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Direct 1,4-difunctionalization of isoquinoline

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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.

Isoquinoline derivatives play an important role in organic chemistry, not only as key structural units in many natural products,[1] but also as building blocks in important pharmaceuticals.[2] Furthermore, they are utilized as chiral ligands for transition metal catalysis,[3] and their iridium complexes are used in organic light-emitting diodes.[4] For these reasons, the efficient synthesis of isoquinoline derivatives is of considerable interest to synthetic and medicinal chemists.[5] 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.[6] Thereafter, several groups showed the utility of this reaction by the synthesis of different substituted pyridines[7] and particular interest was directed on the isolation and characterization of the dihydropyridine intermediate involved in this reaction.[8] 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.[10] 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).[11,12] 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,[13] we report herein our results concerning the 1,4-difunctionalizion of isoquinoline. The undesired N-addition to **2N** was avoided by using electrophiles such as alkyl halides or hexachloro-

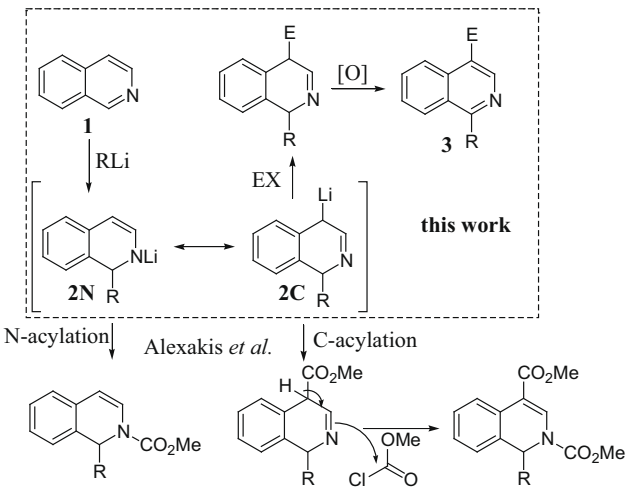

Figure 1. Addition—Electrophilic trapping sequence on isoquinoline.

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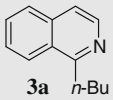
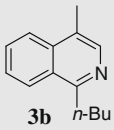
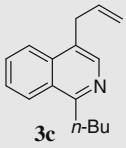
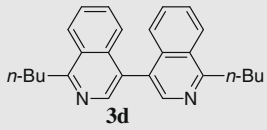
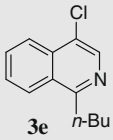
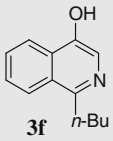
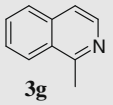
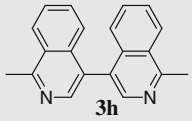
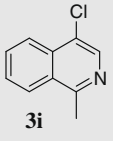
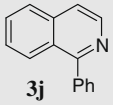
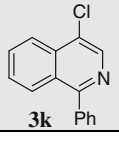
Table 1
Functionalized isoquinoline derivatives **3** produced via the sequence shown in Figure 1[a]

Entry	RLi	EX	Product	Yield (%)
1	*n*-BuLi	MeOH	 **3a**	82
2	*n*-BuLi	MeI	 **3b**	68
3	*n*-BuLi		 **3c**	31
4	*n*-BuLi	C_2Cl_6	 **3d**	72
5	*n*-BuLi	C_2Cl_6[b]	 **3e**	54
6	*n*-BuLi	C_2Cl_6[b,c]	 **3f**	58
7	MeLi	MeOH[d]	 **3g**	74
8	MeLi	C_2Cl_6[d]	 **3h**	64
9	MeLi	C_2Cl_6[b]	 **3i**	42
10	PhLi	MeOH	 **3j**	74
11	PhLi	C_2Cl_6[b]	 **3k**	73

[a] Reaction conditions: (i) 1.2 equiv RLi, 1 equiv DME, Et_2O, 30 °C, 3 h. (ii) 1.5 equiv EX, 2 h. (iii) MeOH (2 equiv), air oxidation.
[b] Reverse addition.
[c] Addition of H_2O at the end of the reaction.
[d] Oxidation with DDQ (1 equiv).

ethylene (C_2Cl_6) (Table 1).[14,15] 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_2Cl_6 was added to the reaction mixture, instead of the expected product **3e**, dimer **3d** was obtained in a good yield of 72% (entry 4).[16] Probably, compound **4** resulting from reaction of the dihydro intermediate **2C/2N** with C_2Cl_6, was trapped immediately by remaining **2C/2N** to give **3d** (Fig. 2).[17] However, compound **3e** could be obtained in 54% yield by performing a reverse addition of the reaction mixture to a solution of C_2Cl_6 in Et_2O following by MeOH addition (entry 5).[18] We then tested the reactivity of **4** toward different nucleophiles but the chlorine displacement was observed only when H_2O was used giving 3-hydroxyquinoline **3f** in a moderate yield of 58% (entry 6).[19] 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.[10] 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**[20] could be obtained in 64% yield by adding C_2Cl_6 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_2Cl_6 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_2O 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.[13b,21]

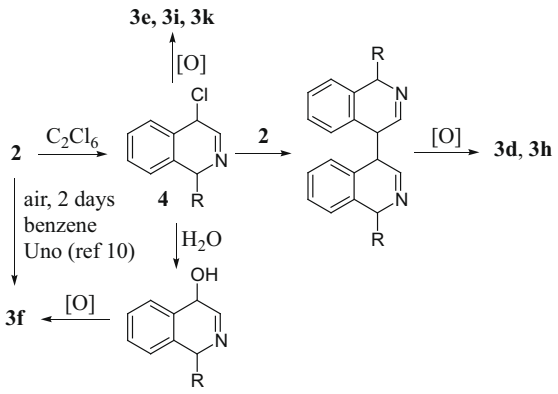


Figure 2. Different pathways for the evolution of intermediate **4**.

Acknowledgment

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Supplementary data

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

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14. The use of TMSCl or aldehydes as electrophiles resulted in inseparable complex mixtures.
15. *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_2O (40 mL) at 30 °C, under argon, was added MeLi (1.6 M in Et_2O, 5.8 mL, 9.3 mmol) and the mixture was stirred for 3 h before it was transferred to a degazed solution of C_2Cl_6 (3.7 g, 11.62 mmol) in Et_2O (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 ^1H NMR of the crude mixture). The reaction mixture was extracted with Et_2O, washed with water, and dried over $MgSO_4$. 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%).^1H NMR (200 MHz, $CDCl_3$) 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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^+, 100%), 142 (26), 115 (45). HRMS m/z calcd for $C_{10}H_8ClN$: 177.0345, found: 178.0418 (MH^+). For analytical data of all other compounds, see the Supplementary data.
16. For a nice application involving this kind of dimer, see: Muraoka, T.; Kinbara, K.; Takuzo, A. *Nature* **2006**, *440*, 512–515.
17. (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.
18. The use of CBr_4 resulted in formation of dimer **3d** in both normal addition and reverse addition.
19. 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**.
20. This product was already isolated by Uno et al. (Ref. 10) but neither the yield nor a proposed mechanism of its formation was reported.
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