# Coupling of Organotin Reagents with Aryl, Acyl and Heteroaryl Halides. Part 2.† Synthesis of Thienylpyridine Derivatives

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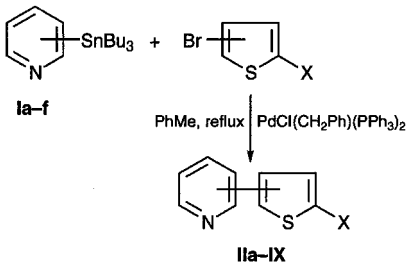
Several new thienylpyridine derivatives are prepared by the Pd-catalysed coupling of organotin compounds with aryl halides; instances of *homo*-coupling of the aryl halides are described.

In our previous works[1,3] we reported the preparation of a variety of 2-and 3-thienyl- and 2- and 3-pyridyl-substituted quinoxalones and pyridazinones. These were prepared by a selection of methods, including palladium-catalysed coupling. This work is extended to include a little-studied class of compound, the thienylpyridines. Previous work on this class of compound[3–5] deals mainly with synthesis of the six isomers, and there is little work on derivatives of the thienylpyridines. More recently, the isomeric thienylpyridines have been studied[6] as potential polymer precursors. In this paper, we describe the preparation and subsequent coupling of the heteroaryltin compounds $Bu_3SnAr$ (Ar = 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl) with appropriately derivatised heterocyclic compounds.

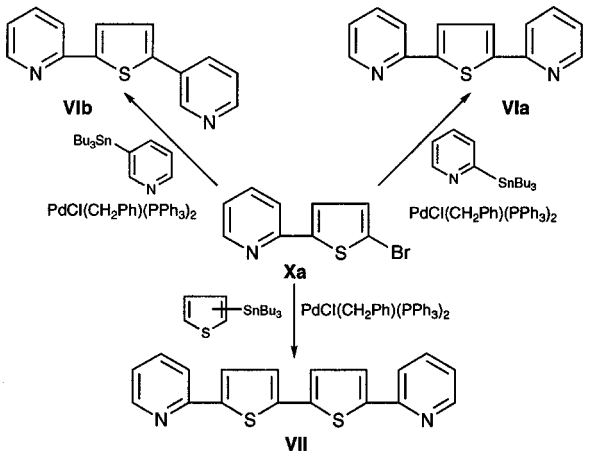
The scope for direct synthesis of derivatives of the thienylpyridines is limited. Palladium-catalysed coupling of organotin reagents has provided a route to a selection of such derivatives. Organotin reagents $R_3SnR^1$ couple with organic halides $R^2X$ in the presence of palladium[12–15] to afford $R^1R^2$. We have shown that this method affords previously inaccessible compounds (Scheme 2, Table).

*Organotin Reagents.*—Organotin compounds (**Ia–f**) were prepared by a variety of methods including the use of tri-*n*-butylstannylsodium, organolithium reagents and Grignard reagents.

*Pd-catalysed Coupling of Organotin Reagents with Aryl Halides.*—Preparation of acetylated and nitrilated thienylpyridines proved to be straightforward: no protection was necessary and yields were between 27 and 95% for the acetylated product, and 60–66% for the nitrile. Preparation of the corresponding aldehydes required protection of the carbonyl group by synthesis of the corresponding acetal by the method described by Sulzbacher *et al.*[16] Without such protection, it is




**Scheme 2**




**Scheme 4**

**Table** Data for compounds described in Scheme 2

| Reaction no. | Product | Yield (%) | Mp/bp (*T*/°C)[a] | $M^+$ (*m*/*z*) | Ar′ | Ar″ | X |
|---|---|---|---|---|---|---|---|
| 1 | **IIa** | 59 | 60–61 | 161 | 2-pyridyl | 2-thienyl | H |
| 2 | **IIb** | 43 | *80*[b] | 161 | 2-pyridyl | 3-thienyl | H |
| 3 | **IIc** | 31 | *94*[c] | 161 | 3-pyridyl | 2-thienyl | H |
| 4 | **IId** | 62 | 76 | 161 | 3-pyridyl | 3-thienyl | H |
| 5 | **IId** | 59 | 76 | 161 | 3-pyridyl | 3-thienyl | H |
| 6 | **IIIa** | 74 | 89 | 203 | 3-pyridyl | 2-thienyl | COMe |
| 7 | **IIIb** | 95 | 122-123 | 203 | 2-pyridyl | 2-thienyl | COMe |
| 8 | **IIIc** | 27 | 105–106 | 203 | 3-pyridyl | 3-thienyl | COMe |
| 9 | **IIId** | 54 | 84–85 | 203 | 2-pyridyl | 3-thienyl | COMe |
| 10 | **IVa** | 66 | 101 | 186 | 3-pyridyl | 3-thienyl | CN |
| 11 | **IVb** | 60 | 105 | 186 | 2-pyridyl | 3-thienyl | CN |
| 12 | **Va** | 39 | 120 | 189 | 2-pyridyl | 2-thienyl | CHO |
| 13 | **Vb** | 33 | 126–127 | 189 | 3-pyridyl | 2-thienyl | CHO |
| 14 | **VIa** | 67 | 198–199 | 238 | 2-pyridyl | 2-thienyl | 2-pyridyl |
| 15 | **VIb** | 81 | 174–176 | 238 | 3-pyridyl | 2-thienyl | 3-pyridyl |
| 16 | **VII** | 13 | 228–229 | 320 | 3-thienyl | 5-bromo-2-(2-pyridyl) | 2-pyridyl (*homo*-coupled) |
| 17 | **VII** | 34 | 228–229 | 320 | 2-pyridyl | 5-bromo-2-(2-pyridyl) | 2-pyridyl (*homo*-coupled) |
| 18 | **VIII** | 62 | 84–86 | 250 | 2-picolyl | 2-thienyl | *homo*-coupled |
| 19 | **IX** | 37 | 239–241 | 217 | 2-picolyl | 2-thienyl | COMe |

[a]Bps in italics. [b]At 0.08 mmHg. [c]At 0.05 mmHg.

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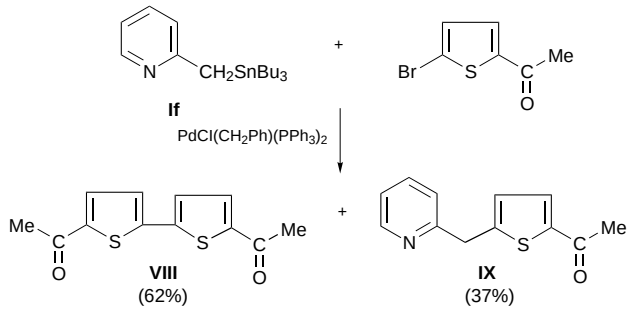
†Part 1 is taken to be ref. 2.

the carbonyl carbon rather than the halogenated site which becomes involved in the coupling, and the eventual result is a secondary alcohol. The aldehyde can alternatively be made by halogenation of the thienylpyridine nucleus followed by lithiation, and reaction *in situ*, with *N*,*N*-dimethylformamide. The range of compounds made in this manner is described in the Table.




**Scheme 5**

*Direct Reaction with Isomeric Thienylpyridines*.—This approach was limited by the constraints of the tolerance of the heterocycles. Halogenation, nitration and synthesis of the aldehyde and acid are shown in Scheme 6.

Techniques used: $^{1}H$ and $^{13}C$ NMR, MS

References: 22

Table 1: Synthesis of tri-n-butylstannyl reagents

Table 2: Synthesis of derivatised thienylpyridines by palladium-catalysed coupling of tri-*n*-butylstannyl heteroaryl reagents with bromopyridines and bromothiophenes

Table 3: Analytical data for derivatised thienylpyridines listed in

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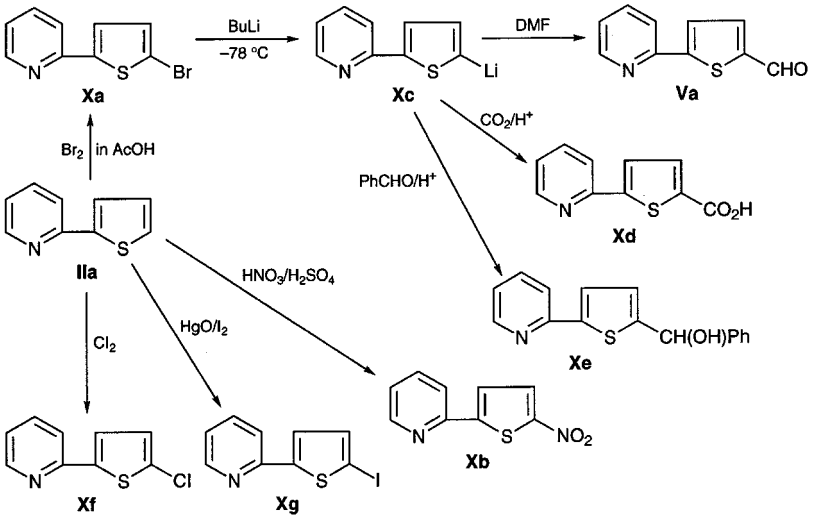


**Scheme 6**

Coupling reactions were extended to afford tri-heterocyclic compounds such as **VIa**,**b**. In the case of attempted preparation of 2-(2-pyridyl)-5-(2-pyridyl)thiophene (**VIa**), coupling proceeded smoothly in low yield (35%), and preparation of the alternative isomer, 2-(2-pyridyl)-5-(3-pyridyl)thiophene (**VIb**) afforded the required product in 81% yield. Attempts to prepare the thiophene analogues resulted in the *homo*-coupling of 5-bromo-2-(2-pyridyl)thiophene (**Xa**), 5,5′-bis(2-pyridyl)-2,2′-bithienyl (**VII**) (Scheme 4).

Similarly, the attempted coupling of 2-[(tri-*n*-butylstannyl)methyl]pyridine (**If**) with 5-bromo-2-acetylthiophene afforded the required cross-coupled product, 5-(2-pyridylmethyl)-2-acetylthiophene (**IX**) and the *homo*-coupled product of the acetylbromothiophene, 5,5′-diacetyl-2,2′-bithienyl (**VIII**) (Scheme 5).

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