Unusual *t*-BuLi Induced Ortholithiation versus Halogen–Lithium Exchange in Bromopyridines: Two Alternative Strategies for Functionalization

Philippe Pierrat, Philippe Gros,* Yves Fort*

Synthèse Organométallique et Réactivité, UMR CNRS-UHP 7565, Faculté des Sciences, Université Henri Poincaré, 54506 Vandoeuvre-lès-Nancy, France
Fax +33(3)83844785; E-mail: Yves.Fort@sor.uhp-nancy.fr; E-mail: Philippe.Gros@sor.uhp-nancy.fr
Received 13 May 2004

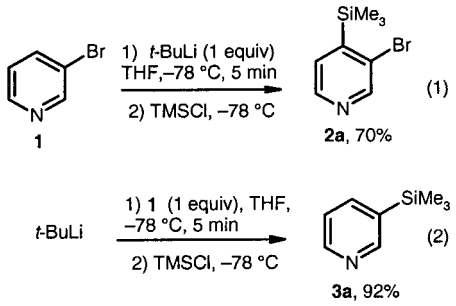
Abstract: The reaction of lithiating agents with various 3-bromopyridines has been investigated. An unprecedented selectivity was observed with *t*-BuLi, which effected a clean lithiation at C-4. With 3-bromo and 2-chloro-3-bromo pyridines, the ortholithiation–exchange ratio was strongly electrophile and addition order dependent while 2-chloro-5-bromopyridine always gave exclusive C-4 substitution.

Key words: bromine–lithium exchange, ortholithiation, bromopyridines, regioselectivity

Bromopyridines are versatile compounds since they can be selectively substituted at various positions using selected lithiating agents. The well-known bromine–lithium exchange is generally achieved with *n*-BuLi[1] or more rarely with *t*-BuLi[2] while ortholithiation is realized with lithium dialkylamides. In most cases, the latter reaction leads to subsequent halogen scrambling or pyridyne formation.[3] Judicious combination of these reactions on dibromopyridines provided efficient routes to new polyfunctional derivatives.[4] During a research program, we have been drawn to investigate regiochemistry in the reaction of various 3-bromopyridines with lithiating agents. Here we report that *t*-BuLi induced an unprecedented ortholithiation instead of the expected bromine–lithium exchange.

Preliminary experiments performed on 3-bromo-pyridine (**1**) gave surprising results. While compounds **2a** and **3a** were expectedly obtained after reaction with LTMP and *n*-BuLi, respectively, *t*-BuLi induced a clean lithiation at C-4 in 70% yield instead of the classical bromine–lithium exchange (Scheme 1), the remaining part was only unreacted **1**. Moreover, the order of reagent introduction had a spectacular effect. Indeed, **2a** was obtained exclusively when *t*-BuLi was added to a THF solution of **1** (1) while the reverse addition led to **3a** (2). This unprecedented bromine tolerant lithiation was very intriguing and we decided to investigate it in more detail under various reaction conditions (Table 1).

As shown, the nature of the electrophile had a dramatic effect. When the medium was quenched with D_2O or dimethyldisulfide (DMDS) bromine–lithium exchange was the main product (entries 6–10). Compounds **3b**–**c** were even obtained as single product using two equivalents of base (entries 7 and 10). The C-4 substituted derivative could be obtained exclusively in the presence of TMSCl (entry 1). In addition, we found that prolonged metallation time had no effect on the **2a**:**3a** ratio when TMSCl was used (entries 1–3) while an increase of temperature favored the formation of **3a** (entry 5).[5] On the other hand, when the medium was quenched with DMDS after 30 or 60 minutes of metallation, the amount of ortholithiation product **2c** was identical to those obtained after five minutes. Starting **1** was then recovered in 80% and no exchange product **3c** was detected (entries 8, 9).



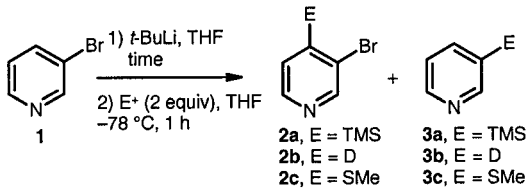
Scheme 1 Effect of order of introduction of *t*-BuLi

These observations suggested the formation of a reactive intermediate evolving towards the C-4 substituted product only when quenched in situ by TMSCl known as a base-compatible electrophile.[6,7] This was supported by the deuteration experiment (entry 6) which indicated the formation of the 4-lithio species only in 21% yield in the medium at the end of metallation time.

We next investigated further the role of the H-4 proton in the mechanistic pathway. Thus, the 4-position was deuterated[8] and subjected to reaction with *t*-BuLi (Scheme 2). As expected, different selectivities were obtained with TMSCl and DMDS. With TMSCl, product **2a**, resulting from deuterium abstraction, was mainly obtained. Interestingly, it was accompanied by a C-2 silylated product probably due to a deuterium induced partial inhibition of deprotonation at C-4. In contrast, deuterium was abstracted only in trace amounts in the presence of DMDS and the reaction led mainly to bromine–lithium exchange product **3c**-d_4.

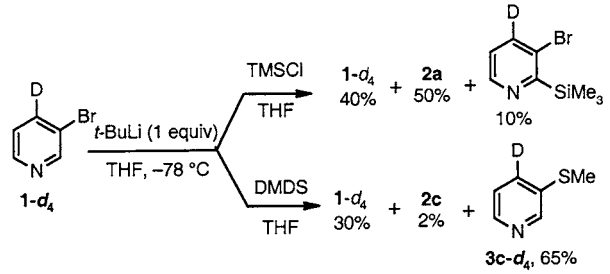
SYNLETT 2004, No. 13, pp 2319–2322
Advanced online publication: 08.09.2004
DOI: 10.1055/s-2004-831337; Art ID: D12004ST

Table 1 Variation of Conditions in Lithiation of **1** with *t*-BuLi[a]

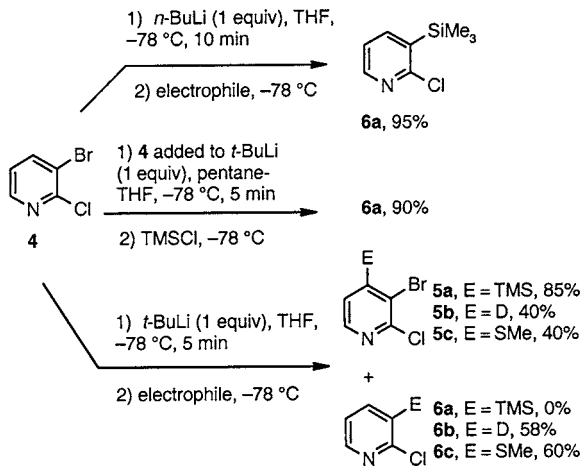


Entry	*t*-BuLi (equiv)	Time (min)	Temp (°C)	E^+	Yield of **1** (%)[b]	Yield of **2** (%)[b]	Yield of **3** (%)[b]
1	1	5	–78	TMSCl	30	**2a**, 70	–
2	1	30	–78	TMSCl	31	**2a**, 69	–
	1	60	–78	TMSCl	30	**2a**, 70	–
4	2	5	–78	TMSCl	–	**2a**, 78	**3a**, 20
5	1	5	–50[c]	TMSCl	–	**2a**, 35	**3a**, 63
6	1	5	–78	D_2O	28[c]	**2b**, 21[d]	**3b**, 49[d]
7	2	5	–78	D_2O	–	–	**3b**, 99[d]
8	1	5	–78	DMDS	30	**2c**, 20	**3c**, 50
9	1	30–60	–78	DMDS	80	**2c**, 20	–
10	2	5	–78	DMDS	–	–	**3c**, 99

[a] All reactions performed on 2 mmol of **1**. All experiments were repeated thrice and gave similar results.
[b] GC yields.
[c] Metallation at –78 °C, 5 min then –50 °C, 5 min.
[d] Ratios determined by ^{1}H NMR.



Scheme 2 Role of the H-4 proton in reaction pathway



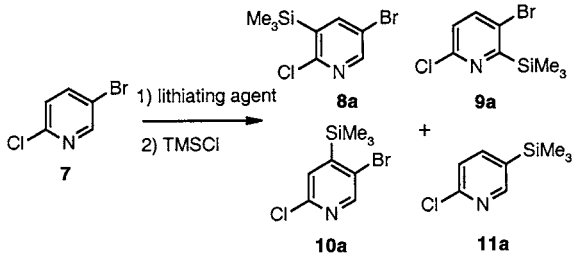
Scheme 3 Reaction of **4** with *t*-BuLi

These results indicated that the H-4 proton played a central role in the evolution of the reactive intermediate. Thus, we examined the effect of pyridine ring substitution especially by introduction of electron-withdrawing chlorine, known to increase the acidity of pyridine protons. The reactivity of 2-chloro-3-bromopyridine (**4**) and 2-chloro-5-bromo-pyridine (**7**) was then investigated (Scheme 3).

At first, very similar reactivities were found for **4** and **1**. *n*-BuLi led only to bromine–lithium exchange. The addition order of reagents was still a key paramater with *t*-BuLi, which had to be added to **4** to obtain ortholithiation. Electrophiles other than TMSCl also led to mixtures of ortholithiation and exchange products. The acidifying effect of chlorine *ortho* to bromine was notable since conversions were generally increased compared to **1**. For example, the silyl derivative **5a** was obtained in 85% yield. The ortholithiation–exchange ratio was also increased from 30:70 for **1** (see Table 1) to 40:60 for **4** when MeSSMe and D_2O were used as electrophiles. This again underlined the role of the H-4 proton into the evolution process of the reactive intermediate since a more acidic H-4 led to higher amount of C-4 substitution.

Then, we turned to lithiation of 2-chloro-5-bromo pyridine (**7**) in order to check the effect of chlorine *para* to bromine (Table 2). In this case, competitive ortholithiation by the chlorine atom could be expected. So the lithi-

Table 2 Reaction of **7** with Various Lithiating Agents[a]

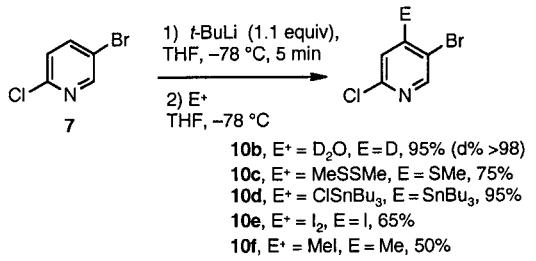


Base (equiv), solvent, temperature, time	Yield of **8a** (%)	Yield of **9a** (%)	Yield of **10a** (%)	Yield of **11a** (%)
LiTMP (3.2 equiv), THF, –78 °C, 2 h	–	–	80	–
LiTMP (1 equiv), THF, –78 °C, 2 h	–	–	7	–
MeLi (1.2 equiv), Et_2O, –78 °C, 15 min	–	–	–	85
n-BuLi (1.2 equiv), THF, –78 °C, 30 min	–	–	–	90
t-BuLi (1 equiv), THF, –78 °C, 5 min	–	–	95[b]	–
t-BuLi (1 equiv), THF, –78 °C, 5 min (reverse addition)	–	–	93	–
s-BuLi (1 equiv), THF, –78 °C, 30 min	–	–	90	–

[a] All reactions were performed on 2 mmol of **7**. All yields are GC yields.
[b] 92% Isolated yield.

ation was also attempted with LTMP, known to promote ortholithiation of both 2-chloro and 3-bromopyridine.

As shown, LiTMP effected exclusive proton abstraction at C-4 (*ortho* to bromine) in agreement with the higher acidity of the H-4 proton.[9] Bromine–lithium exchange was obtained with MeLi and *n*-BuLi. On the other hand, one equivalent of branched alkyllithiums *s*-BuLi and *t*-BuLi led to a clean and efficient C-4 lithiation. In sharp contrast with **1** and **4**, no effect of reagent introduction order was observed with **7** in full agreement with a direct lithiation process. Moreover, the ortholithiation occurred without any bromine–lithium exchange regardless of the electrophile (Scheme 4).[10] The deuteration experiment clearly indicated the quantitative formation of the 3-bromo-4-lithio derivative before the quenching step. The reaction was found of synthetic interest since various substituents were introduced in good yield, particularly iodine and tin moieties giving access to valuable new reactive precursors.



Scheme 4 Lithiation of **7** with *t*-BuLi and reaction with electrophiles

In summary, this study brings new data on the reactivity of *t*-BuLi towards 3-bromopyridines. The reaction of *t*-BuLi with bromopyridines **1** and **4** gave an intermediate evolving mainly towards the ortholithiation product by in situ trapping with the base tolerant TMSCl while incompatible electrophiles DMDS or D_2O led mainly to 3-substituted pyridines. The reason for such an electrophile effect remains unclear. Nevertheless, the deep green color developed during the reaction could be attributed to a radicaloid species.[11] Alternatively, formation of an ate-complex[12] could also explain the unusual behavior compared to classical lithiated intermediates. With 2-chloro-5-bromopyridine, the selectivity was rather governed by the acidity of the H-4 proton leading exclusively to ortholithiation product. The absence of detection of pyridine in the reaction medium ruled out an intermolecular lithiation between 3-lithiopyridine and unreacted **1**. Indeed, pyridine is sluggishly metallated by *t*-BuLi[13] and should be accumulated in the medium.

Finally, this new reactivity of *t*-BuLi is of high synthetic value since all reactions can be performed cleanly with a stoichiometric amount of base. Large excess of lithium dialkylamides (3–4 equiv) are generally required for the same efficiency generating large amounts of side products in the reaction medium. This opens new perspectives in heterocyclic synthesis since retention of both the C-Br and C-Cl bonds provides useful templates for further polyfunctionalization. Work is now under progress to study in more detail the mechanistic pathway as well as the synthetic scope of this new selective lithiation.

References

(1) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485.
(2) Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 6102.
(3) (a) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035. (b) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151. (c) Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835.
(4) Gu, Y. G.; Bayburth, E. K. *Tetrahedron Lett.* **1996**, *37*, 2565.
(5) Temperatures below –78 °C did not change the selectivity.
(6) This kind of reactivity has aleady been observed during our previous works on lithiation of 2-methoxypyridine with BuLi–$Me_2N(CH_2)_2OLi$ reagent. In this case the intermediate evolved towards C-6 lithiation or nucleophilic addition depending on the nature of the electrophile. See: Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *20*, 3071.
(7) TMSCl is known to display some compatibility towards hindered bases. See: (a) Comins, D.; La Munyon, D. *Tetrahedron Lett.* **1988**, *29*, 773. (b) Trécourt, F.; Mallet, M.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 1367.
(8) Compound **1**-*d*4 was obtained in 70% yield (*d* >98%, ^{1}H NMR) by reaction of **1** with LDA (3 equiv) in THF at –78 °C for 0.5 h and condensation with MeOD (5 equiv).
(9) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009.
(10) **General Procedure for Ortholithitaion of 4 with *t*-BuLi.** A solution of 2-chloro-5-bromopyridine (386 mg, 2 mmol) in THF (6 mL) was cooled to –78 °C and *t*-BuLi (1.17 mL, 2 mmol) was added dropwise under nitrogen. After 5 min at –78 °C, the brown solution was treated with a solution of the appropriate electrophile (3 mmol) in THF (4 mL). The reaction medium was then allowed to warm to r.t. (1 h) and the mixture was hydrolyzed at 0 °C with H_2O (10 mL). The aqueous layer was then extracted with Et_2O. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography. Selected data for compound **10c** obtained as an orange oil, (358 mg, 75%), eluent: hexane–EtOAc (90:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.5 (s, 3 H), 6.9 (s, 1 H), 8.3 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 117.7, 118.8, 149.8, 150.4, 154.4. MS (EI): *m/z* (%) = 241 (28), 239 (100) [M^+], 237 (74), 206 (18), 143 (19), 81 (16). Anal. Calcd for $C_6H_5BrClNS$ (%): C, 30.21; H, 2.11; N, 5.87. Found: C, 30.33; H, 2.12; N, 5.78.
(11) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291.
(12) For evidence of formation of ate-complex in halogen-metal exchange see: Jedlicka, B.; Crabtree, R. H. *Organometallics* **1997**, *16*, 6021.
(13) Under these reaction conditions (1 equiv, –78 °C in THF), *t*-BuLi did not metallate pyridine even after 1 h, and gave only 2-*tert*-butylpyridine in 10–15%.