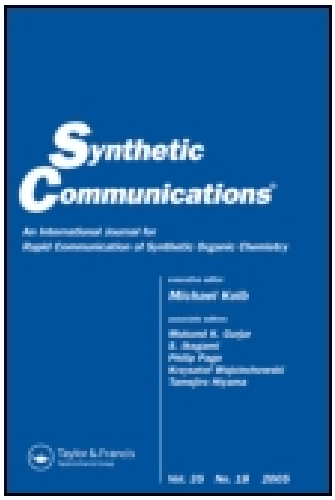

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ABSTRACT

The Stille-type cross-coupling reaction on mesylate, tosylate, and triflate allowed synthesis of symmetrical but also interesting unsymmetrical monofunctionalized 2′2′-bipyridines in possible multigram scales.

Key Words: Stille-type reaction; Bipyridines multigram scale synthesis.

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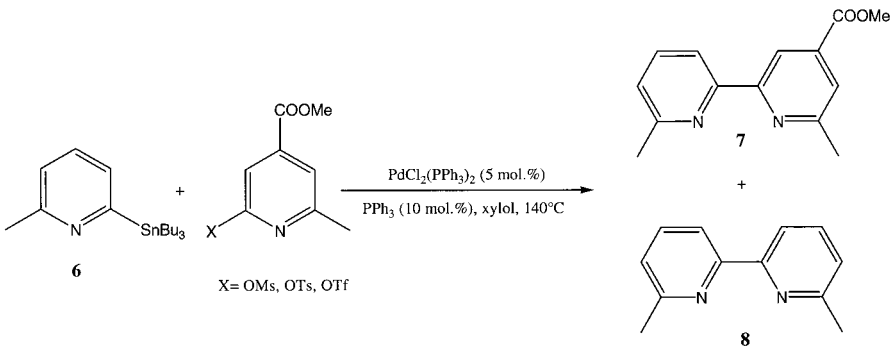
In the course of our ongoing research of new *bis*-heterocycle synthesis, the selective obtention of monofunctionalized systems remains a synthetic challenge until today to gain a simpler way for corresponding heterocyclic cryptate synthesis in bulk than the one previously published.[1a] A survey of the literature revealed a recent high interest on Stille-type cross-coupling methods using either tributyltin-picoline[1b] or tributyltin-diazines[2a,2b] and sometimes triflates[3] to obtain symmetrical or unsymmetrical *bis*-heterocyclic units by stannylation of corresponding halides, followed by a palladium-catalysed reaction.

Here, we report a new two-step efficient coupling reaction between tributyltin-2-picoline **6** and (het) pyridyl mesylate, tosylate, and triflate **2–4**. The tributyl(6-methyl-2-pyridyl)-stannane **6** was prepared in a high yield (86%) by Br–Li exchange transmetallation from 2-bromo-6-methyl pyridine **5** followed by stannylation with tributyltin chloride (THF, −78°C). 2-Methylsulphonyl **2**, 2-(*p*-toluenesulphonyle) **3**, and 2-trifluoromethyl-sulphonyl-4-carboxymethyl-6-methyl pyridin **4** were prepared in good yields from 2-hydroxy-4-carboxymethyl-6-methyl pyridine by classical reactions[4a,4b] except **3** for which a recent modification was used.[4c] Under our conditions[5]; (Sch. 1) the cross-coupling reaction between the stannane **6** and sulphonates **2–4** leads to 2,2′-bipyridines **7** and **8**. As mentioned in Table 1, the mesylate **2** and tosylate **3** afforded a mixture of **7** and **8** in almost equivalent percentage indicating competitive homocoupling and heterocoupling. Note that reactions (realized in triplicate) with the tosylate gave a better yield (93%) than with the mesylate (67%). However, only heterocoupling occurs in the reaction with the triflate **4**, giving the monofunctionalized bipyridine **7** in a good yield (78%).



Scheme 1.

Table 1. Preparation of 2,2′-bipyridines.

Starting Product	Yields (%)[a] **7**	Yields (%)[a] **8**
2	31	36
3	53	40
4	78	0

Reactions realized from 2 mmol of **5**.
[a]Isolated yields.

In summary, we have demonstrated a Stille-type cross-coupling that works with 2-picolinyl mesylate or tosylate and is shown to be a simple and competitive method to afford monofunctionalized *bis*-heterocycles. This methodology potentially improves the synthesis of monofunctionalized supramolecules as e.g., heterocyclic cryptates.

EXPERIMENTAL

General

All compounds gave satisfactory spectral data (^{1}H and ^{13}C NMR) and new compounds gave satisfactory elemental analyses.

4-Carbomethoxy-6-methyl-2-methanesulphonyloxypyridine 2: To 4-carbomethoxy-6-hydroxy-2-methylpyridine (5 g, 29.9 mmol) in dry pyridine (50 mL) at 0°C under Ar was added methanesulphonyl chloride (3.5 mL, 44.8 mmol). The solution was stirred at room temperature for 3 h and then was poured into a separatory funnel containing H_2O (40 mL). The mixture was extracted with CH_2Cl_2 (3 × 60 mL), then combined organic fractions were dried over $MgSO_4$. Filtration and concentration in vacuo, followed by chromatography on silica gel (elution: CH_2Cl_2/MeOH, 97:3), gave a solid. Yield: 5.8 g (85%). M.p. 48–49°C. ^{1}H NMR ($CDCl_3$): $\delta = 7.69$ (s, 1H), 7.45 (s, 1H), 3.95 (s, 3H), 3.51 (s, 3H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 164.3$, 159.1, 157.2, 142.0, 121.6, 112.2, 52.9, 40.8, 23.9. $C_9H_{11}NO_5S$; 0.2 H_2O requires: C, 43.44; H, 4.62; N, 5.63. Found: C, 43.63; H, 4.47; N, 5.50.

4-Carbomethoxy-6-methyl-2-*p*-toluenesulphonyloxypyridine 3: To 4-carbomethoxy-2-hydroxy-6-methylpyridine (5 g, 29.9 mmoles) and Et_3N (4.3 mL, 31.0 mmol) in CH_2Cl_2 (150 mL) at 60°C under Ar was added dropwise a solution of *p*-toluenesulphonyl chloride (recrystallized

in hexane) (5.91 g, 31.0 mmol) in CH_2Cl_2 (50 mL). After the mixture was stirred at 60°C for 8 h. Then the mixture was washed with H_2O (3×50 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by chromatography on aluminium oxide gel (elution: CH_2Cl_2), gave a white powder. Yield: 8.2 g (85%). ^{1}H NMR ($CDCl_3$): $\delta = 7.78$ (d, $J = 8.2$ Hz, 2H), 7.63 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 2H), 3.95 (s, 3H), 2.49 (s, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 165.2$, 159.8, 157.6, 146.1, 142.4, 134.3, 130.2, 129.5, 122.1, 112.7, 53.1, 24.0, 21.9.

4-Carbomethoxy-6-methyl-2-trifluoromethanesulphonyloxypyridine 4: To 4-carbomethoxy-2-hydroxy-6-methylpyridine (1 g, 6.0 mmol) in dry pyridine (40 mL) at 0°C under Ar was rapidly added trifluoromethanesulphonic anhydride (1.21 mL, 7.2 mmol). The solution was stirred at 0°C for 20 min and then was poured into a separatory funnel containing H_2O (40 mL). The mixture was extracted with CH_2Cl_2 (3×30 mL), then combined organic fractions were dried over $MgSO_4$. Filtration and concentration in vacuo, followed by chromatography on silica gel (elution: CH_2Cl_2/acetone, 99:1), gave a colorless oil. Yield: 1.47 g (76%). ^{1}H NMR ($CDCl_3$): $\delta = 7.78$ (s, 1H), 7.50 (s, 1H), 3.97 (s, 3H), 2.61 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 164.5$, 160.8, 156.3, 143.3, 123.9, 119.2 (q, $J_{CF} = 1240$ Hz), 112.3, 53.2, 23.9. $C_9H_8F_3NO_5S$, CH_2Cl_2 requires: C, 31.27; H, 2.62; N, 3.65. Found: C, 31.14; H, 2.33; N, 4.01.

6-Methyl-2-tributylstannylpyridine 6: To 2-bromo-6-methylpyridine (2.5 g, 14.54 mmol) in anhydrous THF (35 mL) at −78°C under Ar was added dropwise *n*-butyllithium (10 mL, 16 mmol; 1.6 M in hexane). After the solution was stirred at −78°C for 90 min, tributyltinchloride (4.73 mL, 17.45 mmol) was added, and the mixture was allowed to warm to room temperature. Water (15 mL) was poured into the reaction mixture, and the phases were separated. The aqueous layer was extracted with diethylether (3×20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting oil was purified by chromatography on aluminium oxide gel (elution: hexanes/acetone, 99.5:0.5) to furnish a colorless oil. Yield: 4.78 g (86%). ^{1}H NMR ($CDCl_3$): $\delta = 7.34$ (t, $J = 7.4$ Hz, 1H), 7.21 (d, $J = 7.4$ Hz, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 2.57 (s, 3H), 1.66–1.52 (m, 6H), 1.41–1.32 (m, 6H), 1.22–1.09 (m, 6H), 1.07–0.87 (m, 9H). ^{13}C NMR ($CDCl_3$): $\delta = 173.7$, 159.3, 134.0, 130.0, 122.2, 29.1, 27.5, 13.8, 10.0.

4-Methoxycarbonyl-6,6′-dimethyl-2,2′-bipyridine 7 and 6,6′-dimethyl-2,2′-bipyridine 8: To a solution of 2-methyl-6-tributylstannylpyridine (764 mg, 2 mmol) in xylol (15 mL) under Ar were added $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol, 5 mol%), PPh_3 (52 mg, 0.2 mmol, 10 mol%) and the

appropriate heteroaromatic compound (2 mmol). The mixture was refluxed for 24 h. After cooling at r.t., the mixture was poured into a saturated solution of EDTA ($2Na^+$) (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (Elution: hexane/acetone, 95:5), gave two products: **4-methoxycarbonyl-6,6′-dimethyl-2,2′-bipyridine 7**: M.p.: 116–117°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.72$ (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 7.71 (s, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.18 (d, $J = 7.6$ Hz, 1H), 3.98 (s, 3H), 2.72 (s, 3H), 2.69 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 166.8$, 159.6, 158.7, 157.7, 155.6, 139.2, 137.7, 124.1, 122.8, 118.9, 118.9, 52.7, 24.8. $C_{14}H_{14}N_2O_2$, 0.5 H_2O requires: C, 66.92; H, 6.02; N, 11.15; Found: C, 66.66; H, 5.78; N, 10.81. **6,6′-dimethyl-2,2′-bipyridine 8**: ^{1}H NMR ($CDCl_3$): $\delta = 8.20$ (d, $J = 7.8$ Hz, 2H), 7.69 (t, $J = 7.6$ Hz, 2H), 7.15 (d, $J = 7.6$ Hz, 2H), 2.64 (s, 6H). ^{13}C NMR ($CDCl_3$): $\delta = 158.5$, 156.6, 137.6, 123.7, 118.8, 24.9.

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