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Synthesis of 5-Pyridyl-2-furaldehydes via Palladium-Catalyzed Cross-Coupling with Triorganozincates

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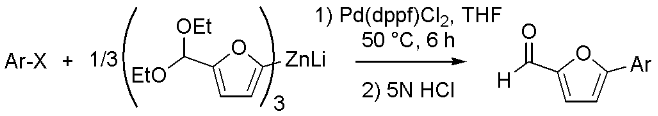
ABSTRACT



5-Pyridyl- and 5-aryl-2-furaldehydes are prepared from furaldehyde diethyl acetal in a four-step, one-pot procedure: (i) deprotonation; (2) Li to Zn transmetalation; (3) Pd-mediated cross-coupling; (4) aldehyde deprotection. Triorganozincate 7 was found to transfer all three groups in the Pd-catalyzed cross-coupling reaction with haloaromatics.

Substituted furans are ubiquitous structural units in natural products and in pharmaceuticals[1] and have often been used as synthetic intermediates.[2] We are interested in 5-pyridyl-2-furaldehydes as synthetic intermediates for pharmaceutically active compounds. Herein we report a scaleable, operationally simple procedure to prepare 5-aryl- and 5-pyridyl-2-furaldehydes from inexpensive, commercially available 2-furaldehyde diethyl acetal.[3] We also report that triorgano- and tetraorganozincates transfers all organic groups in the Pd-catalyzed cross-coupling reaction with aryl halides.

Several transition metal catalyzed biaryl coupling approaches to 5-pyridyl-2-furaldehydes were considered. The ease in which substitution can be incorporated at the 2- and 5-positions made this approach more attractive than cyclization of acyclic precursors.[4] Although 2-halofurans are suitable biaryl coupling partners,[5] the prohibitive cost of the requisite 5-bromo-2-furaldehyde[6] precluded its use on large scale. Thus, we focused instead on using furaldehyde as the nucleophilic component. In a recent report, this strategy was employed using a Heck coupling to prepare 5-aryl-2-furfurals; unfortunately, 2-halopyridines were poor substrates.[7] O'Doherty recently focused on Stille and Negishi couplings to prepare 5-aryl-2-furfurals.[5] A similar approach to 5-pyridyl-2-furaldehydes using a one-pot, four-step sequence is illustrated in Scheme 1: (i) selective deprotonation of furaldehyde diethyl acetal (**1**); (ii) transmetalation to an organometallic nucleophile capable of undergoing transition metal catalyzed cross-coupling;[8] (iii) cross-coupling; (iv) aldehyde deprotection.

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[1] Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Elsevier: New York, 1996; Vol. 2, Chapter 2.08, pp 395−436.

[2] (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795−819. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955−2020.

[3] Available from Aldrich Chemical Co. at $147/25 g, although the cost of raw material 2-furaldehyde is comparable to common solvents.

[4] (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955−2020. (b) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209−215. (c) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Elsevier: New York, 1996; Vol. 2, Chapter 2.07, pp 352−368.

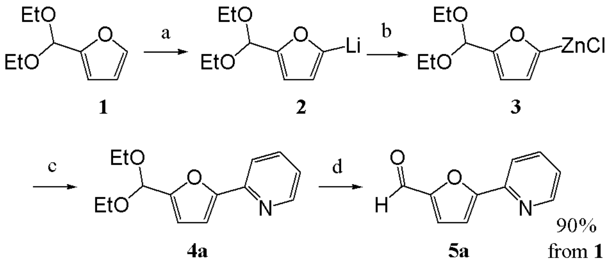
[5] Balachari, D.; Quinn, L.; O'Doherty, G. A. *Tetrahedron Lett.* **1999**, *40*, 4769−4773.

[6] Available from Aldrich Chemical Co. at $11/1 g. For selective bromination of 2-furaldehyde, see: Nazarova, Z. N. *J. Gen. Chem. (U.S.S.R.)* **1954**, *24*, 589−592.

[7] McClure, M.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677−1680.

10.1021/ol0170612 CCC: $22.00

Scheme 1. Four-Step, One-Pot Synthesis of 5-Pyridylfuraldehydes[a]



[a] Reagents and conditions: (a) n-BuLi, THF, TMEDA, −25 °C; (b) $ZnCl_2$, −25 °C to rt; (c) 2-chloropyridine (**9a**), Pd(dppf)Cl_2, 6 h, 50 °C; (d) 5 N HCl.

The deprotonation of furaldehyde diethyl acetal **1** in THF with *n*-BuLi is selective at −78 °C, providing furyllithium **2** (Scheme 1).[9,10] The extreme cryogenics of the deprotonation could be avoided with the addition of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA).[11] Using TMEDA, the deprotonation and subsequent transmetalation steps could be conducted at −20 to −30 °C.[12,13]

Organozinc reagents have seen widespread use due to exceptional functional group tolerance, ease of preparation, and removal of zinc byproducts.[14] Treatment of **2** with $ZnCl_2$ (1.1 equiv) provided organozinc chloride **3**. Several catalysts derived from Ni and Pd were screened to optimize the reaction of **3** with 2-chloropyridine (**9a**). Pd(dppf)Cl_2 [15] (2 mol %) gave the best results, providing **5a** in 90% yield after deprotection. For kilogram-scale runs, catalyst loading was reduced to 0.25 mol % without adverse effects on yield or reaction time.

Commercial bulk sources of "anhydrous" $ZnCl_2$ solid typically contain no less than 1% H_2O.[16] Dissolution in THF and extensive molecular sieve drying was therefore necessary.[17] For this reason, as well as reducing the overall reaction volume and the amount of transition metal reagents,[18] we aimed to minimize the amount of $ZnCl_2$. Thus, diorganozinc **6** was initially prepared by simply adjusting the ratio of reagents (Figure 1). Using the appropriate furyllithium **2**/$ZnCl_2$ stoichiometry, organozincate **7** (3:1) and higher order zincate **8** (4:1) were also prepared.

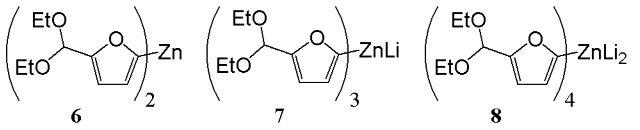


Figure 1.

Diorganozincs are more reactive than organozinc halides toward electrophiles and sometimes transfer only one of the two groups.[19] In cross-coupling reactions, diorganozincs generally transfer both organic groups.[20] Mixed aryl−dialkyl zincates have been shown to selectively transfer an aryl group to an electrophile.[21,22] We report here that triorganozincate **7** transfers all three organic groups in the cross-coupling reaction with 2-chloropyridine (**9a**) and is equally efficient as mono and bis organozincs **3** and **6** (Table 1, entries 1 and 4). However, slightly lower yields were typically obtained with higher order zincate **8** (Table 1, entry 5). We ascribe the lower yields with higher order zincate **8** to its lower thermal stability compared to that of **6** and **7**.[23]

The optimized coupling procedure was applied using organozinc reagents **6** and **7** with chloropyridines **9a**−**g** (Table 1). Since we mainly were interested in chloropyridines, the coupling reaction was also conducted using the

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[8] For synthetic routes to biaryls, see: (a) Stanforth, S. P. *Tetrahedron* **1999**, *54*, 263−303. (b) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 481−516.

[9] (a) Thames, S.; Odom, H. *J. Heterocycl. Chem.* **1966**, *3*, 490−494. (b) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104−109.

[10] The deprotonation step was monitored by HPLC by the following method: an aliquot of solution **2** was quenched with MeI. HPLC typically showed 95% conversion to **2** compared to authentic standards of furaldehyde and 5-methyl-2-furaldehyde.

[11] Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

[12] Furyllithium **2** was stable in THF with TMEDA at −20 °C for several hours. Aging at higher temperatures (e.g., −10 °C, 1 h) resulted in diminished yields of coupled product **5a** (54%).

[13] Without TMEDA, unidentifiable decomposition occurs upon aging the solution of **2** above −40 °C.

[14] (a) Knochel, P.; Jones, P. *Organozinc Reagents, A Practical Approach*; Oxford University Press Inc.: New York, 1999. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boston, 1996.

[15] Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.

[16] Kilogram quantities of solid $ZnCl_2$ can be oven dried at 120 °C, 23 in. Hg with an N_2 purge for 3−5 days. However, handling of a THF solution on scale is preferred to the hygroscopic solid.

[17] Commercial $ZnCl_2$ solution (0.5 M in THF, Aldrich Chemical Co.) contains 0.5% H_2O (~0.3 M) as determined by Karl Fisher titration.

[18] (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry*; Oxford University Press Inc.: New York, 1998, Chapter 4.

[19] (a) Knochel, P. *Synlet* **1995**, 393−403. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

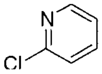
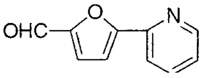
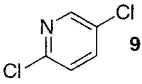
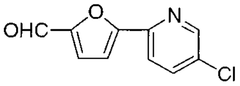
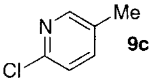
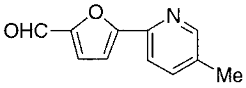
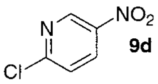
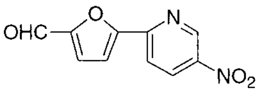
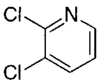
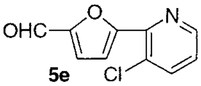
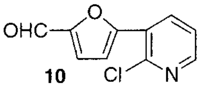
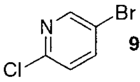
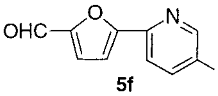
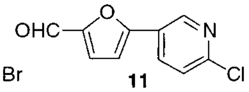
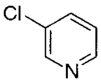
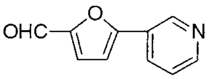
[20] This distinction is sometimes overlooked. See, for example: Perez, I.; Sestelo, J.; Sarandeses, L. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160.

[21] (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539−3540. (b) Kondo, Y.; Komine, T.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Comb. Chem.* **1999**, *1*, 123−126. (c) Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717−4718.

[22] For interesting applications of zincates and higher order zincates, see: (a) Harada, T.; Kaneko, T.; Fujiwara, T.; Oku, A. *J. Org. Chem.* **1997**, *62*, 8966−8967. (b) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377−11390. (c) Harada, T.; Otani, T.; Oku, A. *Tetrahedron Lett.* **1997**, *38*, 2855−2858. (d) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897−4907. (e) Katsuhira, T.; Harada, T.; Maejima, K.; Osada, A.; Oku, A. *J. Org. Chem.* **1993**, *58*, 6166−6168. (f) Harada, T.; Hara, D.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3821−3824. (g) Oku, A.; Harada, T.; Hattori, K.; Nozaki, Y.; Yamaura, Y. *J. Org. Chem.* **1988**, *53*, 3089−3098. (h) McWilliams, J. C.; Armstrong, J. D., III; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11970−11971. (i) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934−4946.

[23] Yield of coupled product **5a** was significantly lower after aging **8** at 25 °C for 1 h.

Table 1. Synthesis of 5-Substituted Pyridylfurals via Pd-Catalyzed Coupling of Pyridylhalide **9a-g** and Organozinc Reagents **6**, **7** and **8**

entry	substrate	Zn reagent[a]	catalyst	% yield	product
1	 **9a**	**6**	Pd(dppf)Cl_2	92	 **5a**
2		**6**	1:1 Pd/(*t*-Bu)$_3$P[b]	91	
3		**7**	1:1 Pd/(*t*-Bu)$_3$P[b]	<5	
4		**7**	Pd(dppf)Cl_2	89	
5		**8**	Pd(dppf)Cl_2	85	
6	 **9b**	**6**	Pd(dppf)Cl_2	82	 **5b**
7		**6**	1:1 Pd/(*t*-Bu)$_3$P[b]	72 (8:1 **5b**/**11**)	
8		**7**	Pd(dppf)Cl_2	85	
9	 **9c**	**6**	Pd(dppf)Cl_2	87	 **5c**
10		**6**	Pd(dppf)Cl_2	90	
11		**7**	Pd(dppf)Cl_2	80	
12	 **9d**	**6**		81	 **5d**
13		**6**	1:1 Pd/(*t*-Bu)$_3$P[b]	73	
14	 **9e**	**6**	1:1 Pd/(*t*-Bu)$_3$P[b]	58 (4:1)	 **5e**  **10**
15		**6**	Pd(dppf)Cl_2	36 (**5e** only)	
16	 **9f**	**6**	Pd(dppf)Cl_2	70 (1:1)	 **5f**  **11**
17		**6**	1:1 Pd/(*t*-Bu)$_3$P[b]	79 (**11** only)	
18		**7**	Pd(dppf)Cl_2	70 (1:1)	
19	 **9g**	**6**	Pd(dppf)Cl_2	30	 **5g**
20		**6**	1:1 Pd/(*t*-Bu)$_3$P[b]	76	
21		**7**	1:1 Pd/(*t*-Bu)$_3$P[b]	<5	
22		**7**	Pd(dppf)Cl_2	<5	

[a] Organozinc reagents were used in the following stoichiometry: **6** (0.6 equiv), **7** (0.35 equiv), and **8** (0.27 equiv). [b] "1:1 Pd/(*t*-Bu)$_3$P" was prepared from a 0.5:1 ratio of $Pd_2(dba)_3$ to (*t*-Bu)$_3$P.

catalyst system derived from (*t*-Bu)$_3$P/$Pd_2(dba)_3$.[24] As discovered by Fu, the (*t*-Bu)$_3$P:Pd ratio is an important parameter.[25] For diorganozinc **6**, a 1:1 ratio gave significantly better yields than commercially available Pd(P(*t*-Bu)$_3$)$_2$.[26] Use of $Pd_2(dba)_3$ with monodentate phosphine ligands such as P(*t*-Bu)$_3$, P(*c*-Hx)$_3$, PPh_3, P(2-furyl)$_3$, and P(*o*-tolyl)$_3$ failed to promote the reaction of halopyridines or haloaromatics with zincates **7** or **8** (Table 1, entries 3 and 21). Bidentate ligands, such as dppf, dppe, dppp, and dppb, promoted the Pd-catalyzed reaction with zincates **7** and **8**, but dppf was superior.

We also examined a series of aryl bromides in the Pd(dppf)Cl_2-catalyzed cross-coupling with organozinc re-

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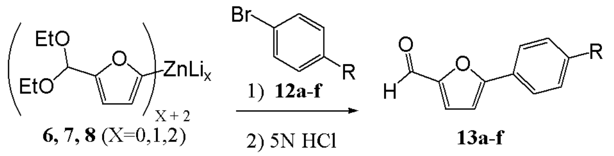
(24) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(25) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(26) Coupling of **6** and **9g** with (*t*-Bu)$_3$P/$Pd_2(dba)_3$ (2 mol % Pd) at 0.5:1, 1:1, 2:1, and 3:1 (ligand: Pd) gave 70%, 76%, 20%, and 20% yields, respectively.

Table 2. Pd(dppf)Cl_2-Catalyzed Preparation of 5-Substituted Arylfurfurals from Aryl Halides **12a**−**f** and Organozinc Reagents **6**, **7**, and **8**



entry	substrate (R)	organozinc reagent[a]	yield (%)[b]
1	**12a** (H)	**6**	77
2		**7**	76
3		**8**	71
4	**12b** (Me)	**6**	88
5		**7**	78
6		**8**	76
7	**12c** (OMe)	**6**	85
8		**7**	79
9		**8**	75
10	**12d** (NO_2)	**6**	75
11		**7**	62
12		**8**	41
13	**12e** (CN)	**6**	84
14		**7**	81
15		**8**	61
16	**12f** (CO_2Et)	**6**	84
17		**7**	63
18		**8**	56

[a] Organozinc reagents were used in the following stoichiometry: **6** (0.6 equiv), **7** (0.35 equiv), and **8** (0.27 equiv). [b] HPLC assay yields base on an authentic standard of each product.

agents **6**, **7**, and **8** (Table 2). Making optimal use of the transition metal reagent $ZnCl_2$ via complex **8** is more efficient than standard Negishi couplings; however, it suffers from less functional group tolerance (Table 2, entries 12, 15, and 18).

Spectroscopic evidence for zincate and higher order zincate formation was relayed to a simpler system generated from PhLi. ^{13}C NMR data indicates a clear trend (Table 3) in that a low-field shift in the ipso Ph-M carbon occurs with increasing electron density in the aromatic ring.[27] In the cross-coupling reaction with 2-chloropyridine, Ph_3ZnLi (0.35 equiv) and Ph_4ZnLi_2 (0.27 equiv) transferred all aryl groups in nearly quantitative yield. To address whether the reaction is catalytic in Zn(II), $ZnCl_2$ (10 mol %) was added to PhLi, followed by 2-chloropyridine and Pd(dppf)Cl_2 (2 mol %). Only a 37% yield was attained, indicating the initial formation of Ph_4ZnLi_2 followed by transfer of all four groups.[28] Interestingly, slow addition of PhLi to a THF solution of $ZnCl_2$ (10 mol %), 2-chloropyridine, and Pd(dppf)Cl_2 (2 mol %) produced an 82% yield of **13a**.[29]

Table 3. Synthesis of 2-Phenylpyridine (**13a**) via Pd(dppf)Cl_2-Catalyzed Coupling of Ph-M with 2-Chloropyridine (1.2 equiv)

entry	δ_{Ph} (ppm)[a]	Ph-M (equiv)	yield (%)
1	187.4	PhLi (1.0)[b]	<5%
2	159.4	PhZnCl (1.0)	98
3	161.8	Ph_2Zn (0.6)	95
4	168.9	Ph_3ZnLi (0.35)	100
5	170.5	Ph_4ZnLi_2 (0.27)	99

[a] Ipso Ph carbon (M−C) ^{13}C data in THF-d_8, with reference to C-2 THF signal at 67.57 ppm. [b] PhLi was prepared from bromobenzene and *s*-BuLi.

An extremely efficient process for the synthesis of 5-aryl- and 5-pyridyl-2-furaldehydes has been demonstrated. The four-step, one-pot procedure takes advantage of using substoichiometric quantities of $ZnCl_2$. A triorganozincate intermediate successfully transfers all three groups in the cross-coupling reaction. Thermally stable higher order zincates (e.g., Ph_4ZnLi_2) transfer all four groups. Efforts to understand and find further application of this chemistry are ongoing.

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Supporting Information Available: Experimental procedures and characterizations for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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[27] This trend is opposite for aliphatic protons, see: Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733−8734.

[28] The reaction appears to stall, and added Pd catalyst failed to produce more product.

[29] The PhLi (1 equiv) was added over 1 h at room temperature to 35 °C. The reaction was then aged at 60 °C for 2 h. Biphenyl (9%) was the only byproduct.