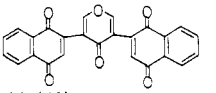
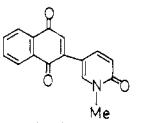
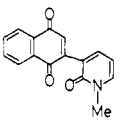
(21) Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1981**, 4899. Rokach, J.; Hamel, P.; Kakushima, M. *Tetrahedron Lett.* **1981**, 4901.
(22) For a preliminary communication concerning sodium peroxodisulfate as a reoxidant, see: Itahara, T. *Chem. Ind. (London)* **1982**, 599.
(23) Eberson, L.; Jönsson, L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 885; *Acta. Chem. Scand., Ser. B* **1976**, *30*, 361; *Ann.* **1977**, 233.

Table II. Oxidative Coupling of 1,4-Naphthoquinone and Aromatic Heterocycles by Palladium Acetate[a]

aromatic heterocycles	mmol	reacn time, h	conv,[b] %	product(s) (yield,[c,d] %)	
	2.0	7	53	 **9** (79)	
	1.5	7	66	 **10** (68)	
	1.5	7	67	 **11** (76)	
	2.0	7	44	 **12** (61)	
	1.0	7	67	 **13** (55)	
	1.0	7	60	 **14** (68)	
	2.0	17	61	 **15** (25)	 **16** (42)
	2.0	17	72	 **17** (56)	 **18** (18)

[a] Conditions used in all experiments: 1,4-naphthoquinone (1.0 mmol), palladium acetate (1.0 mmol), AcOH (50 ml), at reflux temperature, under nitrogen. [b] Conversion of 1,4-naphthoquinone. [c] Yields based on 1,4-naphthoquinone consumed. [d] Isolated.

Table III. Palladium Acetate Catalyzed Arylation of Quinones with Arenes and Reoxidants[a]

				product(s)		
					yields, %	
quinone	$Pd(OAc)_2$, mmol	reoxidant	arene		*b*	*c* (conv,[d] %)
5	0.25	$Na_2S_2O_8$	C_6H_6	**6a**	724	79 (46)
5	0.04	$Na_2S_2O_8$	C_6H_6	**6a**	4025	79 (41)
5	0.25	$K_2S_2O_8$	C_6H_6	**6a**	508	67 (41)
5	0.25	$(NH_4)_2S_2O_8$	C_6H_6	**6a**	680	61 (56)
5	0.25	$Cu(OAc)_2$	C_6H_6	**6a**	228	35 (33)
5	0.25	$FeCl_3$	C_6H_6	**6a**	160	24 (34)
5	0.25	$KMnO_4$	C_6H_6	**6a**	332	33 (51)
5	0.25	$K_2Cr_2O_7$	C_6H_6	**6a**	232	22 (52)
5	0.25	$Na_2S_2O_8$	p-$Me_2C_6H_4$	**6b**	980	60 (81)
1	0.25	$Na_2S_2O_8$	C_6H_6	**2a**	454	36 (63)
				3a	373	15 (63)
				4a	123	5 (63)

[a] Conditions used in all experiments: quinones (5.0 mmol) in a mixture of acetic acid (50 mL) and arenes (50 mL) in the presence of reoxidants (5.0 mmol) at reflux temperature for 15 h in air. [b] Yields based on palladium acetate used. [c] Yields based on quinones 1 or **5** consumed. [d] Conversion of quinones 1 or **5**.

100–200 mesh ASTM, and preparative thin-layer chromatography was performed with Merck silica gel GF-254 or Wako silica gel B-5F.

General Procedure for the Stoichiometric Arylation of Quinones 1, 2a, 5, and 7 with Arenes and Palladium Acetate. A solution of quinones and palladium acetate in acetic acid that contained arenes was heated at reflux temperature under nitrogen. The reaction mixture was evaporated to give a residue, which was then chromatographed on silica gel column, eluted with benzene, to give aryl-substituted quinones and recovered quinones. The results are summarized in Table I. The products 2-phenyl-1,4-benzoquinone (**2a**), 2,5-diphenyl-1,4-benzoquinone (**3a**), and 2-phenyl-1,4-naphthoquinone (**6a**) were identified by comparison with authentic samples obtained commercially. The spectral data of the other products are given below.

2,6-Diphenyl-1,4-benzoquinone (2a): mp 137–138 °C (lit.[24]

mp 136 °C); NMR ($CDCl_3$) δ 6.87 (s, 2 H), 7.4–7.6 (m, 10 H); IR (Nujol) 1660, 1650, 1595 cm^{-1}.

2-(2,5-Dimethylphenyl)-1,4-benzoquinone (2b): mp 77–78 °C; NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.34 (s, 3 H), 6.63–7.3 (m, 6 H); IR (Nujol) 1655 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.85; H, 5.93.

2,5-Bis(2,5-dimethylphenyl)-1,4-benzoquinone (3b): mp 184–185.5 °C; NMR ($CDCl_3$) δ 2.19 (s, 6 H), 2.34 (s, 6 H), 6.76 (s, 2 H), 6.9–7.34 (m, 6 H); IR (Nujol) 1655, 1610 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.79; H, 6.41.

2,6-Bis(2,5-dimethylphenyl)-1,4-benzoquinone (4b): mp 129–130 °C; NMR ($CDCl_3$) δ 2.18 (s, 6 H), 2.33 (s, 6 H), 6.74 (s, 2 H), 6.87–7.34 (m, 6 H); IR (Nujol) 1660, 1610 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.82; H, 6.64.

2-(2,5-Dichlorophenyl)-1,4-benzoquinone (2c): mp 117–118 °C; NMR ($CDCl_3$) δ 6.73–6.95 (m, 3 H), 7.17–7.47 (m, 3 H); IR (Nujol) 1660 cm^{-1}. Anal. Calcd for $C_{12}H_6O_2Cl_2$: C, 56.95; H, 2.39. Found: C, 56.72; H, 2.35.

2,5-Bis(2,5-dichlorophenyl)-1,4-benzoquinone (3c): mp 223–225 °C; NMR ($CDCl_3$) δ 6.92 (s, 2 H), 7.26–7.36 (m, 2 H), 7.4–7.47 (m, 4 H); IR (Nujol) 1670, 1615 cm^{-1}. Anal. Calcd for $C_{18}H_8O_2Cl_4$: C, 54.31; H, 2.03. Found: C, 53.90; H, 1.95.

2,6-Bis(2,5-dichlorophenyl)-1,4-benzoquinone (4c): mp 155–156 °C; NMR ($CDCl_3$) δ 6.89 (s br, 2 H), 7.2–7.47 (m, 6 H); IR (Nujol) 1670 cm^{-1}. Anal. Calcd for $C_{18}H_8O_2Cl_4$: C, 54.31; H, 2.03. Found: C, 54.11; H, 2.29.

2-(2,5-Dichlorophenyl)-5-phenyl-1,4-benzoquinone (3d): mp 159–160 °C; NMR ($CDCl_3$) δ 6.84 (s, 1 H), 6.94 (s, 1 H), 7.19–7.53 (m, 8 H); IR (Nujol) 1650, 1595 cm^{-1}. Anal. Calcd for $C_{18}H_{10}O_2Cl_2$: C, 65.68; H, 3.06. Found: C, 65.61; H, 2.98.

2-(2,5-Dichlorophenyl)-6-phenyl-1,4-benzoquinone (4d): mp 91–92 °C; NMR ($CDCl_3$) δ 6.79 (d, 1 H, J = 2 Hz), 6.92 (d, 1 H, J = 2 Hz), 7.22–7.57 (m, 8 H); IR (Nujol) 1665, 1650, 1595 cm^{-1}. Anal. Calcd for $C_{18}H_{10}O_2Cl_2$: C, 65.68; H, 3.06. Found: C, 66.08; H, 2.99.

2-(2,5-Dimethylphenyl)-1,4-naphthoquinone (6b): mp 83–83.5 °C; NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.34 (s, 3 H), 6.88 (s, 1 H), 6.9–7.0 (m, 1 H), 7.1–7.2 (m, 2 H), 7.64–7.9 (m, 2 H), 8.0–8.25 (m, 2 H); IR (Nujol) 1670, 1595 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.18; H, 5.52. Found: C, 82.42; H, 5.38.

2-(2,5-Dichlorophenyl)-1,4-naphthoquinone (6c): mp 166–168 °C; NMR ($CDCl_3$) δ 6.97 (s, 1 H), 7.23–7.45 (m, 3 H), 7.65–7.9 (m, 2 H), 8.0–8.25 (m, 2 H); IR (Nujol) 1670, 1595 cm^{-1}. Anal. Calcd for $C_{16}H_8O_2Cl_2$: C, 63.26; H, 2.95. Found: C, 63.50; H, 2.66.

2-(2,5-Difluorophenyl)-1,4-naphthoquinone (6d): mp 146.5–148 °C; NMR ($CDCl_3$) δ 6.98–7.14 (m, 3 H), 7.20 (s, 1 H), 7.63–7.93 (m, 2 H), 7.95–8.25 (m, 2 H); IR (Nujol) 1670, 1590 cm^{-1}. Anal. Calcd for $C_{16}H_8O_2F_2$: C, 71.11; H, 2.98. Found: C, 70.82; H, 2.81.

2-(2,4,6-Trimethylphenyl)-1,4-naphthoquinone (6e): mp 155–157 °C; NMR ($CDCl_3$) δ 2.11 (s, 6 H), 2.33 (s, 3 H), 6.84 (s, 1 H), 6.93 (s, 2 H), 7.6–7.9 (m, 2 H), 7.96–8.26 (m, 2 H); IR (Nujol) 1660, 1610, 1590 cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.56; H, 5.95.

2-(2,3,4,5-Tetramethylphenyl)-1,4-naphthoquinone (6f): mp 152–153.5 °C; NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.25 (s, 6 H), 2.27 (s, 3 H), 6.86 (s, 1 H), 6.90 (s, 1 H), 7.63–7.9 (m, 2 H), 7.96–8.26 (m, 2 H); IR (Nujol) 1665, 1650, 1590 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 83.01; H, 6.17.

4-Phenyl-1,2-naphthoquinone (8a): mp 120–121 °C (lit.[8] mp 120–121 °C); NMR ($CDCl_3$) δ 6.37 (s, 1 H), 7.14–7.7 (m, 8 H), 8.1–8.43 (m, 1 H); IR (Nujol) 1690, 1655, 1585 cm^{-1}.

4-(2,5-Dichlorophenyl)-1,2-naphthoquinone (8c): mp 130–131 °C: NMR ($CDCl_3$) δ 6.37 (s, 1 H), 6.82–7.02 (m, 1 H), 7.25–7.7 (m, 5 H), 8.08–8.3 (m, 1 H); IR (Nujol) 1700, 1670, 1590 cm^{-1}. Anal. Calcd for $C_{16}H_8O_2Cl_2$: C, 63.39; H, 2.66. Found: C, 63.33; H, 2.64.

General Procedure for the Stoichiometric Oxidative Coupling of 5 and Aromatic Heterocycles by Palladium Acetate. A solution of **5** (1.0 mmol), aromatic heterocycles (1.0–2.0 mmol), and palladium acetate (1.0 mmol) in acetic acid (50 mL) was heated at reflux temperature under nitrogen. The reaction mixture was evaporated to give a residue which was then chromatographed on silica gel TLC to give 2-heteroaryl-substituted 1,4-naphthoquinones and **5** recovered. These results are summarized in Table II. The spectral and analytical data of the products are given below.

2-(5-Formyl-2-furyl)-1,4-naphthoquinone (9): mp 178–180 °C: NMR ($CDCl_3$) δ 7.35 (d, 1 H, J = 4 Hz), 7.55 (s, 1 H), 7.7–8.28 (m, 5 H), 9.77 (s, 1 H); IR (Nujol) 1675, 1650, 1595 cm^{-1}; mass spectrum, m/e (relative intensity) 252 (M^+, 100), 224 (31), 223 (81), 195 (48), 167 (40), 139 (50). Anal. Calcd for $C_{15}H_8O_4$: C, 71.43; H, 3.20. Found: C, 71.48; H, 3.08.

2-(5-Acetyl-2-furyl)-1,4-naphthoquinone (10): mp 185–187 °C; NMR ($CDCl_3$) δ 2.54 (s, 3 H), 7.24 (d, 1 H, J = 3.5 Hz), 7.47 (s, 1 H), 7.6–8.23 (m, 5 H); IR (Nujol) 1675, 1650, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 266 (M^+, 90), 251 (100), 223 (41). Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 71.91; H, 3.74.

Methyl 5-(1,4-naphthoquinon-2-yl)-2-furancarboxylate (11): mp 176–177.5 °C: NMR ($CDCl_3$) δ 3.93 (s, 3 H), 7.28 (d, 1 H, J = 3.5 Hz), 7.52 (s, 1 H), 7.6–8.23 (m, 5 H); IR (Nujol) 1750, 1675, 1650, 1600, cm^{-1}: mass spectrum, m/e (relative intensity) 282 (M^+, 100), 254 (28), 251 (22), 223 (57). Anal. Calcd for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 68.47; H, 3.43.

2-(5-Acetyl-2-thienyl)-1,4-naphthoquinone (12): mp 202–205 °C: NMR ($CDCl_3$) δ 2.60 (s, 3 H), 7.28 (d, 1 H, J = 4 Hz), 7.74 (s, 1 H), 7.68–8.3 (m, 5 H); IR (Nujol) 1645, 1595 cm^{-1}: mass spectrum, m/e (relative intensity) 282 (M^+, 51), 267 (100). Anal. Calcd for $C_{16}H_{10}O_3S$: C, 68.07; H, 3.57. Found: C, 67.90; H, 3.85.

2-[1-(Phenylsulfonyl)-2-pyrrolyl]-1,4-naphthoquinone (13): mp 201–204 °C; NMR ($CDCl_3$) δ 6.51–6.65 (m, 1 H), 6.95 (s, 1 H), 7.1–7.23 (m, 1 H), 7.4–8.4 (m, 10 H); IR (Nujol) 1670, 1650, 1595, 1580 cm^{-1}; mass spectrum, m/e (relative intensity) 363 (M^+, 80), 222 (47), 141 (36). Anal. Calcd for $C_{20}H_{13}NO_4S$: C, 66.11; H, 3.61; N, 3.85. Found: C, 66.37; H, 3.82; N, 3.62.

2-[1-(Phenylsulfonyl)-3-indolyl]-1,4-naphthoquinone (14): mp 213–215 °C; NMR ($CDCl_3$) δ 7.32 (s, 1 H), 7.2–8.25 (m, 8 H), 8.38 (s, 1 H); IR (Nujol) 1670, 1650, 1600, 1580 cm^{-1}; mass spectrum, m/e (relative intensity) 413 (M^+, 84), 272 (100). Anal. Calcd for $C_{24}H_{15}NO_4S$: C, 69.72; H, 3.66; N, 3.39. Found: C, 69.77; H, 3.70; N, 3.14.

2-(4-Oxopyran-3-yl)-1,4-naphthoquinone (15): mp 217–220 °C; NMR ($CDCl_3$) δ 6.44 (d, 1 H, J = 6 Hz), 7.53 (s, 1 H), 7.81 (d, 1 H, J = 6 Hz), 8.24 (s, 1 H), 7.7–8.3 (m, 4 H); IR (Nujol) 1665, 1655, 1595 cm^{-1}; mass spectrum, m/e (relative intensity) 252 (M^+, 100), 196 (32), 154 (32). Anal. Calcd for $C_{15}H_8O_4$: C, 71.43; H, 3.20. Found: C, 70.96; H, 3.02.

3,5-Di-1,4-naphthoquinon-2-yl-4-pyrone (16): mp 265–268 °C; NMR ($CDCl_3$) δ 7.37 (s, 2 H), 8.13 (s, 2 H), 7.56–8.23 (m, 8 H); IR (Nujol) 1670, 1650, 1595 cm^{-1}; mass spectrum, m/e (relative intensity) 408 (M^+, 100), 324 (28). Anal. Calcd for $C_{25}H_{12}O_6$: C, 73.53; H, 2.96. Found: C, 73.27; H, 3.09.

2-(1,2-Dihydro-1-methyl-2-oxopyridin-5-yl)-1,4-naphthoquinone (17): mp 232–235 °C; NMR ($CDCl_3$) δ 3.62 (s, 3 H), 6.60 (d, 1 H, J = 9 Hz), 6.97 (s, 1 H), 7.3–8.3 (m, 6 H); IR (Nujol) 1670, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 265 (M^+, 100), 236 (21). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.64; H, 4.07; N, 5.24.

2-(1,2-Dihydro-1-methyl-2-oxopyridin-3-yl)-1,4-naphthoquinone (18): mp 222–225 °C; NMR ($CDCl_3$) δ 3.57 (s, 3 H), 6.20 (t, 1 H, J = 7 Hz), 7.18 (s, 1 H), 7.3–8.2 (m, 6 H); IR (Nujol) 1670–1650 (br), 1595, 1550 cm^{-1}; mass spectrum, m/e (relative intensity) 265 (M^+, 100), 237 (37), 236 (29), 209 (54), 208 (21), 181 (22), 180 (29). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.27; H, 4.26; N, 5.19.

Palladium Acetate Catalyzed Arylation of Quinones with Arenes in the Presence of Reoxidants. A mixture of quinones **1** or **5** (5 mmol), palladium acetate (0.25 or 0.04 mmol), and reoxidants (5.0 mmol) in a mixture of acetic acid (50 mL) and arenes (50 mL) was heated at reflux temperature for 15 h under nitrogen with vigorous stirring. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel column, eluted with benzene, to give aryl-substituted quinones and recovered quinones. These results are summarized in Table III.

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Registry No. 1, 106-51-4; **2a**, 363-03-1; **2b**, 79756-66-4; **2c**, 79756-69-7; **3a**, 844-51-9; **3b**, 79756-68-6; **3c**, 79756-71-1; **3d**, 79756-76-6; **4a**, 2887-97-0; **4b**, 79756-67-5; **4c**, 79756-70-0; **4d**, 79756-75-5; **5**, 130-15-4; **6a**, 2348-77-8; **6b**, 79756-72-2; **6c**, 79756-73-3; **6d**, 99113-62-9; **6e**, 99113-63-0; **6f**, 99113-64-1; **7**, 524-42-5; **8a**, 73671-07-5; **8c**, 79756-74-4; **9**, 99113-71-0; **10**, 99113-72-1; **11**, 99113-73-2; **12**, 99113-74-3; **13**, 99113-65-2; **14**, 99113-66-3; **15**, 99113-67-4; **16**, 99113-68-5; **17**, 99113-69-6; **18**, 99113-70-9; C_6H_6, 71-43-2; 2,5-$Me_2C_6H_4$, 106-42-3; 2,5-$Cl_2C_6H_4$, 106-46-7; 2,5-$F_2C_6H_4$, 540-36-3; 2,4,6-$Me_3C_6H_3$, 108-67-8; 2,3,4,5-$Me_4C_6H_2$, 488-23-3; $Pd(OAc)_2$, 3375-31-3; $Na_2S_2O_8$, 7775-27-1; $K_2S_2O_8$, 7727-21-1; $(NH_4)_2S_2O_8$, 7727-54-0; $Cu(OAc)_2$, 142-71-2; $FeCl_3$, 7705-08-0; $KMnO_4$, 7722-64-7; $K_2Cr_2O_7$, 7778-50-9; furfural, 98-01-1; 2-acetylfuran, 1192-62-7; methyl 2-furoate, 611-13-2; 2-acetylthiophene, 88-15-3; 1-(phenylsulfonyl)pyrrole, 16851-82-4; 1-(phenylsulfonyl)indole, 40899-71-6; 4-pyrone, 108-97-4; 1-methyl-2-pyridone, 694-85-9.

Methoxybenzo[*a*]pyrene 4,5-Oxides Labeled with Carbon-13: Electronic Effects in the NIH Shift

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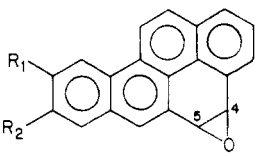
The synthesis of 9-methoxy-4,5-dihydrobenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide and -*5*-^{13}C 4,5-oxide and of 8-methoxy-4,5-dihydrobenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide is reported. The compounds were synthesized in yields of 15% each from unlabeled precursors. ^{13}C NMR analysis of the conversion of the 4,5-oxides to 4-phenols and 5-phenols (NIH shift) revealed a very strong electronic effect of a 9-methoxy substituent, which gave only the 4-phenol, and a significant but weaker effect of an 8-methoxy substituent, which gave both phenols with the 5-phenol predominating.

The environmental carcinogen benzo[*a*]pyrene undergoes microsomal oxidation to form a variety of phenols, quinones, diols, and epoxides.[1] Only a few of these have been shown to bind to DNA, considered by many to be a necessary step in tumor formation.[2] One DNA binding metabolite is 9-hydroxybenzo[*a*]pyrene 4,5-oxide (**1**), which, like the known carcinogenic metabolite 7,8-dihydroxybenzo[*a*]pyrene 9,10-oxide, also causes DNA strand breaks in vitro.[3,4] Despite this similarity, **1** appears to be noncarcinogenic. Why these two compounds show different activities remains an intriguing question whose answer may help elucidate the mechanism of benzo[*a*]pyrene-induced cellular transformation.

The in vitro activity of **1** is also markedly different from that of benzo[*a*]pyrene 4,5-oxide (**2**), which does not bind to DNA,[4] and suggests that the 9-hydroxyl group plays a significant role. Though these differences have been observed in enzymatic systems where the hydroxyl group may affect enzyme binding, another possibility is that the 8-hydroxyl group exerts a through-bond influence within the ring system on epoxide opening.

Using ^{13}C-labeled substrates, Hylarides et al. found that **2** reacted with a variety of nucleophiles, showing no preference for attack at either the 4- or 5-position of the epoxide.[5,6] Likewise, the acid-catalyzed isomerization of **2** to phenol (the NIH shift) produced equal amounts of 4- and 5-phenols. This general lack of regioselectivity was readily determined by the ^{13}C NMR spectra of the crude product mixtures after workup.

As a result of the above study and to compare **1** and **2** under identical experimental conditions, we embarked on the preparation of ^{13}C-labeled 9-hydroxybenzo[*a*]pyrene 4,5-oxide (**1**). Though efforts to synthesize **1** as the free phenol have been unsuccessful, the methyl ether derivative 9-methoxybenzo[*a*]pyrene 4,5-oxide (**3**) has been reported recently[7] and shown to bind to DNA in a manner similar to **1**.[8] The synthesis of **3**, reported by Harvey and Cortez, is not amenable to the incorporation of carbon-13 labels in the epoxide positions. Herein we describe the synthesis of 9-methoxybenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide (**3a**-*4*-^{13}C) and -*5*-^{13}C (**3a**-*5*-^{13}C) and 8-methoxybenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide (**3b**-*4*-^{13}C). These substrates were studied under NIH shift conditions, the results of which are presented below.



1, R_1=OH, R_2=H
2, R_1=R_2=H
3a, R_1=OMe, R_2=H
3b, R_1=H, R_2=OMe

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