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# Preparation of 5-Aryl Furfurals and Aryl Thiophene-2-carboxaldehydes via Palladium-Catalyzed C–C Bond Formation in Aqueous Media[1]

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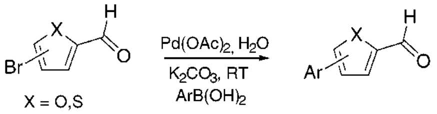
## ABSTRACT



**A series of 5-aryl furfurals and aryl thiophene-2-carboxaldehydes was synthesized. To this end, efficient and effective palladium-catalyzed C–C bond-forming reactions were carried out at room temperature in aqueous media. This mild process allowed the cross-coupling reaction of the bromides to occur in the presence of electrophilic functional groups, which is a valuable advantage over previously reported methods.**

Aryl furans and aryl thiophenes are constituents of a variety of important classes of pharmacologically active compounds. They have been shown to elicit activities as lipoxygenase inhibitors[2] and antiarrhythmics.[3] In particular, 5-aryl furfurals have been shown to be selective antagonists of the 5-HT1D receptor.[4] The direct preparation of such molecules via a C−C bond formation process can be limited when functional group compatibility complicates the synthetic approach.

The Suzuki protocol for the palladium-mediated cross-coupling reaction of aryl boronic acids and aryl halides is an effective method for C−C bond formation.[5] These cross-couplings are particularly powerful when C−C bond formation must be performed in the presence of reactive functional groups. Typical C−C bond formation reactions on halofurans or halothiophenes have traditionally involved the generation of aryl radicals in the presence of these heterocycles.[6] These processes are typically laborious and low yielding. Other reported methods employ nickel(II) catalysis in the homolytic cross-coupling of Grignard reagents to halofurans.[7] Although this process is effective, the method is extremely tedious and limited with respect to functional group compatibility. Herein we report a mild procedure for palladium-catalyzed cross-coupling reactions of bromofurfurals and bromothiophene-2-carboxaldehydes with aryl boronic acids.

Crisp has demonstrated that aryl tin reagents undergo palladium-catalyzed cross-coupling with 2-iodothiophene-carboxaldehydes.[8] These reactions require the more reactive and difficult to obtain iodoheterocycles, high temperatures, and handling of toxic tin reagents. A few simple cases involving the coupling of 2-bromofurans and aryl boronic

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[1] Presented in part at the 216th National Meeting of the American Chemical Society (Boston, August 23−27, 1998). *Book of Abstracts*; American Chemical Society: Washington, DC, 1998; ORGN-624.

[2] Summers, J. B.; Gunn, B. P.; Brooks, Dee W.; Holms, J. H. PCT Int. Appl., WO 8904299 A1 890518, 1989 (71 pp).

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[6] (a) Fisera, L.; Kovac, J.; Komanova, E. *Tetrahedron* **1974**, *30*, 4123. (b) Benati, L.; La Barba, N.; Tiecco, M.; Tundo, A. *J. Chem. Soc B* **1969**, 1253. (c) Antonioletti, R.; D′Auria, M.; D′Onofrio, F.; Piancatelli, G.; Scettri, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1755.

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**Table 1.** Couplings of Aryl Boronic Acids and Thiophenes in Water in the Presence of Tetrabutylammonium Bromide at RT

| Entry | Boronic Acid | Heterocycle | Time (h) | Product | Yield (%)[a] |
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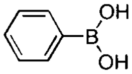
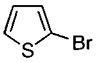
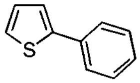
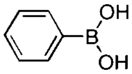
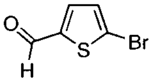
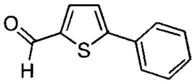
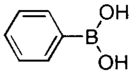
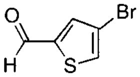
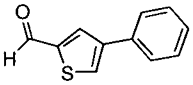
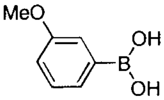
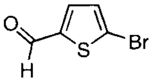
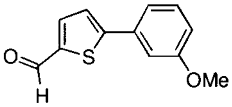
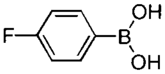
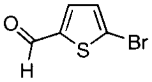
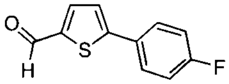
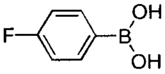
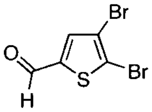
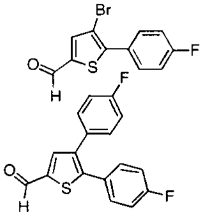
| 1 |  |  | 2.0 |  | 50 |
| 2 |  |  | 2.0 |  | 67 |
| 3 |  |  | 2.0 |  | 75 |
| 4 |  |  | 2.0 |  | 60 |
| 5 |  |  | 2.0 |  | 82 |
| 6 |  |  | 2.0 |  10<br>1 | 80<br>(overall) |

[a] Isolated yield; chromatographed to analytical purity.

acids have been reported by Martin[9] and Sniekus[10] as starting materials for their targets. These couplings were successfully performed using palladium(0) in refluxing ethylene glycol dimethyl ether (DME). In aqueous media, we found C−C bond formation between the aryl boronic acids and bromofurans and thiophenes occurred rapidly in the presence of palladium(II) acetate. In fact, in all cases the reactions were complete after 2 h at room temperature. Utilizing a "ligandless" palladium species in aqueous media repressed the phosphine-related side reactions which are typically encountered in these types of coupling reactions.[11] Under these conditions, bromofurfurals and bromothiophenecarboxaldehydes were coupled with a wide variety of boronic acids in the presence of 2 mol % of palladium(II)acetate, tetrabutylammonium bromide, and potassium carbonate in water.[12] No organic solvents or cosolvents were used or investigated. Although the reaction mixtures were nonhomogeneous and aggregated, the yields were good overall. Some yields appeared to suffer due to the difficulties in the workup extractions.[13] The aggregation, coupled with the high surface tension of water, diminishes the surface contact between hydrophobic species and water molecules.[14] The reaction progress should be aided by a decrease of volume of the reactants along the reaction coordinate. This should ultimately result in an enhanced rate of reaction.

Cross-coupling reactions of the simple heterocycles proceeded at a slower rate. The yields and the reaction rates were considerably lower in comparison to bromofurfural and bromothiophenecarboxaldehyde (Table 1, entry 1 vs entry 2 and Table 2, entry 1 vs entry 2). The electron-withdrawing group present on the aryl halide appears to produce an added electronic advantage for the progression of the cross-couplings. In these instances, increased reaction times resulted in somewhat increased yields. Lower yields and slower reaction rates associated with nonactivated aryl triflates have also been reported.[15] The results of our study are described in Table 1 (thiophenes) and Table 2 (furans).

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(10) Brandao, M. A.; Braga De Oliveira, A.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 15, 2437.

(11) (a) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599. (b) Kong, K. C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313.

(12) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

(13) **Representative Procedure**. 2-Bromo-5-thiophenecarboxaldehyde (1.77 g, 6.16 mmol, 1 equiv), 4-fluorophenyl boronic acid (1.03 g, 7.39 mmol, 1.1 equiv), tetrabutylammonium bromide (1.99 g, 6.16 mmol, 1 equiv), palladium acetate (0.03 g, 1.23 × $10^{-4}$ mol, 2 mol %), and potassium carbonate (2.13 g, 15.40 mmol, 2.5 equiv) were added to a 50 mL round-bottom flask. Deionized water (10 mL) was added, and the reaction was stirred vigorously for 2 h. The reaction mixture became dark and nonhomogeneous. The mixture was diluted with water (30 mL), and the product was extracted with EtOAc (2 × 100 mL). The organics were separated, and the free flowing as well as the syrupy organic layer was collected. The organics were stirred over charcoal (approximately 5 g) for 30 min after which sodium sulfate was added. The organics were dried, filtered, and concentrated. The colorless residue was purified by MPLC, eluting with hexane/EtOAc (4:1, v:v). The reaction yielded 1.046 g (82.3%) as a yellow solid. Calcd for $C_{11}H_7FOS$: 64.06 C, 3.42 H, 15.55 S. Found: 64.00 C, 3.12 H, 15.23 S.

(14) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741.

(15) Perec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060.

**Table 2.** Couplings of Aryl Boronic Acids and Furans in Water in the Presence of Tetrabutylammonium Bromide at RT

| Entry | Boronic Acid | Heterocycle | Time (h) | Product | Yield (%)[a] |
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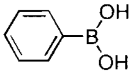
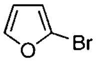
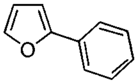
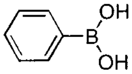
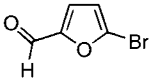
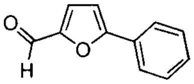
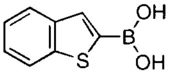
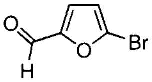
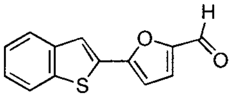
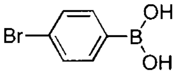
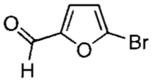
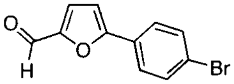
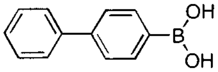
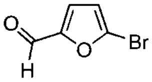
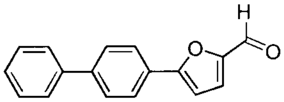
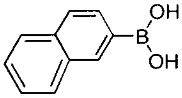
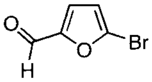
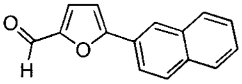
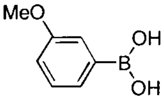
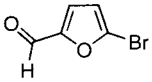
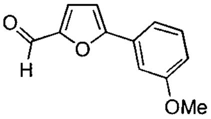
| 1 |  |  | 2.0 |  | 45 |
| 2 |  |  | 1.75 |  | 74 |
| 3 |  |  | 2.0 |  | 61 |
| 4 |  |  | 1.90 |  | 67 |
| 5 |  |  | 1.75 |  | 76 |
| 6 |  |  | 2.0 |  | 48 |
| 7 |  |  | 2.0 |  | 46 |

[a] Isolated yield; chromatographed to analytical purity.

Regiochemical arylation can be selective when the substrate bears multiple bromides. Entry 6 in Table 1 describes such an instance where the C(5) bromide undergoes cross-coupling before the C(4) halide.

In summary, we have found that palladium-catalyzed C−C bond formation of 5-bromofurfurals and bromothiophene-2-carboxaldehydes with aryl boronic acids in water occurs rapidly at room temperature. This mild protocol allows the cross-coupling reaction to occur in the presence of electrophilic functional groups, which is a valuable advantage over previously reported methods.

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