A Convenient Synthesis of Polysubstituted Phenylphenols from Substituted Anilines

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2′ and 4′-Substituted arylfurans react with DMAD in the presence of Lewis acid to afford Diels–Alder adducts with good yields; a subsequent spontaneous or an acid-induced β-elimination leads to polysubstituted phenylphenols.

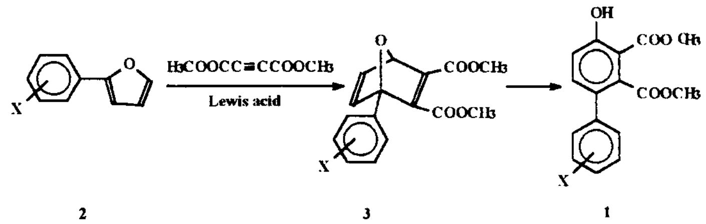
Due to the interest of our group in photochromic compounds,[1,2] such as chromenes, spiropyrans and spirooxazines and particularly polysubstituted ones, we required a general preparation of 4-aryl-2,3-dicarboxyphenols derivatives **1** for further elaboration. There are numerous methods reported in the literature for the preparation of biaryls.[3] Classical examples include Gomberg–Bachmann–Hey[4] and Ulmann[5] reactions or Karasch's coupling of Grignard derived aryl radicals.[6] Recently, a number of newer methods involving organometallic reagents[7] or phase transfer catalytic G.B.H. reactions[8] have become available, some of which afford good to excellent yields. However few results are reported for reactions leading to polysubstituted phenylphenols.

We wish to report here a general approach to the synthesis of **1**; our strategy was to start with 2-arylfurans and to perform the coupling with dimethyl acetylenedicarboxylate[9] (DMAD), with the subsequent opening of **3** leading to the biaryls **1**.

Table 1. Preparation of Arylfurans

Ar	Yield[a] (%)	mp (°C)	Ar	Yield[a] (%)	mp (°C)
-Ph	36	oil	2-naphthyl	28	oil
-Ph	15[b]		2-naphthyl	3[b]	
-Ph	6[c]		4-$NO_2C_6H_4$	29	134[12]
2-ClC_6H_4	40	oil	4-$NO_2C_6H_4$	28[d]	
4-ClC_6H_4	23	74[12]	4-$CH_3COC_6H_4$	29	92
4-BrC_6H_4	20	84[12]	4-$CH_3OC_6H_4$	45	53
4-PhC_6H_4	36	162			

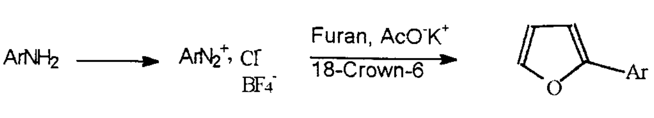
[a] All yields refer to isolated purified products starting from substituted aniline.
[b] Cadogan's conditions[11] (isopentyl nitrite).
[c] Johnson's conditions[12] ($NaNO_2/H_2O$).
[d] Catalyst dibenzo-18-crown-6.



2a X = H 2e X = 4-Ph
b 2-Cl g 4-NO2
c 4-Cl h 4-CH3CO
d 4-Br i 4-CH3O
f PhX = 2-naphthyl

Scheme 1

We first synthesised a wide variety of arylfurans **2** starting from available arylamines, according to the process shown in the equation:



2

The reaction was performed using Korzeniowski's conditions[8,10] unless otherwise specified.

Our results are reported in Table 1.

The Diels–Alder cycloaddition between furan and some dienophiles can be greatly accelerated by addition of a Lewis acid[13] or by using Breslow and Rideout's conditions[14] (heterogeneous sonicated system). We used a Lewis acid catalysis and performed the cycloaddition reaction in the presence of ZnI_2. The reaction of furan with DMAD involves the initial formation of a monoadduct **3**. Further addition of furan[13a] upon the substituted double bond, present in **3**, did not occur under our conditions with our substrates.

Under our conditions, some of the initial adducts **3** are directly converted to the target compounds **1**.

The results are reported in Table 2.

Table 2. Synthesis of Adducts **3** and/or Substituted Phenylphenols

Entry	Ar	Yield[a] (%)	3	1	Entry	Ar	Yield[a] (%)	3	1
1	-Ph	71	0	100	6	4-PhC_6H_4	47[b]	0	100
2	2-ClC_6H_4	67	100	0	7	2-naphthyl	72	3	97
3	4-ClC_6H_4	69	58	42	8	4-$NO_2C_6H_4$	48	100	0
4	4-BrC_6H_4	74	89	11	9	4-$CH_3COC_6H_4$	71	100	0
5	4-PhC_6H_4	81	0	100	10	4-$CH_3OC_6H_4$	51	0	100

[a] All yields refer to isolated purified products.
[b] Catalyst Et_2AlCl.

Table 3. Characterization of Cycloadducts **3** and Polysubstituted Phenylphenols **1**

Product	mp (°C)	Molecular Formula[a]	^{1}H NMR ($CDCl_3$), δ (ppm), *J* (Hz)	^{13}C NMR ($CDCl_3$), δ (ppm)
1a	92	$C_{16}H_{14}O_5$	3.54 (s, 3 H), 3.85 (s, 3 H), 7.04 (d, 1 H, *J* = 8.6), 7.21–7.30 (m, 5 H), 7.37 (d, 1 H, *J* = 8.6), 10.90 (s, 1 H)	51.99 (q), 52.90 (q), 109.01 (s), 118.92 (d), 127.42 (d), 128.11 (d), 128.66 (d), 131.65 (s), 134.34 (s), 136.9 (d), 139.06 (s), 160.75 (s), 168.68 (s), 169.32 (s)
3b	80	$C_{16}H_{13}O_5Cl$	3.59 (s, 3 H), 3.70 (s, 3 H), 5.68 (d, 1 H, d, *J* = 1.9), 7.18–7.30 (m, 4 H), 7.51–7.61 (m, 2 H)	52.24 (q), 52.30 (q), 82.60 (d), 96.66 (s), 127.16 (d), 128.32 (d), 129.87 (d), 129.92 (d), 131.99 (s), 144.25 (d), 144.33 (d), 149.22 (s), 157.08 (s), 162.65 (s), 164.09 (s)
1b	81	$C_{16}H_{13}O_5Cl$	3.48 (s, 3 H), 3.82 (s, 3 H), 5.72 (d, 1 H, *J* = 1.9), 7.04 (d, 1 H, *J* = 8.6), 7.20–7.55 (m, 4 H), 10.92 (s, 1 H)	51.97 (q), 52.87 (q), 109.38 (s), 118.68 (d), 126.06 (d), 128.82 (s), 129.28 (d), 129.36 (d), 131.42 (d), 133.87 (s), 135.21 (d), 137.11 (d), 161.19 (s), 168.45 (s), 169.2 (s)
3c	–	$C_{16}H_{13}O_5Cl$	3.58 (s, 3 H), 3.71 (s, 3 H), 5.76 (d, 1 H, *J* = 1.9), 7.24–7.40 (m, 6 H)	52.44 (q), 52.54 (q), 83.85 (d), 97.46 (s), 128.37 (d), 128.95 (d), 132.48 (s), 135.02 (s), 143.87 (d), 145.32 (d), 149.59 (s), 158.11 (s), 162.53 (s), 164.94 (s)
1c	70	$C_{16}H_{13}O_5Cl$	3.56 (s, 3 H), 3.84 (s, 3 H), 7.02 (d, 1 H, *J* = 10.0), 7.16 (d, 2 H, *J* = 8.6), 7.27 (d, 2 H, *J* = 8.6), 7.31 (d, 1 H, *J* = 8.7), 10.92 (s, 1 H)	52.31 (q), 53.16 (q), 109.30 (s), 119.24 (d), 128.50 (d), 130.22 (d), 130.46 (s), 133.85 (s), 134.56 (s), 136.85 (d), 137.66 (s), 161.14 (s), 168.67 (s), 169.35 (s)
3d	–	$C_{16}H_{13}O_5Br$	3.59 (s, 3 H), 3.72 (s, 3 H), 5.76 (d, 1 H, *J* = 1.9), 7.25–7.50 (m, 6 H)	52.28 (q), 52.37 (q), 83.69 (d), 97.33 (s), 123.17 (s), 128.47 (d), 131.74 (d), 132.82 (s), 143.68 (d), 145.17 (d), 149.41 (s), 157.88 (d), 162.35 (s), 164.76 (s)
1d	77	$C_{16}H_{13}O_5Br$	3.57 (s, 3 H), 3.86 (s, 3 H), 7.04 (d, 1 H, *J* = 8.7), 7.11 (d, 2 H, *J* = 8.5), 7.32 (d, 1 H, *J* = 8.7), 7.44 (d, 2 H, *J* = 8.5), 10.94 (s, 1 H)	52.49 (q), 53.32 (q), 109.46 (s), 119.42 (d), 122.22 (s), 130.69 (d), 131.62 (d), 132.17 (s), 134.65 (s), 136.95 (d), 138.28 (s), 161.32 (s), 168.82 (s), 169.50 (s)
1e	125	$C_{22}H_{18}O_5$	3.49 (s, 3 H), 3.87 (s, 3 H), 7.06 (d, 1 H, *J* = 8.6), 7.30 (d, 1 H, *J* = 8.6), 7.20–7.65 (m, 9 H), 10.89 (s, 1 H)	52.43 (q), 53.28 (q), 109.45 (s), 119.35 (d), 127.15 (d), 127.28 (d), 127.69 (d), 129.06 (d), 129.39 (d), 131.56 (s), 134.65 (s), 137.28 (d), 138.36 (s), 140.55 (s), 140.73 (s), 161.15 (s), 169.01 (s), 169.65 (s)
3f	–	$C_{20}H_{16}O_5$	3.29 (s, 3 H), 3.76 (s, 3 H), 5.89 (d, 1 H, *J* = 1.9), 7.32–7.65 (m, 5 H), 7.72–7.96 (m, 4 H)	
1f	135	$C_{20}H_{16}O_5$	3.24 (s, 3 H), 3.81 (s, 3 H), 7.07 (d, 1 H, *J* = 8.6), 7.24–7.46 (m, 6 H), 7.74–7.79 (m, 2 H), 11.00 (s, 1 H)	51.91 (q), 53.02 (q), 109.26 (s), 118.72 (d), 124.88 (d), 125.94 (d), 126.10 (d), 126.17 (d), 127.68 (d), 128.14 (d), 128.41 (s), 129.93 (s), 132.46 (s), 133.53 (s), 135.83 (s), 136.06 (s), 137.94 (d), 161.19 (s), 168.47 (s), 169.51 (s)
3g	106	$C_{16}H_{13}NO_7$	3.60 (s, 3 H), 3.75 (s, 3 H), 5.82 (d, 1 H, *J* = 1.8), 7.32 (m, 2 H), 7.65 (d, 2 H, *J* = 9.0), 8.21 (d, 2 H, *J* = 9.0)	52.71 (q), 52.81 (q), 84.21 (d), 97.11 (s), 123.99 (d), 128.00 (d), 141.11 (s), 143.76 (d), 145.58 (d), 148.47 (s), 150.14 (s), 157.31 (s), 162.57 (s), 164.66 (s)
1g	–	$C_{16}H_{13}NO_7$	3.58 (s, 3 H), 3.88 (s, 3 H), 7.10 (d, 1 H, *J* = 8.7), 7.37 (d, 1 H, *J* = 8.7), 7.43 (d, 2 H, *J* = 8.8), 8.18 (d, 2 H, *J* = 8.8), 11.00 (s, 1 H)	52.59 (q), 53.42 (q), 109.75 (s), 119.67 (d), 123.68 (d), 129.44 (s), 129.94 (d), 134.80 (s), 136.87 (d), 146.05 (s), 147.51 (s), 161.83 (s), 168.46 (s), 169.26 (s)
3h	77	$C_{18}H_{16}O_6$	2.51 (s, 3 H), 3.55 (s, 3 H), 3.70 (s, 3 H), 5.76 (d, 1 H, *J* = 1.9), 7.26 (dd, 1 H, *J* = 1.9, *J* = 5.2), 7.34 (d, 1 H, *J* = 5.2), 7.52 (d, 2 H, *J* = 8.4), 7.90 (d, 2 H, *J* = 8.4)	26.82 (q), 52.45 (q), 52.57 (q), 83.92 (d), 97.54 (s), 127.09 (d), 128.68 (d), 137.46 (s), 138.90 (s), 143.92 (s), 145.31 (s), 149.61 (s), 158.07 (s), 162.49 (s), 164.80 (s), 197.70 (s)
1h	114	$C_{18}H_{16}O_6$	2.54 (s, 3 H), 3.55 (s, 3 H), 3.84 (s, 3 H) 7.03 (d, 1 H, *J* = 8.6), 7.28–7.38 (m, 3 H), 7.91 (d, 2 H, *J* = 8.7), 10.93 (s, 1 H)	26.75 (q), 52.39 (q), 53.26 (q), 109.52 (s), 119.38 (d), 128.42 (d), 129.11 (d), 130.68 (s), 134.57 (s), 136.23 (s), 136.69 (d), 144.14 (s), 161.35 (s), 168.63 (s), 169.34 (s), 197.79 (s)
1i	105	$C_{17}H_{16}O_6$	3.56 (s, 3 H), 3.75 (s, 3 H), 3.84 (s, 3 H), 6.84 (d, 1 H, *J* = 8.8), 7.01 (d, 2 H *J* = 8.6), 7.16 (d, 2 H, *J* = 8.6), 7.35 (d, 1 H, *J* = 8.8), 10.89 (s, 1 H)	52.26 (q), 53.12 (q), 55.36 (q), 109.18 (s), 113.76 (d), 119.08 (s), 130.04 (d), 131.55 (s), 131.61 (s), 137.33 (s), 159.21 (s), 160.78 (s), 169.18 (s), 169,57 (s)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.30, H ± 0.17.

Inspection of the data in Table 2 reveals that satisfactory yields of [4+2] adducts were obtained in most cases. With 2-(4-nitrophenyl)furan (**2g**) (entry 8), the yield of the reaction was limited to 48% (after 90 hours, 50% of **2g** remains unaffected). With 2-(4-methoxyphenyl)furan (**2i**) (entry 10), after 25 hours, all the starting furan disappeared. However a side product 2-(4-methoxyphenyl)-5-(1,2-dicarboxymethylvinyl)furan was formed by a Michael-type reaction in 14% yield.

The step leading to the synthesis of substituted phenylphenols involving a β-elimination of the heteroatom bridge, appears to be immediate and spontaneous when an electron-releasing group is present on the aryl group.

The presence of an electron-withdrawing group limits β-elimination. This point and also the role of the position of the substituent (see entries 2 and 3 Table 2) are still unclear; we believe that electronic factors are not only responsible for the stability of **3** but that a particular conformation of the aryl-oxygen bridge system is required to give a spontaneous β-elimination.[15]

However, in this case, **3** is easily and quantitatively converted to the biaryl **1** by treatment, at room temperature, with aqueous acid (HCl or H_2SO_4) in diethyl ether. It should be noted that on warming in acetic acid at 90 °C, **3** leads to a retro-Diels–Alder reaction.

[4+2] Addition of Phenylfuran 2a with Dimethyl Acetylenedicarboxylate (DMAD):

A mixture of phenylfuran (216 mg, 1.5 mmol), DMAD (215 mg, 1.5 mmol) and ZnI_2 (48 mg, 0.15 mmol) was stirred under N_2 for 90 h (monitored by TLC on silica gel, hexane/Et_2O 50/50) at r.t. The resulting mixture was then filtered on Celite; the organic solution was washed with 0.1 M $Na_2S_2O_3$ (5 mL), H_2O (10 mL), dried ($MgSO_4$) and evaporated under reduced pression. Flash chromatography on a silica gel column [eluent hexane/Et_2O (0–10%)] afforded **1a** (Table 3).

[4+2] Addition of Arylfurans 2(b–i) with DMAD; Synthesis of 1(c, d, e, f, i):

A mixture of arylfuran (1.5 mmol), DMAD (215 mg, 1.5 mmol), ZnI_2 (48 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was stirred under N_2 at r.t. for 90 h **(2b–h)** or 25 h **(2i)**. An identical workup to that used for **1a** gave **1(c, d, e, f, i)** and **3(b, c, d, f, g, h)** (Table 3).

β-Elimination of 3(b, g, h); Synthesis of 1(b, g, h):

A solution of 0.3 mmol of **3** in Et_2O (3 mL) was stirred at r.t. with conc. H_2SO_4 (0.1 mL). The reaction was monitored by TLC on silica gel [hexane/Et_2O 50/50] (approximately 1 h). The organic phase was washed with brine (2 × 5 mL) dried ($MgSO_4$) and the phenols were purified by flash chromatography [eluent hexane/Et_2O 0–10 %].

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(15) Studies are actually in progress in order to determine the conformation of the different adducts **3**.