Lithiation of 2-Heterosubstituted Pyridines with BuLi−LiDMAE: Evidence for Regiospecificity at C-6

Philippe Gros, Sabine Choppin, Julien Mathieu, and Yves Fort*

Synthèse Organique et Réactivité, UMR CNRS-UHP 7565, Faculté des Sciences, Université Henri Poincaré-Nancy I, BP 239, 54506 Vandoeuvre-Les-Nancy, France

Yves.Fort@sor.uhp-nancy.fr

Received June 21, 2001

The determination of the initial deprotonation site of 2-chloro- and 2-methoxypyridine during reaction with BuLi−LiDMAE has been investigated. A series of experiments on deuterated regioisomers revealed a direct lithiation at C-6 excluding a potential first classical ortholithiation and lithium equilibration in the reaction medium. These results suggested that the formation of lithium aggregates at the neighboring of the pyridinic nitrogen atom favored BuLi delivery at C-6 as well as 6-lithio intermediate stabilization.

Introduction

Lithiation of aromatic and heteroaromatic derivatives has been widely used to create C−C and C−heteroatom bonds allowing the introduction of numerous functionalities. A survey of the literature revealed that main efforts have been focused on the development of the directed orthometalation process (DOM effect).[1] Although continuously debated,[2] the mechanism of this selective reaction was generally assumed to proceed via the well-known complex-induced proximity effect (CIPE)[1b] between the ortho directing group and the lithiating agent promoting introduction of lithium at the ortho position (Scheme 1).

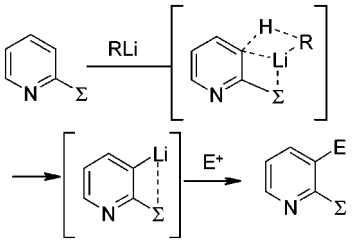
Recently, we have reported a new basic reagent composed of BuLi and $Me_2N(CH_2)_2OLi$. This new unimetal superbase[3] called BuLi−LiDMAE[4] induced a regioselective C-α lithiation of pyridine derivatives even when an ortho-directing group was present on the heterocyclic ring.[4a,b,5]

This unprecedented selectivity was explained by the formation of aggregates between BuLi−LiDMAE and substrates via lithium complexation by the pyridinic nitrogen atom and heteroatom at C-2 (Scheme 2).

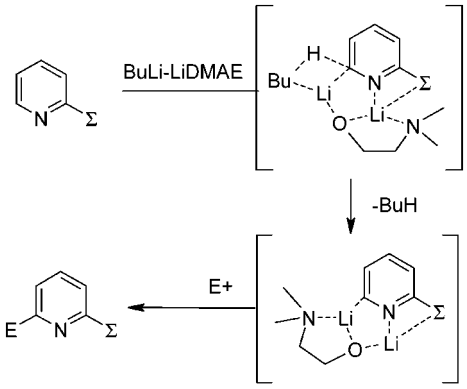
In previous works,[4a,b] we have demonstrated that a bidentate coordination of the lithium alkoxide was essential to obtain such regioselectivity. Indeed, the use of monodentate alkoxides (e.g., *t*-BuOLi) led only to nucleophilic addition products onto the pyridine nucleus in the presence or absence of tertiary amines (e.g., triethylamine). Bidentate tertiary diamines such as TMEDA led also to addition products as well as sterically hindered aminoalkoxides such as 2-diisopropylaminoethoxide. The aggregates were also found to be highly sensitive to solvents. Indeed, the metalation had to be performed in apolar, not coordinating, solvents such as hexane. In THF or DME, classical nucleophilic addition of BuLi was observed due to aggregates disruption.

The presence of two lithium cations in the basic reagent was critical to promote double complexation of the pyridine nucleus. Aggregates were here assumed first to deliver BuLi near the H-6 proton of substrate and second to ensure stabilization of the formed 6-lithiated intermediate.

Scheme 1



Scheme 2



(1) For reviews on orthometalation, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Marsais, F.; Quéguiner, G.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−303.

(2) (a) Schlosser, M.; Mongin, F.; Porwisiak, J.; Dmowski, W.; Büker, H.; Nibbering, N. M. M. *Chem.-Eur. J.* **1998**, *4*, 1281. (b) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553. (c) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640.

(3) Caubère, P. *Chem. Rev.* **1993**, *93*, 2317.

(4) (a) Gros, Ph.; Fort, Y.; Quéguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791. (b) Gros, Ph.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *20*, 3071. (c) Gros, Ph.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *24*, 3597. (d) Gros, Ph.; Ben Younès-Millot, C.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 303. (e) Mathieu, J.; Gros, Ph.; Fort, Y. *Chem. Commun.* **2000**, *11*, 951.

(5) (a) Choppin, S.; Gros, Ph.; Fort, Y. *Org. Lett.* **2000**, *2*, 803−805. (b) Choppin, S.; Gros, Ph.; Fort, Y. *Eur. J. Org. Chem.* **2001**, *3*, 603.

10.1021/jo015855o CCC: $22.00
Published on Web 12/07/2001

Scheme 3

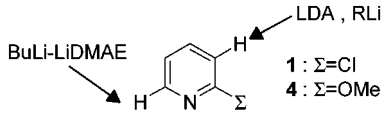
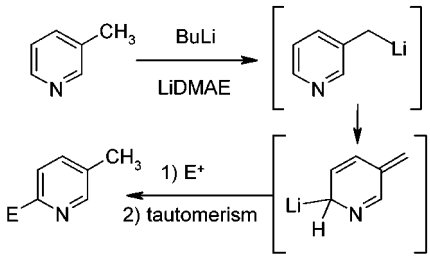


Table 1. PM3-Calculated Mulliken Charges[a]

substrate	H-3	H-6
1	0.125	0.121
4	0.126	0.119

[a] Performed with the Gaussian 98 package.

Scheme 4



This unprecedented selectivity strongly contrasted with those observed with the well-known LDA and lithium alkyls, which abstracted exclusively the H-3 proton in agreement with the DOM effect (Scheme 3).[6,7]

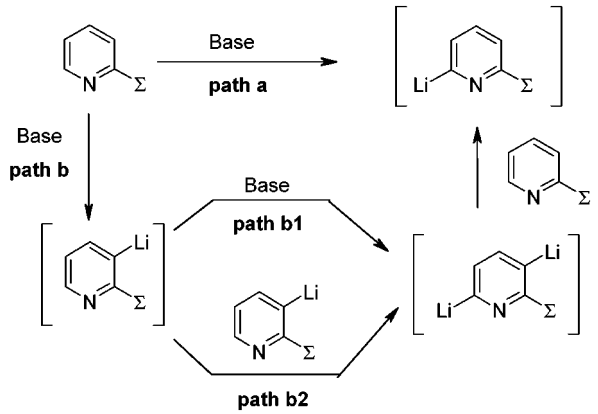
The complete inhibition of the DOM effect with BuLi−LiDMAE was intriguing for several reasons. At first, the Mulliken charges on H-3 and H-6 obtained by PM3 semiempirical calculations were found to be very close in both substrates (Table 1). Then it may be assumed that the unusual selectivity at C-6 should be rather governed by complexation than by proton acidities.

On the other hand, lithiated intermediate equilibrations have been already encountered in the pyridine series. For example, a lithium migration from C-2 toward C-4 was observed via formation of a 2,4-dilithio intermediate during reaction of 3-fluoropyridine and 3-chloropyridine with LDA.[8] In the same way, we have shown that lithiation of the pyridine ring of 3-picoline with BuLi−LiDMAE was not a direct process and was initiated at the side chain (Scheme 4).[4d]

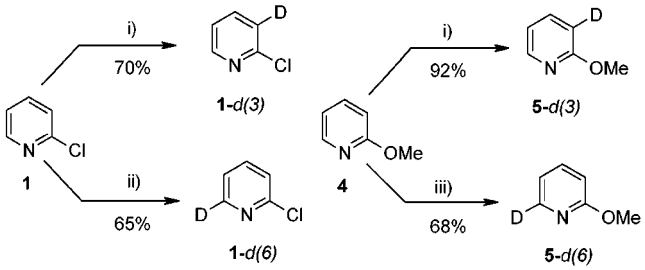
Thus, we had to answer the following question: Is the BuLi−LiDMAE-induced C-6 lithiation a direct process (path a) or the result of a previously formed 3-lithio intermediate equilibration in the reaction medium (paths b1 and/or b2) (Scheme 5)?

Obviously, the key to the problem was the determination of the initial deprotonation site. Thus, we designed a series of lithiation experiments on derivatives of **1** and **4** with prospective hydrogens (H-3 or H-6) replaced by a deuterium exploiting KIE (kinetic isotope effect) protecting ability.[2b,4e,9]

Scheme 5



Scheme 6[a]



[a] Key: (i) (1) LTMP (3.2 equiv), THF, −78 °C, 1.5 h, (2) DCl/D_2O (10 equiv), THF, −78 °C, 1 h; (ii) (1) BuLi−LiDMAE (3 equiv), hexane, −78 °C, 1 h, (2) DCl/D_2O (10 equiv), −78 °C, 15 min; (iii) (1) BuLi−LiDMAE (4 equiv), hexane, 0 °C, 1 h, (2) DCl/D_2O (10 equiv), THF, −78 °C, 1 h.

Results and Discussion

The starting 6-deuterio- and 3-deuteriopyridines (Scheme 6) were prepared in good yields with a deuteration content up to 98% (^{1}H NMR and MS) by selective lithiation-deuteration of 2-chloropyridine **1** and 2-methoxypyridine **4.**[4a,5b,10]

Lithiation of 1, 1-*d(6)*, and 1-*d(3)*. As previously reported,[4a] the lithiation of 2-chloropyridine derivatives was performed with 3 equiv of basic reagent at −78 °C in hexane, and the lithiation mixtures were quenched classically with TMSCl. Although equilibrium displacement should not occur with BuLi−LiDMAE in the presence of TMSCl,[5a] we nevertheless decided to suppress ambiguity using also dimethyl disulfide (DMDS) as electrophile (Scheme 7).

As a general trend, lithiation of **1** and its deuterated derivatives led exclusively to the corresponding 6-substituted compounds in high yields. The strong preference for the C-6 position was clearly demonstrated by the complete deuterium abstraction in **1**-*d(6)* which occurred even in the presence of a proton at C-3. No KIE was observed in this case, and experiments carried out at shorter reaction times (15 min) revealed a very low 1.1 k_H/k_D ratio. Also informative was lithiation of **1**-*d(3)* since deuteration at C-3 did not affect the reaction course at all, which again resulted in C-6 lithiation. The complete

(6) (a) For C-3 lithiation of **1** with LDA, see: (a) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009. (b) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. (c) Trécourt, F.; Marsais, F.; Güngor, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, *9*, 2409−2415.

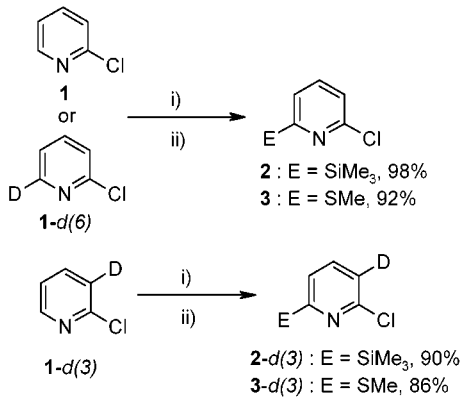
(7) For C-3 lithiation of **4** see: (a) Comins, DL.; La Munyon, D. *Tetrahedron Lett.* **1988**, *29*, 773. (b) Trécourt, F.; Mallet, M.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 1367. (c) Mallet, M. *J. Organomet. Chem.*, **1991**, *406*, 49. (d) Comins, D.; Bavevsky, M.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

(8) (a) Marsais, F.; Bréant, P.; Ginguene, A.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *216*, 139. Marsais, F.; Quéguiner, G. Tetrahedron **1983**, *39*, 2009.

(9) Examples using KIE to elucidate reaction pathways have been reported. See, for instance: (a) Kopach, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 6764. (b) Clayden, J.; Pink, J. Westlund, N.; Wilson, F. *Tetrahedron Lett.* 1998, **39,** 303.

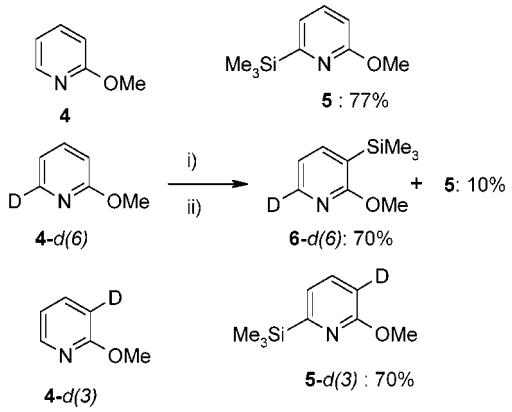
(10) Lempereur, C. Thèse de l'Université de Rouen, France, 2000.

Scheme 7[a]



[a] Key: (i) BuLi−LiDMAE (3 equiv), hexane, −78 °C, 1 h; (ii) TMSCl or DMDS (4 equiv), THF, −78 °C, 1 h.

Scheme 8[a]



[a] Key: (i) BuLi−LiDMAE (4 equiv), hexane, 0 °C, 1 h; (ii) TMSCl (5 equiv), THF, 0 °C, 1 h.

retention of deuterium content (>98%, ^{1}H NMR and MS) in **2**-*d(3)* excluded initial lithiation at C-3 and subsequent equilibration toward C-6. Finally, both electrophiles led to similar yields and selectivities definitely excluding involvement of equilibrium displacements.

Lithiation of 4, 4-*d(6)*, and 4-*d(3)*. The metalation of 2-methoxypyridine derivatives was performed with 4 equiv of BuLi−LiDMAE at 0 °C in hexane according to our previously published procedure (Scheme 8).[3a]

At first, whatever the substrate, products arising from lithiation at C-6 were obtained. However, **4**-*d(6)* led mainly to lithiation at C-3 (70%) and to a low amount (10%) of the 6-silylated derivative **5**. This result contrasted with those obtained with **1**-*d(6)*. An explanation could be a difference of strengh in lithium complexation between MeO and Cl atoms in aggregate presented in Scheme 2.

Since the O−Li interaction is assumed to be stronger than the Cl−Li one, the methoxy group probably more competes than chlorine with pyridine nitrogen in lithium complexation. The consequence is a delivery of butyl base farther from the 6-position with **4**-*d(6)* than with **1**-*d(6)* allowing C-6 and C-3 lithiation in the former case. On the other hand, prevalent complexation by pyridine nitrogen with **1**-*d(6)* puts butyl base closer to the 6-position and subsequent exclusive C-6 lithiation.

The result obtained with **4** and **4**-*d(3)* indicated that deuterium at C-3 did not affect the course of the metalation since **5**-*d(3)* and **5** were obtained in almost identical yields. The complete retention of deuterium content in **5**-*d(3)* once more privileged direct lithiation at C-6.

In summary, the experiments carried out with deuterated 2-chloro and 2-methoxypyridine revealed the strong affinity of BuLi−LiDMAE for the H-6 proton in both substrates and brought evidence for direct lithiation at C-6. This result strongly supported our previous hypothesis of lithium aggregates formation at the neighboring of nitrogen atom preventing orthodirection by the heteroatom at C-2 (Scheme 2). Evidently, such aggregate formation could not be involved with lithium dialkylamides which thus promoted orthodirected lithiation.

Conclusion

As a conclusion, we have shown that BuLi−LiDMAE induced 6-lithiation of 2-chloro and 2-methoxypyridine was an unequivocal direct process. The above experimental study underlined the importance of initial lithiation site knowledge to understand the course of a metalation reaction as well as the crucial role of selective site complexation in directed lithiations. Works are now in progress to extend our experimental approach to other basic reagents and substrates.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, with TMS as internal standard and $CDCl_3$ as solvent. *J* values are given in Hz. GC/MS (EI) spectra were recorded on a HP5871 spectrometer.

Materials and Solvents. BuLi (1.6 M solution in hexane), 2-chloropyridine, 2-methoxypyridine, and dimethylaminoethanol were purchased from Acros. Hexane and THF were distilled and stored on sodium wire before use. All other reagents were commercially available and were purified or used as such. Starting deuterated pyridines **1**-*d(6)*,[5b] **1**-*d(3)*,[6c] **4**-*d(6)*,[4a] and **4**-*d(3)*[7b] and compounds **2**,[5b] **3**,[5b] and **5**[5a] were found to be identical to authentic samples.

Lithiation of 2-Chloropyridines 1, 1-*d(6)*, and 1-*d(3)*. A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in hexane (5 mL) was cooled at ca. −5 °C, and BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 30 min at 0 °C, the solution was cooled at −78 °C, and a solution of the 2-chloropyridine derivative (2.67 mmol) in hexane (5 mL) was added dropwise. After 1 h of stirring, a deep rust-colored solution was observed. Then a solution of TMSCl or DMDS (10.67 mmol) in THF (20 mL) was introduced dropwise. After addition, the reaction medium was allowed to warm slowly at room temperature (1 h). The mixture was hydrolyzed at 0 °C with H_2O (20 mL). The aqueous layer was then extracted with ether (20 mL). After drying ($MgSO_4$) and careful evaporation of solvents, the crude product was purified by column chromatography (hexane/AcOEt 95:5, as eluents).

2-Chloro[3-^{2}H]-6-pyridyl(trimethyl)silane, 2-*d(3)*. ^{1}H NMR δ: 0.3 (s, 9H), 7.40 (d, J = 7 Hz, 1H), 7.55 (d, J = 7 Hz, 1H). ^{13}C NMR δ: −1.9, 122.8, 122.9, 123.0, 127.3, 136.7, 151.3, 170.2 ppm. MS (EI) *m/z*: 188 ($M^+ + 1$) (11), 187 (M^+) (20), 186 ($M^+ - 1$) (31), 171 (100), 151 (44), 93 (59), 72 (44), 63 (19).

2-Chloro[3-^{2}H]-6-methylsulfanylpyridine, 3-*d(6)*. ^{1}H NMR δ: 2.55 (s, 3H), 7.10 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H). ^{13}C NMR δ: 13.7, 118.3, 118.6, 118.9, 119.5, 137.9, 150.7, 160.8 ppm. MS (EI) *m/z*: 161 ($M^+ + 1$) (61), 160 (M^+) (100), 159 ($M^+ - 1$) (60), 127 (11), 114 (46), 79 (61), 51 (20).

Lithiation of 2-Methoxypyridines 4, 4-*d(6)*, and 4-*d(3)*. A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in hexane (5 mL) was cooled at ca. −5 °C, and BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 30 min at 0 °C, a solution of the 2-methoxypyridine derivative

(2 mmol) in hexane (5 mL) was added dropwise. After 1 h of stirring at 0 °C, the orange mixture was treated dropwise with a solution of TMSCl (1.25 mL; 10 mmol) in THF (20 mL). After 0.5 h at 0 °C, the reaction medium was allowed to warm slowly at room temperature (1 h). The mixture was hydrolyzed at 0 °C with H_2O (20 mL). The aqueous layer was then extracted with ether (20 mL). After drying ($MgSO_4$) and careful evaporation of solvents, the crude product was purified by column chromatography (hexane/AcOEt 95:5, as eluents).

2-Methoxy[3-^{2}H]-6-pyridyl(trimethyl)silane, 5-*d(3)*. ^{1}H NMR δ: 7.44 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 3.93 (s, 3H), 0.27 (s, 9H). ^{13}C NMR δ: −1.8, 53.9, 108.7, 109.3, 109.95, 125.7, 130.3, 162.9, 170.7 ppm. MS (EI) m/z: 183 ($M^+ + 1$) (5), 182 (M^+) (30), 167 (100), 137 (42), 59 (13).

2-Methoxy[6-^{2}H]-3-pyridyl(trimethyl)silane, 6-*d(6)*. ^{1}H NMR δ: 7.64 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 3.93 (s, 3H), 0.26 (s, 9H). ^{13}C NMR δ: 2.1, 53.9, 120.2, 127.8, 136.5, 152.9, 153.5, 154.2, 167.3 ppm. MS (EI) m/z: 183 ($M^+ + 1$) (2), 182 (M^+) (14), 167 (40), 137 (100), 59 (11).

JO015855O