Pergamon

Tetrahedron Letters 40 (1999) 4769–4773

TETRAHEDRON
LETTERS

Efficient synthesis of 5-aryl-2-vinylfurans by palladium catalyzed cross-coupling strategies

Devan Balachari, Liam Quinn and George A. O'Doherty *

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

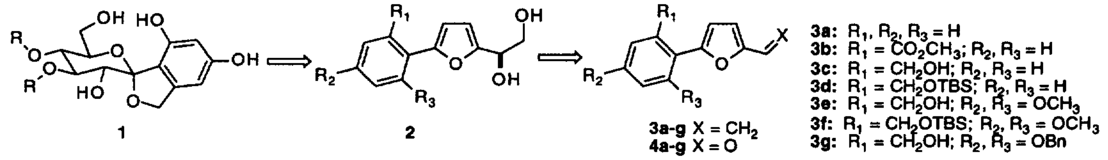
Received 17 February 1999; accepted 16 April 1999

Abstract

The synthesis of substituted 5-aryl-2-furfurals from furfural by three alternative palladium cross coupling strategies are described. The resulting 5-aryl-2-furfurals were converted into their corresponding 5-aryl-2-vinylfurans in good yields by Wittig chemistry. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Stille coupling; cross-coupling; arylfurans; vinylfurans; palladium; organotin; organozinc.

Recently, we discovered a mild route to vinylfuran via Peterson olefination methodology, which has been extended into a versatile synthesis of several hexoses.[1] We were intrigued at the possibility of accessing the papulacandin ring system **1** via an asymmetric dihydroxylation of a protected 5-(2′,4′-dihydroxy-6′-hydroxymethylphenyl)-2-vinylfuran (**3e–g**). This route if realized would allow access to analogs of **1** in both enantiomeric series. For our synthetic approach to this important anti-fungal compound,[2] we required an expeditious route to substituted 5-(2′-hydroxymethylphenyl)-2-vinylfurans **3** and hence the corresponding furaldehydes **4** (Scheme 1).



Scheme 1.

Furans substituted at the 2- and 5- positions are frequently found in nature and exhibit interesting biological and pharmacological properties.[2–7] A particularly interesting class of substituted furans are the aryl furan-2-carbaldehydes **4**, which have been shown to be useful as muscle relaxants[3] and for the treatment of asthma.[4] Similarly, derivatives of **4** have shown wide-spread biological activity as antibacterial,[5] anti-depressant,[6] anti-inflammatory[7] agents, not to mention exhibiting spasmolytic properties.[8] Cross-coupling reactions of aryl halides with metalated furans such as organozincs, organoboranes and organo-

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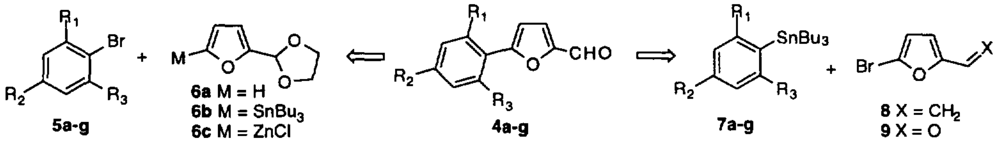
* Corresponding author.

PII: S0040-4039(99)00817-5

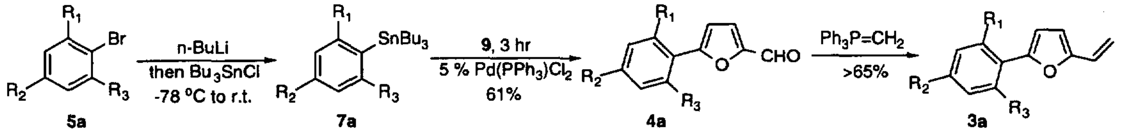
stannanes have long been under the domain of organopalladium chemistry.[9] A survey of the literature for previous syntheses of *ortho* substituted 5-aryl-2-furaldehydes lead us to diazonium chemistry[10a] and the photochemical method of D'Auria.[10b] These procedures are nicely convergent, however, we were concerned about their generality and their ability to be extended to larger scale. Herein, we report our discovery of a convergent one-pot palladium catalyzed coupling method for the synthesis of various substituted 5-(2'-hydroxymethylphenyl)-2-furaldehydes, which can tolerate a wide range of functionality on the phenyl ring.

Due to the compatibility of palladium cross-coupling reactions to a wide range of functionality, we decided to investigate the two coupling strategies outlined in Scheme 2. Collum[11] and others[12] have shown that furyl halides couple with arylstananes under typical Stille conditions. Similarly, arylzincs[13] and boranes[14] have been coupled with bromofurans. These studies, however, were limited in terms of substitution of the arene rings.



Scheme 2.

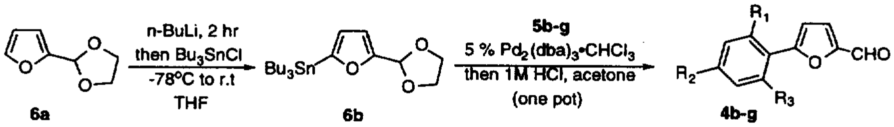
Our initial attempt to synthesize 5-aryl furfurals was with phenyltributyltin **7a** and bromofurfural **9** in the presence of 5% $Pd(PPh_3)_2Cl_2$ in refluxing dichloroethane, resulting in 5-phenyl-2-furfural **4a** in 61% yield (Scheme 3). Furan aldehyde **4a** was easily converted into vinylfuran **3a** upon treatment with the Wittig reagent in >65% yield. In an effort to improve upon this yield, we prepared 5-bromo-2-vinylfuran **8** from **9** via a Wittig reaction, but the 5-bromo-2-vinylfuran **8** proved too unstable for our purposes. A concern with this strategy is that it requires the expensive 5-bromo-2-furfural ($9/g) and that the introduction of a tributylstannyl group to the more substituted arenes (**3b–g** to **7b–g**) was found to be low yielding. Hence, an alternative procedure was sought.



Scheme 3.

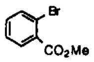
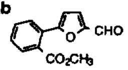
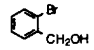
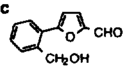
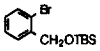
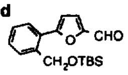
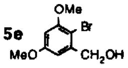
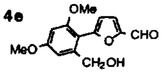
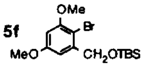
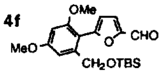
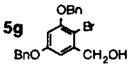
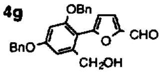
For an alternative procedure we chose to metalate the furan fragment **6a** and cross couple with various arylhalides like **5a–g** (Scheme 2). This was easily accomplished by protecting the aldehyde of furfural and lithiating the 5-position. Treatment of the ethylene glycol acetal of furfural **6a** with *n*-BuLi resulted in formation of the lithio derivative which was subsequently transmetallated to **6b** by adding tributyltinchloride (Scheme 4).[15] Stannane **6b**, after filtering through a plug of silica gel, was used in the Stille reaction without further purification. The resulting product underwent a clean reaction with variously substituted arylbromides (**5b–g**) to yield the 5-aryl-furan-2-carboxaldehydes (**4b–g**) in good yields (Table 1).[16,17] One of the advantages of this procedure is the tolerance of various functional groups on the arene ring (OR, CH_2OH, CO_2CH_3).

To eliminate the use of stoichiometric organotin reagents, we investigated the feasibility of coupling other metallofurans. Our initial attempts to couple the lithiated furan with various arylbromides under palladium(0) catalysis met with no success. We then prepared the furyl zinc reagent **6c** by transmetallating the lithiated **6a** with solid zinc chloride (Scheme 5). When the zinc reagents **6c** and **5b** were subjected to the same Pd(0) coupling condition as in Scheme 4, only poor yields of **4b** were obtained. Neither



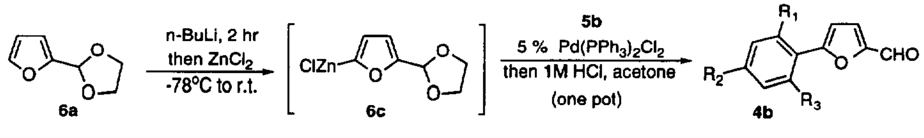
Scheme 4.

Table 1
Pd-catalyzed cross coupling of aryl halides with metallated furans

Entry	ArylX	Furyl-M	Catalyst	Product	yield of 4	yield of 3^D
1	5b 	6b 6c	A B	4b 	65 % 74 %	68 %
2	5c 	6b	A	4c 	66 %	65 %
3	5d 	6b	A	4d 	41 %^{C}	95 %
4	5e 	6b	A	4e 	60 %	62 %
5	5f 	6b	A	4f 	43 %^{C}	99 %
6	5g 	6b	A	4g 	69 %	64 %

A. Reactions were carried out with 2.5 % Pd$_2$(dba)$_3$•CHCl$_3$ and 10 % PPh$_3$ in refluxing toluene. B. Reactions were carried out with 5 % Pd(PPh$_3$)$_2$Cl$_2$ and 2.0 equiv. RZnCl in THF at RT. C. Compounds **4c** and **4e** are also converted into **4d** and **4f** using TBSCl, DMF/DMAP/imidazole/r.t./12h condition. D. Vinylfurans **3a-g** are sensitive to polymerization. All yields were reported after purification and all new compounds were fully characterized.[17]

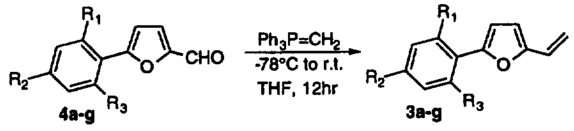
longer reaction time nor higher temperature increased the yield of coupled product. After considerable experimentation we found that at room temperature simply switching the palladium(0) source from $Pd_2(dba)_3 \cdot CHCl_3$ to $Pd(PPh_3)_2Cl_2$ gave us yields of **4b** comparable to the tin procedure[11,18] (see Table 1).



Scheme 5.

Although the zinc cross-coupling procedure gives higher yields of furan **4b**, a drawback to this procedure is its incompatibility with unprotected alcohols and unreactivity towards the less reactive aryl halides. For instance, **6c** under various cross coupling conditions only gave low yields of **4c–g** (<10%). Finally, the substituted furfurals **4a–g** were easily converted to their corresponding vinylfurans **3a–g** by action of the Wittig reagent (Scheme 6 and Table 1).

In conclusion, we have developed mild and efficient methods for the synthesis 5-aryl-2-vinylfurans in



Scheme 6.

large scale with good overall yields. The cross coupling study also showed that many functional groups are tolerated which should be beneficial for further synthetic applications.

Acknowledgements

We thank the University of Minnesota (grant in aid program), the American Cancer Society for an Institutional Research Grant (IRG-58-001-40-IRG-19) and the National Science Foundation for their generous support of our program.

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16. General procedure for Stille coupling: A 10 ml RB-flask under nitrogen was charged with furylstannane (0.466 mmol), substituted bromobenzene (0.512 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), and triphenyl phosphine (12.5 mol%). Toluene (3 ml) was added and the reaction was stirred for 30 min at rt then refluxed overnight. The reaction mixture was cooled to rt, diluted with ether (5 ml) and saturated KF solution (1 ml) was added. The organic layer was separated, washed with water, HCl (1 M), water, brine and dried over sodium sulfate. The crude product without further purification was dissolved in acetone (5 ml) and 1 M HCl (0.2 ml) and stirred at rt overnight. After removal of solvent the crude reaction product was extracted with dichloromethane (10 ml) washed with water, dilute sodium bicarbonate, water, brine and dried (Na_2SO_4). Flash chromatography resulted in the furancarbaldehyde derivatives (**4a–g**). Procedure for zinc coupling: a solution of **6c** (7.24 mmol) was prepared by metallation of furan ethylene acetal **6a** (7.24 mmol) in THF (20 ml) with *n*-BuLi (7.9 mmol, 3.6 ml of 2.5 M solution in hexane) at –78°C under an N_2 atmosphere for 1 h and transmetalation with anhydrous $ZnCl_2$ (0.98 g, 7.24 mmol) which was stirred at rt for 1 h. In a separate flask, bromoester **5b** (0.78 g, 3.62 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol%) were mixed and a solution of **6c** was added via syringe at room temperature. The black solution

was stirred at rt for 12 h and then quenched with saturated aqueous NH_4Cl. Work up and purification through column chromatography yielded compound **4b** (0.62 g, 74%). For preparation of **5e–g** see Barrett et al.[2]

17. Spectral data for selected compounds: compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.71 (d, 1H, *J*=3.6 Hz), 7.28 (d, 1H, *J*=3.6 Hz), 7.44 (dt, 1H, *J*=7.5, 1.5 Hz), 7.52 (dt, 1H, *J*=7.5, 1.5 Hz), 7.66 (dd, 1H, *J*=7.8, 1.2 Hz), 7.73 (dd, 1H, *J*=7.5, 1.5 Hz), 9.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.6, 110.8, 122.7, 128.4, 129.1, 129.5, 129.7, 130.8, 131.2, 152.4, 157.9, 168.4, 177.4. Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.8 (t, 1H, *J*=5.7 Hz), 4.85 (d, 2H, *J*=5.7 Hz), 6.89 (d, 1H, *J*=3.9 Hz), 7.31 (d, 1H, *J*=3.9 Hz), 7.32–7.42 (m, 2H), 7.52–7.55 (m, 1H), 7.73–7.76 (m, 1H), 9.6 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.7, 111.4, 123.6, 127.8, 128.1, 128.5, 129.7, 129.9, 138.3, 152.1, 158.7, 177.3. Compound **4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (br.s, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 4.68 (s, 2H), 6.45 (d, 1H, *J*=2.4 Hz), 6.76 (d, 1H, *J*=2.4 Hz), 6.79 (d, 1H, *J*=3.6 Hz), 7.31 (d, 1H, *J*=3.8 Hz), 9.56 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.8, 63.6, 97.7, 105.2, 109.4, 113.6, 123.5, 143.4, 151.2, 156.1, 159.0, 161.8, 177.0. Compound **4g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (t, 1H, *J*=6.6 Hz), 4.71 (d, 2H, *J*=6.6 Hz), 5.05 (s, 2H), 5.09 (s, 2H), 6.61 (d, 1H, *J*=2.1 Hz), 6.8 (d, 1H, *J*=3.6 Hz), 6.89 (d, 1H, *J*=2.1 Hz), 7.27 (d, 1H, *J*=3.6 Hz), 7.3–7.43 (m, 10H), 9.57 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.2, 70.2, 70.8, 100.2, 107.2, 110.4, 113.7, 123.3, 127.3, 127.6, 128.1, 128.2, 128.6, 128.7, 134.8, 136.2, 136.3, 143.1, 151.2, 155.8, 158.2, 160.9, 176.8. Compound **3g**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29 (t, 1H, *J*=6.6 Hz), 4.72 (d, 2H, *J*=6.6 Hz), 5.06 (s, 2H), 5.09 (s, 2H), 5.17 (dd, 1H, *J*=11.3, 1 Hz), 5.63 (dd, 1H, *J*=17.3, 1 Hz,), 6.36 (d, 1H, *J*=3.4 Hz), 6.54 (dd, 1H, *J*=17.6, 11.2 Hz), 6.62 (t, 2H, *J*=2.8 Hz), 6.86 (d, 1H, *J*=2.2 Hz), 7.34–7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.5, 70.2, 70.6, 98.7, 100.4, 106.6, 110.0, 111.671, 112.3, 112.8, 125.0, 127.1, 127.6, 127.8, 128.1, 128.5, 128.7, 136.6, 142.2, 148.5, 152.0, 157.6, 159.7.
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