COMMUNICATION

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

Philippe Gros and Yves Fort *

Synthèse Organique et Réactivité, ERS-634, Université de Nancy-1, Faculté des Sciences, BP239, F-54506 Vandoeuvre-Les-Nancy, France

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

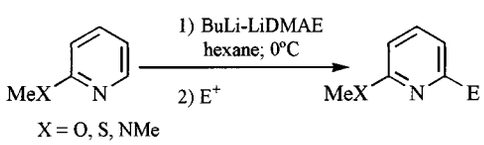
Unsymmetrical bis-heteroaromatic compounds have been synthesized by nucleophilic coupling of C-6 lithiated 2-heterosubstituted pyridines with various heterocycles.

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 homocoupling 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.

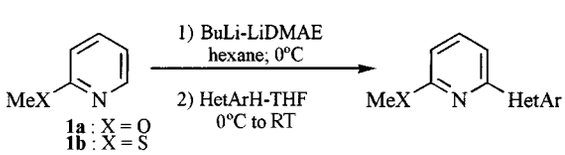
In this context, the nucleophilic addition of a lithiated heterocycle to an electrophilic substrate appeared promising.[6] However, this route has been scarcely used since there is a lack of selective methods for the direct lithiation of heteroaromatics. Indeed, alkyllithiums lead mainly to nucleophilic addition products[7] 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

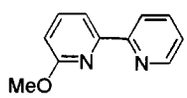
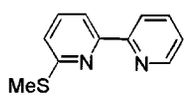
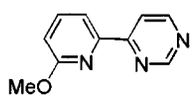
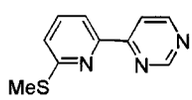
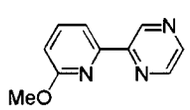
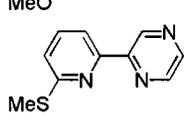
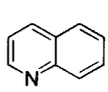
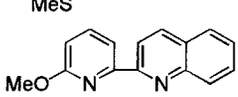
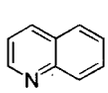
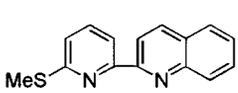
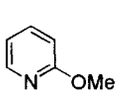
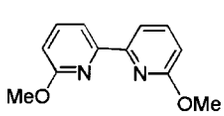
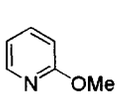
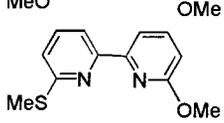
In the course of our ongoing research on coupling reactions,[5c,9] we decided to attempt to perform the nucleophilic addition of the C-6 lithiated 2-heterosubstituted pyridines to heterocyclic compounds (Scheme 2).



Scheme 2

After a preliminary study performed with 2-methoxypyridine as substrate and pyridine as an electrophile, we found that four equivalents[10] of the base BuLi–LiDMAE as well as THF as trapping co-solvent were necessary to obtain the expected 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).

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–$Me_2N(CH_2)_2OLi$, 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.

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 step[6] 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 [^{1}H NMR (400 MHz), ^{13}C 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 ($MgSO_4$) 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 ($M + H^+$) ($C_{10}H_9N_3O$ 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 ($M + H^+$) ($C_{11}H_{10}N_2S$ 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 ($M + H^+$) ($C_{10}H_9N_3S$ 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 ($M + H^+$) ($C_{10}H_9N_3S$ 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 ($M + H^+$) ($C_{12}H_{12}N_2OS$ requires C, 62.07; H, 5.15; N, 12.07. Found: C, 62.36; H, 4.97; N, 12.18%).

References

1 T. Kambara, T. Koshida, N. Saito, I. Kuwajima, K. Kubata and T. Yamamoto, *Chem. Lett.*, 1992, 583.
2 K. V. Rao, K. Biemann and R. B. Woodward, *J. Am. Chem. Soc.*, 1963, **85**, 2532.
3 T. Meyer, *Acc. Chem. Res.*, 1989, **22**, 165.
4 (*a*) P. E. Fanta, *Chem. Rev.*, 1964, **64**, 613; (*b*) A. L. Papet and A. Marsura, *Synthesis*, 1993, 478; (*c*) Y. Fort, S. Becker and P. Caubère, *Tetrahedron*, 1994, **50**, 11893.
5 (*a*) Y. Yamamoto, Y. Azuma and H. Mitoh, *Synthesis*, 1986, 564; (*b*) V. Kalin, *Synthesis*, 1991, 413; (*c*) Y. Yamamoto, T. Tanaka, M. Yagi and M. Inamoto, *Heterocycles*, 1996, **42**, 189.
6 (*a*) T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 1; (*b*) G. Newkome and D. Hager, *J. Chem. Soc., Chem. Commun.*, 1981, 858; (*c*) R. Van der Stoel, H. Van der Plas and H. Jogejan, *Recl. Trav. Chim. Pays-Bas*, 1983, **102**, 364.
7 (*a*) J. Verbeck, A. George, R. de Jong and L. Brandsma, *J. Chem. Soc., Chem. Commun.*, 1984, 257; (*b*) E. W. Thomas, *J. Org. Chem.*, 1986, **51**, 2184.
8 (*a*) P. Gros, Y. Fort and P. Caubère, *J. Chem. Soc., Perkin Trans. 1*, 1997, **20**, 3071; (*b*) P. Gros, Y. Fort and P. Caubère, *J. Chem. Soc., Perkin Trans. 1*, 1997, **24**, 3597.
9 (*a*) Y. Fort, *Tetrahedron Lett.*, 1995, **36**, 6051; (*b*) E. Brenner and Y. Fort, *Tetrahedron Lett.*, 1998, **39**, 5359.
10 This amount of basic reagent was also found as necessary in the metallation of nitrogen-containing heterocycles by LiTMP. See for example, N. Plé, A. Turck, K. Couture and G. Queguiner, *J. Org. Chem.*, 1995, **60**, 3781.
11 P. M. Pojer and L. A. Summers, *J. Heterocycl. Chem.*, 1974, **11**, 303.
12 R. Held, F. Dietz and P. Thomas, *Z. Chem.*, 1972, **12**, 346.

Communication 8/07161F