Pergamon

Tetrahedron Letters 40 (1999) 4555–4558

TETRAHEDRON
LETTERS

# A General Synthesis of 2-Formyl-3-Arylpyrroles

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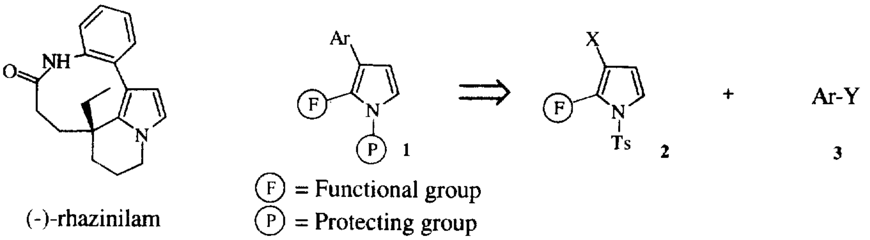
Received 13 April 1999; accepted 24 April 1999

***Abstract*** : 2-Formyl-3-iodo-1-tosylpyrrole **2** has been prepared in four steps from cinnamaldehyde. It was coupled with a wide variety of arylboronic acids to give the corresponding biaryl compounds in high yields. © 1999 Published by Elsevier Science Ltd. All rights reserved.

*Keywords : pyrrole derivatives, biaryls, coupling reactions, arylboronic acids, palladium catalyst*

In the context of a research program aiming at the synthesis of the alkaloid (-)-rhazinilam and analogs which mimic the cellular properties of Paclitaxel (Taxol®),[1] we were looking for an easy and convergent access to 2-substituted-3-arylpyrroles **1**. To our surprise, only few methods of synthesis of this type of pyrrole derivatives have been reported and they give low yields and also lack generality.[2] An obvious strategy for the synthesis of **1** would be a palladium-catalysed coupling reaction between partners of general structures **2** and **3** (Scheme 1). Although coupling reactions involving pyrrole derivatives are known,[3] none of them involve 2,3-disubstituted pyrroles. The synthetic route we were looking for had to fulfil the following requirements : (a) allow for a wide diversity of aryl and heteroaryl substituents, (b) be compatible with functional groups such as -CHO, -COR, -COOR at position 2 of the pyrrole, (c) be applicable to solid-phase synthesis for the construction of combinatorial library. Since the Suzuki reaction has been shown to be applicable to the coupling of hindered partners,[4] we decided to study the palladium-catalysed coupling of pyrrole **4** with various arylboronic acids. The aldehyde function would allow for numerous transformations after the coupling reactions. A tosyl group on nitrogen would be a good model for a polymer-bond aryl sulfonyl group.



Scheme 1

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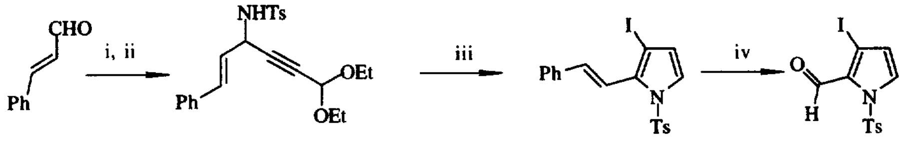


**5** (76%) **6** (71%) **4** (48%)

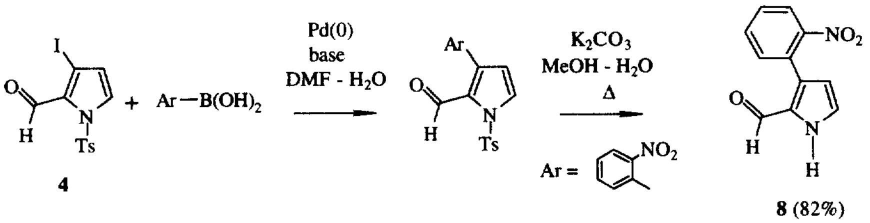
Reagents and Conditions : i, $TsNH_2$, $BF_3$-$OEt_2$, toluene, Δ ; ii, propiolaldehyde diethylacetal, *n*-BuLi, ether, -78°C then $ZnCl_2$ - ether, -78°C ; iii, HI aq. (7eq.), -10°C ; iv, $KMnO_4$ aq. (3eq.), 4 hrs.

Scheme 2

2-formyl-3-iodopyrrole **4** had been obtained in less than 5% yield from a complex mixture of products resulting from the iodination of 2-formyl pyrrole.[5] We found that compound **5** which was readily prepared by a known procedure from *trans*-cinnamaldehyde,[6] reacted with a concentrate aqueous solution of hydrogen iodide to give the pyrrole derivative **6** (Scheme 2). The oxidative cleavage of the double bond of **6** was not trivial in view of the high sensitivity of the pyrrole nucleus towards oxidants.[7] After screening several reagents and reaction conditions, we found potassium permanganate to be most convenient : oxidation took place in 4 hrs at room temperature to give pure 2-formyl-3-iodopyrrole **4** in 48% yield.

Suzuki reaction was first performed with tetrakis(triphenylphosphine)palladium(0) in the presence of sodium carbonate in DMF - $H_2O$ at 80°C. These conditions had been successfully used for the coupling of various halopyrroles with arylboronic acids.[3b,3f] However, when applied to the coupling of **4** with *o*-nitrophenylboronic acid, these conditions gave only moderate yields of the desired product (Scheme 3, Table, entry a). The use of a stronger base[1,4b,4c] as $Ba(OH)_2$ gave no coupling (entry b), perhaps as a result of the reaction of the base with the aldehyde group. No improvement was obtained by using a palladium(0) complex generated in situ from $PdCl_2(PPh_3)_2$[8] (entry c). We then considered a palladium catalyst bearing the bidentate ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf).[9, 3a] With this catalyst, the coupling of **4** with *o*-nitrophenylboronic acid took place in 5 min at 80°C to give **7** in 98% yield (entry d).[10]

High yields of coupling products were also obtained with phenylboronic acid and with the meta and para isomers of nitrophenylboronic acid (entry e, f, g). The reaction was also efficient with an electron-rich aryl group (entry h) and with 2-thienylboronic acid (entry i). Even the highly hindered mesitylboronic acid gave a coupling product in acceptable yields (entry j). As expected,[11] the tosyl group on the pyrrole nitrogen could be easily removed as illustrated by the high yield conversion of **7** into the free pyrrole **8** (Scheme 3).

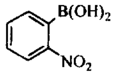
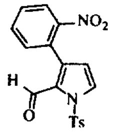
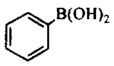
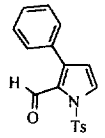
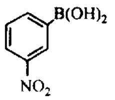
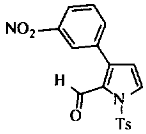
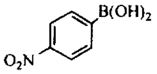
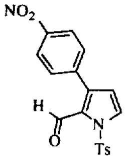
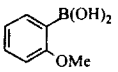
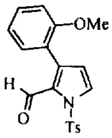
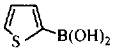
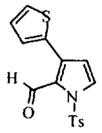
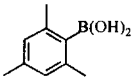
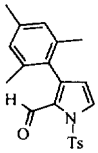


**4** **8** (82%)

Scheme 3

These results demonstrate the generality and practibility of the coupling process. The method should offer the possibility of building readily libraries of 2-substituted-3-arylpyrroles from a polystyrene bound 2-formyl-3-iodo-1-sulfonylpyrrole. Still it would certainly benefit from a more direct synthesis of **4**. This is presently being examined in our group.

**Table - Coupling of 2-Formyl-3-Iodo-1-Tosylpyrrole 3 with Arylboronic Acids**

| Entry | $ArB(OH)_2$ | Conditions(a) | Product(b) | Yield, % |
|---|---|---|---|---|
| a |  | $Pd(PPh_3)_4$, $Na_2CO_3$, 3 hrs |  7 | 42 |
| b |  | $Pd(PPh_3)_4$, $Ba(OH)_2$, 3 hrs |  | 0 |
| c |  | $PdCl_2(PPh_3)_2$, $Ba(OH)_2$, 2 hrs |  | 0 |
| d |  | $PdCl_2dppf$, $Ba(OH)_2$, 5 min (A) |  | 98 |
| e |  | A |  | 92 |
| f |  | A |  | 88 |
| g |  | A |  | 84 |
| h |  | A |  | 88 |
| i |  | A |  | 85 |
| j |  | A |  | 61 |

(a) All reactions were performed at 80°C with $DMF\text{-}H_2O$ (4:1) with 10% of catalyst - (b) All compounds have been caracterised by $^1H$ and $^{13}C$ NMR, IR, MS and elemental analyses.

**Acknowledgments** : These studies were generously supported by a grant from the European Community (fellowship to C.F.), the "Fonds National de la Recherche Scientifique" (fellowship to F.D.) and the "Ministère de l'Education et de la Recherche scientifique de la Communauté française de Belgique (Action concertée 96/01-197)".

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10. Representative procedure : A mixture of degassed DMF (6 ml) and water (1.5 ml) was added to 2-formyl-3-iodo-1-tosylpyrrole **3** (120 mg, 0.32 mmol), *o*-nitrophenyl boronic acid (80 mg, 0.48 mmol), barium hydroxide octahydrate (150 mg, 0.48 mmol) and [1.1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (23 mg, 0.03 mmol) in a three-necked flask under argon. The mixture was heated for 5 min in an oil bath previously warmed at 80°C and then allowed to cool to room temperature. 20 ml of AcOEt and 3 ml of water were added before filtration through celite. The organic phase was successively washed with water (5 X 10 ml) and brine (1 X 15ml) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (40% of $Et_2O$ in petroleum ether). 120 mg (98%) of pale yellow solid were obtained. m.p. 143°C. $^{1}H$ NMR ($CDCl_3$, 500 MHz) δ 9.88 (*s*, 1H); 8.04 (*dd*, $^{3}J$ = 8.1Hz, $^{4}J$ = 1.5Hz, 1H); 7.79 (*d*, $^{3}J$ = 8.1Hz, 2H); 7.67 (*d*, $^{3}J$ = 3.3Hz, 1H); 7.59 (*ddd*, $^{3}J$ = 7.7Hz, $^{4}J$ = 1.4Hz, 1H); 7.52 (*ddd*, $^{3}J$ = 7.7Hz, $^{4}J$ = 1.4Hz, 1H); 7.35 (*d*, $^{3}J$ = 8.1Hz, 2H); 7.33 (*dd*, $^{3}J$ = 7.7Hz, $^{4}J$ = 1.4Hz, 1H); 6.39 (*d*, $^{3}J$ = 3.3Hz, 1H); 2.43 (*s*, 3H). $^{13}C$ NMR (CDCl3, 125 MHz) δ 178.91; 148.99; 145.99; 135.42; 135.26; 132.45; 132.26; 130.16; 129.21; 128.48; 128.35; 128.34; 127.25; 124.39; 113.86; 21.58. IR cm$^{-1}$ (KBr) 3074; 1678; 1536; 1269; 740. EI +Q1MS (70 eV): 369 $(M\text{-}H)^+$; 341 $(M\text{-}CO)^+$; 324 $(M\text{-}NO2)^+$; 215 $(M\text{-}C7H7SO2)^+$; 187 $(215\text{-}CO)^+$; 155 $(C7H7SO2)^+$; 91 $(C7H7)^+$. *Anal.* calcd. : C 58.37%; H 3.81%; N 7.56%. Found : C 58.23%; H 3.56%; N 7.37%.
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