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5-(1,3-Dioxolan-2-yl)-2-furanylzinc bromide; direct preparation, and its application for the synthesis of 5-substituted furan derivatives

ABSTRACT

good to excellent yields.

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5-(1,3-Dioxolan-2-yl)-2-furanylzinc bromide was easily prepared by the direct insertion of active zinc to

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Due to the particular interest in the furan moiety in natural products,¹ numerous studies have focused on the development of a versatile synthetic methodology for the preparation of furan derivatives, especially for the 2,5-disubstituted furan compounds. Among the well-known procedures, palladium-catalyzed crosscoupling reactions of metalated furans are one of the predominant approaches.² O'Doherty described the preparation of 5-aryl-2-furaldehydes using palladium-catalyzed cross-coupling reaction of protected furylstannes and/or furylzincs.³ A similar approach using a cross-coupling reaction of triorganozincates was also reported by Gauthier.⁴ The organometallic reagents used in these studies were prepared by the lithiation of the protected furans followed by transmetallation with zinc halide. Generally, cryogenic conditions are required for the lithiation of organic compounds. McClure also reported the regioselective palladium-catalyzed direct arylation of 2-furaldehyde.⁵ More recently, a convenient synthetic route for 5arylsubstituted 2-furaldehydes utilizing the coupling reaction of various organozinc reagents with 5-bromo-2-furaldehyde was reported.⁶ Even though this route could provide a variety of 5-substituted furaldehydes, a drawback to this procedure is that some of organozinc reagents are not readily available. Therefore, in spite of the present methodologies, there is still a need to explore a versatile synthetic methodology for the preparation of 5-substituted furan derivatives.

We herein would like to report a convenient synthetic route for the preparation of 5-substituted furan derivatives. It is of interest

* Corresponding author. E-mail address: kimsemail@dankook.ac.kr (S.-H. Kim). that this methodology provides a unique way of preparing highly functionalized 2-furaldehydes.

2-bromo-5-(1,3-dioxolane)furan under mild conditions. Of interest, the resulting organozinc was suc-

cessfully coupled with aryl halides and acid chlorides affording the corresponding coupling products in

As shown in Scheme 1 and 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide **1** was easily prepared by the direct insertion of active zinc to 2-(5-bromofuran-2-yl)-1,3-dioxolane under mild conditions.⁷ To confirm the formation of the corresponding organozinc reagent, the reaction mixture was quenched with iodine and analyzed by GC and GC–MS. Both analyses clearly showed the formation of 2-(5-iodofuran-2-yl)-1,3-dioxolane. From this result, it could be inferred that the corresponding organozinc reagent (**1**) was successfully obtained. To find out the usefullness of the resulting organozinc reagent, subsequent coupling reactions have been performed with a variety of different types of electrophiles such as aromatic halides, haloamines, halophenols, and carboxylic acid chlorides.

Prior to the general applications of 5-(1,3-dioxolan-2-yl)-2furanylzinc bromide **1**, a typical Pd-catalyzed C–C bond-forming reaction with 1-bromo-4-iodobenzene was carried out. As described in Scheme 2, two derivatives were achieved depending upon the work-up procedure.

The coupling reaction was completed in 1 h at room temperature in THF in the presence of 1 mol % Pd(PPh₃)₄. As is typical, an acidic work-up procedure gave rise to the 5-(4-bromophenyl)-2-furaldehyde **B** in 89% isolated yield. Meanwhile, a protected furaldehyde **A** was obtained from the work-up procedure using ammonium chloride in excellent yield.

As described in aforementioned report,⁶ these types of molecules are easily accessible via the cross-coupling reaction of 2-bromo-5-furaldehyde with the corresponding organozinc regents. Therefore, we have tried somewhat different types of coupling





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Scheme 1. Preparation of 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide.



Scheme 2. Preparation of 5-aryl-substituted furans.

reactions to achieve complex molecules. Table 1 shows the results observed from Pd-catalyzed cross-coupling reactions with a variety of aryl bromides.

In an effort to evaluate the overall feasibility of the organozinc **1**, coupling reaction with 2-bromo-5-furaldehyde was carried first under the conditions depicted in Table 1. The reaction proceeded

Table 1

Pd-catalyzed coupling reaction

smoothly at room temperature and was completed in 30 min. Even though the formation of the cross-coupling product was confirmed by GC and GC-MS, unfortunately, the separation of coupling product failed due to the instability of the product in the atmosphere (Table 1, entry 1). However, a similar compound **1b** which has an ester functionality was successfully obtained in 63% isolated yield (Table 1, entry 2). The next attempt was to couple some aromatic bromides that the corresponding organozinc reagents were not readily available from the direct insertion method using active zinc route. Use of Pd(OAc)₂/SPhos catalytic system successfully afforded the coupling product 1c in 73% isolated yield (Table 1, entry 3). It is of importance that no extra ligand was necessary for the coupling reaction in the presence of Pd(PPh₃)₂Cl₂. It worked effectively in the coupling reaction at room temperature with tetramethylphenyl, tert-butylphenyl, and acenaphthyl bromides leading to the corresponding products, 1d, 1e, and 1f in excellent yields (Table 1, entries 4-6), respectively. This condition was also very effective with an electron-rich phenyl bromide (Table 1, entry 7).



^a Isolated yield (based on aryl halide) otherwise mentioned.

^b Conversion by GC, no isolated product.

Table 2

Coupling reaction with alcohols and amines



Entry	Halide	Conditions	Product	Yield ^a (%)
1	OH 0.4 eq	rt/30 min	CONTRACTOR 2a	92
2	0.4 eq	rt/30 min	O OH 2b	72
3	OH	rt/30 min		(>98%) ^b
4	0.8 eq	rt/30 min	CONTRACTOR 2d	(>98%) ^b
5	0.8 eq	rt/30 min	O O NH ₂ 2e	80

^a Isolated (based on halide), otherwise mentioned.
 ^b Conversion by GC, no isolated product.

Table 3

Copper-catalyze coupling reaction



Entry	Electrophile	Conditions	Product	Yield ^a (%)
1	COCI	0 °C to rt/1 h	Contraction 3a	93
2	Br	0 °C to rt/1 h	Br 3b	83
3	COCI	0 °C to rt/1 h		90
4	→ coci	0 °C/1 h	∠o → → → → → → → → → → → → → → → → → → →	89
5	COCI S	0 °C to rt/1 h	Co → S → 3e	75
6	CI N COCI	rt/1 h		83

Table 3	(continued)
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Entry	Electrophile	Conditions	Product	Yield ^a (%)	
7	(CF ₃ CO) ₂ O	0 °C/1 h	CF ₃ 3g	65	
8	Br	rt/1 h	o sh	70	

^a Isolated yield (based on electrophile).

We then attempted the coupling reaction with haloaromatic compounds containing an alcohol or an amine functional group which would be more challenging. Even though there are very limited examples of coupling reactions of organozinc compounds with haloaromatic alcohols and amines,⁸ to our knowledge, no report revealed the coupling reaction with furanylzinc bromide.

en our study, the coupling reaction was easily accomplished using 2 mol % Pd(OAc)₂ and 4 mol % SPhos in THF at room temperature. As described in Table 2, it was found that some of the coupling products were not stable enough to be isolated as a coupling product in the atmosphere. Interestingly, the stability of the coupling product is depending upon the position of functional group. For instance, 4-iodophenol and 3-iodophenol were coupled well with 1 under mild conditions affording the corresponding products, 2a and 2b, in 92% and 72% isolated yields, respectively (Table 2, entries 1 and 2). However, no isolated product was obtained from the reaction using 2-iodophenol even though the coupling reaction proceeded smoothly under the same conditions (Table 2, entry 3). In the case of employing aniline, a similar result was also observed. Again, we were not able to isolate the coupling product 2d using 4-iodoaniline (Table 2, entry 5). Meanwhile, 3-iodoaniline was coupled with 1 giving rise to the coupling product 2e in 80% isolated yield (Table 2, entry 6). In our study, no further investigations on the stability of the unstable compounds were executed.

Subsequent investigation of this chemistry was focused on introducing a carbonyl group on the 5-position of furan. To this end, copper-catalyzed coupling reactions with an acid chloride were applied since this methodology has been one of the most widely used strategies in acylation. The first attempt was carried out with benzovl chloride in a standard fashion (10 mol % Cul and 20 mol % LiCl). The coupling product 3a was achieved in excellent isolated yield (93%, Table 3, entry 1). Alkyl acid chlorides (Table 3, entries 3 and 4) were also coupled with 1 to generate ketones 3c and 3d in good yields. Interestingly, heterocyclic acid chlorides were also successfully employed in the coupling reaction with 1 providing unsymmetrical heterocyclic ketones 3e and 3f in moderate to good yields (Table 3, entries 5 and 6), respectively. It was observed that trifluoroacetic anhydride was also a good coupling partner and the coupling reaction with 1 gave ketone 3g in moderate yield (Table 3, entry 7). Finally, a S_N2' -type reaction was performed with allyl bromide resulting in the formation of 2-(5allylfuran-2-yl)-1,3-dioxolane 3h in 70% yield (Table 3, entry 8).

In conclusion, an efficient synthetic procedure for the synthesis of a wide range of 5-substituted furaldehydes via either Pd- or copper-catalyzed cross-coupling reactions of 5-(1,3-dioxolan-2yl)-2-furanylzinc bromide with readily available halides and acid chlorides has been revealed. Of special note is the very mild reaction conditions used in this study.⁹ Further applications of this methodology are under investigation.

A. Supplementary data

Experimental procedures and copies of ¹H, ¹³C NMR data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.006.

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- (a) Preparation of 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide (1); In an oven-9. dried 50 mL round-bottomed flask equipped with a stir bar was added 0.93 g of active zinc (Zn*, 14.25 mmol). 2-(5-Bromofuran-2-yl)-1,3-dioxolane (2.08 g, 9.5 mmol) was then cannulated neatly into the flask at room temperature. The resulting mixture was stirred for 3 h. The whole mixture was settled down and then the supernatant was used for the subsequent coupling reactions. (b) Representative coupling reaction procedure; Into a 50 mL round-bottomed flask were added Pd(PPh3)2Cl2 (0.17 g, 5 mol %) and 3-bromo-N,N-dimethylaniline (0.60 g, 3 mmol) under an argon atmosphere. Next, 10 mL of 5-(1,3-dioxolan-2yl)-2-furanylzinc bromide (0.5 M in THF, 5 mmol) was added via a syringe. The resulting mixture was stirred at rt for 3.0 h. Quenched with saturated NH4Cl solution, then extracted with ethyl acetate (10 mL \times 3). Washed with saturated Na₂S₂O₃ solution and brine, then dried over anhydrous MgSO₄. Purification by column chromatography on silica gel (20% ethyl acetate/80% heptane) afforded 3-(5-(1,3-dioxolan-2-yl)furan-2-yl)-N,N-dimethylaniline (1g, 0.71 g) in 92% isolated vield.