Cross-Coupling Reactions for the Preparation of 2-Arylfurans, 2-Benzylfuran and 2-Cinnamylfuran

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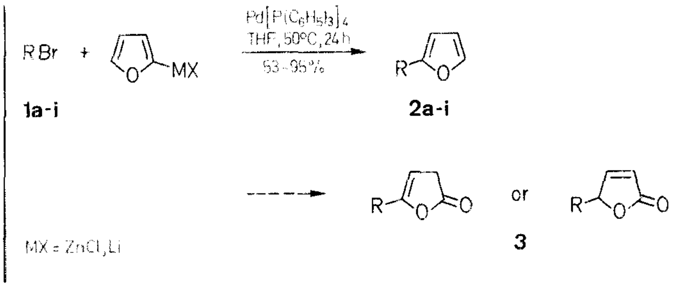
Pd[0] catalysed coupling between organyl bromides and either 2-lithofuran or 2-furylzinc chloride are described. Arylation by a wide variety of aromatic bromides can be carried out in high yields and on a large scale. Benzylation and cinnamylation are also successful.

Due to our interest in butenolides,[1] particularly those related to the fadyenolides[2] and the piperolides,[3] as well as our requirement for synthons for lignan synthesis,[4] we have been searching for methods for the production of 2-organylfurans **2** and their conversion to 5-organylbutenolides **3**.



1, 2	R	1, 2	R
a	C_6H_5	**f**	$3,4\text{-}(CH_3O)_2C_6H_3$
b	$4\text{-}CH_3C_6H_4$	**g**	$4\text{-}O_2NC_6H_4$
c	$3\text{-}CH_3C_6H_4$	**h**	$C_6H_5CH_2$
d	$4\text{-}CH_3OC_6H_4$	**i**	$C_6H_5CH{=}CHCH_2$
e	$3\text{-}CH_3OC_6H_4$		

In particular, we were interested in the synthesis and reactions of 2-aryl, 2-benzyl and 2-cinnamylfurans.

After searching the literature and trying various methods,[5] we were unable to find a satisfactory, high-yield synthesis of 2-arylfurans that was applicable to the large scale synthesis of a wide range of 2-arylfurans as well as to the production of 2-benzyl- and 2-cinnamylfurans. This paper describes such a general method, which should find wide application.

Transition metal catalysed cross coupling of organic halides with organometallics are well known.[6] Aromatic,[7] benzylic[7] and alkenyl[8] halides participate in this type of reaction, which may be catalysed by nickel, palladium[6,7,8] or ion[8a] salts. The organometallic may be a Grignard reagent, an organozinc derivative[6,7,8] or may be derived from the transition metal.[7c] The coupling of heteroatomatic nuclei is less well known, but the selective coupling of aryl halides to dibromothiophenes using $NiCl_2$ $(dppp)_2$ [where dppp $= (C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$] has been well investigated and used for lignan synthesis.[9] The reaction (using $PdCl_2$ + dppp) has been extended to the selective crossed coupling of dihalopyridines and dibromothiophenes with a variety of other nuclei, including the sole example of such a reaction with a furan moiety.[10]

Table 1. The Preparation of 2-Organylfurans

Exp. No.	MX in 2-Furyl Deriv.	Halide	Catalyst[a]	Product	Yield[b,c] %
1	Li	**1b**	None	**2b**	0
2	ZnCl	**1b**	None	**2b**	0
3	Li	**1b**	$Pd[PC_6H_5)_3]_4$	**2b**	0
4	Li	**1b**	$Ni[P(C_6H_5)_3)_2Cl_2$	**2b**	0
5	ZnCl	**1b**	$Ni[P(C_6H_5)_3]_2Cl_2$	**2b**	19
6	ZnCl	**1b**	$Pd[P(C_6H_5)_3]_4$	**2b**	95
7	ZnCl	**1a**	$Pd[P(C_6H_5)_3]_4$	**2a**	81
8	ZnCl	**1c**	$Pd[P(C_5H_5)_3]_4$	**2c**	91
9	ZnCl	**1d**	$Pd[P(C_6H_5)_3]_4$	**2d**	69
10	ZnCl	**1e**	$Pd[P(C_6H_5)_3]_4$	**2e**	71
11	ZnCl	**1f**	$Pd[P(C_6H_5)_3]_4$	**2f**	76
12	ZnCl	**1g**	$Pd[P(C_6H_5)_3]_4$	**2g**	77
13[d]	ZnCl	**4**	$Pd[P(C_6H_5)_3]_4$	**5**	76
14	Li	**1h**	$Pd[P(C_6H_5)_3]_4$	**2h**	76
15	Li	**1i**	$Pd[P(C_6H_5)_3]_4$	**2i**	53[e,f]

[a] 0.5 mmol of catalyst to 150 mmol of bromo-compound.
[b] Yield of purified product.
[c] Yield based on bromo-compound.
[d] 3 equiv. of furan used.
[e] 15% of $(C_6H_5CH{:}CHCH_2)_2$ isolated.
[f] Reaction at room temperature for 18 h.

Table 2. Physical and Spectral Data for 2-Organylfurans Prepared.

Product	m.p. (°C) or b.p. (°C)/torr[a]	Molecular Formula[b] or Lit. Data	UV (MeOH)[c] λ_{max} (log ε)	^{1}H-NMR (CDCl$_3$)[d] δ (ppm)	^{13}C-NMR (CDCl$_3$)[d]				MS (70 eV)[e] m/e (%)	HRMS[f] Found (Calc.)
					C-5	C-4	C-3	C-2		
2a	74–76/2.5	b.p. 94°C/ 10 torr[5a,11]	208 (4.14), 279 (4.30)	6.42 (1H, q, J = 2 Hz); 6.60 (1H, d, J = 3 Hz); 7.2 (2H, q, J = 1 Hz); 7.0–7.4 (3H, m); 7.31 (1H, d, J = 2 Hz)	142	111.6	105	154	144 (100) 89 (8) 115 (81) 65 (3) 116 (20) 77 (2) 145 (11) 105 (2)	–
2b	72–75/2	b.p. 56°C/ 0.5 torr[5a]	210 (4.13), 278 (4.29)	2.25 (3H, s); 6.35 (1H, q, J = 2 Hz); 6.50 (1H, d, J = 3 Hz); 7.08 (2H, d, J = 8 Hz); 7.35 (1H, d, J = 2 Hz); 7.51 (2H, d, J = 8 Hz)	141.6	111.6	104.3	154.3	158 (100) 134 (10) 129 (39) 91 (8) 115 (18) 78 (4) 159 (12) 104 (2)	–
2c	46/0.05	$C_{11}H_{10}O$ (158.2)	210 (3.8) 280 (3.9)	2.30 (3H, s); 6.35 (1H, q, J = 2 Hz); 6.55 (1H, d, J = 3 Hz); 6.9–7.6 (5H, m)	141.9	111.6	104.8	154.3	158 (100) 51 (27) 129 (80) 39 (27) 115 (63) 63 (20) 128 (40) 77 (19)	158.0733 (158.0732)
2d	52–53 (MeOH)	m.p. 52–53°C[5a]	208 (3.71), 284 (4.03)	3.82 (3H, s); 6.44 (1H, q, J = 2 Hz); 6.51 (1H, d, J = 3 Hz); 6.94 (2H, d, J = 9 Hz); 7.42 (1H, d, J = 2 Hz); 7.63 (2H, d, J = 9 Hz)	141.4	111.5	103.5	154.1	174 (100) 102 (14) 159 (85) 103 (13) 131 (33) 175 (13) 77 (26) 145 (12)	–
2e	48/0.1	$C_{11}H_{10}O_2$ (174.2)	218 (3.74), 275 (3.81)	3.7 (3H, s); 6.35 (1H, q, J = 2 Hz); 6.55 (1H, d, J = 3 Hz); 6.70 (1H, m); 7.2 (3H, m); 7.35 (1H, d, J = 2 Hz)	142.0	109.3	105.3	153.9	174 (100) 77 (16) 145 (26) 103 (15) 131 (21) 102 (13) 115 (17) 175 (11)	174.0681 (174.0681)
2f	65–66 (MeOH)	$C_{12}H_{12}O_3$ (204.2)	208 (3.84), 285 (4.01)	3.88 (3H, s); 3.92 (3H, s); 6.4 (1H, q, J = 2 Hz); 6.48 (1H, d, J = 3 Hz); 6.82 (1H, d, J = 9 Hz); 7.16 (1H, s); 7.20 (1H, d, J = 9 Hz); 7.38 (1H, d, J = 2 Hz)	141.6	108.8	103.9	154.4	204 (100) 51 (13) 189 (35) 205 (13) 161 (19) 143 (11) 63 (14) 133 (11)	204.0762 (204.0786)
2g	122–124 (sublimed)	$C_{10}H_7NO_3$[g] (189.2)	358 (3.68)	6.6 (1H, q, J = 2 Hz); 7.08 (1H, d, J = 3 Hz); 7.68 (1H, d, J = 2 Hz); 7.88 (2H, d, J = 9 Hz); 8.26 (2H, d, J = 9 Hz)[h]	145.5	113.4	110.3	152.6[h]	189 (100) 63 (20) 115 (75) 131 (17) 89 (23) 143 (16) 159 (20) 39 (14)	189.0428 (189.0428)
5	148–150 (sublimed)	$C_{14}H_{10}O_2$ (210.2)	338 (4.02)	6.4 (1H, q, J = 2 Hz); 6.6 (2H, d, J = 3 Hz); 7.4 (2H, d, J = 2 Hz); 7.6 (4H, s)[h]	142.2	111.1	105.2	154.1[h]	210 (100) 105 (10) 181 (42) 115 (9) 153 (25) 76 (9) 152 (22)	210.0681 (210.0681)
2h	95/0.5	b.p. 90°C/ 8 torr[12]	226 (3.62)	3.9 (2H, s); 5.95 (1H, m); 6.20 (1H, m); 7.19 (5H, s); 7.25 (1H, m)	141.4	110.2	106.2	154.6	158 (100) 91 (16) 128 (77) 81 (11) 130 (28) 77 (9) 115 (23) 78 (8)	–
2i	92/0.15	b.p. 82°C/ 0.2 torr[12]	218 (4.03), 253 (4.08)	3.5 (2H, d, J = 6 Hz); 6.0–6.5 (4H, m); 7.1–7.3 (6H, m)	141.3	110.3	105.7	153.9	184 (100) 117 (30) 155 (45) 141 (26) 115 (33) 128 (25) 91 (32) 153 (21)	–

[a] B.p. are of bath temp. using Kugelrohr distillation.

[b] Satisfactory microanalyses obtained: C ±0.4, H ±0.3; and for **2g**: N ±0.2; except for **2c**: C −0.6.

[c] Recorded on a Unicam SP1805 spectrophotometer.

[d] Recorded on a Varian HA100 (1H) and on a Varian XL100 (^{13}C)spectrometers.

[e] Eight most abundant peaks. Recorded on a AEI MS9 spectrometer.

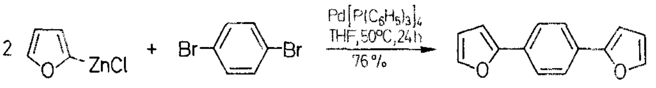
[f] Recorded on a AEI MS9 spectrometer at 70 eV.

[g] Known compound.[11] Analysis obtained due to discrepancy with literature m.p. of 134–135°C.

[h] Run in $(CD_3)_2CO$.

We decided to investigate the cross-coupling of organyl halides with 2-lithiofuran and 2-furylzinc chloride in some depth. The results are presented in Table 1. From experiments 1 to 6 it is clear that a combination of 2-furylzinc chloride with tetrakistriphenylphosphine palladium must be used to obtain a good yield of 2-(4′-methylphenyl)furan. Importantly for large scale preparations, surprisingly small quantities of catalyst are required as compared with those used for thiophene couplings. The optimal conditions found were then applied to a variety of aryl halides.

Experiments 6 and 8 show that metal exchange with an aromatic methyl group does not occur, whilst experiments 9–12 show that both electron donating and withdrawing groups are tolerated by the reaction. Interestingly, we were able to use 1,4-dibromobenzene (**4**) to give the doubly coupled product **5**, which could presumably be further coupled at will.



4 **5**

2-Lithiofuran could be used directly for the production of 2-benzyl- and 2-cinnamylfurans **2h** and **2i** (experiments 14 and 15). The yield of 2-cinnamylfuran was lowered by the production of a dimeric product, assigned structure $(C_6H_5CH{=}CHCH_2)_2$, which had to be separeted by careful, double distillation.

All of these 2-substituted furans are subject to rapid oxidation and elemental analyses must be performed immediately after purification. The physical data and analyses for the products are given in Table 2. The assignment of signals in the ^{13}C-NMR of 2-phenylfuran was accomplished by specific decoupling experiments and the results extrapolated to the other furans. The successful conversions of compounds **2** *via* furylboronates into butenolides **3** will be published separately.

2-Phenylfuran (2a); Typical Procedure:

A hexane solution of *n*-butyllithium (125 ml, 1.2 molar, 150 mmols) is added from a pressure equalising funnel to a stirred solution of dry furan (10.2 g, 150 mmol) in dry tetrahydrofuran (100 ml) at 0°C under argon. The mixture is allowed to stir for 3 h at 0°C and is then added, *via* a double-ended needle, to a stirred solution of dry zinc chloride (20.1 g, 150 mmol) in tetrahydrofuran (100 ml) at room temperature. The mixture is stirred for a further hour.

$Pd[P(C_6H_5)_3]_4$ (0.57 g, 0.5 mmol) is weighed into a 1 litre round-bottomed flask under argon and dissolved in tetrahydrofuran (250 ml). Redistilled bromobenzene (15.7 g, 100 mmol) is added *via* a syringe to the stirred catalyst solution followed by the solution of 2-furylzinc chloride. The temperature is then slowly raised to 50°C and the reaction stirred at that temperature for 24 h. Dilute hydrochloric acid (100 ml, 0.1 molar) is added to the cooled reaction mixture followed by ether (100 ml). The aqueous layer is separated and washed with ether (2 × 100 ml). The combined organic phase is washed with aqueous sodium hydrogencarbonate (100 ml), water (3 × 100 ml), dried with magnesium sulfate, filtered and concentrated. Distillation of the residue gives *2-phenylfuran*; yield: 11.62 g (81 %); b.p. 74–76°C/2.5 torr (Lit.[5a] b.p. 94°C/10 torr).

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