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Straightforward access to methyl-polyheterocycles from direct *para*-lithiation of 3-picoline

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Abstract—Various heterocycles have been introduced on the 3-picoline nucleus via a regioselective BuLi-$Me_2N(CH_2)_2OLi$ (BuLi-LiDMAE) mediated *para*-lithiation. Useful methyl-polyheterocycles were efficiently prepared by a one-pot lithiation–stannylation-Stille coupling sequence. © 2001 Published by Elsevier Science Ltd.

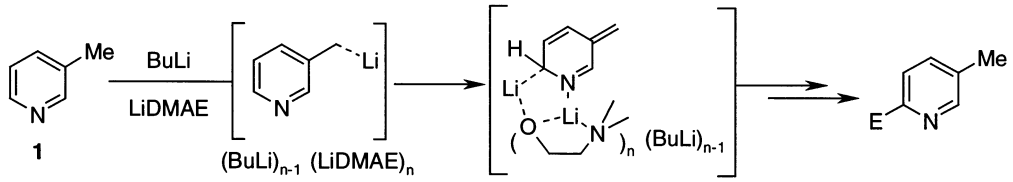
Polyheterocycles are involved in many application fields such as medicinal chemistry,[1] transition metal chemistry,[2] asymmetric synthesis,[3] supramolecular chemistry[4] and materials for optoelectronic.[5] These applications imply the elaboration of sophisticated compounds and particularly those offering the possibility of further structural and electronic modifications. As a representative example of our ongoing research in this area we have shown that many reactive 2-chloro-6,*x*′-bisheterocycles could be efficiently prepared from a C–Cl bond tolerating lithiation-stannylation of 2-chloropyridine and subsequent Stille coupling reaction.[6] More recently, we have discovered that 3-picoline **1** could be regioselectively *para*-functionalised with the BuLi-$Me_2N(CH_2)_2OLi$ (BuLi-LiDMAE) reagent via a methyl to C-2 lithium shift (Scheme 1).[7]

We thought that this selective pyridine nucleus versus base-sensitive methyl group[8] metallation could be valuable to prepare 5-methyl-2,*x*′-bisheterocycles. In this letter, we report the straightforward synthesis of these compounds using a one-pot lithiation-stannylation-coupling of 3-picoline.

At first, we prepared tributyl(5-methyl-2-pyridyl)-stannane **2** by transmetallation of lithiated 3-picoline in situ generated from **1** (Scheme 2).

After kugelrohr distillation, **2** was obtained in a very good 85% isolated yield.[9] This result was similar to those obtained by Lehn and co-workers.[3a] from 2-bromo-5-methyl-pyridine. However, our method advantageously used the cheap parent 3-picoline **1** as a starting material. After having demonstrated the efficiency of the BuLi–LiDMAE induced lithiation procedure to prepare **2**, we turned to its coupling in the Stille conditions. For a practical purpose and in order to limit exposure to toxic tin derivatives, we decided to bypass the purification step of **2** and a one-pot coupling process was investigated. After a series of preliminary experiments, the conditions reported on Scheme 3 were retained to examine the one-pot coupling with various (hetero)aromatic halides (Table 1).[10]

As shown, the one-pot process was efficient and compounds **3a**–**h** were obtained in acceptable to good yields (46–73%) from chloro-, bromoheterocycles or iodoben-



Scheme 1.

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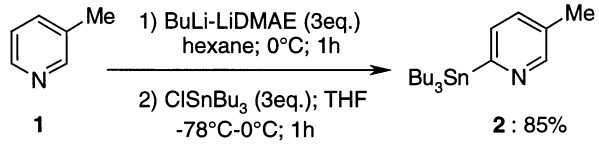
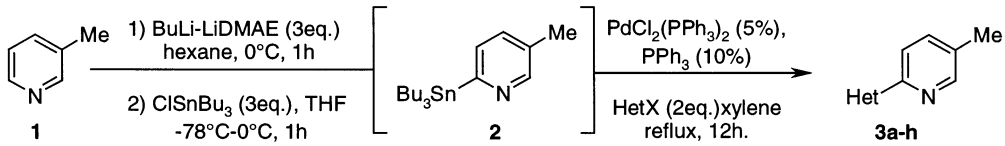


Scheme 2.

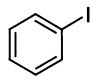
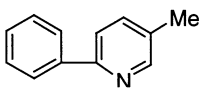
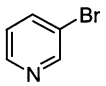
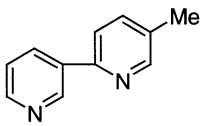
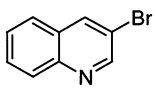
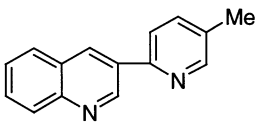
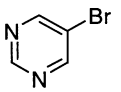
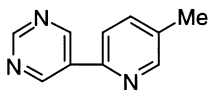
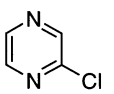
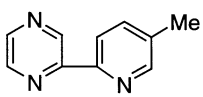
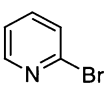
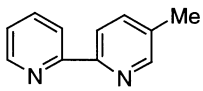
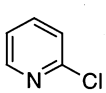
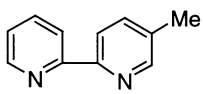
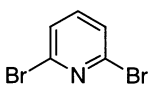
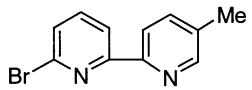
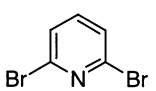
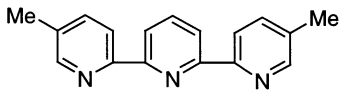
zene. The picoline moiety was introduced selectively at various positions of the heterocycles. The natural product **3b**[11] was prepared in a good 70% yield. Diazines and quinoline nuclei were also efficiently coupled leading to the new dissymmetrical products **3c–e**. Finally, by simply adjusting the amount of 2,6-dibromopyridine, we also succeeded in preparing bromobipyridine **3g**[3b] and terpyridine **3h**[12] in 50 and 46% yields, respectively. The one-pot synthesis of these supramolecular edifices building blocks was as efficient (overall yields) as the three step procedures proposed in the literature from 2-amino-5-methylpyridine.[3b,11]

In summary we have demonstrated that a series of methyl-polyheterocycles can be efficiently prepared in a one-pot way by simply using the easily available inexpensive 3-picoline as a starting material. This new process limited the handling of tin derivatives and was found to be competitive with a multistep synthesis proposed in the literature.



Scheme 3.

Table 1. Preparation of methylpolyheterocycles by one-pot cross-coupling of **1**[a]

HetX	Product		Yield %[b]
		**3a**	65
		**3b**	70
		**3c**	50
		**3d**	73
		**3e**	60
		**3f**	52
		**3f**	49
		**3g**	50
		**3h**	46[c]

[a] All reactions performed on 2 mmoles of 1. [b] Isolated yields after flash-chromatography. [c] 0.6 eq. of 2,6 dibromopyridine were used.

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9. Note that purification by chromatography led to lower yield; see Ref. 6.
10. General procedure for the preparation of **3a**–**h**. *n*-BuLi (7.5 mL of a 1.6 M solution in hexanes; 12 mmole) was added dropwise to a solution of 2-dimethylaminoethanol (0.54 g; 6 mmole) in hexane (5 mL) cooled at 0°C, under a nitrogen atmosphere. After 30 min at 0°C a solution of 3-picoline (0.19 g; 2 mmole) in hexane (5 mL) was added dropwise. After 1 h at 0°C, the red solution was cooled at −78°C and treated dropwise with a solution of tributyltin chloride (1.95 g; 6 mmole) in THF (20 mL). After 1 h at −78°C, the reaction medium was then allowed to warm slowly to room temperature. Xylene (20 mL) was added and the hexane–THF mixture was evaporated under reduced pressure. $PdCl_2(PPh_3)_2$ (70 mg; 0.1 mmole), triphenylphosphine (52 mg; 0.2 mmole) and the appropriate (hetero)aromatic halide (generally 4 mmole) were then added. The reaction mixture was refluxed under nitrogen for 12 h. After cooling at room temperature, xylene was evaporated under reduced pressure and the residue dissolved in dichloromethane (20 mL). The obtained solution was treated with aqueous hydrochloric acid (20 mL, 6N). The aqueous phase was treated with aqueous ammonia (30 mL; 10%) and the product extracted twice with dichloromethane (20 mL). After aqueous work-up, drying ($MgSO_4$) and solvent evaporation, the crude products were purified by flash-chromatography with hexane/AcOEt mixtures. Selected analytical data. **3c**: brown solid, mp 105°C, δ_H 2.36 (s, 3H), 7.55 (m, 2H), 7.72 (m, 2H), 7.87 (d, *J* 8, 1H), 8.13 (d, *J* 8, 1H), 8.56 (s, 1H), 8.69 (s, 1H), 9.51 (d, *J* 2, 1H); δ_C 18.1, 120.1, 126.8, 127.8, 128.3, 129.1, 129.6, 131.7, 132.4, 133.2, 137.4, 147.9, 149.1, 140.4, 151.9; MS (EI) *m*/*z* 220 (100, M^+), 219 (54), 205 (8) ($C_{15}H_{12}N_2$ requires C, 81.82; H, 5.45; N, 12.72. Found: C, 81.93; H, 5.38; N, 12.96%). **3d**: white solid, mp 149°C, δ_H 2.41 (s, 3H), 7.64 (dd, *J* 6.8 and 1.2 , 1H), 7.67 (d, *J* 8, 1H), 8.57 (s, 1H), 9.24 (s, 1H), 9.31 (s, 2H); δ_C 18.2, 119.8, 132.2, 133.4, 137.5, 149.0, 150.8, 154.7, 158.1. MS (EI) *m*/*z*: 171 (100, M^+), 144 (57%), 143 (35%), 118 (14%), 93 (50%), 89 (27%), 63 (23%), 51 (14%). ($C_{10}H_9N_3$ requires: C, 70.18; H, 5.26; N, 24.56. Found: C, 70.16; H, 5.41; N, 24.32%). **3e**: white solid, mp 52°C. δ_H 2.39 (s, 3H), 7.55-7.65 (m, 1H), 8.23 (d, *J* 8, 1H), 8.44 (d, *J* 0.8, 1H), 8.57 (m, 2H), 9.59 (s, 1H), δ_C 18.3, 120.8, 134.1, 137.3, 142.9, 143.3, 143.9, 149.8, 151.1, 151.5. MS (EI) *m*/*z*: 171 (100, M^+), 143 (5%), 119 (64%), 93 (39%), 65 (7%). ($C_{10}H_9N_3$ requires: C, 70.18; H, 5.26; N, 24.56. Found: C, 70.31; H, 5.39; N, 24.29%).
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