Arylation of 2-Furyl 4-Fluorophenyl Ketone: An Extension of Heck Chemistry towards Novel Integrase Inhibitors

Luigi Franchi,[a] Marta Rinaldi,[a] Giulia Vignaroli,[a] Anna Innitzer,[a] Marco Radi,[a] Maurizio Botta*[a,b]

[a] Dipartimento Farmaco Chimico Tecnologico, University of Siena, Via Alcide de Gasperi 2, 53100 Siena, Italy

[b] Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, BioLife Science Bldg., Suite 333, 1900 N 12th Street, Philadelphia, PA 19122, USA
Fax +39(577)234306; E-mail: botta.maurizio@gmail.com

Received 28 July 2010; revised 2 August 2010

Abstract: An optimized procedure for the direct and regioselective arylation of 2-acylfurans has been developed. The versatility of this protocol has been evaluated on a series of aryl and heteroaryl halides, thus obtaining a small collection of 2,5-disubstituted furans in moderate to good yields. Finally, the optimized protocol has been successfully applied to the synthesis of the HIV-1 integrase inhibitor **3** and could be further exploited for the generation of novel substituted furans as potential integrase inhibitors.

Key words: Heck reaction, direct arylation, 2-acylfurans, catalysis, integrase inhibitors

HIV-1 integrase (IN) is an essential enzyme involved in viral replication cycle related to the integration of viral DNA into host cell genome. HIV-1 integrase represents an interesting target for the development of new anti-HIV therapies because it has no known counterpart in the host cell. During the last twenty years many efforts have been devoted to the identification of HIV-1 integrase inhibitors (INIs). These efforts have recently culminated in the FDA approval of raltegravir (**1**, Figure 1) as the first INI on the market.[1] During the last few years, our research group has been involved in the search for novel INIs that led to the identification of an interesting hit compound **2** having a micromolar activity both on enzymatic and cellular assays (Figure 1).[2a,b]

Structure activity relationship (SAR) studies showed that the 2,5-disubstituted furan moiety was essential for the biological activity,[2a,b] and the exploration of the C5-functionalization has recently led to the identification of a promising carbinol analogue **3** (Figure 1) endowed with a moderate activity against IN (IC50: 43 μM). [3] Unfortunately, the strategy used for the synthesis of the latter compound, based on a Suzuki coupling and next Grignard reaction on the 2-formyl moiety, suffered from a lack of efficiency due to low yields and poor tolerance towards several functional groups.[4] Organometallic reactions (e.g., Meerwein and Suzuki coupling) have been previously used by us to build 2-arylated furans.[2b,c] However, the requirements of diazonium salts or boron species limit the versatility of the above mentioned procedures since each organometallic species should be prepared separately before each coupling reaction. Accordingly, we envisioned an alternative and more versatile route for the synthesis of the IN inhibitor **3** (Scheme 1): the latter compound could be obtained by reduction of **5a** followed by ester deprotection while the intermediate **5a** could in turn be achieved via direct arylation of the easily obtainable 2-furyl 4-fluorophenyl ketone (**4**) and commercially available methyl 4-iodosalicylate.

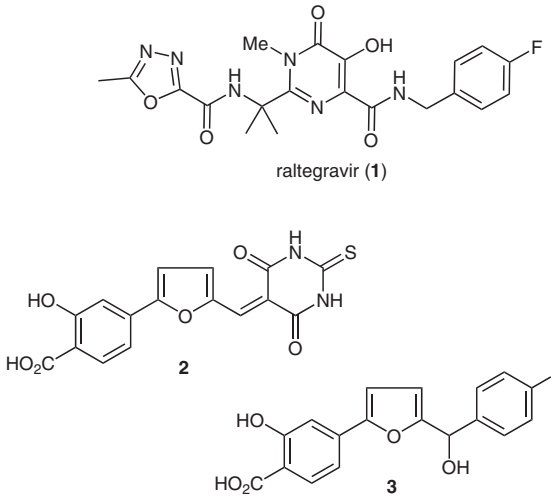
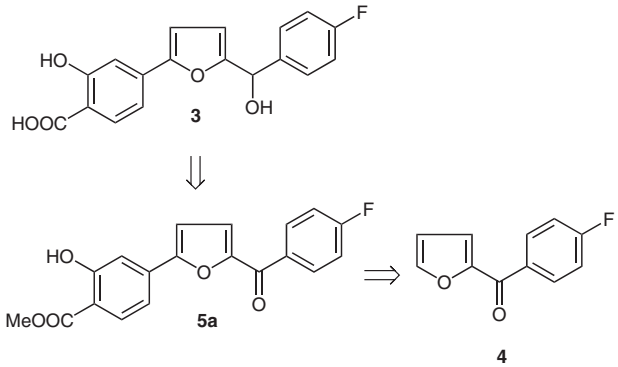


Figure 1 Structure of raltegravir (**1**) and integrase inhibitors **2** and **3** recently developed by us

Direct arylation[5] has recently emerged as a valuable approach for the functionalization of various pentatomics heterocycles.[6] Several examples on the application of Heck coupling for the selective 2-arylation of functional-

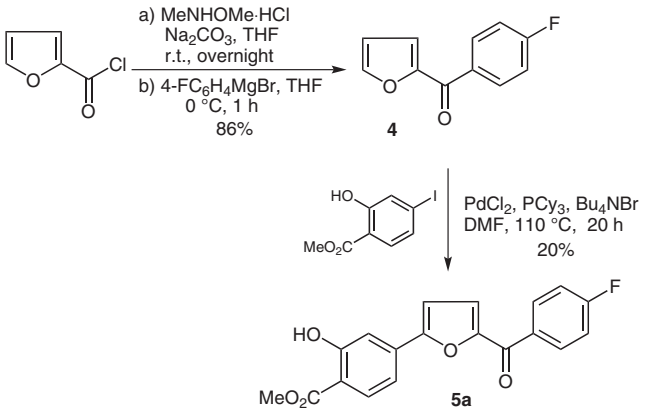


Scheme 1 Retrosynthetic approach for the synthesis of the carbinol derivative **3**

SYNTHESIS 2010, No. 22, pp 3927–3933
Advanced online publication: 07.09.2010
DOI: 10.1055/s-0030-1258247; Art ID: Z19310SS

ized furans are reported in the literature.[5,7] However, only a few efficient examples are known on the application of such approach for the direct arylation of 2-acylfurans.[8] Herein, an improved general method for the direct arylation of the 2-furyl 4-fluorophenyl ketone (**4**) has been developed and applied to the synthesis of the IN inhibitor **3**. The versatility of this protocol has been also evaluated on a series of aryl and heteroaryl halides and its exploitation could allow to generate novel 2,5-disubstituted furans as potential IN inhibitors.

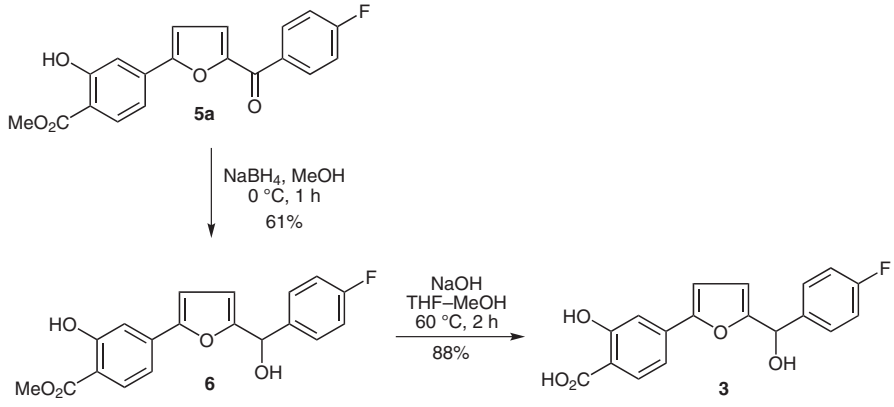
The 2-acylfuran **4** was synthesized in two steps starting from commercially available 2-furoyl chloride, which was initially converted into the corresponding Weinreb amide in quantitative yield. The latter intermediate was then used in the next Grignard reaction without any further purification to give the desired compound **4** in 86% overall yield (Scheme 2). The 2-furyl 4-fluorophenyl ketone (**4**) was then used as substrate for the optimization of the Heck coupling reaction (Table 1). The first attempt of direct arylation was conducted according to the standard McClure protocol:[9] commercially available methyl 4-iodosalicylate was added over 10 hours to a solution of catalyst ($PdCl_2$), ligand (PCy_3), additive (Bu_4NCl), and the 2-acylfuran **4** in DMF at 110 °C. The resulting mixture was stirred for an additional 10 hours to give the desired compound **5a** even if in low yields (20%), after a long reaction time (20 h) and using an high catalyst loading (10 mol%) (Scheme 2; Table 1, entry 1). In order to optimize this coupling protocol, the influence of each parameter on the outcome of the reaction was thoroughly investigated (Table 1). The optimal temperature for the coupling was proved to be 110 °C (higher temperatures gave the same results) and the reaction was completed within 2 hours, as revealed by the consumption of the aryl iodide on TLC. The halide species were added to the reaction mixture as last step and no differences were evidenced with or without cannulation. A profitable completion of the optimization of the reaction was guaranteed by the use of different Pd(0) catalysts such as $Pd_2(dba)_3$ or precatalyst forms such as $Pd(OAc)_2$, and $PdCl_2$ (Table 1, entries 1–18). However, the best results were obtained using $Pd(PPh_3)_2Cl_2$ as catalyst (Table 1, entry 18). Tricyclohexylphosphine, triphenylphosphine, triethyl phosphite, and tri-*o*-tolylphosphine



Scheme 2 Direct arylation of **4** following the McClure protocol

were tested as monodentate ligands while dppp, dppf, and Xantphos were used as bidentates.

Results with PCy_3 and PPh_3 were comparable, but a loss of efficacy was found with triethyl phosphite and dppp (Table 1, entries 2–9). It was interesting to note that no reaction occurred with both P(*o*-tolyl)$_3$ and bidentate ligands such as dppf or Xantphos (Table 1, entries 10–14). $NiCl_2$ also proved to catalyze the Heck coupling,[10] but its application to our reaction was unsuccessful (Table 1, entry 15). Ligand-free conditions[11,12] were also attempted in combination with $PdCl_2$, but poor results were obtained (Table 1, entries 17). Among the tetralkylammonium salts, used as additive in the 'Jeffery conditions',[13] Bu_4NCl gave the best results in our hands both in terms of yield and easiness of purification (Table 1, entry 19). LiCl[14] and pivalic acid[15] were also considered as suitable additives for the Heck reaction, but they gave poor results in our reaction (Table 1, entry 20, 21). Ag_2CO_3 was tested for its double action as halide scavenger and base,[16] but low yield and several side products were obtained (Table 1, entry 23). Et_3N and K_2CO_3 were used as base giving worst results compared to KOAc (Table 3, entries 24, 25). Particularly anhydrous conditions were not generally required. Among the solvents, DMF had the best impact on the reaction outcome while DMF–H_2O, DMSO, toluene, MeCN, and ethanol always gave lower yields (Table 1, entries 26–30). Microwave conditions



Scheme 3 Synthesis of the integrase inhibitor **3**

Table 1 Optimization of the Coupling Reaction[a]

Entry	Catalyst (0.1 equiv)	Ligand (0.2 equiv)	Base (3 equiv)	Solvent (0.1 M)	Additive (1 equiv)	Heating (°C)	Time (h)	Yield (%)[b]
1[c]	$PdCl_2$	PCy_3	KOAc	DMF	Bu_4NBr	110	20	20
2	$PdCl_2$	PCy_3	KOAc	DMF	Bu_4NBr	110	2	19
3	$Pd(OAc)_2$	PCy_3	KOAc	DMF	Bu_4NBr	110	2	20
4	$PdCl_2$	PPh_3	KOAc	DMF	Bu_4NBr	110	2	28
5	$Pd(OAc)_2$	PPh_3	KOAc	DMF	Bu_4NBr	110	2	26
6	$PdCl_2$	$P(OEt)_3$	KOAc	DMF	Bu_4NBr	110	2	15
7	$Pd(OAc)_2$	$P(OEt)_3$	KOAc	DMF	Bu_4NBr	110	2	11
8	$PdCl_2$	dppp	KOAc	DMF	Bu_4NBr	110	2	10
9	$Pd(OAc)_2$	dppp	KOAc	DMF	Bu_4NBr	110	2	5
10	$PdCl_2$	P(*o*-tolyl)$_3$	KOAc	DMF	Bu_4NBr	110	12	–
11	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	KOAc	DMF	Bu_4NBr	110	12	–
12	$PdCl_2$	dppf	KOAc	DMF	Bu_4NBr	110	12	–
13	$Pd(OAc)_2$	dppf	KOAc	DMF	Bu_4NBr	110	12	–
14	$PdCl_2$	Xantphos	KOAc	DMF	Bu_4NBr	110	12	–
15	$NiCl_2$	PPh_3	KOAc	DMF	Bu_4NBr	110	12	–
16	$Pd_2(dba)_3$	PPh_3	KOAc	DMF	Bu_4NBr	110	12	12
17	$PdCl_2$	–	KOAc	DMF	Bu_4NBr	110	12	5
18	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	Bu_4NBr	110	2	29
19	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	Bu_4NCl	110	2	40
20	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	pivalic acid	110	2	14
21	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	LiCl	110	2	–
22	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	–	110	12	30
23	$Pd(PPh_3)_2Cl_2$	–	–	DMF	Ag_2CO_3	110	2	18
24	$Pd(PPh_3)_2Cl_2$	–	Et_3N	DMF	Bu_4NCl	110	12	–
25	$Pd(PPh_3)_2Cl_2$	–	K_2CO_3	DMF	Bu_4NCl	110	12	–
26	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF–H_2O	Bu_4NCl	110	2	23
27	$Pd(PPh_3)_2Cl_2$	–	KOAc	MeCN	Bu_4NCl	110	2	19
28	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMSO	Bu_4NCl	110	2	25
29	$Pd(PPh_3)_2Cl_2$	–	KOAc	toluene	Bu_4NCl	110	2	17
30	$Pd(PPh_3)_2Cl_2$	–	KOAc	EtOH	Bu_4NCl	110	2	–
31	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	Bu_4NCl	80–100 MW	3 × 30′	30
32	$Pd(PPh_3)_2Cl_2$	–	KOAc	DMF	pivalic acid	80–100 MW	3 × 30′	10

[a] The reaction between methyl 4-iodosalicylate (1 equiv) and the 2-furyl 4-fluorophenyl ketone (**4**; 2 equiv) (Scheme 2) was monitored by TLC analysis and stopped after consumption of the aryl iodide.
[b] Isolated yield.
[c] Reaction conditions are those of the standard McClure protocol (ref. 9).

had no effect in speeding up the reaction and low yields were obtained even after repeated irradiation cycles (Table 1, entries 31, 32). Catalyst stoichiometry was also investigated, and the best results were obtained under 1 mol% loading (Table 2, entry 4).

Table 2 Effect of $Pd(PPh_3)_2Cl_2$ Loading on the Yield of **5a**[a]

Entry	Catalyst loading (equiv)	Yield (%)[b]
1	0.100	40
2	0.050	36
3	0.030	41
4	0.010	52
5	0.005	37

[a] Reaction conditions are those reported in Table 1, entry 19.
[b] Isolated yield.

Overall, the optimized protocol for the direct arylation of **4** employed $Pd(PPh_3)_2Cl_2$ (1 mol%), Bu_4NCl as additive, KOAc as base, and DMF as solvent. An excess of 2-furyl 4-fluorophenyl ketone (**4**; 2 equiv) should also be used in order to prevent undesired homocoupling reaction. The main advantages of this protocol are represented by the low catalyst loading, the short reaction time, and no need of cannulation.

This optimized protocol has been then exploited for the synthesis of the integrase inhibitor **3** as shown in Scheme 3. Compound **5a** obtained via direct arylation in 52% yield (Table 2, entry 4), was initially reduced to the corresponding carbinol **6** using $NaBH_4$ at 0 °C. Saponification of the latter intermediate gave the desired compound **3** in good overall yield.

Finally, the versatility of the optimized coupling protocol was evaluated on a series of aryl and heteroaryl iodides in place of methyl 4-iodosalycilate: a small collection of 2,5-disubstituted furans was thus obtained (Table 3). Aromatic substituents such as cyano, nitro, methoxy, carboxyethyl, amino, and fluoro were well tolerated giving the desired products in moderate to high yields (Table 3, entries 2–9). Heterocyclic iodides such as *N*,*N*-dimethyl-5-iodouracil gave also good yields of the corresponding product (Table 3, entry 10).

In summary, an optimized protocol for the direct and regioselective arylation of 2-acylfurans has been developed. This procedure proved to be a suitable tool for the easy derivatization of the 2-furyl 4-fluorophenyl ketone (**4**), giving access to the 2,5-disubstituted furan **5a** in high yields, short reaction time and using a low catalyst loading. The latter compound was then easily converted into the HIV-1 integrase inhibitor **3** with good overall yield. The versatility of the coupling protocol was finally proved on different aryl and heteroaryl iodides and its exploitation could allow to generate novel 2,5-disubstituted furans as novel potential integrase inhibitors.

Table 3 Application of the Optimized Heck Protocol to Different Aryl and Heteroaryl Iodides[a]

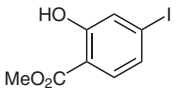
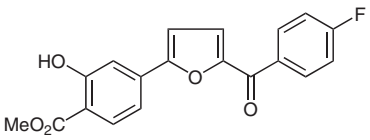
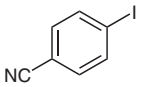
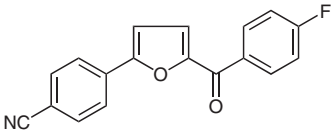
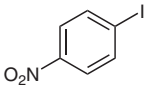
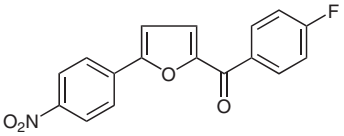
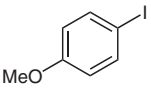
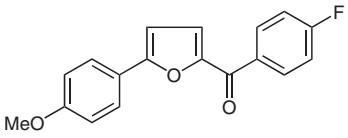
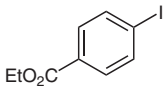
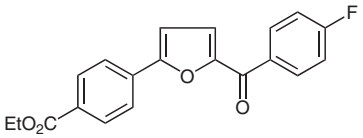
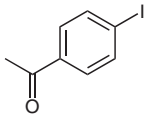
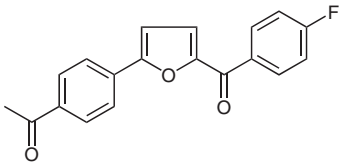
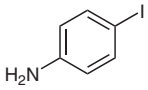
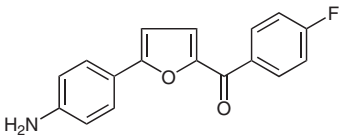
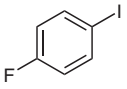
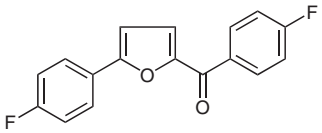
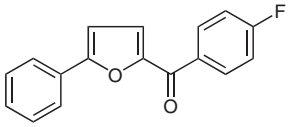
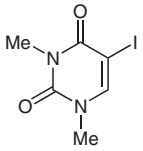
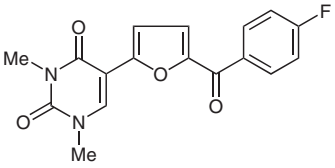
Entry	Halide	Product	Yield (%)[b]
1		**5a** 	52
2		**5b** 	80
3		**5c** 	87
4		**5d** 	72
5		**5e** 	78

Table 3 Application of the Optimized Heck Protocol to Different Aryl and Heteroaryl Iodides[a] (continued)

Entry	Halide	Product	Yield (%)[b]
6		**5f** 	68
7		**5g** 	31
8		**5h** 	84
9		**5i** 	83
10		**5j** 	51

[a] Conditions: aryl/heteroaryl iodide (1 equiv), 2-furyl 4-fluorophenyl ketone (**4**; 2 equiv), KOAc (3 equiv), Bu_4NCl (1 equiv), DMF (0.1 M), 110 °C, 2 h.
[b] Isolated yield.

All commercially available chemicals were used as purchased. Anhydrous reactions were run under a positive pressure of dry N_2. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. TLC was carried out using Merck TLC plates silica gel 60 F254. Chromatographic purifications were performed on columns packed with Merck 60 silica gel, 23–400 mesh, for flash technique. ^1H and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker Avance DPX400 spectrometer. Chemical shifts are reported relative to $CDCl_3$ at δ = 7.24 and TMS at δ = 0.00. Melting points were taken using a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer PE 2004 elemental analyzer, and the data for C, H, and N are within 0.4% of the theoretical values. Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 MeOH–H_2O. UV detection was monitored at 254 nm. Mass spectra were acquired in positive mode scanning over the mass range of 50–1500. The following ion source parameters were used: drying gas flow, 9 mL/min; nebulizer pressure, 40 psig; drying gas temperature, 350 °C.

Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

4-Fluorophenyl(furan-2-yl)methanone (4, 2-Furyl 4-Fluorophenyl Ketone)

2-Furoyl chloride (130.5 mg, 1 mmol) was added to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (195 mg, 2 mmol), pyridine (cat), and Na_2CO_3 (424 mg, 4 mmol) in THF (2 mL, 0.5 M) and the resulting mixture was stirred overnight at r.t. Aq 1 M NaOH (20 mL) and EtOAc (20 mL) were added and the two-phase solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated. The oily residue was dissolved in THF (2 mL, 0.5 M) and then 4-fluorophenylmagnesium bromide (1 M in THF, 1.2 mmol, 1.2 mL) was added dropwise. The solution was stirred for 1 h at r.t., cooled to 0 °C, diluted with EtOAc (20 mL) and sat. aq NH_4Cl (20 mL) was then added. The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography (EtOAc–PE, 1:4) to give the desired product **4** (163 mg, 86%) as an orange oil; R_f = 0.40 (EtOAc–PE, 1:8).

^1H NMR ($CDCl_3$): δ = 8.05 (dd, J_1 = 8.55 Hz, J_2 = 5.42 Hz, 2 H), 7.70 (s, 1 H), 7.26 (m, 1 H), 7.17 (t, J_1 = 8.55 Hz, 2 H), 6.61 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 180.40, 165.20 (J_F = 253.05 Hz), 151.92, 146.82, 137.88, 131.65 (J_F = 8.59 Hz), 120.11, 115.24 (J_F = 21.91 Hz), 112.03.

MS (ESI): *m*/*z* = 213 $[M + Na]^+$.

Anal. Calcd for $C_{11}H_7FO_2$: C, 69.47; H, 3.71. Found: C, 69.66; H, 3.70.

Heck Coupling of 2-Furyl 4-Fluorophenyl Ketone (4) with Aryl/Heteroaryl Iodides; General Procedure

A solution of $Pd(PPh_3)_2Cl_2$ (1.8 mg, 1 mol%, 0.0025 mmol), Bu_4NCl (70 mg, 0.25 mmol, 1 equiv), KOAc (74 mg, 0.75 mmol, 3 equiv), and 2-furyl 4-fluorophenyl ketone (**4**; 95 mg, 0.50 mmol, 2 equiv) in DMF (2.5 mL, 0.1 M) was stirred and degassed at r.t. for 15 min. The respective aryl/heteroaryl iodide (0.25 mmol, 1 equiv) was then added and the resulting mixture was heated at 110 °C under N_2 for 2 h. TLC analysis revealed a complete consumption of the iodide after 2 h and the reaction was quenched by diluting with EtOAc (20 mL) and adding sat. aq NH_4Cl (20 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography using a mixture of EtOAc–PE.

Methyl 4-[5-(4-Fluorobenzoyl)furan-2-yl]-2-hydroxybenzoate (5a)

Yield: 52%; white solid; mp 178 °C; R_f = 0.31 (EtOAc–PE, 1:6).

IR ($CHCl_3$): 1678, 16414, 1601 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 10.86 (s, 1 H), 8.09 (dd, J_1 = 8.35 Hz, J_2 = 5.43 Hz, 2 H), 7.90 (d, J_1 = 8.15 Hz, 2 H), 7.39 (d, J_1 = 1.08 Hz, 1 H), 7.35 (d, J_1 = 3.80 Hz, 1 H), 7.32 (dd, J_1 = 8.15 Hz, J_2 = 1.08 Hz, 1 H), 7.21 (t, J_1 = 8.35 Hz, 2 H), 6.95 (d, J_1 = 3.80 Hz, 1 H), 3.98 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 180.40, 169.98, 162.97 (J_F = 245.10 Hz), 161.76, 156.38, 152.13, 135.55, 133.32, 131.89 (J_F = 8.55 Hz), 130.64, 122.00, 115.64, 115.63 (J_F = 21.54 Hz), 113.44, 112.59, 109.78, 52.37.

MS (ESI): *m*/*z* = 363 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{13}FO_5$: C, 67.06; H, 3.85. Found: C, 66.95; H, 3.83.

4-[5-(4-Fluorobenzoyl)furan-2-yl]benzonitrile (5b)

Yield: 80%; white solid; mp 217 °C; R_f = 0.29 (EtOAc–PE, 1:4).

IR ($CHCl_3$): 2230, 1644, 1601 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.06 (dd, J_1 = 8.46 Hz, J_2 = 5.64 Hz, 2 H), 7.90 (d, J_1 = 8.05 Hz, 2 H), 7.73 (d, J_1 = 8.05 Hz, 2 H), 7.34 (d, J_1 = 3.63 Hz, 1 H), 7.22 (t, J_1 = 8.55 Hz, 2 H), 6.99 (d, J_1 = 3.63 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 180.50, 165.52 (J_F = 254.03 Hz), 155.66, 152.21, 133.03, 132.90, 132.72, 131.81 (J_F = 8.08 Hz), 125.24, 122.07, 118.32, 115.69 (J_F = 21.31 Hz), 112.37, 109.86.

MS (ESI): *m*/*z* = 314 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{10}FNO_2$: C, 74.22; H, 3.46; N, 4.81. Found: C, 74.12; H, 3.48; N, 4.79.

4-Fluorophenyl[5-(4-nitrophenyl)furan-2-yl]methanone (5c)

Yield: 87%; pale yellow solid; mp 202 °C; R_f = 0.21 (EtOAc–PE, 1:7).

IR ($CHCl_3$): 1645, 1601, 1521, 1340 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.31 (d, J_1 = 9.15 Hz, 2 H), 8.07 (dd, J_1 = 8.54 Hz, J_2 = 5.49 Hz, 2 H), 7.95 (d, J_1 = 9.15 Hz, 2 H), 7.36 (d, J_1 = 3.66 Hz, 1 H), 7.22 (t, J_1 = 8.54 Hz, 2 H), 7.05 (d, J_1 = 3.66 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 180.49, 165.56 (J_F = 252.55 Hz), 155.31, 152.49, 147.66, 134.77, 133.20, 131.83 (J_F = 10.30 Hz), 125.41, 124.37, 122.05, 115.73 (J_F = 22.66 Hz), 110.45.

MS (ESI): *m*/*z* = 334 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{10}FNO_4$: C, 65.60; H, 3.24; N, 4.50. Found: C, 65.73; H, 3.24; N, 4.46.

4-Fluorophenyl[5-(4-methoxyphenyl)furan-2-yl]methanone (5d)

Yield: 72%; pale yellow solid; mp 114 °C; R_f = 0.37 (EtOAc–PE, 1:6).

IR ($CHCl_3$): 1634, 1611, 1601, 1479 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.05 (dd, J_1 = 7.98 Hz, J_2 = 5.85 Hz, 2 H), 7.75 (d, J_1 = 8.52 Hz, 2 H), 7.31 (d, J_1 = 3.72 Hz, 1 H), 7.19 (t, J_1 = 7.98 Hz, 2 H), 6.97 (d, J_1 = 8.52 Hz, 2 H), 6.71 (d, J_1 = 3.72 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 180.22, 165.23 (J_F = 254.13 Hz), 160.57, 158.72, 150.82, 133.84, 131.71 (J_F = 8.13 Hz), 126.55, 123.07, 122.06, 115.45 (J_F = 22.18 Hz), 114.35, 106.06, 55.31.

MS (ESI): *m*/*z* = 319 $[M + Na]^+$, 615 $[2 M + Na]^+$.

Anal. Calcd for $C_{18}H_{13}FO_3$: C, 72.97; H, 4.42. Found: C, 73.09; H, 4.43.

Ethyl 4-[5-(4-Fluorobenzoyl)furan-2-yl]benzoate (5e)

Yield: 78%; white solid; mp 124 °C; R_f = 0.24 (EtOAc–PE = 1:7).

IR ($CHCl_3$): 1712, 1641, 1601 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.05 (d, J_1 = 8.30 Hz, 2 H), 8.01 (m, 2 H), 7.79 (d, J_1 = 8.30 Hz, 2 H), 7.27 (d, J_1 = 3.69 Hz, 1 H), 7.14 (t, J_1 = 8.30 Hz, 2 H), 6.89 (d, J_1 = 3.69 Hz, 1 H), 4.33 (q, J_1 = 6.92 Hz, 2 H), 1.35 (t, J_1 = 6.92 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 180.42, 165.85, 165.40 (J_F = 255.55 Hz), 156.92, 151.87, 133.41, 132.91, 131.82 (J_F = 10.04 Hz), 130.13, 124.68, 122.29, 115.59 (J_F = 22.03 Hz), 109.13, 61.12, 14.22.

MS (ESI): *m*/*z* = 339 $[M + H]^+$, 361 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{15}FO_4$: 71.00; H, 4.47. Found: C, 70.89; H, 4.44.

1-{4-[5-(4-Fluorobenzoyl)furan-2-yl]phenyl}ethanone (5f)

Yield: 68%; pale yellow solid; mp 146 °C; R_f = 0.26 (EtOAc–PE, 2:7).

IR ($CHCl_3$): 1682, 1641, 1601 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.08 (dd, J_1 = 8.78 Hz, J_2 = 5.54 Hz, 2 H), 8.03 (d, J_1 = 8.32 Hz, 2 H), 7.89 (d, J_1 = 8.32 Hz, 2 H), 7.35 (d, J_1 = 3.70 Hz, 1 H), 7.21 (t, J_1 = 8.78 Hz, 2 H), 6.98 (d, J_1 = 3.70 Hz, 1 H), 2.63 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 197.05, 180.46, 165.44 (J_F = 255.85 Hz), 156.76, 151.98, 137.08, 133.11, 131.82 (J_F = 10.08 Hz), 128.95, 127.34, 124.93, 122.27, 115.62 (J_F = 21.64 Hz), 109.33, 26.55.

MS (ESI): *m*/*z* = 331 $[M + Na]^+$, 347 $[M + K]^+$.

Anal. Calcd for $C_{19}H_{13}FO_3$: C, 74.02; H, 4.25. Found: C, 73.90; H, 4.27.

5-(4-Aminophenyl)furan-2-yl(4-fluorophenyl)methanone (5g)

Yield: 31%; dark red solid; mp 132 °C; R_f = 0.13 (EtOAc–PE, 2:7).

IR ($CHCl_3$): 1622, 1601, 1477 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.04 (dd, J_1 = 8.65 Hz, J_2 = 5.98 Hz, 2 H), 7.62 (d, J_1 = 8.65 Hz, 2 H), 7.30 (d, J_1 = 3.99 Hz, 1 H), 7.18 (t, J_1 = 8.65 Hz, 2 H), 6.72 (d, J_1 = 8.65 Hz, 2 H), 6.64 (d, J_1 = 3.99 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 180.22, 165.20 (J_F = 252.41 Hz), 159.74, 150.40, 147.84, 134.05, 131.75 (J_F = 9.57 Hz), 126.78, 123.61, 119.65, 115.48 (J_F = 21.53 Hz), 114.97, 105.22.

MS (ESI): *m*/*z* = 304 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{12}FNO_2$: C, 72.59; H, 4.30; N, 4.98. Found: C, 72.73; H, 4.29; N, 5.00.

4-Fluorophenyl[5-(4-fluorophenyl)furan-2-yl]methanone (5h)
Yield: 84%; white solid; mp 129 °C; R_f = 0.39 (EtOAc–PE, 1:7).

IR ($CHCl_3$): 1643, 1601 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.98 (dd, J_1 = 9.16 Hz, J_2 = 5.73 Hz, 2 H), 7.72 (dd, J_1 = 8.59 Hz, J_2 = 5.73 Hz, 2 H), 7.24 (d, J_1 = 4.01 Hz, 1 H), 7.10 (m, 4 H), 6.72 (d, J_1 = 4.01 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 180.42, 165.96 (J_F = 253.29 Hz), 164.23 (J_F = 248.17 Hz), 157.45, 151.23, 133.61, 131.74 (J_F = 9.22 Hz), 126.99 (J_F = 8.07 Hz), 125.56, 116.76, 116.09 (J_F = 21.90 Hz), 115.52 (J_F = 21.68 Hz), 107.13.

MS (ESI): m/z = 307 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{10}F_2O_2$: C, 71.83; H, 3.55. Found: C, 71.66; H, 3.60.

4-Fluorophenyl(5-phenylfuran-2-yl)methanone (5i)
Yield: 83%; white solid; mp 119 °C; R_f = 0.42 (EtOAc–PE, 1:8).

IR ($CHCl_3$): 1639, 1600 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.06 (dd, J_1 = 8.71 Hz, J_2 = 5.50 Hz, 2 H), 7.78 (d, J_1 = 7.33 Hz, 2 H), 7.43 (t, J_1 = 7.33 Hz, 2 H), 7.37 (d, J_1 = 7.33 Hz, 1 H), 7.32 (d, J_1 = 3.66 Hz, 1 H), 7.18 (dd, J_1 = 8.71 Hz, 2 H), 6.82 (d, J_1 = 3.66 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 180.35, 165.28 (J_F = 251.07 Hz), 158.31, 151.36, 133.65, 131.80 (J_F = 8.00 Hz), 129.29, 129.21, 128.88, 125.00, 122.53, 115.50 (J_F = 21.72 Hz), 107.45.

MS (ESI): m/z = 267 $[M + H]^+$, 289 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{11}FO_2$: C, 76.68; H, 4.16. Found: C, 76.49; H, 4.20.

5-[5-(4-Fluorobenzoyl)furan-2-yl]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (5j)
Yield: 51%; pale orange solid; mp 194 °C; R_f = 0.50 (EtOAc–PE, 1:1).

IR ($CHCl_3$): 1710, 1666 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.00 (s, 1 H), 7.86 (dd, J_1 = 8.65 Hz, J_2 = 5.32 Hz, 2 H), 7.21 (d, J_1 = 3.99 Hz, 1 H), 7.13 (d, J_1 = 3.99 Hz, 1 H), 7.12 (t, J_1 = 8.65 Hz, 2 H), 3.49 (s, 3 H), 3.37 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 180.65, 165.24 (J_F = 253.29 Hz), 159.98, 151.79, 150.63, 149.30, 140.20, 133.86, 131.39 (J_F = 9.86 Hz), 123.74, 115.61 (J_F = 20.02 Hz), 110.86, 104.17, 37.50, 28.12.

MS (ESI): m/z = 351 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{13}FN_2O_4$: C, 62.19; H, 3.99; N, 8.53. Found: C, 62.01; H, 4.07; N, 8.62.

Methyl 4-[5-(4-Fluorophenyl)(hydroxymethyl)furan-2-yl]-2-hydroxybenzoate (6)
$NaBH_4$ was added portionwise to a solution of **5a** (18 mg, 0.053 mmol) in MeOH (1 mL) until TLC indicated a complete consumption of the starting material. The solution was diluted with H_2O (10 mL) and EtOAc (10 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (EtOAc–PE, 1:4) to give the desired product (11 mg, 61%) as a white solid; R_f = 0.27 (EtOAc–PE, 1:4).

^1H NMR ($CDCl_3$): δ = 10.80 (s, 1 H), 7.81 (d, J_1 = 8.42 Hz, 2 H), 7.46 (d, J_1 = 8.69 Hz, J_2 = 5.33 Hz, 2 H), 7.23 (s, 1 H), 7.14 (d, J_1 = 8.42 Hz, 2 H), 7.08 (d, J_1 = 8.69 Hz, 2 H), 6.70 (d, J_1 = 3.36 Hz, 1 H), 6.22 (d, J_1 = 3.36 Hz, 1 H), 5.87 (s, 1 H), 3.95 (s, 3 H).

MS (ESI): m/z = 365 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{15}FO_5$: C, 66.66; H, 4.42. Found: C, 66.81; H, 4.49.

4-[5-(4-Fluorophenyl)(hydroxymethyl)furan-2-yl]-2-hydroxybenzoic Acid (3)
A solution of **6** (0.030 mmol) in THF (1 mL) at 60 °C was treated dropwise with aq 1 M NaOH until TLC analysis indicated a complete consumption of the starting material. The solution was cooled to 0 °C and diluted with Et_2O (5 mL) and aq 1 M NaOH (5 mL). The organic layer was separated and the aqueous layer was acidified with concd HCl until pH <1 and finally extracted with EtOAc (5 mL). The organic phase was dried (Na_2SO_4) and evaporated to give the desired product (9 mg, 88%) as a white solid; mp 162 °C (dec.).

^1H NMR (MeOD): δ = 7.83 (d, J_1 = 8.76 Hz, 1 H), 7.49 (d, J_1 = 8.41 Hz, J_1 = 5.45 Hz, 2 H), 7.10 (t, J_1 = 8.76 Hz, 2 H), 7.04 (m, 2 H), 6.84 (d, J_1 = 3.25 Hz, 1 H), 6.25 (d, J_1 = 3.25 Hz, 1 H), 5.82 (s, 1 H).

MS (ESI): m/z = 327 $[M - 1]^-$.

Anal. Calcd for $C_{18}H_{13}FO_5$: C, 65.85; H, 3.99. Found: C, 65.99; H, 3.92.

Acknowledgment

This work was supported by the European Union (TRIoH Consortium, LSHB-2003-503480 and THINC, HEALTH-2007-2.3.2-1).

References

(1) Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore, F.; Gardelli, C.; Gonzalez Paz, O.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteaguado, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley, M. *J. Med. Chem.* **2008**, *51*, 5843.
(2) (a) Tintori, C.; Corradi, V.; Magnani, M.; Manetti, F.; Botta, M. *J. Chem. Inf. Model.* **2008**, *8*, 2166. (b) Rajamaki, S.; Innitzer, A.; Falciani, C.; Tintori, C.; Christ, F.; Witvrouw, M.; Debyser, Z.; Massa, S.; Botta, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3615. (c) Mugnaini, C.; Rajamaki, S.; Tintori, C.; Corelli, F.; Massa, S.; Witvrouw, M.; Debyser, Z.; Veljkovic, V.; Botta, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5370.
(3) Manuscript in preparation.
(4) Data not shown.
(5) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Chen, X.; Engle, K. M.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.
(6) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
(7) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(8) Dong, J. J.; Roger, J.; Pozgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 1832.
(9) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677.
(10) Kelkar, A. A.; Hanaoka, T.; Kubota, Y.; Sugi, Y. *Catal. Lett.* **1994**, *29*, 69.
(11) De Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; De Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.
(12) Douchet, H.; Pozgan, F.; Roger, J. *ChemSusChem* **2008**, *1*, 404.
(13) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
(14) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(15) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
(16) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.