

Direct synthesis of unsymmetrical bis-heterocycles from 2-heterosubstituted 6-lithiopyridines

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Received (in Cambridge) 14th September 1998, Accepted 22nd September 1998

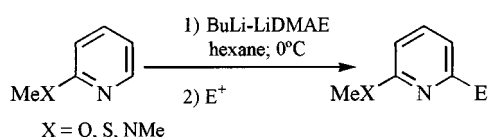
Unsymmetrical bis-heteroaromatic compounds have been synthesized by nucleophilic coupling of C-6 lithiated 2-heterosubstituted pyridines with various heterocycles.

Bis-heterocyclic compounds have been the focus of a great deal of attention. They have found numerous applications as electrical materials,¹ biologically active molecules,² chelating agents and metal ligands.³

Two major synthetic methods are generally used to prepare these compounds. The palladium- or nickel-catalyzed homo-coupling of heteroaryl halides leads to symmetrical products,⁴ while the use of intermediate organotin or organozinc species allows the preparation of unsymmetrical compounds.⁵ The main drawbacks of these processes are generally the cost and availability of halogenated heterocycles as well as the formation of side-products.

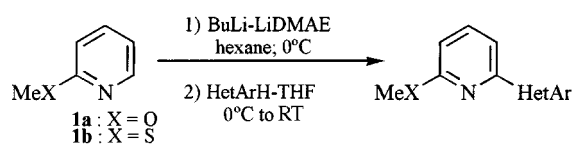
In this context, the nucleophilic addition of a lithiated heterocycle to an electrophilic substrate appeared promising.⁶ However, this route has been scarcely used since there is a lack of selective methods for the direct lithiation of heteroaromatics. Indeed, alkylolithiums lead mainly to nucleophilic addition products⁷ and a prior halogen-metal exchange step is often necessary.

Recently,⁸ we have shown that the basicity/nucleophilicity ratio of BuLi was considerably increased by association with lithium 2-dimethylaminoethanolate (LiDMAE). As a consequence, the newly formed base BuLi-LiDMAE^{8a} allowed an unusual and regioselective metallation of 2-heterosubstituted pyridines (**1a, b**) at their C-6 position, affording the corresponding C-6 substituted 2-heterosubstituted pyridines in good yields (Scheme 1).



Scheme 1

In the course of our ongoing research on coupling reactions,^{5c,9} we decided to attempt to perform the nucleophilic addition of the C-6 lithiated 2-heterosubstituted pyridines to heterocyclic compounds (Scheme 2).



Scheme 2

After a preliminary study performed with 2-methoxypyridine as substrate and pyridine as an electrophile, we found that four equivalents¹⁰ of the base BuLi-LiDMAE as well as THF as trapping co-solvent were necessary to obtain the expected

Table 1 Coupling of pyridines **1a** and **1b** with heteroaromatic compounds^a

Substrate	HetArH	Product	Yield (%) ^b
1a			2a ¹¹ 64 ^c
1b			2b 75 ^d
1a			3a 62
1b			3b 60
1a			4a 60
1b			4b 45
1a			5a 25
1b			5b 30
1a			6a ¹² 58
1b			6b 63

^a Reaction performed on 4 mmol of substrate; metallation: 4 equiv. of BuLi-Me₂N(CH₂)₂OLi, hexane, 0°C, 1 h; coupling: 4 equiv. of HetArH in THF, 0°C to RT, 2 h. ^b Isolated yields after purification (flash chromatography or Chromatotron). ^c 50% of 2,2'-bipyridine was isolated. ^d 42% of 2,2'-bipyridine was isolated.

2-methoxy-6,6'-bipyridine **2a** in good yield. The above determined conditions were used to perform reactions starting from 2-methoxypyridine **1a** and 2-methylthiopyridine **1b** (Table 1).

The obtained results show that the methoxy and methylthio substituted bis-heterocycles were obtained in acceptable to

good yields. It is worthy of note that it is not necessary to carry out an oxidation step⁶ to obtain products since the dihydro intermediates aromatized readily in the reaction medium or upon aqueous work-up.

In these reactions, pyridine displayed particularly interesting behavior. Whatever the conditions used (unreported here), 2,2'-bipyridine was obtained as a by-product. This side-reaction could be expected according to our previous work.^{8b} Indeed, the reaction of BuLi–LiDMAE with pyridine at 0 °C gave 82% of 2,2'-bipyridine after addition of THF. However, 2,2'-bipyridine was easily separated from **2a** and **2b** by classical flash-chromatography.

On the other hand, quinoline which is known to be very sensitive to nucleophilic attack by BuLi^{7a} led surprisingly to the lowest yields. This may be interpreted as a consequence of a strong complexation of lithiopyridines by the formed compounds **3a** and **3b**, weakening their nucleophilicity.^{6a}

Finally, the method was also successful in the preparation of symmetrical products leading to 6,6'-dimethoxy-2,2'-bipyridine **6a** in 58% yield. This result is far better than those obtained in our previous work. Indeed, **6a** was obtained in 30% yield after addition of THF in a mixture of BuLi–LiDMAE with 2-methoxypyridine.^{8a}

In conclusion, we have shown that the direct condensation of heterocycles with 2-heterosubstituted 6-lithiopyridines is an efficient and simple method and has to be considered for the synthesis of new and not easily accessible bis-heterocycles.

Experimental

All new compounds have been satisfactorily characterized [¹H NMR (400 MHz), ¹³C NMR (100 MHz), MS and elemental analysis].

Typical experimental procedure

To a solution of 2-dimethylaminoethanol (720 mg, 16 mmol) in hexane (10 mL) cooled at 0 °C, was added dropwise BuLi (1.6 M solution in hexane, 20 mL, 32 mmol). After 15 min, a solution of 2-methoxypyridine (436 mg, 4 mmol) in hexane (10 mL) was added dropwise (10 min) and the reaction mixture stirred at 0 °C for 1 h. The orange solution was cooled at –20 °C and a solution of pyrimidine (1.28 g, 16 mmol) in THF (40 mL) was added dropwise, and the mixture stirred for 1 h at 0 °C and 1 h at room temperature. Hydrolysis was performed at 0 °C with water (20 mL). After aqueous work-up, the organic layer was dried (MgSO₄) and the solvents evaporated. The residue was purified on a Chromatotron (AcOEt–hexane, 5:95), yielding 463 mg (62%) of **3a**. δ_{H} 4.06 (s, 3H), 6.88 (d, *J* 8, 1H), 7.74 (t, *J* 7.5, 1H), 8.11 (d, *J* 7.5, 1H), 8.33 (d, *J* 5, 1H), 8.84 (d, *J* 5, 1H), 9.26 (s, 1H); δ_{C} 53.8, 113.9, 115.1, 117.6, 139.9, 151.5, 158.0, 158.9, 163.1, 164.1; *m/z* (CI) 188 (M + H⁺) (C₁₀H₉N₃O requires C, 64.16; H, 4.85; N, 22.45. Found: C, 64.25; H, 5.17; N, 22.12%).

Selected data

2b: δ_{H} 2.69 (s, 3H), 7.15 (d, *J* 8, 1H), 7.25 (dt, *J* 5 and 2, 1H), 7.57 (t, *J* 8, 1H), 7.75 (dt, *J* 8 and 2, 1H), 8.07 (d, *J* 8, 1H), 8.42 (d, *J* 8, 1H), 8.62 (d, *J* 4, 1H); δ_{C} 13.6, 117.1, 121.2, 121.3, 132.1, 136.5, 148.8, 155.3, 156.0, 157.1; *m/z* (CI) 203 (M + H⁺) (C₁₁H₁₀N₂S requires C, 65.32; H, 4.98; N, 13.85. Found: C, 65.45; H, 5.02; N, 14.16%); **3b**: δ_{H} 2.69 (s, 3H), 7.32 (d, *J* 8, 1H), 7.68 (t, *J* 7.5, 1H), 8.21 (d, *J* 7.5, 1H), 8.40 (d, *J* 4.5, 1H), 8.87 (d, *J* 4.5, 1H), 9.30 (s, 1H); δ_{C} 13.6, 117.5, 117.8, 124.0, 137.2, 153.6, 158.3, 159.1, 160.3, 162.9; *m/z* (CI) 204 (M + H⁺) (C₁₀H₉N₃S requires C, 59.09; H, 4.46; N, 20.67. Found: C, 59.16; H, 4.73; N, 20.32%); **4b**: δ_{H} 2.65 (s, 3H), 7.26 (d, *J* 8, 1H), 7.63 (t, *J* 7.5, 1H), 8.05 (d, *J* 7.5, 1H), 8.59 (br s, 2H), 9.68 (s, 1H); δ_{C} 13.5, 116.6, 122.9, 137.1, 143.7, 143.9, 144.8, 151.2, 154.0, 160.0; *m/z* (CI) 204 (M + H⁺) (C₁₀H₉N₃S requires C, 59.09; H, 4.46; N, 20.67. Found: C, 59.36; H, 4.61; N, 20.43%); **6b**: δ_{H} 2.57 (s, 3H), 4.18 (s, 3H), 6.50 (dd, *J* 8 and 1, 1H), 6.85 (dd, *J* 7.5 and 1, 1H), 7.45 (t, *J* 7, 1H), 7.46 (t, *J* 8 and 2, 1H), 8.30 (dd, *J* 7.5 and 1, 1H), 8.40 (dd, *J* 7.2 and 1, 1H); δ_{C} 12.3, 54.4, 113.1, 117.1, 120.5, 125.4, 132.8, 135.6, 153.4, 155.9, 156.3, 161.3; *m/z* (CI) 233 (M + H⁺) (C₁₂H₁₂N₂O₂ requires C, 62.07; H, 5.15; N, 12.07. Found: C, 62.36; H, 4.97; N, 12.18%).

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Communication 8/07161F