A Shorter Synthesis of Dithienopyridines Through Pd(0)-Catalyzed Coupling of 2-(2-Trimethylstannyl-3-thienyl)-1,3-dioxolane with *tert*-Butyl *N*-(*ortho*-Halothienyl)carbamates

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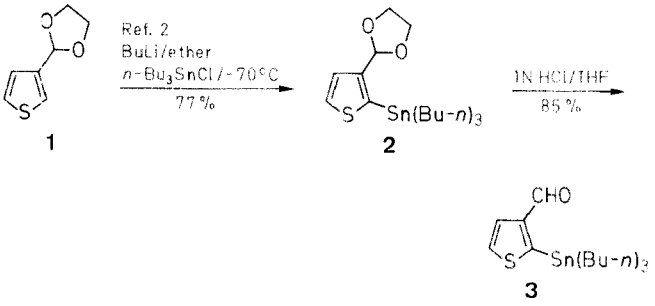
Less sterically crowded 2-(2-trimethylstannyl-3-thienyl)-1,3-dioxolane **(4)** was prepared and coupled with *tert*-butyl *N*-(*ortho*-halothienyl) carbamates, catalyzed by Pd(0) complex, to give dithieno[3,2-*b*; 2',3'-*d*]pyridine **(5)**, dithieno[3,4-*b*; 2',3'-*d*]pyridine **(6)**, and dithieno[2,3-*b*; 2',3'-*d*]pyridine **(7)** in good yields.

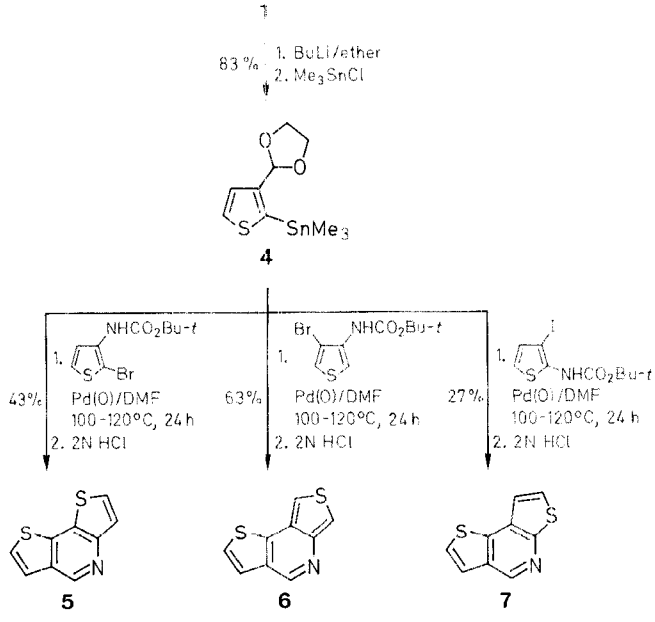
In a previous paper,[2] we described a synthesis of dithienopyridines through a Pd(0)-catalyzed coupling reaction of 2-tri-*n*-butyl-stannyl-3-thiophenecarboxaldehyde **(3)** with *tert*-butyl *N*-(*ortho*-halothienyl)carbamates, in which a protection-deprotection procedure was needed (Scheme **A**).



1 2 3

Scheme **A**

In order to shorten the synthetic route, we investigated the coupling of **2** with *tert*-butyl *N*-(*ortho*-halothienyl)carbamates. However, all attempts to couple **2**, even with the reactive *tert*-butyl *N*-(4-iodo-3-thienyl)carbamate, were unsuccessful. The sharp difference in reactivity in the coupling reactions between **2** and **3** could be caused by steric effects, since **2** is more sterically crowded than **3**. But it could also be caused by electronic effects, since the formyl group is more electron-withdrawing than the acetal group.



5 6 7

Scheme **B**

In order to probe the real cause of the difference in reactivity, we prepared the less sterically crowded 2-(2-trimethylstannyl)-1,3-dioxolane **(4)** by metalation of 2-(3-thienyl)-1,3-dioxolane with butyllithium, followed by reaction with trimethyltin chloride at −70 °C (Scheme **B**). We found that **4** can indeed be coupled with the three *ortho*-halothienylcarbamates to give dithienopyridines **5**, **6**, and **7** in 43%, 63% and 27% yields, respectively (Scheme **B**). The reason for the low yield of **7** is unknown.

From the different reactivities in the coupling reactions between the trimethylorganostannane **4** and tri-*n*-butylorganostannane **2**, it is evident that the yields of the coupling reaction are influenced by the alkyl groups attached to tin. In the catalytic cycle, both the organotin reagent and the organic halide are involved in the transmetalation step, and thus it is reasonable that steric crowding will affect this process. When both the coupling partners are sterically crowded, the transmetalation process may be restricted by steric hindrance. Although tri-*n*-butylorganostannanes have been successfully coupled with a number of organic halides,[3] trimethylorganostannanes should be preferred, as long as steric effects have to be considered.

In conclusion, this procedure provides a short synthesis of dithienopyridines using a less sterically crowded trimethylorganostannane. Another advantage is that the by-product trimethyltin bromide can be easily removed from the reaction mixture by washing with water.

Melting points are uncorrected. ^{1}H-NMR spectra were recorded with a Varian XL-300 spectrometer. The MS were recorded on a Finnigan 4021 spectrometer. GC analyses were carried out on a Varian 1400 gas chromatograph using OV-17 (3%, 2 m) column. The elemental analyses were made at the Analytical Department of the Chemical Center, Lund.

2-(2-Trimethylstannyl-3-thienyl)-1,3-dioxolane (4):
To a stirred solution of 2-(3-thienyl)-1,3-dioxolane[4] (20 g, 0.128 mol) in dry ether (100 mL), 1.51 N BuLi in hexane (91.4 mL, 0.138 mol) is added dropwise under nitrogen at room temperature. After refluxing for 10 min, the mixture is cooled to −70 °C, and Me_3SnCl (25.5 g, 0.128 mol) in dry ether (100 mL) is added dropwise. After the addition is complete, the mixture is warmed to room temperature, and the precipitate (LiCl) is filtered off. The filtrate is distilled at reduced pressure to give **4** as a yellowish liquid; yield: 33.8 g (83%); bp 116–120 °C/0.045 mbar, which solidified on cooling, mp 58–59.5 °C (after passing twice through a column of silica gel 60, eluent: EtOAc/cyclohexane (5:95)).

$C_{10}H_{16}O_2SSn$ (319.0)	calc.	C 37.65	H 5.06	S 10.05
	found	38.0	5.21	10.0

MS (DEI): $m/z = 321$ ($M^+ + 2$).

IR (film): $\nu = 2970$, 2880, 1400, 1100, 770 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 0.37$ (m, 9 H, CH_3, $J = 55.18$ Hz); 4.05 (m, 4 H, CH_2CH_2); 5.88 (t, 1 H, CH, $J = 4.85$ Hz); 7.29 (d, 1 H, H-5, $J = 4.70$ Hz); 7.58 (d, 1 H, H-4, $J = 4.75$ Hz).

Dithienopyridines 5, 6, 7; General Procedure:
A 250 mL two-necked flask, equipped with a condenser, magnetic stirrer and nitrogen inlet, is charged with 2-(2-trimethylstannyl-3-thienyl)-1,3-dioxolane (3.19 g, 0.01 mol), *tert*-butyl *N*-(*ortho*-bromothienyl)carbamate[5] (0.01 mol), tetrakis(triphenylphosphine)palladium(0)[6] (0.34 g, 0.003 mol) and dry DMF (60 mL). The mixture is stirred at 100–120 °C for 24 h, whereupon 2 N HCl (30 mL) is added, and the mixture is refluxed for 1 h. After cooling to room temperature, the mixture is treated with 2 N NaOH (30 mL) and stirring is continued for 5 min. The solvent is evaporated, and the residue extracted with ether (3 × 50 mL). The combined ether phase is washed with water, and dried ($MgSO_4$). After removal of ether, the residue is chromatographed on silica gel 60, using a mixture of EtOAc/cyclohexane (1:1 for **5**, 1:3 for **6** and **7**) as eluent.

5; yield: 43%; mp 78–80 °C (Lit.[2] mp 78–80 °C).

6; yield: 63%; mp 80–82 °C (Lit.[2] mp 80–81.5 °C).

7; yield: 27%; mp 92–93 °C (Lit.[2] mp 92–93 °C).

The IR and ^{1}H-NMR are identical to the previously prepared samples.

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