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PALLADIUM-CATALYZED ARYLATION OF FURAN, THIOPHENE, BENZO[b]FURAN AND BENZO[b]THIOPHENE

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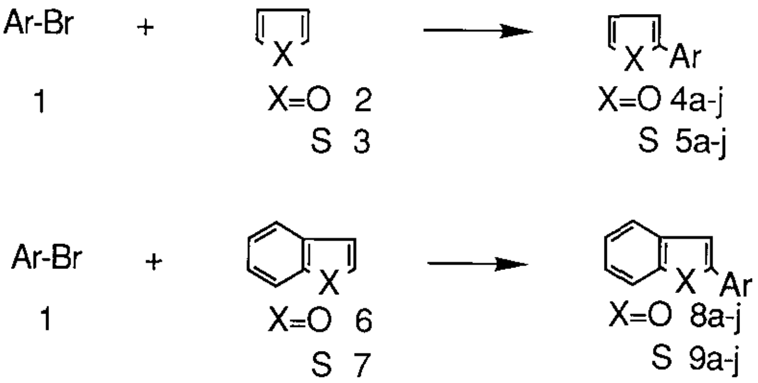
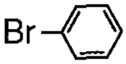
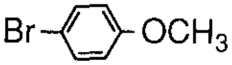
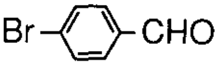
Abstruct - Treatment of π-electron sufficient aromatic heterocycles such as furan, thiophene, benzo[b]furan and benzo[b]thiophene with aryl bromides in the presence of tetrakis(triphenylphosphine)palladium gave the corresponding 2-aryl aromatic heterocycles.

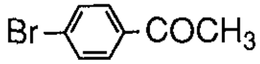
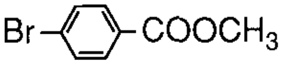
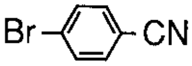
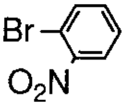
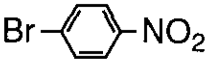
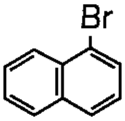
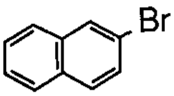
Aryl-substituted aromatic heterocycles are of interest as naturally occurring compounds such as pterofuran,[1] 2-phenylpropynylthiophene,[2] neolignans.[3,4] Palladium-catalyzed cross-coupling reactions between organometallic reagents and organic halides are now very efficient means for carbon-carbon bond formation.[5] A few reports are available on the arylation of aromatic heterocycles, such as that of benzo[b]furan <u>via</u> organopalladium intermediates[6] and reactions of aromatic heterocycles with arenes in the presence of palladium (II) acetate.[7] Cross-coupling reactions of 2-lithiofuran, 2-furylzinc chloride[8] and thienylmagnesium bromide[9] with aryl halides have also been reported. In all these cases, the conversion of aromatic heterocycles to the corresponding organometallic reagents is required. It was previously found that indoles react with 2-chloropyrazines directly to give 2-(2-indolyl)pyrazines[10,11] without conversion of indoles to the corresponding organometallic reagents. In the present study, palladium-catalyzed direct cross-coupling reactions of aryl bromides were conducted with π-electron sufficient aromatic heterocycles such as furan, thiophene, benzo[b]furan and benzo[b]thiophene. In the presence of tetrakis(triphenylphosphine)palladium, a mixture of aryl bromides, excess aromatic heterocycles such as furan and thiophene, potassium acetate and N,N-dimetylacetamide (DMA) was heated at 150°C in a sealed tube, in consideration of the volatility of furan and thiophene, and under an atmosphere of argon. Benzo[b]furan or benzo[b]thiophene was used as the reaction substrate in a stoichiometric quantity followed by refluxing the reaction mixture under argon. The results are summarized in Table 1.

Table 1. Palladium-Catalyzed Cross-Coupling Reactions of Aryl Bromides with Furan, Thiophene, Benzo[b]furan and Benzo[b]thiophene



Ar-Br (1)	Product (Yield %)	mp (°C) or bp (°C/torr)	
	4a (--)[a]	--	
	5a (69)	34-35	[34-35][12]
	8a (23)	118-119	[120.8-121.2][13]
	9a (35)	170-172	[175.5-176.0][12]
	4b (--)[a]	--	
	5b (46)	106-107	[107-108][14]
	8b (12)	153-154	[152][15]
	9b (11)	200-202	[193-194][16]
	4c (40)	41-42	
	5c (63)	67-68	
	8c (--)[a]	--	
	9c (40)	170-174	

(continued)

	4d (48)	102-103	
	5d (47)	117-119	
	8d (20)	169-170	
	9d (64)	210-212	
	4e (52)	120-121	[121-122][17]
	5e (38)	139-140	[141-142][14]
	8e (25)	172-174	[176.5-177][18]
	9e (31)	221-223	
	4f (33)	61-63	
	5f (52)	84-85	
	8f (--)[a]	--	
	9f (36)	87-88	
	4g (60)	125-130/3	[121-126/2][19]
	5g (53)	118-120/1[b]	[51-52][20]
	8g (50)	160-170/4	
	9g (65)	85-86.5	[86-88][21]
	4h (59)	135.5-136.5	[134-135][22]
	5h (66)	134-135	[138][14]
	8h (20)	181-182	[182][23]
	9h (55)	215-217	[214-215][24]
	4i (18)	114-117/0.2	[90-91/0.02][22]
	5i (72)	118-121/0.2	[126-127/0.25][25]
	8i (--)[a]	--	
	9i (62)	105	[120-121][26]
	4j (--)[a]	--	
	5j (55)	102-103	[104-105][25]
	8j (--)[a]	--	
	9j (32)	209-211	[213-214][27]

a: many products

b: Although it has been reported that compound 8g is crystalline, we obtained this compound as an oil, which was pure enough for elemental analysis.

The reactions of furan with bromobenzene, 4-bromoanisole and 2-bromonaphthalene gave many products that could not be separated, as also noted on reacting benzo[b]furan with 4-bromobenzaldehyde, 4-bromobenzonitrile, 1- and 2-bromonaphthalenes. On the whole, the arylation of thiophene and benzo[b]thiophene gave better results than that of furan and benzo[b]furan. Structural determination was made on the basis of a comparison with physical data of known compounds(See Table 1). The 400 MHz H^1-nmr spectra of compounds 8a and 9a were identical with those of compounds, 2-phenylbenzo[b]furan and 2-phenylbenzo[b]thiphene, respectively, synthesized *via* an alternative route.[28,29] Consequently, arylation was conducted to occur at the 2-position of π-electron sufficient aromatic heterocycles such as furan, thiophene, benzo[b]furan and benzo[b]thiophene.

The reactions may be summarized as follows:

1) Cross-coupling reactions of aryl bromides with electron-withdrawing groups proceed in moderate yields.
2) There occurs a simple and regioselective arylation of π-sufficient aromatic heterocycles such as furan, thiophene, benzo[b]furan and benzo[b]thiophene.

At the present, this chemistry is also being extended to the synthesis of natural products.

EXPERIMENTAL

No correction was made for any melting points. ^{1}H-Nmr spectral data of new compounds were obtained by either a Varian EM-390 using TMS as the internal standard or a Brucker AM-400. The following instruments were used to acquire other spectral data. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80B spectrometer. Column chromatography was carried out under medium pressure with a UVILOG 5-IIIa as the uv detector (Oyo-Bunko Kiki Co. LTD. Tokyo), and Kiesel Gel 60 (Merk. AG., Darmstadt) as the packing material.

General Procedure for Preparation of 2-Arylfurans (3a-j) and 2-Arylthiophenes (4a-j)

A mixture of aryl bromides (2 mmol), furan (1 ml, ca. 13.8 mmol) or thiophene (1 ml, ca. 12 mmol), CH_3COOK (294 mg, 3 mmol), $Pd(PPh_3)_4$ (116 mg, 5 mol%), and DMA (5 ml) in a sealed tube was heated at 150°C for 12 h. The solvent was evaporated *in vacuo* and the residue was triturated with H_2O (20 ml) and extracted with CH_2Cl_2 (15 ml x 3). The organic phase was dried over Na_2SO_4, filterd and concentrated. The crude product was purified by medium pressure liquid chromatography using hexane-CH_2Cl_2 or hexane-Et_2O.

2-(p-Formylphenyl)furan(4c): pale yellow prisms; mp 41-42 °C (n-hexane); ms: m/z 172 (M^+); ^{1}H-nmr: δ 6.53 (1H, dd, J=3.4 and 1.8 Hz, furan H), 6.83 (1H, d, J = 3.4 Hz, furan H), 7.55 (1H, d, J = 1.8 Hz, furan H), 7.78 (4H, m, benzene H), 9.98 (1H, s, CHO) ppm; ir (film): 1705 cm^{-1} (CHO); *Anal*. Calcd for $C_{11}H_8O_2$: c, 76.73; h, 4.68. Found: C, 76.89; H, 4.67.

2-(p-Acetylphenyl)furan(4d): colorless needles; mp 102-103 °C (n-hexane); ms: m/z 186 (M^+), 171 (M^+-CH_3); ^{1}H-nmr: δ 2.57 (3H, s, $COCH_3$), 6.48 (1H, dd, J = 1.5 and 3.5 Hz, furan H), 6.77 (1H, dd, J = 0.8 and 3.5 Hz, furan H), 7.47 (1H, dd, J = 0.8 and 1.5 Hz, furan H), 7.70 (2H, d, J = 7.0 Hz, benzene H), 7.93 (2H, d, J = 7.0 Hz, benzene H) ppm; ir (KBr); 1705 cm^{-1} (C=O); High-resolution ms calcd for $C_{12}H_{10}O_2$: 186.0657. Found: 186.0668.

2-(p-Cyanophenyl)furan(4f): pale yellow crystals; mp 61-63 °C (n-hexane); ms: m/z 169 (M^+); ^{1}H-nmr: δ 6.50 (1H, dd, J = 1.5 and 3.0 Hz, furan H), 6.77 (1H, dd, J = 1.0 and 3.0 Hz, furan H), 7.47 (1H, dd, J = 1.0 and 1.5 Hz, furan H), 7.57 (2H, d, J = 7.5 Hz, benzene H), 7.72 (2H, d, J = 7.5 Hz, benzene H) ppm; ir (KBr): 2210 cm^{-1} (CN); *Anal*. Calcd for $C_{11}H_7NO$: C, 78.08; H, 4.17; N, 8.28. Found: C, 78.23; H, 4.19; N, 8.28.

2-(p-Formylphenyl)thiophene(5c): colorless needles; mp 67-68 °C (i-PrOH); ms: m/z 188 (M^+); ^{1}H-nmr: δ 7.03 (1H, dd, J = 1.5 and 5.5 Hz, thiophene H), 7.32 (2H, m, thiophene H), 7.67 (2H, d, J = 15 Hz, benzene H), 7.77 (2H, d, J = 15 Hz, benzene H), 9.95 (1H, s, CHO) ppm; ir (KBr): 1690 cm^{-1} (CHO); *Anal*. Calcd for $C_{11}H_8OS$: C, 70.17; H, 4.28. Found: C, 70.47; H, 4.31.

2-(p-Acetylphenyl)thiophene(5d): colorless needles; mp 112-114 °C (i-PrOH); ms: 202 (M^+), 187 (M^+-CH_3); ^{1}H-nmr: δ 7.07 (1H, dd, J = 3.0 and 6.0 Hz, thiophene H), 7.33 (2H, m, thiophene H), 7.65 (2H, d, J = 9.0 Hz, benzene H), 7.93 (2H, d, J = 9.0 Hz, benzene H) ppm; ir (KBr): 1675 cm^{-1}(C=O); High-resolution ms Calcd for $C_{12}H_{10}OS$: 202.0445. Found: 202.0448.

2-(p-Cyanophenyl)thiophene(5f): colorless needles; mp 84-85 °C (n-hexane); ms: 185 (M^+); ^{1}H-nmr: δ 7.13 (1H, dd, J = 3.5 and 4.5 Hz, thiophene H), 7.40 (2H, m, thiophene H), 7.68 (4H, s, benzene H) ppm; ir (KBr): 2230 cm^{-1} (CN); Anal. Calcd for $C_{11}H_7NS$: C, 71.32; H, 3.81; N, 7.56. Found: C, 71.49; H, 3.80; N, 7.74.

2-(o-Nitrophenyl)thiophene(5g): pale yelow oil; bp 118-120 °C/1 torr (oil bath temp.); ms: m/z 205 (M^+); ^{1}H-nmr: δ 7.07-7.22 (2H, m), 7.30-7.70 (4H, m), 7.73-7.81 (1H, m) ppm; ir (film): 1530, 1355 cm^{-1} (NO_2); Anal. Calcd for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.83. Found: C, 58.22; H, 3.57; N, 6.78.

General Procedure for Preparation of 2-Aryl Benzo[b]furans (8a-j) and Benzo[b]thiophene (9a-j)

A mixture of aryl bromides (2 mmol), benzo[b]furan (283 mg, 2.4 mmol) or benzo[b]thiophene (295 mg, 2.4 mmol), CH_3COOK (294 mg, 3 mmol), $Pd(PPh_3)_4$ (116 mg, 5 mol%), and DMA (4 ml) was refluxed under argon atmosphere until the aryl bromides could no longer be detected on a tlc plate. The reaction mixture was worked up according to the general procedure for the synthesis of 4a-j and 5a-j.

2-(p-Acetylphenyl)benzo[b]furan(8d): colorless scales; mp 169-170 °C (i-PrOH); ms: m/z 236 (M^+), 221 (M^+-CH_3); ^{1}H-nmr: δ 2.64 (3H, s, $COCH_3$), 7.17 (1H,d, J = 0.81 Hz, benzo[b]furan 3-H), 7.26 (1H, td, J = 7.6 and 1.0 Hz, benzo[b]furan H), 7.34 (1H, td, J = 7.2 and 1.3 Hz, benzo[b]furan H), 7.55 (1H, dd, J = 8.2 and 0.8 Hz, benzo[b]furan H), 7.63 (1H, dd, J = 7.4 and 0.5 Hz, benzo[b]furan H), 7.95 (2H, d, J = 8.6 Hz, benzene H), 8.04 (2H, d, J = 8.7 Hz, benzene H) ppm; ir (KBr): 1725 cm^{-1} (C=O); Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.27; H, 5.08.

2-(o-Nitrophenyl)benzo[b]furan(8g): pale yellow viscous oil, bp 160-170 °C/4 torr (oil bath temp.); ms: m/z 239 (M^+); ^{1}H-nmr: δ 7.02 (1H, d, J = 0.78 Hz, benzo[b]furan 3-H), 7.23-7.99 (8H, m) ppm; ir (film): 1555, 1380 cm^{-1} (NO_2); High-resolution ms Calcd for $C_{14}H_9NO_3$: 239.0581. Found: 239.0558.

2-(p-Formylphenyl)benzo[b]furan(9c): pale yellow crystals; mp 170-174 °C (i-propyl ether); ms: m/z 238 (M^+); ^{1}H-nmr: δ 7.21 (1H, d, 0.8 Hz, benzo[b]furan 3-H), 7.27 (1H, td, J = 7.7 and 0.9 Hz, benzo[b]furan H), 7.35 (1H, td, J = 7.7 and 1.3 Hz, benzo[b]furan H), 7.56 (1H, dd, J = 8.6 and 0.7 Hz, benzo[b]furan

H), 7.63 (1H, dd, J = 7.9 and 0.5 Hz, benzo[b]furan H), 7.96 (2H, d, J = 8.6 Hz, benzene H), 8.03 (2H, d, J = 8.4 Hz, benzene H), 10.05 (1H, s, CHO) ppm; ir (KBr): 1700 cm^{-1} (C=O); Anal. Calcd for $C_{15}H_{10}OS$: C, 75.60; H, 4.23. Found: C, 75.71; H, 4.24.

2-(p-Acetylphenyl)benzo[b]thiophene(9d): colorless scales; mp 210-212 °C (i-PrOH); ms: m/z 252 (M^+), 237 (M^+-CH_3); ^{1}H-nmr: δ 2.46 (3H, s, $COCH_3$), 7.37 (2H, m, benzo[b]thiophene H), 7.67 (1H, s, benzo[b]thiophene H), 7.79 - 7.86 (2H, m, benzo[b]thiophene H), 7.80 (2H, d, J = 8.6 Hz, benzene H), 8.02 (2H, d, J = 8.5 Hz, benzene H) ppm; ir (KBr): 1690 cm^{-1} (C=O); Anal. Calcd for $C_{16}H_{12}OS$: C, 76.16; H, 4.79. Found: C, 76.12; H, 4.67.

2-(p-Methoxycarbonylphenyl)benzo[b]thiophene(9e): colorless scales; mp 221-223 °C (i-PrOH); ms: m/z 268 (M^+); ^{1}H-nmr: δ 3.95 (3H, s, $COOCH_3$), 7.36 (2H, m, benzo[b]thiophene H), 7.65 (1H, s, benzo[b]thiophene 3-H), 7.54-7.86 (2H, m, benzo[b]thiophene H), 7.78 (2H, d, J = 8.6 Hz, benzene H), 8.60 (2H, d, J = 8.6 Hz, benzene H) ppm; ir (KBr): 1720 cm^{-1} (C=O); Anal. Calcd for $C_{10}H_{12}O_2S$: C, 71.62; H, 4.51. Found: C, 71.52; H, 4.58.

2-(p-Cyaophenyl)benzo[b]thiophene(9f): colorless crystals, mp 87-88 °C (i-PrOH); ms: m/z 235 (M^+); ^{1}H-nmr: 7.38 (2H, m, benzo[b]thiophene H), 7.66 (1H, s, benzo[b]thiophene H), 7.70 (2H, d, J = 8.4 Hz, benzene H), 7.80 (2H, d, J = 8.5 Hz, benzene H), 7.80 - 7.86 (2H, m, benzo[b]thiophene H) ppm; ir (KBr): 2240 cm^{-1} (CN); Anal. Calcd for $C_{15}H_9NS$: C, 76.56; H, 3.86; N, 5.95. Found: C, 76.85; H, 3.75; N, 5.90.

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