A Practical One-Pot Synthesis of 5-Aryl-2-furaldehydes

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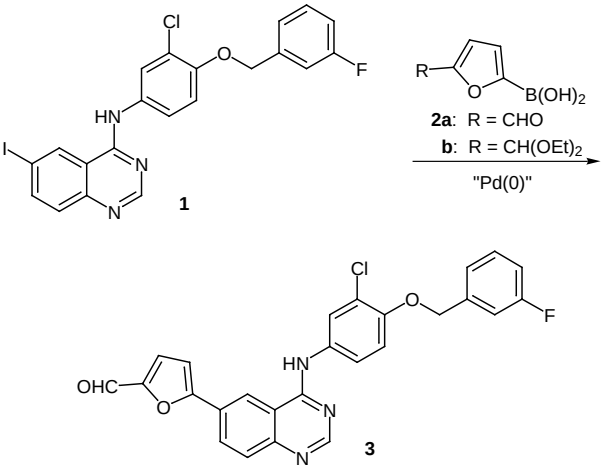
Abstract: A useful one-pot synthesis of 5-aryl-2-furaldehydes via palladium-mediated Suzuki coupling of aryl halides with in situ generated 5-(diethoxymethyl)-2-furylboronic acid is described. The procedure has general applicability, delivers high yields, and is amenable to scale-up.

Key words: furylboronic acids, Suzuki cross-coupling, Pd/C, 5-aryl-2-furaldehydes

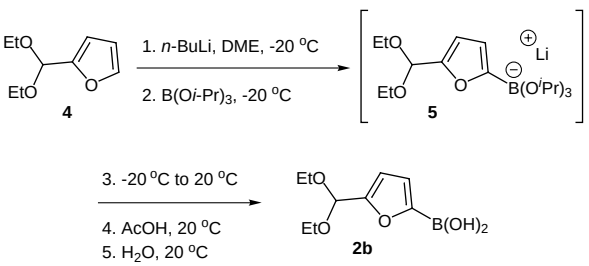
The synthesis of substituted furans continues to stimulate the interest of synthetic organic chemists, as is reflected by a number of recent review articles.[1] In particular, 5-aryl-2-furaldehydes and their derivatives are key structural units in natural products[2] and important pharmacologically active compounds,[3] and therefore render themselves as valuable synthetic targets. Our interest in the preparation of 5-aryl-2-furaldehyde moieties derived from the need to assemble 5-(4-{3-chloro-4-[(3-fluorobenzyl)oxy]anilino}-6-quinazolinyl)-2-furaldehyde (**3**, Scheme 1). This compound has been identified as an important building block for the synthesis of compounds of GlaxoSmithKline's erbB family of protein tyrosine kinase inhibitors, which are potential targets for the treatment of solid tumors.[4] Our objective was to develop a synthetic route that would minimize raw material costs and be amenable to the preparation of multi-kilogram quantities of **3**. Typical approaches to the 5-aryl-2-furaldehyde moiety include coupling of aryldiazonium salts with 2-furaldehyde in the presence of cupric chloride,[5] photochemical arylation of 5-halo-2-furaldehydes,[6] oxidative cross-coupling between 2-furaldehyde and arenes by palladium(II) salts,[7] palladium-catalyzed coupling of 5-bromo-2-furaldehyde with arylboronic acids,[8] as well as palladium-catalyzed coupling of 5-(tributylstannyl)-2-furaldehyde[9] or 5-formyl-2-furylboronic acid (**2a**) with aryl halides and triflates.[9,10] Other less direct methods rely on the regioselective Vilsmeier formylation[11] of air-sensitive[12] 2-arylfurans, which can be prepared by palladium-catalyzed cross-coupling of chloro(2-furyl)zinc or 2-furyllithium with aryl halides and triflates.[12,13] For our purpose, it appeared most appropriate to assemble 5-(4-anilino-6-quinazolinyl)-2-furaldehyde **3** through a Suzuki coupling of readily available *N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-iodo-4-quinazolinamine (**1**) with 5-formyl-2-furylboronic acid (**2a**) or its corresponding diethyl acetal **2b**.[14]



Scheme 1

Although furylboronic acid **2a** was available from a single chemical supplier, its use was considered cost-prohibitive.[15] Furthermore, the scant number of published[10,16] and patented[17] reports describing the preparation of **2a**/**b** suffer from low temperature requirements, capricious reproducibility, tedious workup, as well as unsuitably low purity and isolated yields (26–45%). Indeed, we experienced the aforementioned problems when following literature procedures using THF as the reaction solvent, and typically observed 71% of 5-(diethoxymethyl)-2-furylboronic acid (**2b**) and 24% of 2-(diethoxymethyl)furan (**4**; Scheme 2) prior to isolation, as determined by HPLC.[18] Raising the reaction temperature above –40 °C gave less favorable results.[19]

A significant process improvement was achieved by solvent change from THF to DME. Not only did DME allow



Scheme 2

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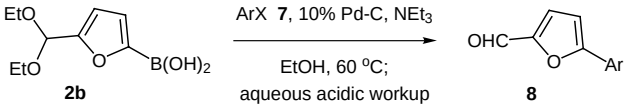
for lithiation of 2-(diethoxymethyl)furan (**4**) at higher temperatures (–20 °C), but treatment of the resulting [5-(diethoxymethyl)-2-furyl]lithium intermediate with triisopropyl borate also provided substantially higher conversion to furylboronic acid **2b** (92%, plus 3% of unreacted furan **4**) (Scheme 2). The higher conversion obtained with DME may be attributable to its increased ability to coordinate to the lithiated furan.[20] Upon resolving the issue of reaction efficiency, we faced the problem of product isolation. It is well known that the relatively high solubility of boronic acids in aqueous media often complicates their isolation and purification. In fact, numerous attempts in our own laboratories to improve the isolation of **2a/b** were unsuccessful. However, the crude solution of 5-(diethoxymethyl)-2-furylboronic acid (**2b**), liberated from the presumed boron "ate" complex **5**[21] by acidic hydrolysis, displayed only modest signs of decomposition upon storage at ambient temperature.[22] Consequently, advancement of the in situ generated solution of **2b** to the Suzuki coupling was investigated.[23]

Fortunately, it proved unnecessary to isolate the boronic acid. Its crude solution could successfully be utilized in the subsequent Suzuki reaction, even several weeks after preparation and without affecting the purity profile. Initially, we employed standard Suzuki coupling conditions[24] using organophosphorous complexes of palladium. While these transformations turned out to be efficient, isolated 5-(4-anilino-6-quinazolinyl)-2-furaldehyde **3**, prepared using dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)], was contaminated with residual palladium at undesirably high levels of 520–850 ppm as determined by Inductively Coupled Plasma (ICP) analysis. Removal of residual palladium is a major concern in the pharmaceutical industry and often necessitates involved workup procedures utilizing Pd-complexing agents.[25] To minimize palladium contamination and to avoid potential phosphine-related side-reactions,[26] we considered phosphine-free and ligandless heterogeneous palladium catalysts which had successfully been employed in Suzuki coupling reactions. These catalysts include palladium(II) acetate,[8,27] palladium(II) chloride,[28] and palladium supported on activated carbon.[29] Indeed, we were able to develop a highly efficient process for the Suzuki coupling of in situ generated 5-(diethoxymethyl)-2-furylboronic acid (**2b**) with *N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-iodo-4-quinazolinamine (**1**) using a catalytic amount of Pd/C.[30] The fact that solvent degassing is not required illustrates the robustness of the aforementioned Pd/C catalyzed coupling. The use of Pd/C greatly facilitated the removal of palladium during product isolation by simple filtration through a Celite pad or a 0.45 micron filter. The solvent of choice is DME, whose superiority over THF extended from the boronic acid generation to the Suzuki coupling by providing more consistent yields, shorter reaction times, and enhanced purity profiles. Interestingly, addition of EtOH was required for optimum conversion.[31] The one-pot boronic acid generation/Suzuki coupling was successful on scales of up to 1.1 kg with isolated yields ranging from 79 – 88%. The product, 5-(4-{3-chloro-4-[(3-fluorobenzyl)oxy]anilino}-6-quinazolinyl)-2-furaldehyde (**3**), displayed a typical purity of 96.7% (HPLC, 220 nm) with low levels of palladium contamination (19–52 ppm).

To evaluate the scope and limitations of this procedure, we investigated the coupling of several aryl and heteroaryl halides **7** with in situ generated 5-(diethoxymethyl)-2-furylboronic acid (**2b**) as illustrated in Scheme 3. The results are shown in the Table.



Scheme 3

We observed that electron-deficient aryl iodides **7a**–**f** (entries 1–6) afforded facile and clean conversion with the heterogeneous Pd/C catalyst, while electron-rich aryl iodides such as 4-methoxyanisole **7g** (entry 7) required prolonged reaction times and yielded incomplete conversions. Interestingly, none of the aryl bromides **7a** and **h**–**j** (entry 1, X = Br, and entries 8–10) reacted under the Pd/C conditions, not even highly reactive 1-bromo-4-nitrobenzene. However, use of the $PdCl_2$(dppf) catalyst in these instances provided excellent conversion (entries 7–10). With either catalyst, reactive functional groups such as the ester and formyl moieties were well tolerated (entries 4 and 8).

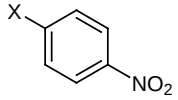
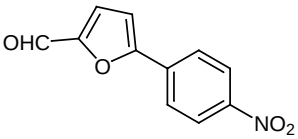
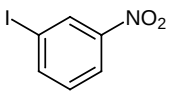
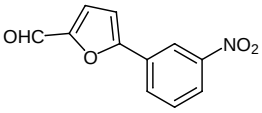
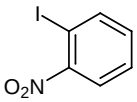
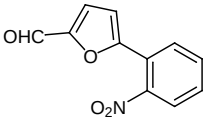
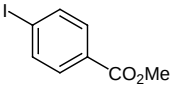
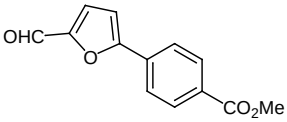
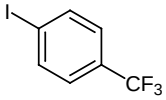
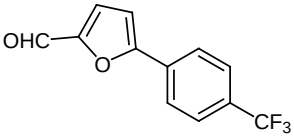
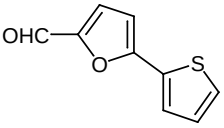
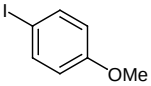
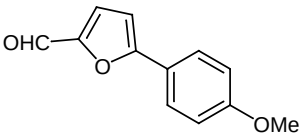
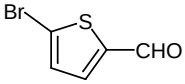
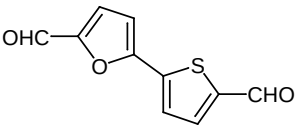
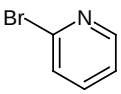
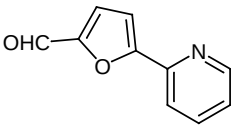
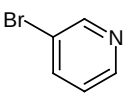
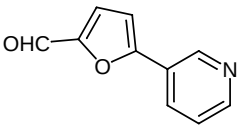
In summary, we have developed a practical and efficient one-pot synthesis of 5-aryl-2-furaldehydes utilizing in situ generated boronic acid in a Suzuki coupling strategy. This has been shown to have general applicability and has been used to prepare kilogram quantities of the elaborate 5-(4-anilino-6-quinazolinyl)-2-furaldehyde **3**. The key advantages of this synthesis are the improved generation of 5-(diethoxymethyl)-2-furylboronic acid (**2b**), its direct advancement into the coupling step, and the use of inexpensive and readily removable Pd/C for the Suzuki reaction.

Melting points were determined on a Electrothermal IA9100 digital melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 20DXC FT-IR spectrometer. ^{1}H NMR and ^{13}C spectra were obtained in $CDCl_3$ with Varian INOVA 300 and Varian INOVA 400 NMR instruments, respectively, and chemical shifts are reported in δ values (ppm) relative to the internal reference of $CDCl_3$ (δ 7.25 for ^{1}H and δ 77.0 for ^{13}C spectra). Exact mass data were obtained with a modified Finnigan MAT 311A with an AMD hard and software data acquisition system. Elemental analyses were performed by Atlantic Microlab, Inc. Methyl-4-iodobenzoate was purchased from Avocado. All other reagents and solvents were purchased from Aldrich, and were used without purification or degassing.

5-(Diethoxymethyl)-2-furylboronic Acid (2b)

To a cooled (–20 °C) solution of 2-(diethoxymethyl)furan (**4**; 33.8 mL, 200 mmol) in DME (340 mL) was added BuLi (2.5 M solution

Table One-Pot Synthesis of 5-Aryl-2-formylfuran Derivatives **8a**–**j**[a]

Entry	Aryl Halide	Catalyst	Time (h)	5-Aryl-2-formylfuran **8**	Yield[b] (%)
1	**7a** 	10% Pd/C	2	**8a** 	X = Br: 0 X = I: 81
2	**7b** 	10% Pd/C	2	**8b** 	91
3	**7c** 	10% Pd/C	16	**8c** 	84
4	**7d** 	10% Pd/C	18	**8d** 	78
5	**7e** 	10% Pd/C	6	**8e** 	91
6	**7f** 	10% Pd/C[c]	36	**8f** 	79
7	**7g** 	$PdCl_2(dppf)$[d,e]	20	**8g** 	63
8	**7h** 	$PdCl_2(dppf)$ [f]	2	**8h** 	90
9	**7i** 	$PdCl_2(dppf)$[e,f]	36	**8i** 	83
10	**7j** 	$PdCl_2(dppf)$[f]	18	**8j** 	84

[a] All reactions were performed at 60 °C in the presence of 10 wt% 10% Pd/C or 5 mol% $PdCl_2(dppf)$ and 2.0 equiv of Et_3N.
[b] Yields of isolated pure products.
[c] Additional 10% Pd/C (10 wt%) was required to effect complete conversion.
[d] Only 61% conversion was achieved with 10% Pd/C.
[e] Additional $PdCl_2(dppf)$ (2.5 mol%) was required to effect complete conversion.
[f] No conversion with 10% Pd/C.

in hexanes, 96 mL, 240 mmol) at a rate such that the internal temperature was maintained below –15 °C. The reaction mixture was stirred at –20 °C for 2 h before adding triisopropyl borate (55.4 mL, 240 mmol). The cooling was suspended, and the mixture was allowed to warm to 20 °C. To this mixture was added, at 20 °C, AcOH (15 mL, 260 mmol) followed by H_2O (18 mL, 1000 mmol). The solution of 5-(diethoxymethyl)-2-furylboronic acid (**2b**) was analyzed for purity by HPLC[18] and then used directly in the Suzuki coupling reaction.

5-Aryl-2-furaldehydes 8; General Procedure

To the crude boronic acid solution **2b** (ca 0.27 M assuming 100% yield; 40 mL, 10.8 mmol) was added aryl halide **7** (4.32 mmol). The resulting mixture was then treated successively with EtOH (14 mL), Et_3N (1.21 mL, 8.64 mmol), and 10% Pd/C (50% water wet, Degussa type E101NE/W, 108 mg). It was heated to 60 °C (internal) and stirred at this temperature until the reaction was deemed completed by HPLC. The mixture was cooled to 25 °C, and the precipitates were removed by vacuum filtration through Hyflo Super Celite and washed with DME (3 × 5 mL or until the wash was colorless). The filtrate was treated with deionized water (20 mL) and trifluoroacetic acid (1.66 mL, 21.5 mmol) and stirred until complete acetal removal was verified by HPLC. The resulting solution was washed with a 1:4 mixture of aq sat. NaCl and aq sat. $NaHCO_3$ solutions (2 × 100 mL). The organic layer was dried (Na_2SO_4) and vacuum filtered, and the filtrate was concentrated in vacuo. The crude 5-aryl-2-formylfuran **8** was purified by flash column chromatography (silica gel, 200–400 mesh, 60 Å) using an appropriate solvent system (R_f value of ca 0.2).

5-(5-Formyl-2-thienyl)-2-furaldehyde (8h)

Yield: 90%; yellow powder; mp 184–185 °C.

IR (neat): ν = 3113, 2841, 1656, 1530, 1439, 1393, 1384, 1279, 1228, 1027, 965, 890, 812, 807, 770, 672 cm^{-1}.

^1H NMR (300 MHz): δ = 9.93 (s, 1 H, OCCHO), 9.69 (s, 1 H, SCCHO), 7.74 [d, 1 H, *J* = 4.0 Hz, SC(CHO)=CHC*H*], 7.58 [d, 1 H, *J* = 4.0 Hz, SC(CHO)=C*H*], 7.31 [d, 1 H, *J* = 3.8 Hz, OC(CHO)=CHC*H*], 6.88 [d, 1 H, *J* = 3.8 Hz, OC(CHO)=C*H*].

^{13}C NMR (100 MHz): δ = 182.8, 177.6, 153.0, 152.7, 144.3, 140.1, 136.9, 126.5, 122.8, 110.7.

HRMS (FAB pos.): *m/z* Calcd for $C_{10}H_7O_3S$ ($M + H^+$): 207.0116. Found: 207.0115.

Anal. Calcd for $C_{10}H_6O_3S$ (206.2): C, 58.24; H, 2.93; S, 15.55. Found: C, 58.71; H, 3.25; S, 15.42.

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(14) Although initial investigations indicated 2-(2-furyl)-1,3-dioxolane to be superior to 2-(diethoxymethyl)furan (**4**) for boronic acid generation, it has limited availability, and the resulting in situ generated boronic acid is less reactive in the Suzuki coupling. Therefore, our studies were focused on acetal **4**.

(15) 5-Formyl-2-furylboronic acid (**2a**), available from Frontier Scientific, costs ca. $26,000/mol, while 2-(diethoxymethyl)furan (**4**) retails at Aldrich for ca. $1,000/mol ($340/kg for bulk quantities).

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(18) Column: Phenomenex Luna C18(2) 50 mm × 2.0 mm 3 micron. Mobile phase: A = 0.05 % (v/v) TFA in H_2O, B = 0.05 % (v/v) TFA in MeCN. Gradient Profile: 0% to 95% B over 8 min. UV detection at λ = 280 nm. 1.0 mL/min flowrate with injection volume of 1.0 μL.

(19) The palladium-catalyzed preparation of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furaldehyde from 5-bromo-2-furaldehyde may have been an attractive alternative approach: (a) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (d) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508; however, the high price tag of 5-bromo-2-furaldehyde and the boron

reagent [4,4,5,5-tetramethyl-1,3,2-dioxaborolane or bis(pinacolato)diboron] presented a significant drawback.

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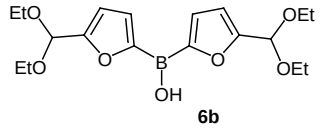
(22) Typical degradation products observed upon prolonged standing were 2-(diethoxymethyl)furan (**4**) and the putative "dimer" **6** (LC-MS) as shown in the Figure below:



6b

Figure

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(30) The only type of Pd/C employed for this and all other experiments described herein was 10 wt% (dry basis)palladium on activated carbon, 50% water wet, Degussa type E101NE/W; it was used as purchased from Aldrich.

(31) It is conceivable that EtOH enhances solubilization of the reaction components. We determined that omission of EtOH or use of EtOH–DME ratios less than 1:2 resulted in competitive degradation of 5-(diethoxymethyl)-2-furylboronic acid (**2b**) to 2-(diethoxymethyl)furan (**4**), thereby preventing complete conversion.