ChemComm

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

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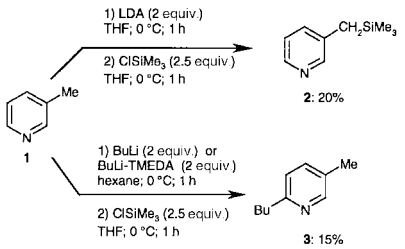
Received (in Liverpool, UK) 28th February 2000, Accepted 13th April 2000

BuLi–$Me_2N(CH_2)_2OLi$ (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 competitivity 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 protons[1] 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–$Me_2N(CH_2)_2OLi$ (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 group[1] giving **2** while BuLi or BuLi–TMEDA led to complex mixtures containing the nucleophilic addition product **3**.



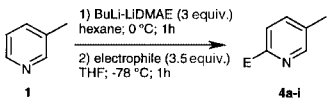
Scheme 1

In contrast, when **1** was treated with BuLi–LiDMAE (3 equiv.),[4] after subsequent quenching with $ClSiMe_3$, 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 electrophiles[5] (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.

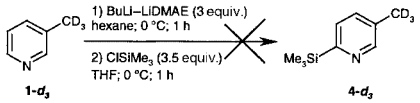
Our attention then focused on the interpretation of the obtained regioselectivity. At first we felt that owing to the known higher acidity of side-chain protons,[6] lithiation at the methyl group could be considered as the initial step of the reaction pathway. Thus, we attempted the metallation of

Table 1 Preparation of 2,5-disubstituted pyridines[a]



Electrophile	Product E		Yield (%)[b]
Me_3SiCl	Me_3Si	**4a**	91
DCl/D_2O	D	**4b**	100[c]
MeSSMe	MeS	**4c**	90
Me_2NCOPh	PhCO	**4d**	60
Bu^tCHO	Bu^tCHOH	**4e**	75
MeCOEt	Me(Et)COH	**4f**	50
$ClSnBu_3$	Bu_3Sn	**4g**	50[d]
C_2Cl_6	Cl	**4h**	70
CBr_4	Br	**4i**	65
I_2	I	**4j**	68

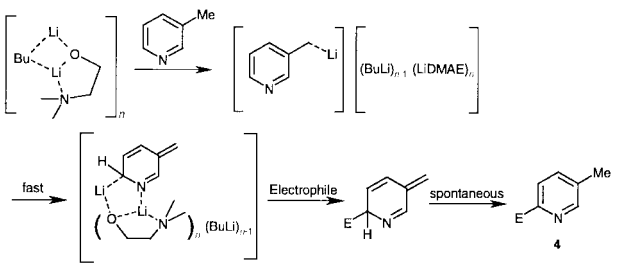
[a] Reactions performed using 4 mmol of **1**. [b] Isolated yields after purification. [c] Deuterium content determined by ^1H NMR. [d] Loss of material upon chromatographic purification (^1H NMR yield was 95%).



Scheme 2

3-(methyl-d_3)pyridine **1**-d_3 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**-d_3 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

DOI: 10.1039/b001690j

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spontaneous aromatisation[8] 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 (^{1}H, ^{13}C 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 $MgSO_4$. 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($CDCl_3$, TMS), 0.32 (s, 9H), 2.31 (s, 3H); 7.41 (s, 1H), 7.42 (s, 1H), 8.62 (s, 1H). δ_C($CDCl_3$, 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%).

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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.

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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.