Efficient and Regioselective Access to Bis-heterocycles via Palladium-Catalysed Coupling of Organostannanes and Organozincates Derived from C-6 Lithiated 2-Methoxypyridine

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Abstract: The efficient and regioselective synthesis of various bis-heterocyclic compounds was performed using a regioselective one-pot lithiation–transmetallation–cross-coupling of 2-methoxypyridine.

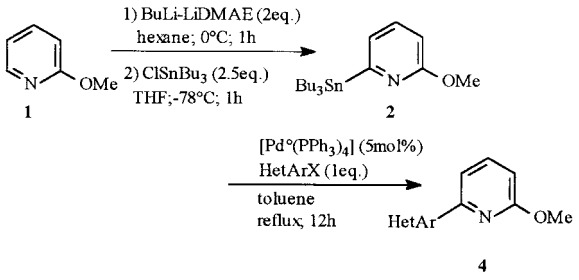
Key words: C-6 lithiation, cross-coupling of heterocycles, 2-methoxy-6-(tributylstannyl)pyridine, 6-bromozinc-2-methoxypyridine

In the course of our ongoing research on the synthesis of new bis-heterocycles,[1–3] we have developed a new basic system BuLi–$Me_2N(CH_2)_2OLi$ (BuLi–LiDMAE) allowing an unusual and regioselective metallation of 2-hetero-substituted pyridines at their C-6 position.[3a,b] This led us to envision the use of the intermediate 2-alkoxy-6-lithiopyridine as a precursor for coupling reactions with heteroaromatic compounds. In this context, we have recently shown that 2-alkoxy-6-lithiopyridine and 6-lithio-2-methylsulfanylpyridine underwent nucleophilic coupling reactions.[3c] Indeed, these intermediates were reactive enough to perform a direct addition onto the azomethine bond of pyridines, pyrimidines, pyrazines and quinolines. This method was found particularly simple and convenient to prepare 2,2'-bis-heterocyclic compounds.

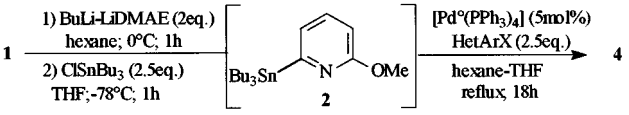
On the other hand, the palladium-catalysed coupling[4] of organozincates[5] or organostannanes[6] with (het)aryl halides appeared as an efficient way to obtain unsymmetrical compounds. Thus, we thought that this method could be efficiently used to prepare 2,x'-bis-heterocycles from 6-lithio-2-methoxypyridine. In this paper we present the in situ preparation of 2-methoxy-6-(tributylstannyl)pyridine and 6-bromozinc-2-methoxypyridine and their coupling reactions with various heterocyclic compounds.

We first examined the reactivity of isolated 2-methoxy-6-tributylstannylpyridine **2** (method A) obtained in 78% yield by transmetallation of lithiated 2-methoxypyridine with $ClSnBu_3$ in THF at –78 °C (Scheme 1).[3a]

In the presence of 5 mol% of Pd° ($Pd(PPh_3)_4$), we found that **2** reacted with various brominated heterocycles in moderate 43–57% yields (Table). In addition, the cross-coupling proceeded as well with 2-pyridyltriflate. The main drawback of this method was the isolation of organostannane **2**. Consequently we tried to perform the corresponding one-pot reaction (Method B) (Scheme 2).



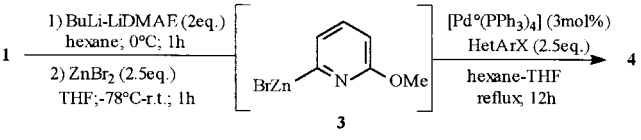
Scheme 1



Scheme 2

In these conditions, bis-heterocycles were obtained in yields comparable to the overall ones obtained from isolated **2** (31–46%, see Table). Note that the reaction was performed in a hexane–THF mixture and not in the classical aromatic solvents (toluene or xylene).

These first results were promising but the moderate yields appeared as limiting for a synthetic purpose. Thus, we decided to study the reactivity of in situ generated 6-bromozinc-2-methoxypyridine (Scheme 3) since organozinc species are well known as highly reactive intermediates in palladium-catalysed coupling reactions.[5]



Scheme 3

After some exploratory experiments we determined that 2.5 equivalents of $ZnBr_2$ led to the best results with both heterocyclic bromide and triflate. In addition, only 3

mol% of Pd° ($Pd(PPh_3)_4$) were necessary to obtain the products in good 64–74% yields (see Table).

It appeared that, in all examples, the yields were higher than those obtained with the organotin derivative **2**. This observation was in agreement with those of Queguiner and co-workers during the coupling of other methoxy-bearing heterocycles.[4c] In addition, the organozinc species offered good stability. Indeed, no loss of efficiency was observed even when coupling was performed after stirring the white suspension of organozincate for 12 h at room temperature. Finally, the efficient recovery of the coupling products was another practical advantage as zincated side products were much more easily eliminated than organotin ones.

As a conclusion, we have shown that the direct C-6 metallation of 2-methoxypyridine allowed the efficient preparation of organotin and organozinc species. Their one-pot palladium-catalysed coupling afforded various new bis-heterocyclic compounds in a regioselective way.

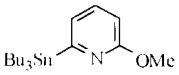
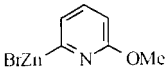
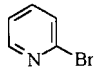
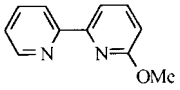
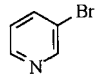
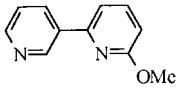
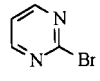
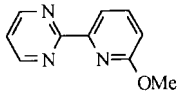
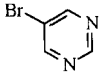
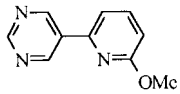
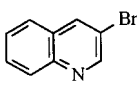
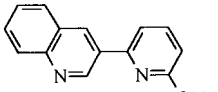
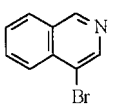
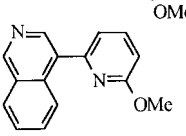
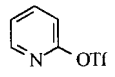
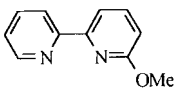
^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 M Hz, respectively, with TMS as internal standard and $CDCl_3$ as solvent. GC-MS measurements (EI) were performed on a HP5971A spectrometer. Elemental analyses were performed by the Service Central d'Analyses du CNRS (Vernaison, France). 2-Pyridyl trifluoromethanesulfonate was prepared according to reference 7. All other reagents were commercially available and were purified or used as such. Hexane, THF and toluene were distilled and stored over sodium wire before use.

2-Methoxy-6-(tributylstannyl)pyridine (2)[3a]; General Procedure

A solution of 2-(dimethylamino)ethanol (720 mg, 8 mmoles) in hexane (5mL) was cooled at ca. –5 °C and BuLi was (10 mL, 16 mmoles) was added dropwise under N_2. After 30 min at 0 °C, a solution of 2-methoxypyridine (430 mg, 4 mmoles) in hexane (5 mL) was added dropwise. After 1 h a deep green color was observed. The solution was cooled at –78 °C and a solution of $ClSnBu_3$ (3.25 g, 10 mmoles) in THF (20 mL) was added dropwise. After 1 h at this temperature, the mixture was treated in order to isolate **2** (Method A) or used as such (Method B).

^1H NMR: δ = 0.92 (t, *J* = 7 Hz, 9H), 1.10–1.25 (m, 6H), 1.35 (m, 6H), 1.5 (t, *J* = 8 Hz, 6H), 3.90 (s, 3H), 6.55 (d, 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H).

Table Palladium-Catalysed Coupling of 2-Methoxy-6-(tributylstannyl)pyridine (**2**) and 6-Bromozinc-2-methoxypyridine (**3**) with HetArX

			Organometallic Reagent		
			 **2**	 **3**	
HetArX	Product		Method[a]	Yield%[c]	Yield%[b,c]
		**4a**	A B	56 46	 64
		**4b**	A B	57 37	 70
		**4c**	A B	53 43	 65
		**4d**	A B	55 40	 74
		**4e**	A B	43 35	 68
		**4f**	A B	46 31	 65
		**4a**	A B	53 45	 70

[a] Method A: coupling performed on 2 mmoles of **2**; Method B: one-pot coupling performed on 4 mmoles of 2-methoxypyridine;
[b] one-pot coupling performed on 4 mmoles of 2-methoxypyridine;
[c] Isolated yields after purification on a Chromatotron (hexane-EtOAc).

^{13}C NMR: δ = 9.6, 13.4, 27, 28.7, 52.8, 108.6, 125.6, 135.5, 162.8, 170.3.

Coupling with 2-Methoxy-6-(tributylstannyl)pyridine (2)
Method A
To a solution of isolated 2-methoxy-6-tributyltinpyridine **2** (796 mg, 2 mmoles) in toluene (20 mL) were added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol, 5mol%) and the appropriate triflate or halide (2 mmoles). The mixture was refluxed for 12 h. After cooling at r.t. the mixture was poured into a sat. KF (25 mL). The organic layer was then separated, washed with H_2O (25 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified on a chromatotron using hexane/EtOAc mixtures as eluents.

Coupling with 2-Methoxy-6-(tributylstannyl)pyridine (2)
Method B
The solution of **2** in hexane/THF was heated to 25 °C and $Pd(PPh_3)_4$ (230 mg, 0.2 mmol, 5mol%) and the appropriate triflate or halide (10 mmoles) were added. The mixture was refluxed for 18 h. After cooling at r.t. the mixture was poured into a sat. KF (25 mL). The organic layer was then separated, washed with H_2O (25 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified on a chromatotron using hexane/EtOAc mixtures as eluents.

Coupling with 6-Bromozinc-2-methoxypyridine (3)
A solution of 2-(dimethylamino)ethanol (720 mg, 8 mmoles) in hexane (5mL) was cooled at ca –5 °C and BuLi was (10 mL, 16 mmols) was added dropwise under N_2. After 30 min at 0 °C, a solution of 2-methoxypyridine (430 mg, 4 mmols) in hexane (5 mL) was added dropwise. After 1 h a deep green color was observed. The solution was cooled at –78 °C and a solution of anhyd $ZnBr_2$ (2.24 g, 10 mmols) in THF (20mL) was added dropwise. After 30 min at –78 °C and 30 min at r.t., $Pd(PPh_3)_4$ (140 mg, 0.12 mmol, 3mol%) and the appropriate triflate or halide (10 mmols) were added. The mixture was refluxed for 12 h. After cooling at r.t. the mixture was quenched with a sat. NH_4Cl (25 mL). The organic layer was then separated, washed with H_2O (25 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified on a chromatotron using hexane/EtOAc mixtures as eluents.

6-methoxy-2,2'-bipyridine (**4a**)[8] and 6-methoxy-2,3'-bipyridine (**4b**)[9] were found identical (spectroscopic data) to authentic samples.

2-(6-Methoxy-2-pyridyl)pyrimidine (4c)
Oil, ^{1}H NMR: δ = 4.09 (s, 3H), 6.87 (dd, 8.75, *J* = 0.75 Hz, 1H), 7.25 (t, *J* = 4.8 Hz, 1H), 7.70 (dt, 7.5, *J* = 0.75 Hz, 1H), 8.06 (dd, *J* = 7, 0.75 Hz, 1H), 8.87 (d, *J* = 4.5 Hz, 2H).

^{13}C NMR: δ = 53.9, 113.2, 117.5, 120.4, 139.6, 152.8, 157.9, 164.2, 164.7.

MS (EI) m/z 188 (6, M^++1), 187 (58, M^+), 186 (100, M^+-1), 156 (32), 130 (11), 104 (11), 93 (7), 78 (8), 53 (6).

5-(6-Methoxy-2-pyridyl)pyrimidine (4d)
Mp 120 °C.

^{1}H NMR: δ = 4.03 (s, 3H), 6.80 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.70 (dt, *J* = 7, 0.8 Hz, 1H), 9.23 (s, 1H), 9.35 (s, 2H).

^{13}C NMR: δ = 53.9, 111.8, 113.4, 132.4, 139.9, 149.5, 155.3, 158.8, 164.6, MS (EI) m/z 188 (10, M^++1), 187 (100, M^+), 186 (70, M^+–1), 159 (33), 143 (14), 132 (12), 130 (17), 103 (12), 76 (15), 63 (8), 51 (8).

3-(6-Methoxy-2-pyridyl)quinoline (4e)
Mp 87 °C.

^{1}H NMR: δ = 4.07 (s, 3H), 6.75 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.53 (dt, *J* = 7, 1 Hz, 1H), 7.65 (dt, *J* = 7.5, 0.5 Hz, 1H), 7.70 (dt, *J* = 7.5, 0.5 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 9.60 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR: δ = 53.8, 110.6, 113.5, 127.3, 128.2, 128.8, 129.6, 130.15, 131.9, 133.7, 139.7, 148.5, 149.8, 152.4, 164.4.

MS (EI) *m/z* = 237 (15, M^++1), 236 (100, M^+), 235 (91, M^+–1), 207 (22), 192 (5), 177 (3), 151 (4), 140 (3), 118 (8), 103 (7), 89 (6), 76 (10), 63 (4), 51 (3).

4-(6-Methoxy-2-pyridyl)isoquinoline (4f)
Mp 95 °C.

^{1}H NMR: δ = 3.99 (s, 3H), 6.84 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 7 Hz, 1H), 7.62 (dt, *J* = 7, 0.8 Hz, 1H), 7.71 (dt, *J* = 7, 1.5 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H), 8.37 (d, 8.5 Hz, 1H), 8.70 (s, 1H), 9.30 (s, 1H).

^{13}C NMR: δ = 53.9, 110.3, 118.1, 125.4, 127.6, 128.3, 129.0, 131.0, 131.8, 134.2, 139.6, 143.9, 153.4, 154.2, 164.2.

MS (EI) m/z 237 (14, M^++1), 236 (94, M^+), 235 (100, M^+–1), 221 (26), 205 (23), 192 (17), 151 (6), 76 (10), 63 (4), 51 (2).

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