AN EXPEDIENT PALLADIUM-MEDIATED ROUTE TO 3-ARYLFURANS[†]

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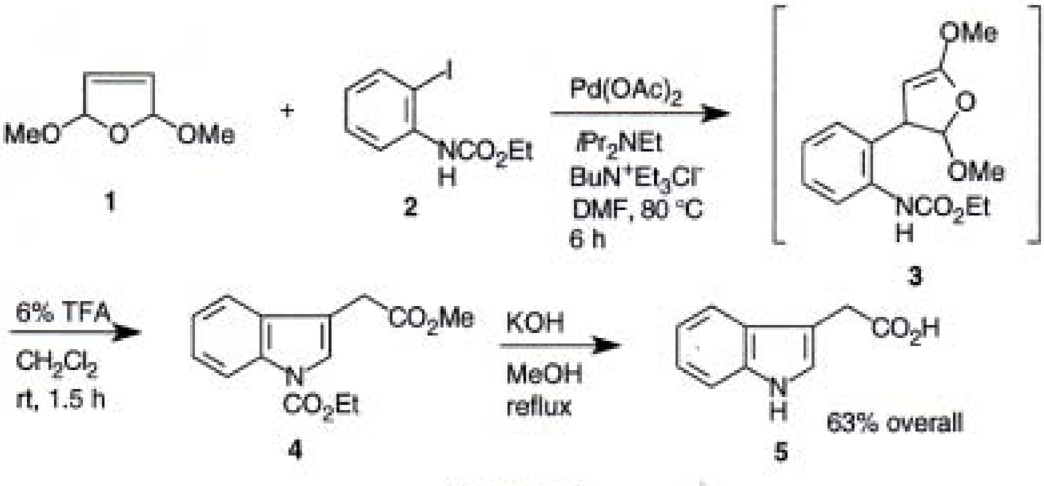
Abstract — A facile route to 3-arylfurans has been developed by employing the Heck reaction between 2,5-dihydro-2,5-dimethoxyfuran and aryl iodides as the key step.

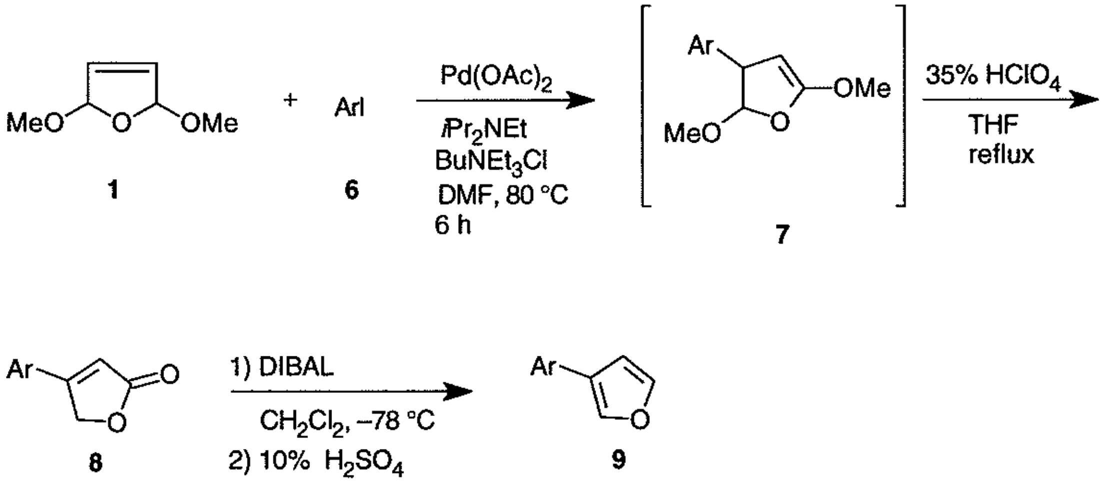
In relation to our recent project, we required a substantial amount of 3-arylfurans. Since no simple procedure has been reported,[1] we investigated the synthesis of 3-arylfurans by application of our previously established procedure[2] for the preparation of indoleacetic acid derivatives. In our indoleacetic 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[3] (3 mol %) in DMF containing diisopropylethylamine (0.31 equiv.) and benzyltriethylammonium chloride (1.0 equiv.) at 80 °C

[†] 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**) Ar=	3-Arylbutenolide (**8**)[a] (%) : (mp)	3-Arylfuran (**9**)[a] (%) : (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-phenanthlyl	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).[4] By following the reported procedure the butenolides (**8a~l**) were treated with 2 equiv. of DIBAL at –78 °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 $CDCl_3$.

8	IR (cm^{-1})	^1H NMR (δ) (300 MHz)	^{13}C NMR (δ) (75 MHz)
a	1787, 1747	7.54-7.48 (m, 5H), 6.39 (t, 1H, *J*=1.9 Hz), 5.24 (d, 2H, *J*=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, *J*=1.9 Hz), 5.19 (d, 2H, *J*=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, *J*=1.9 Hz), 5.22 (d, 2H, *J*=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, *J*=8.2 Hz), 7.28 (d, 2H, *J*=8.2 Hz), 6.32 (t, 1H, *J*=1.6 Hz), 5.21 (d, 2H, *J*=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, *J*=1.6 Hz), 5.28 (d, 2H, *J*=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, *J*=8.2, 8.1 Hz), 7.11-7.00 (m, 3H), 6.37 (t, 1H, *J*=1.6 Hz), 5.21 (d, 2H, *J*=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, *J*=8.8, 1.7 Hz), 6.98 (dt, 2H, *J*=8.8, 1.7 Hz), 6.25 (t, 1H, *J*=1.6 Hz), 5.20 (d, 2H, *J*=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, *J*=7.7 Hz), 7.18 (t, 1H, *J*=7.7 Hz), 7.08 (d, 1H, *J*=7.7 Hz), 6.17 (t, 1H, *J*=1.9 Hz), 5.11 (d, 2H, *J*=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, *J*=8.0 Hz), 7.15 (s, 1H), 7.10 (d, 1H, *J*=8.0 Hz), 6.23 (br.s, 1H), 5.18 (d, 2H, *J*=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, *J*=1.9 Hz), 5.20 (d, 2H, *J*=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, *J*=1.9 Hz), 5.19 (d, 2H, *J*=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, *J*=8.8, 0.8 Hz), 8.72 (d, 1H, *J*=8.2 Hz), 8.15 (dd, 1H, *J*=8.2, 1.4 Hz), 7.93 (dd, 1H, *J*=8.0, 1.4 Hz), 7.80-7.64 (m, 5H), 6.50 (t, 1H, *J*=1.9 Hz), 5.34 (d, 2H, *J*=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 $CDCl_3$.

9	^1H NMR (δ) (300 MHz)	^{13}C NMR (δ) (75 MHz)
a	7.74 (t, 1H, J=1.1 Hz), 7.52-7.47 (m, 3H), 7.41-7.35 (m, 2H), 7.28 (m, 1H), 6.71 (dd, 1H, J=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, J=1.6, 0.8 Hz), 7.48 (t, 1H, J=1.6 Hz), 7.33 (m, 1H), 7.28-7.18 (m, 3H), 6.58 (dd, 1H, J=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, J=0.8 Hz), 7.47 (m, 1H), 7.32-7.22 (m, 3H), 7.08 (br.d, 1H, J=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, J=1.6 Hz), 7.38 (d, 2H, J=8.2 Hz), 7.18 (d, 2H, J=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, J=7.4, 1.9 Hz), 7.39 (t, 1H, J=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, J=1.6, 0.8 Hz), 7.47 (m, 1H), 7.29 (t, 1H, J=7.7 Hz), 7.08 (m, 1H), 7.02 (m, 1H), 6.82 (ddd, 1H, J=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, J=1.6 Hz), 7.41 (dt, 2H, J=8.8, 1.7 Hz), 6.91 (dt, 2H, J=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, J=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, J=7.7 Hz), 7.07 (s, 1H), 7.02 (d, 1H, J=7.7 Hz), 6.55 (dd, 1H, J=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, J=0.8 Hz), 7.33 (t, 1H, J=1.6 Hz), 7.15 (br.s, 1H), 7.11 (d, 1H, J=7.7 Hz), 7.01 (d, 1H, J=7.7 Hz), 6.56 (dd, 1H, J=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, J=1.6, 0.8 Hz), 7.43 (t, 1H, J=1.6 Hz), 7.09 (br.s, 2H), 6.89 (m, 1H), 6.66 (dd, 1H, J=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, J=8.2 Hz), 8.70 (d, 1H, J=8.0 Hz), 8.18 (dd, 1H, J=8.0, 1.1 Hz), 7.88 (dd, 1H, J=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_2O, the organic layer was washed with 5% $NaHCO_3$ followed by brine and dried over $MgSO_4$. 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% $HClO_4$ (60 mL) for 48 h. After cooling, the mixture was extracted with Et_2O and the extract was washed sequentially with brine, 5% $NaHCO_3$, brine and dried over $MgSO_4$. 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_2O and treated with 10% H_2SO_4 (16 mL) and the stirring was further continued for 10 min at rt. The organic layer was separated and washed with 5% $NaHCO_3$, brine and dried over $MgSO_4$. 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 ary iodides by employing the Heck reaction as the key step.

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REFERENCES AND NOTES

1. T. Usui, Y. Tsubone, and A. Tanaka, *J. Heterocycl. Chem.*, 1985, **22**, 849; Y. Yang, *Synth. Commun.*, 1989, **19**, 1001; P. Wipf, L. T. Rahman and S. R. Rector, *J. Org. Chem.*, 1998, **63**, 7132.
2. K. Samizu and K. Ogasawara, *Synlett*, 1994, 499; K. Samizu and K. Ogasawara, *Heterocycles*, 1994, **38**, 1745.
3. R. F. Heck, "Palladium Reagents in Organic Syntheses", Academic Press, London, 1985.
4. H. Minato and T. Nagasaki, *Chem.& Ind.* (London), 1965, 899; P. A. Grieco, C. S. Pogonowski, and S. Burke, *J. Org. Chem.*, 1975, **40**, 542.

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