

Unprecedented C-6 functionalisation of 3-picoline induced by a methyl to C-6 lithium shift

Julien Mathieu, Philippe Gros 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. E-mail: yves.fort@sor.uhp-nancy.fr

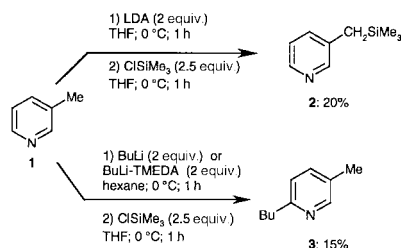
Received (in Liverpool, UK) 28th February 2000, Accepted 13th April 2000

BuLi–Me₂N(CH₂)₂OLi (BuLi–LiDMAE) promoted the clean C-6 functionalisation of 3-picoline via a methyl to C-6 lithium shift.

The selective lithiation-functionalisation of 3-picoline **1** remains a synthetic challenge since the potential electrophilicity of the azomethine bond towards alkyllithium reagents as well as a competitiveness between acidic protons of the methyl group and those of the heteroaromatic ring must be considered. In fact, a survey of the literature revealed that major studies concern the abstraction of side-chain protons¹ while the selective lithiation of the pyridinic ring has been performed only *via* halogen–metal exchange on the corresponding brominated derivatives.² To our knowledge, direct lithiation of the cheap and easily available parent **1** has not yet been described.

Recently, we have reported the usefulness of BuLi–Me₂N(CH₂)₂OLi (denoted BuLi–LiDMAE) for the metallation of pyridine derivatives in apolar solvents. This new reagent prevented the classical nucleophilic addition of BuLi while promoting the regioselective lithiation at C- α of the pyridinic ring.³ Herein, we describe our investigations on the selective metallation of 3-picoline **1** with BuLi–LiDMAE and its efficiency for the synthesis of 2-substituted-5-methylpyridines.

All our initial attempts to metallate the pyridinic ring of **1** with classical lithium reagents failed (Scheme 1). Reaction with LDA affected exclusively the methyl group¹ giving **2** while BuLi or BuLi–TMEDA led to complex mixtures containing the nucleophilic addition product **3**.



Scheme 1

In contrast, when **1** was treated with BuLi–LiDMAE (3 equiv),⁴ after subsequent quenching with ClSiMe₃, neither silylation of the methyl group nor addition products were detected. Moreover, exclusive C-6 silylation of the pyridinic ring occurred and **4a** was isolated in 90% yield. The versatility of this unprecedented reaction was further nicely illustrated by condensation of representative electrophiles⁵ (Table 1).[†]

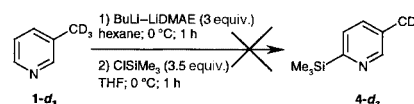
As shown, clean C-6 functionalisation was observed and products **4b–h** were isolated in good to very good yields. Note that the derivatives **4g–j** are of particular interest as potentially reactive precursors for further chemical modifications.

Our attention then focused on the interpretation of the obtained regioselectivity. At first we felt that owing to the known higher acidity of side-chain protons,⁶ lithiation at the methyl group could be considered as the initial step of the reaction pathway. Thus, we attempted the metallation of

Table 1 Preparation of 2,5-disubstituted pyridines^a

Electrophile	E	Product	Yield (%) ^b
Me ₃ SiCl	Me ₃ Si	4a	91
DCI/D ₂ O	D	4b	100 ^c
MeSSMe	MeS	4c	90
Me ₂ NCOPh	PhCO	4d	60
Bu ^t CHO	Bu ^t CHOH	4e	75
MeCOEt	Me(Et)COH	4f	50
ClSnBu ₃	Bu ₃ Sn	4g	50 ^d
C ₂ Cl ₆	Cl	4h	70
CBr ₄	Br	4i	65
I ₂	I	4j	68

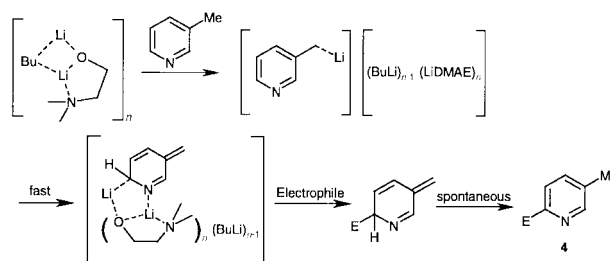
^a Reactions performed using 4 mmol of **1**. ^b Isolated yields after purification. ^c Deuterium content determined by ¹H NMR. ^d Loss of material upon chromatographic purification (¹H NMR yield was 95%).



Scheme 2

3-(methyl-*d*₃)pyridine **1-d₃** with BuLi–LiDMAE. Deuterium was here expected to act as a carbon protecting group preventing methyl proton abstraction owing to a kinetic isotope effect (KIE).⁷ As shown in Scheme 2, no silylated product **4-d₃** was detected.

This strong KIE clearly indicated that the availability of methyl protons was critical to ensure functionalisation of the pyridinic ring. An eventual direct metallation at C-6 was thus excluded and the reaction pathway probably involves a fast lithium migration from the side chain to the 6 position. According to our previous observations,³ this unusual shift is assumed to be favoured by a strong complexation of BuLi–LiDMAE aggregates in the neighbourhood of the pyridine nitrogen atom. Subsequent electrophilic quenching followed by



Scheme 3

spontaneous aromatisation⁸ would then afford product **4** (Scheme 3).

In summary, we have shown that BuLi–LiDMAE promoted the unprecedented regioselective C-6 functionalisation of 3-picoline. This efficient method was found to be a direct and simple route to functional picolinic derivatives which constitute the key structure of many biologically active compounds.

Notes and references

† All compounds gave satisfactory spectral data (¹H, ¹³C NMR) and new compounds gave satisfactory elemental analyses. The preparation of **4a** is given as a typical procedure. To a solution of 2-dimethylaminoethanol (1.07 g; 12 mmol) in hexane (5 mL) cooled at 0 °C, was added dropwise BuLi (24 mmol; 15 mL of a 1.6 M solution in hexanes). After 15 min, a solution of 3-picoline (0.37 g; 4 mmol) in hexane (5 mL) was added dropwise and the orange solution stirred for 1 h at 0 °C. After cooling at –78 °C, a solution of TMSCl (1.55 g, 14 mmol) in THF (25 mL) was added dropwise. The reaction mixture was maintained at –78 °C for 1 h and then allowed to warm to room temperature. Hydrolysis at 0 °C with water (15 mL) was followed by extraction with diethyl ether (20 mL) and drying over MgSO₄. After evaporation of solvents, the crude product was purified by flash-chromatography using hexane–AcOEt (85:15) as eluent. **4a** was obtained as an oil (0.59 g, 90%). δ_H(CDCl₃, TMS), 0.32 (s, 9H), 2.31 (s, 3H); 7.41 (s, 1H), 7.42 (s, 1H), 8.62 (s, 1H). δ_C(CDCl₃, TMS), –1.3, 18.95, 128.7,

132.7, 135.0, 151.2, 164.8. *m/z* (EI): 165 (M⁺, 59%), 164 (54%), 150 (100%), 93 (18%), 73 (36%), 65 (47%).

- 1 M. L. Davis, B. J. Wakefield and J. A. Wadell, *Tetrahedron*, 1992, **5**, 939; W. M. Stalick and J. H. Murray, *Org. Prep. Proced. Int.*, 1994, **26**, 677.
- 2 F. Effenberger, A. Krebs and P. Willrett, *Chem. Ber.*, 1992, **125**, 1131; G. A. Kraus and J. Malpert, *Synlett*, 1997, **1**, 107; G. Hanan, U. Schubert, D. Volkmer, E. Rivière, J.-M. Lehn, N. Kyritsakas and J. Fisher, *Can. J. Chem.*, 1997, **75**, 169.
- 3 Ph. Gros, Y. Fort and P. Caubère, *J. Chem. Soc., Perkin Trans. 1*, 1997, **20**, 3071; Ph. Gros, Y. Fort and P. Caubère, *J. Chem. Soc., Perkin Trans. 1*, 1997, **24**, 3597; Ph. Gros, C. Ben Younès-Millot and Y. Fort, *Tetrahedron Lett.*, 2000, **41**, 303; S. Choppin, Ph. Gros and Y. Fort, *Org. Lett.*, 2000, in press.
- 4 The reaction with 2 equiv. of BuLi–LiDMAE led also to clean C-6 substitution but in lower yield (76%).
- 5 Condensation with epoxides (styrene oxide and propylene oxide) was also attempted but was found to be unsuccessful and 3-picoline was recovered quantitatively in both cases.
- 6 R. Fraser, T. Mansour and S. Savard, *J. Org. Chem.*, 1985, **50**, 3232.
- 7 Examples using KIE to control the regioselectivity of lithiations have been reported. See, for example: M. Kopach and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 6764; J. Clayden, J. Pink, N. Westlund and F. Wilson, *Tetrahedron Lett.*, 1998, **39**, 303.
- 8 Despite all our efforts we were unable to isolate the hydro intermediate.