



## Direct 1,4-difunctionalization of isoquinoline

Frédéric Louërat, Yves Fort, Victor Mamane \*

Laboratoire SRS-MC-SOR, UMR CNRS-UHP 7565, Nancy Université, BP 70239, Bd des Aiguillettes, 54506 Vandoeuvre-les-Nancy, France

### ARTICLE INFO

#### Article history:

Received 25 June 2009

Revised 17 July 2009

Accepted 22 July 2009

Available online 26 July 2009

#### Keywords:

Isoquinoline  
Functionalization  
'One-pot' reaction

### ABSTRACT

The synthesis of 1,4-disubstituted isoquinoline derivatives was achieved in one step starting from isoquinoline. The process involved a nucleophilic addition in 1-position followed by an electrophilic trapping in 4-position. Interesting features were noted when  $C_2Cl_6$  was used as the electrophile since different compounds could be isolated selectively only by adjusting the reaction parameters.

© 2009 Elsevier Ltd. All rights reserved.

Isoquinoline derivatives play an important role in organic chemistry, not only as key structural units in many natural products,<sup>1</sup> but also as building blocks in important pharmaceuticals.<sup>2</sup> Furthermore, they are utilized as chiral ligands for transition metal catalysis,<sup>3</sup> and their iridium complexes are used in organic light-emitting diodes.<sup>4</sup> For these reasons, the efficient synthesis of isoquinoline derivatives is of considerable interest to synthetic and medicinal chemists.<sup>5</sup> For fine-tuning of the biological and/or physical properties of these compounds for final application, a general and flexible functionalization method that allows a rapid access to diversely substituted compounds from the inexpensive and readily available isoquinoline is highly desirable.

The 2,5-difunctionalization of pyridine through a nucleophilic attack at C-2 followed by an electrophilic trapping at C-5 was first reported nearly four decades ago.<sup>6</sup> Thereafter, several groups showed the utility of this reaction by the synthesis of different substituted pyridines<sup>7</sup> and particular interest was directed on the isolation and characterization of the dihydropyridine intermediate involved in this reaction.<sup>8</sup> Curiously, there is no report concerning this reaction with isoquinoline although it would represent a rapid way of functionalization of the isoquinoline core. Indeed, the direct addition on isoquinoline is too slow and the resulting dihydro derivative re-aromatizes rapidly by loss of  $LiH^9$  before it can react with an electrophile. In order to facilitate the nucleophilic addition, one way could be electrophilic N-activation.<sup>10</sup> However the dihydro intermediates would be too stable to react with an electrophile. We then reasoned that the best way to succeed in the 1,4-difunctionalization of isoquinoline could be via activation of the nucleophile. Alexakis and co-workers observed that the reaction of  $MeLi$  with isoquinoline

was accelerated by adding a stoichiometric amount of a lithium coordinating compound such as DME (dimethoxyethane).<sup>11,12</sup> During their work, they observed that, when using methyl chloroformate as the electrophile, along with the expected N-acylation product, a non-separable by-product incorporating two ester groups was also observed, probably resulting from the initial C-acylation followed by N-acylation (Fig. 1).

On the basis of these considerations and pursuing our efforts toward the synthesis and functionalization of polyheterocyclic systems,<sup>13</sup> we report herein our results concerning the 1,4-difunctionalization of isoquinoline. The undesired N-addition to **2N** was avoided by using electrophiles such as alkyl halides or hexachloro-

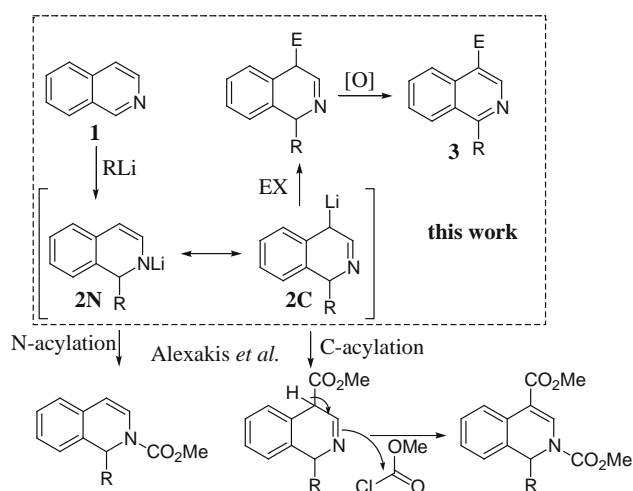
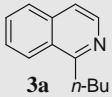
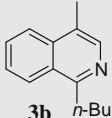

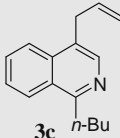
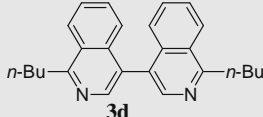
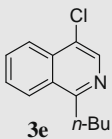
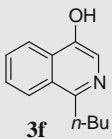
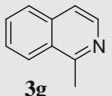
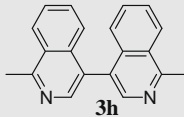
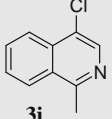
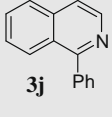
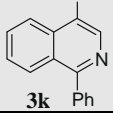


Figure 1. Addition–Electrophilic trapping sequence on isoquinoline.

\* Corresponding author. Tel.: +33 3 83 68 43 20; fax: +33 3 83 68 47 85.  
E-mail address: [victor.mamane@srsmc.uhp-nancy.fr](mailto:victor.mamane@srsmc.uhp-nancy.fr) (V. Mamane).

**Table 1**  
Functionalized isoquinoline derivatives **3** produced via the sequence shown in Figure 1<sup>a</sup>

Entry	RLi	EX	Product	Yield (%)
1	<i>n</i> -BuLi	MeOH		82
2	<i>n</i> -BuLi	MeI		68
3	<i>n</i> -BuLi			31
4	<i>n</i> -BuLi	C <sub>2</sub> Cl <sub>6</sub>		72
5	<i>n</i> -BuLi	C <sub>2</sub> Cl <sub>6</sub> <sup>b</sup>		54
6	<i>n</i> -BuLi	C <sub>2</sub> Cl <sub>6</sub> <sup>b,c</sup>		58
7	MeLi	MeOH <sup>d</sup>		74
8	MeLi	C <sub>2</sub> Cl <sub>6</sub> <sup>d</sup>		64
9	MeLi	C <sub>2</sub> Cl <sub>6</sub> <sup>b</sup>		42
10	PhLi	MeOH		74
11	PhLi	C <sub>2</sub> Cl <sub>6</sub> <sup>b</sup>		73

<sup>a</sup> Reaction conditions: (i) 1.2 equiv RLi, 1 equiv DME, Et<sub>2</sub>O, 30 °C, 3 h. (ii) 1.5 equiv EX, 2 h. (iii) MeOH (2 equiv), air oxidation.

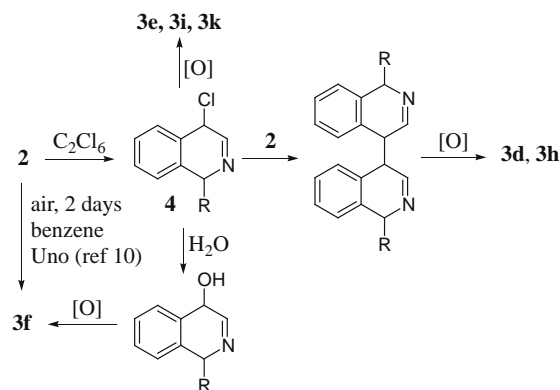
<sup>b</sup> Reverse addition.

<sup>c</sup> Addition of H<sub>2</sub>O at the end of the reaction.

<sup>d</sup> Oxidation with DDQ (1 equiv).

ethylene (C<sub>2</sub>Cl<sub>6</sub>) (Table 1).<sup>14,15</sup> The reaction of **1** with 1.2 equiv of *n*-BuLi in the presence of 1 equiv of DME resulted in clean C1-addition after 3 h in diethyl ether at 30 °C under argon. After addition of MeOH (2 equiv), the mixture was opened to air producing compound **3a** in 82% yield (entry 1). The dihydro intermediate **2C** could be trapped by iodomethane followed by addition of MeOH and air oxidation to give **3b** in 68% yield (entry 2). Trapping with allylbromide afforded a mixture containing the expected product along with products of the double bond isomerization. Nevertheless, compound **3c** could be isolated in 31% yield (entry 3). When C<sub>2</sub>Cl<sub>6</sub> was added to the reaction mixture, instead of the expected product **3e**, dimer **3d** was obtained in a good yield of 72% (entry 4).<sup>16</sup> Probably, compound **4** resulting from reaction of the dihydro intermediate **2C/2N** with C<sub>2</sub>Cl<sub>6</sub>, was trapped immediately by remaining **2C/2N** to give **3d** (Fig. 2).<sup>17</sup> However, compound **3e** could be obtained in 54% yield by performing a reverse addition of the reaction mixture to a solution of C<sub>2</sub>Cl<sub>6</sub> in Et<sub>2</sub>O following by MeOH addition (entry 5).<sup>18</sup> We then tested the reactivity of **4** toward different nucleophiles but the chlorine displacement was observed only when H<sub>2</sub>O was used giving 3-hydroxyquinoline **3f** in a moderate yield of 58% (entry 6).<sup>19</sup> It is worth noting that **3f** and related compounds were already observed by Uno and co-workers after air oxidation of the hydrolyzed dihydro derivative **2C/2N** for 2 days in benzene.<sup>10</sup> MeLi was then used as the nucleophile and we observed the same reactivity toward isoquinoline **1** compared to *n*-BuLi. However, it was noted that the resulting dihydro intermediates were not completely re-aromatized after addition of MeOH under air thus requiring the addition of DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) in order to achieve reaction completion. Under these conditions, compound **3g** was isolated in 74% yield (entry 7). The dimer **3h**<sup>20</sup> could be obtained in 64% yield by adding C<sub>2</sub>Cl<sub>6</sub> to the reaction mixture before DDQ oxidation (entry 8). The reverse addition procedure allowed the isolation of compound **3i** in 42% yield (entry 9). Finally, the reaction of PhLi was performed under the standard conditions allowing the synthesis of products **3j** and **3k** with respective yields of 74% and 73% (entries 10 and 11).

In conclusion, we have described a straightforward access to 1,4-disubstituted isoquinoline compounds by a simple addition–electrophilic trapping sequence. The use of DME during the addition of RLi (*n*-BuLi, MeLi and PhLi) was important to accelerate the reaction and to allow electrophilic trapping before rearomatization. Among the electrophiles tested, C<sub>2</sub>Cl<sub>6</sub> was very interesting because it allowed the selective formation of three different compounds depending on the order of addition (normal or reverse) and on the quenching method (H<sub>2</sub>O instead of MeOH). It is interesting to note that in case of **3i**, the presence of a methyl group and a chlorine atom should allow for further transformations to occur.<sup>13b,21</sup>



**Figure 2.** Different pathways for the evolution of intermediate **4**.

## Acknowledgment

We gratefully acknowledge the CNRS and Nancy Université for financial support.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2009.07.125.

## References and notes

- Bentley, K. W. In *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998; Vol. 1.
- (a) Yoon, T.; De Lombaert, S.; Brodbeck, R.; Gulianello, M.; Chandrasekhar, J.; Horvath, R. F.; Ge, P.; Kershaw, M. T.; Krause, J. E.; Kehne, J.; Hoffman, D.; Doller, D.; Hodgetts, K. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 891–896; (b) Örtqvist, P.; Peterson, S. D.; Åkerblom, E.; Gossas, T.; Sabnis, Y. A.; Fransson, R.; Lindeberg, G.; Danielson, U. H.; Karlén, A.; Sandström, A. *Bioorg. Med. Chem.* **2007**, *15*, 1448–1474; (c) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954–6957.
- (a) Clayden, J.; Fletcher, S. P.; McDouall, J. J. W.; Rowbottom, S. J. *M. J. Am. Chem. Soc.* **2009**, *131*, 5331–5343; (b) Luesse, S. B.; Counciller, C. M.; Wilt, J. C.; Perkins, B. R.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 2445–2447; (c) Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* **2007**, *48*, 3915–3917.
- (a) Fang, K.-H.; Wu, L.-L.; Huang, Y.-T.; Yang, C.-H.; Sun, L.-W. *Inorg. Chim. Acta* **2006**, *359*, 441–450; (b) Liu, S.-J.; Zhao, Q.; Chen, R.-F.; Deng, Y.; Fan, Q.-L.; Li, F.-Y.; Wang, L.-H.; Huang, C.-H.; Huang, W. *Chem. Eur. J.* **2006**, *12*, 4351–4561; (c) Zhao, Q.; Liu, S.; Shi, M.; Wang, C.; Yu, M.; Li, L.; Li, F.; Yi, T.; Huang, C. *Inorg. Chem.* **2006**, *45*, 6152–6160.
- (a) Yang, H. *Tetrahedron Lett.* **2009**, *50*, 3081–3083; (b) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458–3461; (c) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, W.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 2893–2896; (d) Fisher, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2009**, *130*, 15720–15725.
- (a) Giam, C. S.; Stout, J. L. *Chem. Commun.* **1970**, 478; (b) Doyle, P.; Yates, R. *Tetrahedron Lett.* **1970**, *11*, 3371–3374.
- (a) Zhang, L.-H.; Tan, Z. *Tetrahedron Lett.* **2000**, *41*, 3025–3028; (b) Finch, N.; Gemenden, C. W. *J. Org. Chem.* **1975**, *40*, 569–574; (c) Giam, C. S.; Knaus, E. E.; Pasutto, F. M. *J. Org. Chem.* **1974**, *39*, 3565–3568.
- (a) Marsais, F.; Granger, P.; Quéguiner, G. *J. Org. Chem.* **1981**, *46*, 4494–4497; (b) Francis, R. F.; Howell, H. M.; Fetzer, D. T. *J. Org. Chem.* **1981**, *46*, 2213–2215; (c) Francis, R. F.; Crews, C. D.; Scott, B. S. *J. Org. Chem.* **1978**, *43*, 3227–3230.
- (a) Abramovitch, R. A.; Poulton, G. A. *Chem. Commun.* **1967**, 274–275; (b) Fraenkel, G.; Copper, J. C. *Tetrahedron Lett.* **1968**, *8*, 1825–1830.
- Uno, H.; Okada, S.; Suzuki, H. *J. Heterocycl. Chem.* **1991**, *28*, 341–346.
- Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117–2122.
- Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 1568–1572.
- (a) Mamane, V.; Louërât, F.; Iehl, J.; Abboud, M.; Fort, Y. *Tetrahedron* **2008**, *64*, 10699–10705; (b) Mamane, V.; Aubert, E.; Fort, Y. *J. Org. Chem.* **2007**, *72*, 7294–7300; (c) Mamane, V.; Fort, Y. *Tetrahedron Lett.* **2006**, *47*, 2337–2340; (d) Mamane, V.; Fort, Y. *J. Org. Chem.* **2005**, *70*, 8220–8223.
- The use of TMSCl or aldehydes as electrophiles resulted in inseparable complex mixtures.
- General experimental procedure: preparation of 1-methyl-4-chloro-isoquinoline 3i.** To a solution of isoquinoline **1** (1 g, 7.75 mmol) and DME (0.8 mL, 7.75 mmol) in degassed Et<sub>2</sub>O (40 mL) at 30 °C, under argon, was added MeLi (1.6 M in Et<sub>2</sub>O, 5.8 mL, 9.3 mmol) and the mixture was stirred for 3 h before it was transferred to a degassed solution of C<sub>2</sub>Cl<sub>6</sub> (3.7 g, 11.62 mmol) in Et<sub>2</sub>O (10 mL) at 30 °C. After 2 h of stirring, MeOH (15 mmol, 0.6 mL) was added and the mixture was stirred under open air for 30 min (complete aromatization was observed by performing <sup>1</sup>H NMR of the crude mixture). The reaction mixture was extracted with Et<sub>2</sub>O, washed with water, and dried over MgSO<sub>4</sub>. After concentration, the residue was purified by chromatography on silica gel (hexanes/ethyl acetate 9:1) to give compound **3i** as a reddish syrup (580 mg, 42%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 8.37 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 6.8 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 2.87 (s, 3H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 157.2, 140.0, 133.0, 130.6, 127.8, 127.6, 126.4, 125.7, 123.5, 21.9. MS (EI) m/z 177 (M<sup>+</sup>, 100%), 142 (26), 115 (45). HRMS m/z calcd for C<sub>10</sub>H<sub>8</sub>ClN: 177.0345, found: 178.0418 (MH<sup>+</sup>). For analytical data of all other compounds, see the Supplementary data.
- For a nice application involving this kind of dimer, see: Muraoka, T.; Kinbara, K.; Takuzo, A. *Nature* **2006**, *440*, 512–515.
- (a) Ref. 8c; An analogous mechanism was proposed for this dimerization process in the pyridine series: (b) Giam, C. S.; Knaus, E. E.; Lockhart, R. A.; Keener, I. G. *Can. J. Chem.* **1975**, *53*, 2305–2310; (c) Knaus, E. E.; Ondrus, T. A.; Giam, C. S. *J. Heterocycl. Chem.* **1976**, *13*, 789–792.
- The use of CBr<sub>4</sub> resulted in formation of dimer **3d** in both normal addition and reverse addition.
- Piperidine or sodium methanolate did not give the expected substitution but instead we observed the formation of a large amount of **3a** probably resulting from HCl elimination in the dihydro intermediate **4**.
- This product was already isolated by Uno et al. (Ref. 10) but neither the yield nor a proposed mechanism of its formation was reported.
- (a) Desmaret, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029–3036; (b) Desmaret, C.; Schneider, R.; Fort, Y. *Tetrahedron* **2001**, *57*, 7657–7664; (c) Desmaret, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247–250.