A FACILE SYNTHESIS OF THE PRODRUG 2,5-BIS(4-*O*-METHOXYAMIDINOPHENYL)FURAN AND ANALOGS

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Abstract: A convenient synthesis of the prodrug 2,5-bis(4-*o*-methoxyamidinophenyl)furan and analogs using 2,5-bis(tri-*n*-butylstannyl)furan and palladium catalyzed cross-coupling reactions is described.

Introduction

2,5-Bis(4-*O*-methoxyamidinophenyl)furan (**1**), a prodrug of furamidine, which is effective when administered orally in an immunosupressed rat model for *Pneumocystis carinii* pneumonia (PCP) and it is also effective against mouse models of human African trypanosomiasis.[1 2] Currently, **1** is in Phase II clinical trials against both of these diseases.[2] A previous report showed that 2,5-bis(4-*O*-methoxyamidinophenyl)furan (**1**) and 2,5-bis(4-hydroxyamidinophenyl)furan (**4**) were approximately equally effective against PCP when given orally, however the closely related analog 2,5-bis(4-*O*-ethoxyamidinophenyl)furan (**2**) was not effective.[1] The prior synthesis of **1** and analogs involved reaction of 2,5-bis (4-cyanophenyl)furan under Pinner-type conditions to form the corresponding imidate ester that was then allowed to react with the appropriate hydroxylamine.[1] The Pinner process is cumbersome since rigorous exclusion of water is essential. For the compounds under discussion the process is further complicated due to the very low solubility of 2,5-bis(4-cyanophenyl)furan, necessitating quite long reaction times (3-7 days). A synthesis of these prodrugs which avoids use of the Pinner approach would be quite useful. We reported the use of Stille coupling for the preparation of several 2,5-diarylfurans, however, coupling of amidoximes was not explored by us[3] nor does Stille coupling of amidoxime aryl halides appear to have been studied. We describe here the successful application of Stille cross-coupling chemistry for the preparation of 2,5-bis (4-hydroxy and 4-*O*-alkylamidinophenyl)furans.

Results and Discussion

The palladium catalyzed reactions of 2,5-bis(tri-*n*-butylstannyl)furan with amidoxime aryl bromides in dioxane solution at 90-100 °C for 14-18 hours gave 2,5-diarylfurans in good yields; ranging from 61 to 70% (Scheme 1 and Table 1).[4] Interestingly, coupling of the 4-bromobenzamidoxime gave the corresponding bis-amidoxime **4** in good yield. In contrast, we noted under *N*-coupling conditions that benzamidoxime was converted to benzonitrile[5] and that attempted Heck coupling of 4-bromobenzamidoxime with 2(4-cyanophenyl)furan yielded 2,5-bis(4-cyanophenyl)furan.[6]

Scheme 1

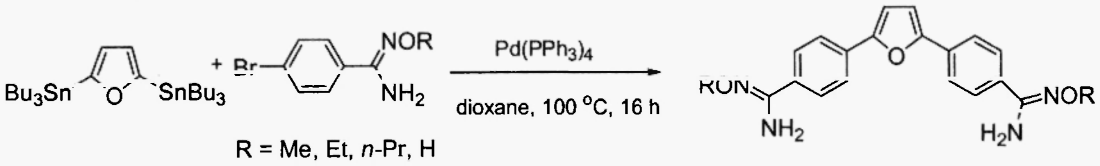

Table 1. Synthesis of Amidoxyfurans.

Entry	R[a]	Temp (C^0)	Reaction Time (h)	% Yield	Mp (°C)
1	Me	100	16	61	192.5-193
2	Et	100	14	65	164-165
3	*n*-Pr	100	14	70	158.5-159.1
4	H	100	18	67	Over 350

a) Catalyst 5 mol % $Pd(PPh_3)_4$ based on 2,5-bis(tri-*n*-butylstannyl)furan ; dioxane used as solvent .

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 these prodrug molecules which are difficult to obtain by the Pinner approach. This method provides an attractive, potentially scalable, approach to these amidoximes.

Acknowledgement

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References and Notes

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(4) Typical procedure: An oven-dried 25 mL round-bottomed flask was charged with 678 mg (1.05 mmol) of 2,5-bis(tributylstannyl)furan and 456 mg (2 mmol) of *O*-*n*-propyl-*p*-bromobenzamidoxime under nitrogen. To that was added 10 mL of anhydrous dioxane and 115 mg of tetrakis(triphenylphosphene)palladium(0) and the mixture was heated at reflux for 16 hours. After complete consumption of the amidoxime by TLC, the reaction mixture was cooled and the solvent was removed using a rotary evaporator. The residue was diluted with EtOAc and filtered through celite, the celite layer was washed with EtOAc. Then the combined EtOAc layers were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using 35-40% ethyl acetate in hexane to yield 294 mg (70%) of **3**. ^1H NMR ($CDCl_3$) δ 0.98 (t, 6H, $2CH_3$, J = 4.5 Hz), 1.75 (m, 4H, $2CH_2$), 4.09 (t, 4H, $2CH_2$, J = 4.5 Hz), 4.82 (br, 4H, $2NH_2$), 6.78 (s, 2H, Furan), 7.70 (d, 4H, Ar, J = 6.7 Hz), 7.75 (d, 4H, Ar, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 10.8, 22.8, 75.6, 108.6, 124.1, 126.4, 131.7, 132.0, 151.5, 153.4. MS (EI) 421 (M+1, 100%), 405 (5%), 363 (17%), 347 (5%), 288 (10%). Anal. Calcd for $C_{24}H_{28}N_4O_3$: C 68.57; H 6.66; N 13.33. Found: C 68.49; H 6.72; N 13.36.

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