ORGANIC LETTERS

2000
Vol. 2, No. 6
803−805

Unusual C-6 Lithiation of 2-Chloropyridine-Mediated by BuLi–$Me_2N(CH_2)_2OLi$. New Access to 6-Functional-2-chloropyridines and Chloro-bis-heterocycles

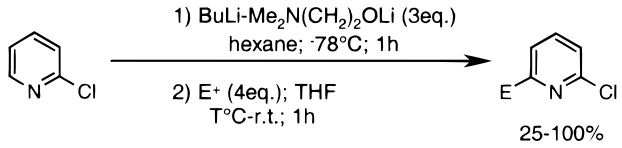
Sabine Choppin, Philippe Gros, and Yves Fort*

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

yves.fort@sor.uhp-nancy.fr

Received January 12, 2000

ABSTRACT



The reaction of 2-chloropyridine with alkylithium generally results in nucleophilic addition leading to the loss of chlorine atom while exclusive directed ortho metalation is obtained using LDA. Herein it is shown that the BuLi–$Me_2N(CH_2)_2OLi$ (BuLi–LiDMAE) superbase promotes an unprecedented regioselective C-6 lithiation. The method was successfully applied to the preparation of potentially useful chlorinated pyridinic and bis-heterocyclic synthons.

Among pyridine derivatives, 2-chloropyridine appears as a particularly versatile compound. Indeed, the presence of a C−Cl bond makes it potentially reactive toward nucleophiles allowing the introduction of functional groups.[1] The pyridinic protons are also of interest since base abstraction could give a metalated pyridine potentially reactive toward electrophilic reagents. Unfortunately, the reaction with BuLi was troublesome since only addition products onto the azomethine bond were obtained with, in some cases, untimely elimination of the chlorine atom.[2] Thus, the design of new methods allowing metalation of 2-chloropyridine with retention of the C−Cl bond could be of great synthetic value. From our knowledge, only LDA efficiently accomplished this reaction inducing exclusive lithiation at the C-3 position[3,4] as a consequence of the chlorine atom directing effect (DoM effect).[5] All these reactions were performed in THF and metalation in apolar solvents was never reported.

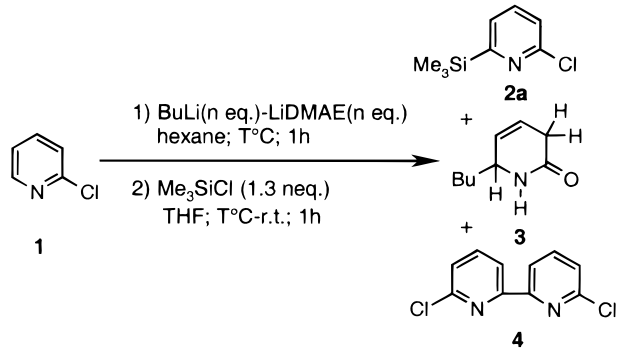
In our recent works,[6,7] we have shown that the basicity/nucleophilicity ratio (B/N ratio) of BuLi could be significantly increased in hexane by association with lithium dimethylamino ethoxide (noted LiDMAE). As a consequence, the obtained base BuLi−LiDMAE efficiently metalated sensitive heterocycles.[7] Moreover, 2-hetero-substituted pyridines were regioselectively metalated at the unusual C-6 position.[6,8] This prompted us to investigate the metalation of 2-chloropyridine with BuLi−LiDMAE in apolar solvents.

(1) Shepherd, R. G.; Fedrick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145.
(2) Trécourt, F.; Marsais, F.; Güngor, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, *9*, 2409−2415.
(3) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009−2021.
(4) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137−4140.
(5) For reviews on directed orthometalation, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Marsais, F.; Quéguiner, G.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−303.
(6) (a) Gros, Ph.; Fort, Y.; Quéguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791−4794. (b) Gros, Ph.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 20, 3071−3080.
(7) Gros, Ph.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *24*, 3597−3600.
(8) Gros, Ph.; Ben Younès-Millot, C.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 303−306.

10.1021/ol005538o CCC: $19.00
Published on Web 02/23/2000

At first, we performed a series of exploratory experiments of which the more significant results are reported in Table 1.

Table 1. C-6 Lithiation of 2-Chloropyridine Mediated by BuLi−LiDMAE[a]

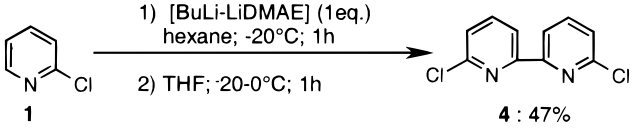


entry	BuLi (equiv)	LiDMAE (equiv)	T (°C)	**1**[b] (%)	**2a**[b] (%)	**3**[b] (%)	**4**[b] (%)
1	1		0			5	
2	1		−78	20		30	
3	1	1	0	60			10
4	1	1	−40	30	12	10	15
5	1	1	−78	27	57	10	5
6	2	2	−78	15	75	2	tr
7	3	3	−78		98[c]		

[a] All reactions performed on 2.7 mmol of **1**. [b] GC yields. [c] 90% isolated yield.

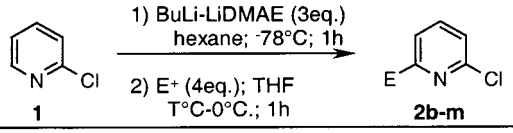
The results obtained with BuLi at 0 or −78 °C were in agreement with those reported in the literature for reactions in THF[2] since only **3** and a large amount of tarry products were obtained (entries 1 and 2). In contrast, entries 3−7 underlined the role of LiDMAE on the B/N ratio. Indeed, C-6 lithiation was generally observed when BuLi−LiDMAE was used. As expected,[6] the yield of **2a** was critically dependent on the temperature and amount of base. When 1 equiv of BuLi−LiDMAE was used, notable amounts of dimer **4** were obtained. Since **4** was never isolated with BuLi, we deduced that it probably results from the electrophilic trapping of a part of 6-lithio-2-chloropyridine by unreacted 2-chloropyridine. According to this observation, we performed the reaction in the absence of electrophile and found a one-step convenient way to prepare **4** from 2-chloropyridine (Scheme 1).[9]

Scheme 1



From Table 1, it appeared that the best yield in **2a** was obtained by performing the lithiation with 3 equiv of BuLi−LiDMAE for 1 h at −78 °C. Under these conditions (entry 7), the reaction proceeded cleanly and **2a** was obtained as a single product (90% isolated).[10] To illustrate the versatility and synthetic value of the reaction for the preparation of 6-functional-2-chloropyridines, we examined the condensation with various representative electrophiles (Table 2). As shown, products **2b**−**l** were generally obtained in good yields. The deuterated product **2b** was obtained in 100% yield (^{1}H NMR), nicely evidencing the quantitative formation of 6-lithio-2-chloropyridine in the reaction medium. Despite all our efforts, product **2d** always remained contaminated by

Table 2. C-6 Functionalization of 2-Chloropyridine[a]



Electrophile	Product, E=		Yield %[b]
MeOD	D	**2b**	100[c]
MeSSMe	MeS	**2c**	92
MeI	Me	**2d**	70[d]
Me_2SO_4			60[d]
t-BuCHO	*t*-BuCH(OH)	**2e**	90
MeEtCO	MeEtC(OH)	**2f**	60
DMF	CHO	**2g**	15[e]
Me_2NCOPh	PhCO	**2h**	84
$ClSnBu_3$	$SnBu_3$	**2i**	84
C_2Cl_6	Cl	**2j**	74
CBr_4	Br	**2k**	70[f]
I_2	I	**2l**	80
		**2m**	30[g]
		**2n**	25[g]

[a] Reaction performed on 2.7 mmol of **1**. [b] Isolated yields after purification on Chromatotron. [c] Deuterium content determined by ^{1}H NMR. [d] 2-Chloro-6-ethylpyridine was obtained as a side product (10% (GC)). [e] **2g** was found to be highly unstable. [f] CBr_4 was added as a hexane solution. [g] The diazines were reacted at −20 °C.

(9) Compound **4** was obtained in 20% overall yield from 2-bromo-6-chloropyridine: Newkome, G. R.; Hager, D. C. *J. Am. Chem. Soc.* **1978**, *100*, 5567−5568.

(10) **Typical Procedure for C-6 Functionalization of 1.** To a solution of 2-dimethylaminoethanol (0.72 g; 8 mmol) in hexane (5 mL) cooled at 0 °C, under a nitrogen atmosphere, was added dropwise *n*-BuLi (10 mL of a 1.6 M solution in hexanes; 16 mmol). After 30 min at 0 °C, the reaction medium was cooled at −78 °C and a solution of 2-chloropyridine (0.3 g; 2.67 mmol) in hexane (5 mL) was added dropwise. After 1 h at this temperature, the red solution was treated with a solution of the appropriate electrophile (10.67 mmol) in THF (20 mL). The reaction medium was then allowed to warm slowly to 0 °C. Hydrolysis was then performed at this temperature with water. After usual aqueous workup, the products were purified by flash chromatography.

10% of the corresponding ethyl derivative even using Me_2SO_4 to prevent lithium−halogen exchange. This side product thus probably arose from the subsequent lithiation of **2d** in the reaction medium. Compounds **2i**−**l** were particularly attractive since they bear potentially reactive functional groups. The introduction of heteroaromatic groups by nucleophilic coupling of 6-lithio-2-chloropyridine with electrophilic heterocycles was also examined. Although the lithio intermediate reacted only moderately with pyrimidine and pyrazine, it gave access to the new chlorinated unsymmetric bis-heterocyles **2m**−**n**.

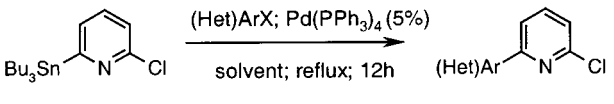
Note that these direct coupling processes were found to be less efficient than those previously obtained with 2-methoxypyridine[11] and may be attributed to a weaker nucleophilicity of 6-lithio-2-chloropyridine.

Finally, since our method was particularly efficient to introduce tributyltin at the C-6 position, we investigated the ability of stannane **2i** to undergo Stille cross-coupling.[12] The results obtained with various (hetero)aromatic halides are reported in Table 3.

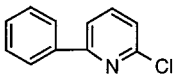
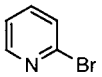
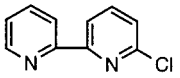
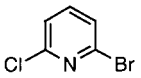
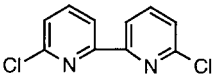
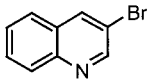
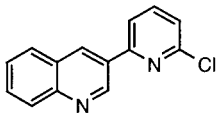
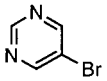
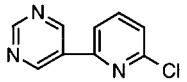
As shown, efficient coupling reactions were obtained. While the choice of temperature was not critical with iodobenzene, refluxing xylene had to be used to ensure efficient cross-coupling with bromoheterocycles. In addition to the efficient preparation of the new compounds **5c**,**d**, we succeeded in improving the overall yields (calculated from **1**) of the known **4**[8] and **5b**.[13] Note that the synthesis of **4** was a nice illustration of the usefulness of the prepared 2-chloro-6-functional pyridines **2i** and **2k**.

As a conclusion, we have shown that the metalation of 2-chloropyridine by BuLi−LiDMAE was chemo- and regioselective. Indeed, lithiation occurred exclusively at the C-6 position while nucleophilic addition on the pyridine ring and displacement of the chlorine atom were suppressed. Thus, it allowed the preparation of new useful pyridinic and bis-heterocyclic synthons.

Table 3. Stille Cross-Coupling of Stannane **2i**[a]



2i **5**

(Het)ArX	Solvent	Product		Yield %[b]
PhI	Toluene		**5a**	58
	Xylene			60
	Toluene		**5b**	20
	Xylene			60
	Xylene		**4**	53
	Xylene		**5c**	65
	Xylene		**5d**	80

[a] All reactions performed on 1.1 mmol of **2i** and 1.3 mmol of (Het)ArX in the presence of 5 mol % of $Pd(PPh_3)_4$. [b] Isolated yields after flash chromatography.

Supporting Information Available: Text giving detailed experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005538O

(11) Gros, Ph.; Fort, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, *10*, 1685−1689.

(12) For a recent review on the Stille coupling reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. In *The Stille Reaction*; John Wiley and Sons: New York, 1998.

(13) Compound **5b** has been prepared in 32% yield from the corresponding pyridylpyridone. Field, J. S.; Haines, R. J.; Parry, C. J.; Sookraj, S. H. *S. Afr. J. Chem.* **1993**, *46*(3/4), 70−74.