Pergamon

Tetrahedron Letters, Vol. 37, No. 19, pp. 3247-3250, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00530-8

A General Synthesis of β-Aryl and Heteroarylpyrroles by Palladium-catalyzed Coupling Reaction of β-Tributylstannylpyrrole with Aryl and Heteroaryl Halides

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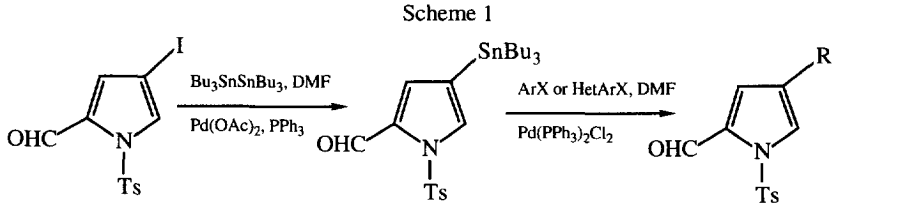
Abstract: Several β-aryl and heteroarylpyrroles have been synthesized by palladium-catalyzed coupling reaction of β-tributylstannylpyrroles with aryl and heteroaryl halides in 62-89% yields. These precursors may be readily converted into β-aryl and heteroaryl substituted porphyrins for the study of the oxophlorin to oxaporphyrin conversion in heme catabolism, catalyzed by heme oxygenase. Copyright © 1996 Elsevier Science Ltd

Attention has been drawn to β-aryl substituted porphyrins for the study of the oxophlorin to oxaporphyrin conversion in heme catabolism, catalyzed by heme oxygenase.[1,2] However, due to lack of general methods for the synthesis of the necessary β-arylpyrrole precursors only a few β-aryl substituted porphrins[3] are known. Recently, Chang has shown that the β-phenyl substituted pyrroles could be prepared from β-bromopyrroles and phenylboric acid by Suzuki cross coupling in excellent yield, [4] whereas our laboratory demonstrated that β-vinylpyrroles could be prepared by Stille coupling reaction of β-iodopyrroles with vinyltributyltin also in excellent yield.[5] Although these two methods have been shown to be efficient for the synthesis of a wide range of β-unsaturated substituted pyrroles, their success depends largely on the availability of the starting materials, arylboric acids and alkenyltributyltin respectively, whose preparation may be problematic when other sensitive functional groups are present. To avoid such disadvantages we report herein a general and highly efficient synthesis of β-aryl and heteroarylpyrroles by palladium-catalyzed coupling reaction of the readily prepared N-protected-β-tributylstannylpyrrole **2** with aryl and heteroaryl halides (Scheme 1).

Scheme 1



1 **2** **3** R = Ar, HetAr

The starting material, 2-formyl-4-iodo-1-tosylpyrrole **1** was prepared following known procedures.[6] Tributylstannylpyrrole **2** required for the coupling was synthesized as follows. A mixture of **1** (5.63 g, 15 mmol), $Bu_3SnSnBu_3$ (9.01 ml, 18 mmol), $Pd(OAc)_2$ (100 mg, 0.45 mmol), and PPh_3 (235 mg, 0.9 mmol) was stirred at 80°C for 15 min under N_2. The reaction mixture was then diluted with brine and extracted with ethyl acetate (3 x 100 ml). The organic phase was washed brine with (4 x 100 ml), dried over anhydrous Na_2SO_4 and evaporated. Chromatography of the residue on silica gel using n-hexane/AcOEt=20:1 as eluent afforded compound **2** (7.31 g, 91%) as light yellow oil.[7] It is worth noting that stannane **2** was quite stable and could be stored in the refrigerator for several weeks without significant decomposition. Following the above procedure several other β-tributylstannylpyrroles have been prepared in good yields in our laboratory. These results will be published elsewhere.

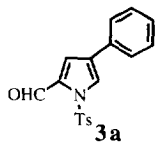
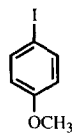
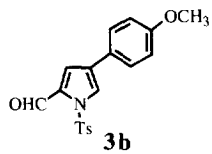
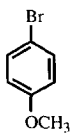
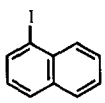
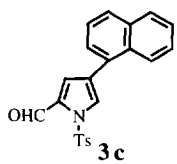
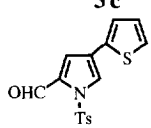
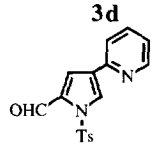
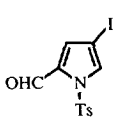
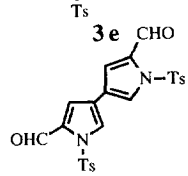
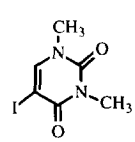
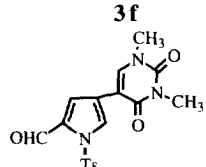
As shown in Scheme 1, a series of aryl and heteroaryl halides was successfully cross-coupled with β-tributylstannylpyrrole **2** to give the expected products **3**. The yields of products **3a-3f** were satisfactory when toluene was used as solvent. However, under the same reaction conditions, in the cases of **3f** and **3g**, very poor yields were observed due to solubility of the starting materials, 2-formyl-4-iodo-1-tosylpyrrole and 5-iodo-1,3-dimethyluracil, in toluene. This problem was solved by using DMF as solvent and the expected products were obtained in good yields. In a typical experiment, a mixture of compound **2** (1.19 g, 2.2 mmol), aryl or heteroaryl halide (2.0 mmol) and bis(triphenylphosphine)palladium(II) chloride (42 mg, 3 mol%) in toluene (10 ml) was refluxed under N_2 untill the starting material disappeared (TLC). During the course of the reaction the color changed from yellow to black as Pd° was formed. The reaction mixture was cooled to room temperature, CH_2Cl_2 (50 ml) added and the resulting solution washed with saturated aqueous NaCl (50 ml) and water (50 ml). The organic phase was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent and chromatography on silica gel, eluting with ethyl acetate/n-hexane (1:5), gave the product. The results are listed in Table 1.

The major advantages of this method include good to excellent yields and readily prepared starting material, tributylstannylpyrrole which is stable to air and moisture. Since arylboric acids or aryltributyltin are avoided, aryl and heteroaryl bromides and iodides possessing varied and sensitive substitutents could be used directly as starting materials and gave the expected products. Moreover, the method tolerates an aldehyde group at the pyrrolic α-position during the formation of β-tributylstannylpyrroles, which will be essential for further conversion of these precursors into β-aryl and heteroaryl porphyrins.

Summary: The above catalytic procedure provides a general construction of otherwise barely accessible β-aryl and heteroarylpyrroles from β-tributylstannylpyrrole and aryl or heteroaryl halides.

Acknowledgement: We would like to thank the NIH and the Robert A. Welch Foundation for financial support of this work.

Table 1. Palladium-complex catalyzed synthesis of β-aryl and heteroaryl substituted pyrroles

Entry	Halide	Solvent	Condition	Product[(a)]	Yield (%)[(b)]
1		toluene	reflux, 0.5 h	 **3a**	85
2		toluene	reflux, 0.5 h	 **3b**	79
3		toluene	reflux, 5 h	**3b**	68
4		toluene	reflux, 0.5 h	 **3c**	76
5		toluene	reflux, 0.5 h	 **3d**	89
6		toluene	reflux, 5 h	 **3e**	67
7		DMF	120°C, 6 h	 **3f**	70
8		DMF	120°C, 6 h	 **3g**	62

(a) For ^{1}H, ^{13}C-NMR and +FAB-MS data see References and Note 7. (b) Isolated yields.

References and Notes.

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7. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker-WM300MHz spectrometer with TMS as internal standard, $CDCl_3$ as solvent, chemical shift in ppm, coupling constants J in Hz. Compound **2**: ^{1}H-NMR δ 9.98 (s, 1H, CHO), 7.80 (d, ^{3}J = 8.4, 2H, H-Ph), 7.48 (d, ^{4}J = 1.9, 1H, H-pyrrole), 7.31 (d, ^{3}J = 8.4, 2H, H-Ph), 7.18 (d, ^{4}J = 1.9, 1H, H-pyrrole), 2.34 (s, 3H, CH_3); ^{13}C-NMR δ 178.9 (CHO), 145.6, 137.8, 135.8, 134.8, 134.4, 131.9, 130 (2C), 127.3 (2C), 120.0, 29.9 (3C), 27.1 (3C), 22.4, 17.4 (3C), 13.6 (3C); +FAB/DP-MS m/e 540 (M^{+}+ 1, 74), 482 (32), 426 (17), 368 (55), 291 (29), 235 (53), 179 (100). Compound **3b**: ^{1}H-NMR δ 10.01 (s, 1H, CHO), 7.82 (d, ^{3}J = 8.4, 2H, H-Ph), 7.77 (d, ^{4}J = 1.6, 1H, H-pyrrole), 7.45 (d, ^{3}J = 9.2, 2H, H-Ph), 7.39 (d, ^{4}J = 1.6, 1H, H-pyrrole), 7.33 (d, ^{3}J = 8.4, 2H, H-Ph), 6.94 (d, ^{3}J = 9.2, 2H, H-Ph), 3.84 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C-NMR δ 179.3 (CHO), 146.0, 133.9, 130.2 (2C), 129.4, 128.0, 127.3 (2C), 126.8 (2C), 124.1, 124.0, 121.2, 114.4 (2C), 112.4, 55.3, 21.7; +FAB/DP-MS m/e 356 (M^{+}+ 1, 15), 250 (18), 201 (12), 154 (100). Compound **3c**: ^{1}H-NMR δ 10.11 (s, 1H, CHO), 7.91 (d, ^{3}J = 8.4, 2H, H-Ph), 7.82 (d, ^{4}J = 1.7, 1H, H-pyrrole), 7.53-7.15 (m, 10H), 2.47 (s, 3H, CH_3); ^{13}C-NMR δ 179.2 (CHO), 146.1, 134.5-122.5 (20C), 21.7; +FAB/DP-MS m/e 376 (M^{+}+ 1, 8), 307 (15), 221 (6), 154 (100). Compound **3d**: ^{1}H-NMR δ 9.96 (s, 1H, CHO), 7.75 (d, ^{3}J = 8.5, 2H, H-Ph), 7.68 (d, ^{4}J = 1.6, 1H, H-pyrrole), 7.25 (d, ^{3}J = 8.5, 2H, H-Ph), 7.23 (d, ^{4}J = 1.6, 1H, H-pyrrole), 7.18-6.95 (m, 3H, H-thiophene), 2.34 (s, 3H, CH_3); ^{13}C-NMR δ 179.1 (CHO), 146.2, 133.7, 130.2 (2C), 129.0, 127.7, 127.4 (2C), 125.6, 124.6, 124.0 (2C), 122.3, 121.3, 21.7; +FAB/DP-MS m/e 332 (M^{+}+ 1, 25), 307 (18), 177 (12), 154 (100).Compound **3f**: ^{1}H-NMR δ 10.03 (s, 2H, CHO), 7.83(d, ^{3}J = 8.3, 4H, H-Ph), 7.75 (d, ^{4}J = 1.6, 2H, H-pyrrole), 7.35 (d, ^{3}J = 9.2, 4H, H-Ph), 7.26 (d, ^{4}J = 1.6, 2H, H-pyrrole), 2.43 (s, 6H, 2xCH_3); ^{13}C-NMR δ 179.0 (2xCHO), 145.6 (2C), 134.2 (2C), 130.3 (4C), 128.1 (2C), 127.5 (4C), 124.6 (2C), 120.9 (2C), 110.2 (2C), 21.7 (2C); +FAB/DP-MS m/e 497 (M^{+}+ 1, 5), 460 (10), 391 (12), 307 (22), 250 (8), 154 (100). Compound **3g**: ^{1}H-NMR δ 10.08 (s, 1H, CHO), 8.32 (d, ^{4}J = 1.8, 1H, H-pyrrole), 7.83 (d, ^{3}J = 8.3, 2H, H-Ph), 7.46 (s, 1H), 7.32 (d, ^{3}J = 8.3, 2H, H-Ph), 7.29 (d, ^{4}J = 1.8, 1H, H-pyrrole), 3.49 (s, 3H, NCH_3), 3.43 (s, 3H, NCH_3), 2.42 (s, 3H, CH_3); ^{13}C-NMR δ 179.4 (CHO), 161.6, 151.3, 146.1, 138.7, 135.1, 133.2, 130.2 (2C), 127.4 (2C), 127.1, 119.5, 119.2, 106.1, 37.4, 27.8, 21.71; +FAB/DP-MS m/e 388 (M^{+}+ 1, 11), 307 (23), 233 (8), 154 (100).

(*Received in USA* 7 *February* 1996; *revised* 6 *March* 1996; *accepted* 13 *March* 1996)