

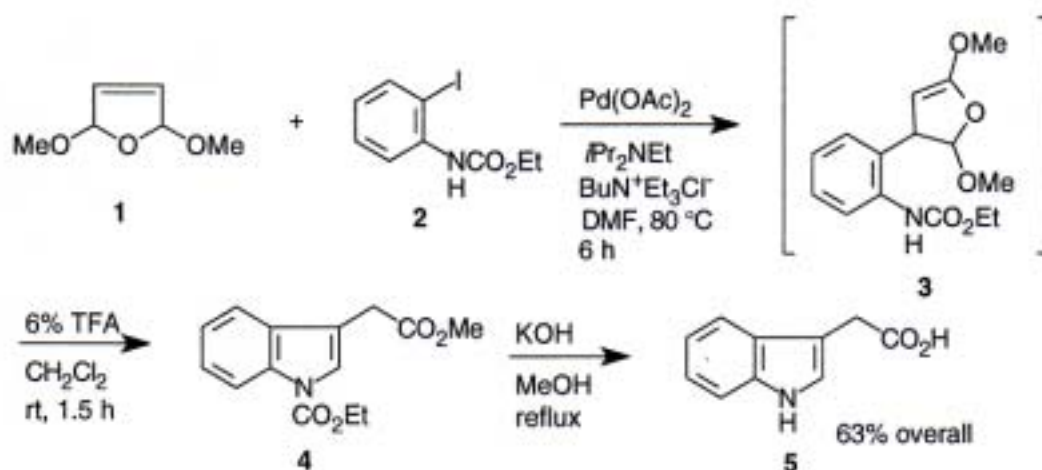
## AN EXPEDIENT PALLADIUM-MEDIATED ROUTE TO 3-ARYLFURANS<sup>†</sup>

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**Abstract** — A facile route to 3-arylfurans has been developed by employing the Heck reaction between 2,5-dihydro-2,5-dimethoxyfuran and aryl iodides as the key step.

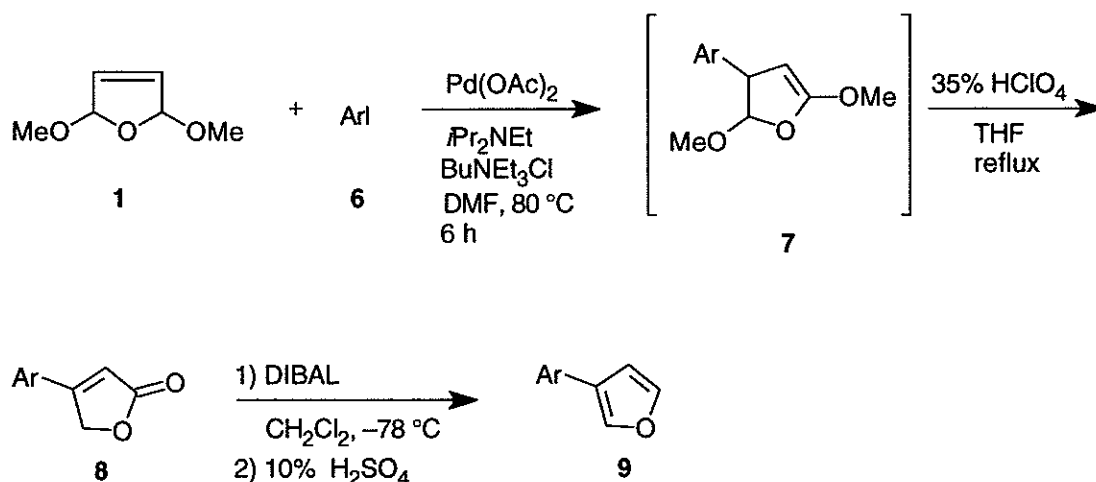
In relation to our recent project, we required a substantial amount of 3-arylfurans. Since no simple procedure has been reported,<sup>1</sup> we investigated the synthesis of 3-arylfurans by application of our previously established procedure<sup>2</sup> for the preparation of indoleacetic acid derivatives. In our indoleacetic acid synthesis we treated commercially available 2,5-dihydro-2,5-dimethoxyfuran (**1**) and *N*-carbethoxy-2-iodoaniline (**2**) under the Heck conditions to give the 3-aryl-4,5-dihydro-2,5-dimethoxyfuran (**3**) which, on exposure to trifluoroacetic acid followed by hydrolysis, furnished indoleacetic acid (**5**) in acceptable yield (**Scheme 1**).



**Scheme 1**

By following the indoleacetic acid synthesis, we treated 2 equiv. of 2,5-dihydro-2,5-dimethoxyfuran (**1**) with aryl iodides (**6a–o**) in the presence of a catalytic amount of palladium (II) acetate<sup>3</sup> (3 mol %) in DMF containing diisopropylethylamine (0.31 equiv.) and benzyltriethylammonium chloride (1.0 equiv.) at 80 °C

<sup>†</sup> Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 73rd birthday.



Scheme 2

**Table 1:** Preparation of 3-Arylfuran (9)

| Entry | Aryl Iodide (6)<br>Ar=   | 3-Arylbutenolide (8) <sup>a</sup><br>(%) : (mp) | 3-Arylfuran (9) <sup>a</sup><br>(%) : (mp) |
|-------|--------------------------|---|--|
| 1     | (a) : phenyl             | 58 : 91-93 °C                                   | 89 : 55-56 °C                              |
| 2     | (b) : 2-methylphenyl     | 58 : 68-69 °C                                   | 83 : oil                                   |
| 3     | (c) : 3-methylphenyl     | 56 : 86-87 °C                                   | 84 : oil                                   |
| 4     | (d) : 4-methylphenyl     | 66 : 113-115 °C                                 | 98 : 53-55 °C                              |
| 5     | (e) : 2-methoxyphenyl    | 80 : 95-97 °C                                   | 74 : oil                                   |
| 6     | (f) : 3-methoxyphenyl    | 51 : 81-83 °C                                   | 87 : oil                                   |
| 7     | (g) : 4-methoxyphenyl    | 51 : 117-119 °C                                 | 81 : oil                                   |
| 8     | (h) : 2,3-dimethylphenyl | 53 : 65-67 °C                                   | 80 : oil                                   |
| 9     | (i) : 2,4-dimethylphenyl | 61 : 112-114 °C                                 | 78 : oil                                   |
| 10    | (j) : 3,4-dimethylphenyl | 66 : 132-134 °C                                 | 93 : oil                                   |
| 11    | (k) : 3,5-dimethylphenyl | 52 : 137-139 °C                                 | 89 : oil                                   |
| 12    | (l) : 9-phenanthryl      | 48 : 149-150 °C                                 | 83 : oil                                   |
| 13    | (m) : 2-nitrophenyl      | 0   | —  |
| 14    | (n) : 3-nitrophenyl      | 0   | —  |
| 15    | (o) : 4-nitrophenyl      | 0   | —  |

a) All new compounds have satisfactory analytical data (high resolution MS and/or combustion).

for 6 h. Although the three aryl iodides (6m, n, o) having a nitro functionality decomposed to give complex mixtures, the other substrates afforded the 4-aryl-4,5-dihydro-2,5-dimethoxyfurans (7a-l) as diastereomeric mixtures which, after filtration through a silica gel column, were refluxed in THF containing 35% hydroperchloric acid (1:1 v/v) for 48 h to give the 3-arylbutenolides (8a-l) in good to moderate yields (Table 1).

Transformation of a butenolide to the corresponding furan has been achieved by using diisobutylaluminum hydride (DIBAL).<sup>4</sup> By following the reported procedure the butenolides (8a-l) were treated with 2 equiv. of DIBAL at  $-78^\circ\text{C}$ , followed by diluted 10% sulfuric acid to give the corresponding 3-arylfurans (9a-l) in excellent yields (Scheme 2: Table 1).

**Table 2:** NMR Spectral Data of 3-Arylbutenolide (**8**) in CDCl<sub>3</sub>.

| <b>8</b> | IR (cm <sup>-1</sup> ) | <sup>1</sup> H NMR (δ) (300 MHz)  | <sup>13</sup> C NMR (δ) (75 MHz)  |
|----------|------------------------|---|---|
| a        | 1787, 1747             | 7.54-7.48 (m, 5H), 6.39 (t, 1H, <i>J</i> =1.9 Hz), 5.24 (d, 2H, <i>J</i> =1.9 Hz)   | 174.1, 164.1, 131.9, 129.7, 129.4, 126.5, 113.0, 71.0   |
| b        | 1786, 1748             | 7.42-7.25 (m, 4H), 6.28 (t, 1H, <i>J</i> =1.9 Hz), 5.19 (d, 2H, <i>J</i> =1.9 Hz), 1.57 (s, 3H)   | 174.1, 164.0, 137.4, 132.0, 130.8, 129.7, 127.4, 126.6, 117.1, 72.7, 21.8   |
| c        | 1785, 1745             | 7.40-7.28 (m, 4H), 6.36 (t, 1H, <i>J</i> =1.9 Hz), 5.22 (d, 2H, <i>J</i> =1.9 Hz), 2.41 (s, 3H)   | 174.1, 164.3, 139.2, 132.7, 129.6, 129.2, 127.1, 123.7, 112.8, 71.1, 21.2   |
| d        | 1788, 1731             | 7.41 (d, 2H, <i>J</i> =8.2 Hz), 7.28 (d, 2H, <i>J</i> =8.2 Hz), 6.32 (t, 1H, <i>J</i> =1.6 Hz), 5.21 (d, 2H, <i>J</i> =1.6 Hz), 2.42 (s, 3H)  | 174.2, 164.1, 142.6, 130.0, 126.4, 111.9, 71.0, 21.4  |
| e        | 1730                   | 7.49-7.41 (m, 2H), 7.07-7.00 (m, 2H), 6.57 (t, 1H, <i>J</i> =1.6 Hz), 5.28 (d, 2H, <i>J</i> =1.6 Hz), 3.93 (s, 3H)  | 174.8, 161.1, 158.5, 133.0, 128.4, 121.0, 118.6, 114.7, 111.7, 72.7, 55.4   |
| f        | 1794, 1734             | 7.39 (dd, 1H, <i>J</i> =8.2, 8.1 Hz), 7.11-7.00 (m, 3H), 6.37 (t, 1H, <i>J</i> =1.6 Hz), 5.21 (d, 2H, <i>J</i> =1.6 Hz), 3.86 (s, 3H)   | 174.0, 164.0, 160.2, 131.0, 130.5, 118.9, 117.1, 113.4, 112.2, 71.1, 55.4   |
| g        | 1731                   | 7.46 (dt, 2H, <i>J</i> =8.8, 1.7 Hz), 6.98 (dt, 2H, <i>J</i> =8.8, 1.7 Hz), 6.25 (t, 1H, <i>J</i> =1.6 Hz), 5.20 (d, 2H, <i>J</i> =1.6 Hz), 3.87 (s, 3H)  | 174.6, 163.8, 162.6, 128.4, 122.4, 114.8, 110.7, 71.0, 55.5   |
| h        | 1786, 1743             | 7.26 (d, 1H, <i>J</i> =7.7 Hz), 7.18 (t, 1H, <i>J</i> =7.7 Hz), 7.08 (d, 1H, <i>J</i> =7.7 Hz), 6.17 (t, 1H, <i>J</i> =1.9 Hz), 5.11 (d, 2H, <i>J</i> =1.9 Hz), 2.36 (s, 3H), 2.32 (s, 3H)  | 174.1, 165.8, 138.6, 135.2, 132.1, 130.7, 126.1, 125.2, 118.0, 73.2, 20.7, 17.1   |
| i        | 1807, 1732             | 7.18 (d, 1H, <i>J</i> =8.0 Hz), 7.15 (s, 1H), 7.10 (d, 1H, <i>J</i> =8.0 Hz), 6.23 (br.s, 1H), 5.18 (d, 2H, <i>J</i> =0.5 Hz), 2.45 (s, 3H), 2.37 (s, 3H)   | 174.5, 163.7, 141.4, 137.6, 133.0, 127.3, 126.8, 116.1, 72.7, 22.0, 21.2  |
| j        | 1728                   | 7.28-7.21 (m, 3H), 6.31 (t, 1H, <i>J</i> =1.9 Hz), 5.20 (d, 2H, <i>J</i> =1.9 Hz), 2.32 (s, 6H)   | 174.3, 164.3, 141.4, 137.8, 130.5, 127.6, 127.3, 124.0, 111.7, 71.0, 19.8, 19.6   |
| k        | 1789, 1738             | 7.14 (s, 1H), 7.11 (s, 2H), 6.32 (t, 1H, <i>J</i> =1.9 Hz), 5.19 (d, 2H, <i>J</i> =1.9 Hz), 2.37 (s, 6H)  | 174.2, 164.5, 139.1, 133.6, 129.7, 124.3, 112.7, 71.1, 21.1   |
| l        | 1725                   | 8.80 (dd, 1H, <i>J</i> =8.8, 0.8 Hz), 8.72 (d, 1H, <i>J</i> =8.2 Hz), 8.15 (dd, 1H, <i>J</i> =8.2, 1.4 Hz), 7.93 (dd, 1H, <i>J</i> =8.0, 1.4 Hz), 7.80-7.64 (m, 5H), 6.50 (t, 1H, <i>J</i> =1.9 Hz), 5.34 (d, 2H, <i>J</i> =1.9 Hz) | 173.9, 164.3, 131.1, 130.9, 130.4, 129.4, 128.8, 128.6, 127.6, 127.5, 127.4, 127.2, 125.2, 123.8, 123.6, 122.8, 119.3, 73.3 |

**Table 3:** NMR Spectral Data of 3-Arylfuran (**9**) in CDCl<sub>3</sub>.

| <b>9</b> | <sup>1</sup> H NMR (δ) (300 MHz)  | <sup>13</sup> C NMR (δ) (75 MHz)  |
|----------|---|---|
| a        | 7.74 (t, 1H, <i>J</i> =1.1 Hz), 7.52-7.47 (m, 3H), 7.41-7.35 (m, 2H), 7.28 (m, 1H), 6.71 (dd, 1H, <i>J</i> =1.9, 0.8 Hz)  | 143.8, 138.6, 132.6, 129.0, 127.1, 126.7, 126.0, 109.0  |
| b        | 7.52 (dd, 1H, <i>J</i> =1.6, 0.8 Hz), 7.48 (t, 1H, <i>J</i> =1.6 Hz), 7.33 (m, 1H), 7.28-7.18 (m, 3H), 6.58 (dd, 1H, <i>J</i> =1.6, 0.8 Hz), 2.39 (s, 3H)   | 142.7, 140.1, 135.9, 132.4, 130.8, 129.4, 127.3, 126.1, 125.7, 111.6, 21.1  |
| c        | 7.72 (d, 1H, <i>J</i> =0.8 Hz), 7.47 (m, 1H), 7.32-7.22 (m, 3H), 7.08 (br.d, 1H, <i>J</i> =6.6 Hz), 6.69 (m, 1H), 2.38, (s, 3H)   | 143.7, 138.62, 138.56, 132.5, 128.9, 127.9, 126.8, 126.7, 123.1, 109.0, 21.4  |
| d        | 7.70 (br.s, 1H), 7.46 (t, 1H, <i>J</i> =1.6 Hz), 7.38 (d, 2H, <i>J</i> =8.2 Hz), 7.18 (d, 2H, <i>J</i> =8.2 Hz), 6.68 (m, 1H), 2.36 (s, 3H)   | 143.7, 138.3, 136.8, 129.7, 129.6, 126.5, 125.9, 109.0, 21.0  |
| e        | 7.92 (br.s, 1H), 7.42 (dd, 1H, <i>J</i> =7.4, 1.9 Hz), 7.39 (t, 1H, <i>J</i> =1.9 Hz), 7.17 (m, 1H), 6.96-6.86 (m, 2H), 6.72 (m, 1H), 3.84 (s, 3H)  | 156.6, 142.3, 141.7, 128.0, 127.8, 121.8, 121.3, 120.8, 111.1, 109.5, 55.2  |
| f        | 7.72 (dd, 1H, <i>J</i> =1.6, 0.8 Hz), 7.47 (m, 1H), 7.29 (t, 1H, <i>J</i> =7.7 Hz), 7.08 (m, 1H), 7.02 (m, 1H), 6.82 (ddd, 1H, <i>J</i> =8.2, 2.7, 0.8 Hz), 6.69 (m, 1H), 3.84 (s, 3H)                            | 160.2, 143.8, 138.8, 134.0, 130.0, 126.6, 118.6, 112.4, 111.9, 109.0, 55.2  |
| g        | 7.65 (br.s, 1H), 7.45 (t, 1H, <i>J</i> =1.6 Hz), 7.41 (dt, 2H, <i>J</i> =8.8, 1.7 Hz), 6.91 (dt, 2H, <i>J</i> =8.8, 1.7 Hz), 6.65 (m, 1H), 3.82 (s, 3H)   | 158.9, 143.6, 137.8, 127.1, 126.2, 125.1, 114.3, 108.9, 55.2  |
| h        | 7.48-7.44 (m, 2H), 7.17-7.09 (m, 3H), 6.52 (dd, 1H, <i>J</i> =1.6, 0.8 Hz), 2.33 (s, 3H), 2.27 (s, 3H)  | 142.6, 140.1, 137.5, 134.8, 132.8, 129.2, 127.7, 126.3, 125.6, 112.2, 20.7, 16.9  |
| i        | 7.49 (m, 1H), 7.45 (m, 1H), 7.21 (d, 1H, <i>J</i> =7.7 Hz), 7.07 (s, 1H), 7.02 (d, 1H, <i>J</i> =7.7 Hz), 6.55 (dd, 1H, <i>J</i> =1.9, 0.8 Hz), 2.34 (s, 3H), 2.33 (s, 3H)  | 142.6, 139.9, 137.0, 135.7, 131.6, 129.4, 129.3, 126.8, 125.7, 111.6, 20.99, 20.96  |
| j        | 7.57 (t, 1H, <i>J</i> =0.8 Hz), 7.33 (t, 1H, <i>J</i> =1.6 Hz), 7.15 (br.s, 1H), 7.11 (d, 1H, <i>J</i> =7.7 Hz), 7.01 (d, 1H, <i>J</i> =7.7 Hz), 6.56 (dd, 1H, <i>J</i> =1.9, 0.8 Hz), 2.17 (s, 3H), 2.15 (s, 3H) | 143.6, 138.3, 137.0, 135.5, 130.2, 130.1, 127.3, 126.6, 123.4, 109.0, 19.7, 19.4  |
| k        | 7.68 (dd, 1H, <i>J</i> =1.6, 0.8 Hz), 7.43 (t, 1H, <i>J</i> =1.6 Hz), 7.09 (br.s, 2H), 6.89 (m, 1H), 6.66 (dd, 1H, <i>J</i> =1.6, 0.8 Hz), 2.32 (s, 6H)   | 143.6, 138.6, 138.5, 132.4, 128.8, 126.7, 123.9, 109.1, 21.2  |
| l        | 8.76 (d, 1H, <i>J</i> =8.2 Hz), 8.70 (d, 1H, <i>J</i> =8.0 Hz), 8.18 (dd, 1H, <i>J</i> =8.0, 1.1 Hz), 7.88 (dd, 1H, <i>J</i> =7.7, 1.6 Hz), 7.76-7.56 (m, 7H), 6.75 (m, 1H)                                       | 143.1, 140.8, 131.7, 131.2, 130.8, 130.2, 129.4, 128.7, 127.7, 127.0, 126.8, 126.78, 126.7, 126.5, 125.0, 123.1, 122.7, 112.7 |

Typical procedure is as follows. A solution of 2,5-dihydro-2,5-dimethoxyfuran (2.22 mL, 18.3 mmol), 4-iodotoluene (**6d**) (2.0 g, 9.17 mmol), diisopropylethylamine (2.40 mL, 13.8 mmol) and benzyltriethylammonium chloride (2.09 g, 9.17 mmol) in DMF (9.2 mL) was heated at 80 °C for 6 h in the presence of a catalytic amount of palladium (II) diacetate (62 mg, 3 mol %). After dilution with Et<sub>2</sub>O, the organic layer was washed with 5% NaHCO<sub>3</sub> followed by brine and dried over MgSO<sub>4</sub>. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel column (60 g, elution with 1:2 v/v AcOEt-hexane) to give 4-phenyl-4,5-dihydro-2,5-dimethoxyfuran (**7d**) as a diastereomeric mixture. The mixture without separation was then refluxed in THF (60 mL) and 35% HClO<sub>4</sub> (60 mL) for 48 h. After cooling, the mixture was extracted with Et<sub>2</sub>O and the extract was washed sequentially with brine, 5% NaHCO<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (70 g, elution with 1:10 v/v AcOEt-hexane) to give the 4-arylbutenolide (**8d**) (1.05 g, 66%) as colorless crystals (**Table 1: Entry 4**).

To obtain the 3-(4-methylphenyl)furan (**9d**), the butenolide (**8d**) (1.0 g, 5.74 mmol) was stirred in dichloromethane (20 mL) at -78 °C and to this solution was added DIBAL (1.5 M in toluene, 5.67 mL, 11.5 mmol) and stirring was continued at the same temperature for 2 h. The mixture was diluted with Et<sub>2</sub>O and treated with 10% H<sub>2</sub>SO<sub>4</sub> (16 mL) and the stirring was further continued for 10 min at rt. The organic layer was separated and washed with 5% NaHCO<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel column (50 g, elution with 1:50 v/v AcOEt-hexane) to give the 3-(4-methylphenyl)furan (**9d**) (887 mg, 98%) as colorless crystals (**Table 1: Entry 4**).

In conclusion, we have developed an expedient route to 3-arylfurans starting from 2,5-dihydro-2,5-dimethoxyfuran and aryl iodides by employing the Heck reaction as the key step.

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