



## A convenient synthesis of 5-aryl- and 5-heteroaryl-2-furaldehydes by the cross-coupling reaction of organozincs

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### ABSTRACT

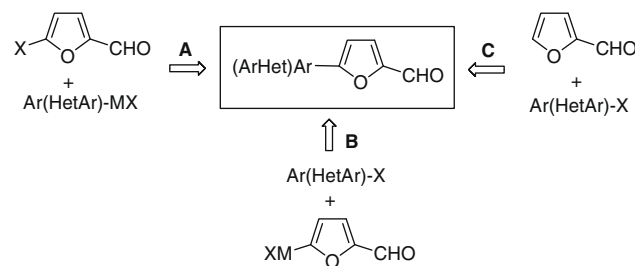
An efficient synthetic route for the preparation of 5-heteroaryl- and 5-aryl-2-furaldehydes has been developed. It has been accomplished by the palladium(0)-catalyzed cross-coupling reaction of hetero-arylzinc and arylzinc reagents with 5-bromo-2-furaldehyde under very mild conditions.

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The furan moiety is an interesting structural unit playing a prominent role in natural products which show a wide range of biological activity.<sup>1</sup> Of special interest are aryl-substituted furan intermediates which have been intensively used in the preparation of furan-containing pharmaceuticals.<sup>2</sup> Due to the particular interest in this area, studies have focused on the development of a versatile synthetic methodology for the preparation of 2,5-disubstituted furan derivatives. As depicted in Scheme 1, palladium-catalyzed cross-coupling reactions of metalated furans are one of the predominant approaches.<sup>3</sup> In contrast, little work has been performed using arylmetallic reagents. For example, O'Doherty described the preparation of 5-aryl-2-furaldehydes using palladium-catalyzed cross-coupling reaction of protected furylstannes and/or furylzincs (routes **A** and **B**, Scheme 1).<sup>4</sup> Recently, a similar approach using an one-pot, four-step sequence palladium-catalyzed cross-coupling reaction of triorganozincates was also reported by Gauthier et al. (route **B**, Scheme 1).<sup>5</sup> The organometallic reagents used in these studies were prepared by the lithiation of the protected furans followed by transmetalation. Generally, cryogenic conditions are required for the lithiation of organic compounds. McClure has also reported the regioselective palladium-catalyzed direct arylation of 2-furaldehyde (route **C**, Scheme 1).<sup>6</sup> In spite of the present methodologies, there is still a need to explore a convenient route for the preparation of a variety of 5-substituted furaldehydes.

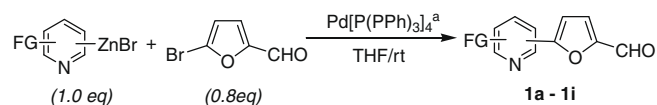
We herein would like to report a convenient synthetic route for the preparation of 5-aryl- and 5-heteroaryl-2-furaldehydes. All the reactions were efficiently carried out in the presence of a catalytic amount of Pd(0)-catalyst under very mild conditions affording the cross-coupling products in good to excellent yield. Significantly, a wide range of 5-substituted-2-furaldehydes were provided since various organozinc reagents were readily available.

As described in a previous Letter,<sup>5</sup> 5-pyridyl-2-furaldehydes have been used for synthetic intermediates in pharmaceuticals. Therefore, the first coupling attempt in our study was performed using several pyridylzinc bromides with 5-bromo-2-furaldehyde.<sup>7</sup> These organozinc reagents were easily prepared by the direct oxidative addition of active zinc to the corresponding halides.<sup>8</sup> It is well-known that the use of organozinc reagents is advantageous over the other organometallics such as the Grignard, Suzuki, and Stille couplings mainly because of the functional group tolerance. As summarized in Table 1, the coupling reaction was carried out in the presence of a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> at rt in THF. An excellent yield was obtained from the reaction of simple 2-pyridylzinc bromide in 1 h (Table 1, entry 1). Sterically hindered organozinc, 3-methyl-2-pyridylzinc bromide, required a prolonged reaction time affording **1b** in lower yield (Table 1, entry 2). The coupling reaction of 5-methyl-2-pyridylzinc bromide, however, was completed in 6 h at rt to produce **1c** in good yield (Table 1, entry 3). An extended time (24 h) was required for the methoxy-substituted pyridylzinc at rt in THF (Table 1, entry 4). 2-Pyridylzinc bromide containing a fluorine was also successfully employed in the coupling reaction with 5-bromo-2-furaldehyde to give the coupled product **1e** in 60% yield (Table 1, entry 5). Along with the 2-pyridylzinc reagents, 3-pyridylzinc bromides (Table 1, entries 6–8) were also easily reacted with



Scheme 1. Synthetic routes for 5-substituted 2-furaldehydes.

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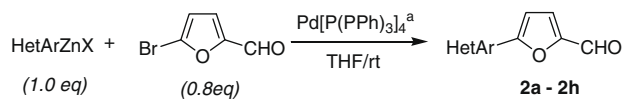
**Table 1**  
Preparation of 5-pyridyl-2-furaldehyde

Entry	Electrophile	Time (h)	Product	Yield <sup>b</sup> (%)
1		1		92
2		24		56
3		6		80
4		24		50
5		6		60
6		6		85
7		1		95
8		6		72
9		6		66

<sup>a</sup> 1 mol % used.<sup>b</sup> Isolated yield (based on furaldehyde).

5-bromo-2-furaldehyde at rt in THF to afford the corresponding products (**1f**, **1g**, and **1h**, Table 1) in good to excellent yields. Even in the reaction with 2-chloro-4-pyridylzinc bromide, the coupling reaction proceeded smoothly to give **1i** in 66% yield (Table 1, entry 9).

Moreover, the Pd(0)-catalyzed coupling reaction is also applicable to the synthesis of several different types of 5-heteroaryl-2-furaldehydes. Again, the aforementioned mild reaction conditions worked well for this coupling. The results are summarized in Table 2. Expansion of this strategy was conducted by the coupling reaction of thienylzinc bromides containing a halogen, 1,3-dioxane, and ester functionalities. As described in entries 1–3 in Table 2, the corresponding products (**2a**, **2b**, and **2c**, respectively) were obtained in good to excellent isolated yields. Significantly, these functionalities derived from organozinc reagents could be used for the further modification along with the aldehyde at the 2-position of the furan ring. Unfortunately, product **2b** appears to be an unstable compound, which leads to the formation of a mixture of products upon storage at rt. It is of interest that an unsymmetrical furan–furan linkage (**2d**, Table 2) has been obtained in 83% isolated yield

**Table 2**  
Synthesis of 5-heteroaryl-2-furaldehydes

Entry	Organozinc	Time (h)	Product	Yield <sup>b</sup> (%)
1		1.0		75
2		0.5		95
3		0.5		92
4		1.0		83
5		24		43
6		24		33
7		24		41

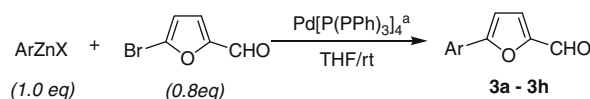
<sup>a</sup> 1 mol % used.<sup>b</sup> Isolated yield (based on furaldehyde).

by treatment with 5-ethoxycarbonyl-2-furylzinc bromide (Table 2, entry 4). We also investigated the use of heteroarylzinc bromides possessing two hetero atoms such as 2-thiazoylzinc and 5-pyrimidylzinc bromides. As noted in entries 5 and 6 in Table 2, yields (43% and 33%) were somewhat lower than other heteroarylzincs. 3-Quinolinylzinc bromide also appeared to be a good coupling partner for 5-bromo-2-furaldehyde resulting in the formation of **2g** in moderate yield (Table 2, entry 7).

Many functionalized arylzinc halides also underwent the coupling reaction with 5-bromo-2-furaldehyde under the same conditions and successfully gave 5-aryl-2-furaldehydes. In the case of electron-withdrawing groups (Table 3, entries 1–4), excellent yields (82–93%) were achieved with the exception of 3-cyanophenylzinc iodide (42%, **3d**, entry 4, Table 3). For most of the cases, the reactions were completed in 1 h at rt. From the treatment of 4-methylphenylzinc bromide (Table 3, entry 7) under the same conditions (rt, 1 h) used above, the coupling product (**3g**, Table 3) was obtained in slightly reduced yields (55%). It was found that the coupling reaction with 4-methoxyphenylzinc bromide required a longer reaction time yielding **3h** in 70% isolated yield (Table 3, entry 8).

In conclusion, an efficient synthetic procedure for the synthesis of a wide range of 5-aryl- and 5-heteroaryl-2-furaldehydes via Pd-catalyzed cross-coupling reactions of readily available organozinc reagents has been revealed.<sup>9</sup> Also, of special note are the very mild reaction conditions used in this study. This protocol offers another synthetic strategy for the preparation of 5-substituted

**Table 3**  
Preparation of 5-aryl-2-furaldehydes



Entry	Arylzinc	Time (h)	Product	Yield <sup>b</sup> (%)
1		1.0		93
2		0.5		82
3		1.0		91
4		0.5		42
5		0.5		92
6		1.0		90
7		1.0		55
8		24		70

<sup>a</sup> 1 mol % used.

<sup>b</sup> Isolated yield (based on furaldehyde).

2-furaldehyde derivatives. Further applications of this methodology are under investigation.

### Supplementary data

Supplementary data (copies of <sup>1</sup>H, <sup>13</sup>C NMR data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.035.

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- Representative coupling procedure*: Into a 50 mL rbf were added Pd(PPh<sub>3</sub>)<sub>4</sub> (0.10 g, 1 mol %) and 5-bromo-2-furaldehyde (1.40 g, 8 mmol) under an argon atmosphere. Next, 20 mL of 2-pyridylzinc bromide (0.5 M in THF, 10 mmol) was added via a syringe. The resulting mixture was stirred at rt for 1.0 h. The reaction was quenched with saturated NH<sub>4</sub>Cl solution and then the reaction mixture was extracted with ethyl acetate (10 mL × 3), washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and brine, and then dried over anhydrous MgSO<sub>4</sub>. Purification by column chromatography on silica gel (20% ethyl acetate/80% heptane) afforded 5-(2-pyridyl)-2-furaldehyde (**1a**, 1.28 g) as a white solid in 92% isolated yield.