PALLADIUM CATALYZED CROSS-COUPLING REACTIONS FOR THE SYNTHESIS OF 2,5-DISUBSTITUTEDFURANS

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Abstract: : A convenient synthesis of 2,5-bisarylfurans, 2,5-bisbenzylfurans and 2,5-bisbenzoylfurans employing 2,5-bis(tri-n-butylstannyl)furan and palladium catalyzed cross-coupling reactions is described.

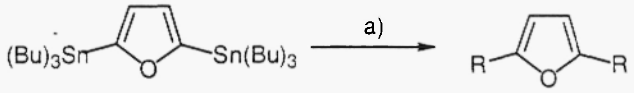
Introduction

The synthesis and chemistry of furans remains of considerable current interest as a consequence of the their presence in natural products and their utility as pharmaceuticals and synthetic tools (1). We have an interest in 2,5-diarylfurans and related compounds as DNA minor-groove binding agents which show promise as chemotherapeutic agents (2-6). A classical approach, the Paal-Knorr method, of synthesis of 2,5-diarylfurans employs acid catalyzed cyclodehydration of 1,4-diketones (7). Often synthesis of a requisite 1,4-diketone represents a considerable synthetic challenge. The methodology of Stetter which employs thiazolium catalyzed nucleophilic addition of arylaldehydes to divinylsulfone represented a significant advance in the convenient synthesis of 1,4-diaryl-1, 4-diketones (8). Despite the utility of the Stetter approach it has limitations, for example, when strong electron withdrawing groups are present on the aryl rings the method results in very low yields or fails (9). A classical method for formation 2,5-bisbenzylfurans and 2,5-bisbenzoylfurans, which also is limited by the presence of strong electron withdrawing groups, uses Friedel-Crafts strategies (10). This approach is also limited due to the high reactivity of furan and therefore these reactions are often difficult to control (10). 2,5-Diarylfurans bearing cyano or nitro groups on the aryl rings are important for our program of synthesis of DNA minor-groove binders (2-6). A potential approach for preparation of 2,5-diarylfurans, which has not been extensively explored, involves the use of palladium catalyzed cross-coupling reactions using Stille chemistry. The coupling of arylstannanes with 2,5-dibromofuran has been reported(11); however, the latter compound is not readily available and this route requires the inconvenience of individual preparation of arylstannanes. The preparation of 2,5-bis (trimethylstannyl) furan (12) and 2,5-bis (tri-*n*-butylstannyl) furan (13) has been reported. The two stannylfurans, respectively, were converted to halofurans and to polyphenylene-*co*-

furan. The use of bis-stannyl compounds in Stille reactions has been rather limited(14), with the exception of the detailed studies with 3,4-bis (tri-n-butylstannyl) furan (15). We describe here the successful application of Stille cross-coupling chemistry for the preparation of 2,5-disubstitutedfurans.

Results and Discussion

The palladium catalyzed reactions of 2,5-bis(tri-*n*-butylstannyl)furan with aryl bromides (**2-7**) in dioxane solution at 90-100°C for 12-24 hours gave 2,5-diarylfurans in good yields; ranging from 70 to 86%(see Scheme 1 and Table 1) (16). One case, that of **8**, gave a 50% yield. The two aryl iodides used in coupling reactions **1** and **9** gave 58% and 77% yield , respectively, of the expected 2,5-bisarylfurans. However, in these cases it was necessary to use DMF as the solvent since when dioxane was employed only modest yields (~20%) were obtained. Interestingly, Yang and Wong (15) noted that 3,4-bis (tri-n-butylstannyl)furan coupled poorly with aryl iodides and had to use CuI as a co-catalyst along with Pd $(PPh_3)_4$ to obtain a good yield of the bisarylfurans. In our cases, a simple change of solvent to DMF gave useful yields. Cross-coupling with heteroaryl bromides (**10-13**) also gave good yields in the approximately 70% range; thus providing a convenient method for preparation of aromatic triheterocyles.



Scheme 1. a) RX, $Pd(PPh_3)_4$, dioxane or DMF (See Table 1)

Stille cross-coupling reactions employing benzyl halides are well documented (17). The reaction of 2,5-bis(tri-*n*-butylstannyl)furan with benzyl chlorides **14** and **15** gave the expected 2,5-disubstitutedfuran products, however the yields were only moderate; in the 50% range. Cross-coupling using the benzyl bromide **16** gave a somewhat higher yield, 69%, of the 2,5-disubstitutedfuran product. This approach provides a simple method for obtaining these bis-benzylfurans.

The coupling of arylstannanes with carboxylic acid chlorides is a useful approach, under mild conditions, for ketone synthesis (18). In the case of 2,5-bis (tri-*n*-butylstannyl) furan coupling with aryl acid chlorides worked reasonably well, however, the yields were only in the 40% range(see example **17** and **18**).

Table 1. Synthesis of 2.5-Disubstitutedfurans[a].

Entry	R	X	Temp (C°)	Rx Time (Hr)	% Yield	Mp°C(lit.mp)
1[b]	Ph	I	100	18	58	87 (88)[1]
2	$4\text{-CNC}_6\text{H}_4$	Br	100	15	75	284-285(284-285)[2]
3	$3\text{-CNC}_6\text{H}_4$	Br	100	20	70	159-160
4	$4\text{-CN-2-CH}_3\text{C}_6\text{H}_3$	Br	100	12	80	244-245
5	$4\text{-NO}_2\text{C}_6\text{H}_4$	Br	100	18	86	269-270(270-272)[3]
6	$4\text{-NO}_2\text{-3-CH}_3\text{C}_6\text{H}_3$	Br	90	16	80	230-231
7	$4\text{-NO}_2\text{-2-CH}_3\text{C}_6\text{H}_3$	Br	100	18	85	242-243
8	$4\text{-COOEtC}_6\text{H}_4$	Br	100	24	50	164-165
9[b]	$3\text{-NO}_2\text{C}_6\text{H}_4$	I	100	16	77	195-196(190-193)[4]
10	5-CNfuran-2-yl	Br	100	14	70	167-168
11	4-CNfuran-2-yl	Br	100	12	72	212-213
12	5-CNthiophene-2-yl	Br	100	12	75	187-188
13	2-CNthiophene-4-yl	Br	100	12	72	205-206
14	benzyl	Cl	100	16	56	49.5-52 (51)[5]
15	4-NO_2benzyl	Cl	90	8	46	154-155.5
16	4-CNbenzyl	Br	90	10	69	190-191
17	benzoyl	Cl	75	48	58	106-107
18	4-NO_2benzoyl	Cl	75	18	41	166-168

a) Catalyst 5 mol % $Pd(PPh_3)_4$ based on 2.5-bis(tri-*n*-butylstannyl)furan ; dioxane used as solvent b) for cases 1 and 9 DMF was used as solvent. 1) F. Barba. M. D. Velasco, A. Guirado. *Synthesis*. 593(1984). 2) B. P. Das and D. W. Boykin. *J. Med. Chem.*. 20, 531 (1977). 3) V. Amarnath and K . Amarnath, *J. Org. Chem.* 60, 301 (1995). 4) C. Ling and P. M. Lahti. *J. Am. Chem. Soc.* 116. 8784 (1994). 5) L. M. Gomes. *C. R. Acad. Sci., Ser. C.* 270, 750, (1970).

The use of 2.5-bis(tri-*n*-butylstannyl)furan in palladium catalyzed cross-coupling reactions provides a convenient one step process for preparation of a range of 2.5-disubstitutedfurans which are often difficult to obtain. This method provides an attractive alternative to other approaches we have employed for the preparation of 2.5-diarylfurans(19), especially for those containing strong electron withdrawing groups.

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(16) Typical procedure for preparation of 2,5-disubstitutedfuran: The 2,5-bis (tri-*n*-butylstannyl) furan used in this work was prepared using s-butyllithium, as described by Seitz(12), in a 70% yield in contrast to the 40% yield reported(13) using n- butyllithium. A mixture of 2,5-bis (tri-*n*-butylstannyl)furan (3.23 g , 0.005 mole), 4-bromo-3-methylbenzonitrile (1.96 g , 0.01mole) and 80 mg $Pd(PPh_3)_4$ in 60 ml of dry dioxane was heated under nitrogen at 100°C for 12 hr (reaction course followed by TLC). The volume of the reaction mixture was reduced under vacuum; 100 ml of $CHCl_3$ and 50 ml of 10% aqueous KF was added and the mixture was stirred for 0.5 h. The organic layer was separated, dried over magnesium sulfate and the solvent was removed under vacuum. The crude product was chromatographed over neutral alumina; elution with $CHCl_3$: ether(1:1) , followed by $CHCl_3$. A bright yellow solid(1.2 g, 80 %), mp 244-245°C, was obtained. ^{1}HNMR (DMSO-d_6) 7.9 (d, 2H, J = 8.4 Hz), 7.76 (s, 2H), 7.71 (d, 2H, J = 8.4 Hz), 7.16 (s, 2H), 2.59 (s, 6H). ^{13}CNMR (DMSO-d_6) 151.3, 135.0, 134.4, 132.7, 129.4,126.8, 118.1 113.6, 109.7, 20.8. Ms m/z 298. Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.72; N, 9.38. Found: C, 80.43; H, 4.73; N, 9.33.

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