Regioselective Introduction of Ethoxycarbonylmethyl and Cyanomethyl Groups into Quinoline and Isoquinoline†

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Micheline Grignon-Dubois* and Faïza Diaba

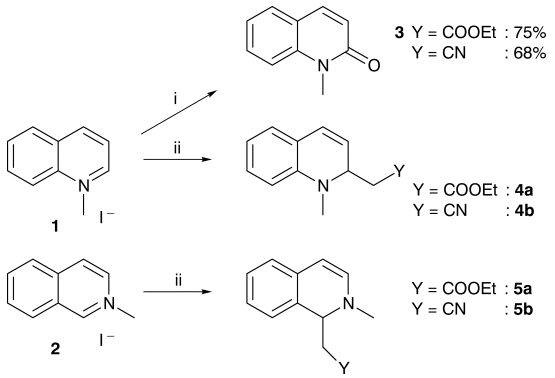
Laboratoire de Chimie Organique et Organométallique, CNRS UMR 5802, Université Bordeaux I, 351, Cours de la Libération, F-33405 Talence-Cedex, France

A new regioselective route to ethoxycarbonylmethyl- and cyanomethyl-1,2-dihydro-*N*-methyl-quinolines and -isoquinolines starting from methyl-quinolinium or -isoquinolinium iodides and commercially available trimethylsilyl reagents is presented.

As part of a programme directed toward the synthesis of new drugs from functionalized heterocyclic derivatives, we needed to introduce ethoxycarbonylmethyl and cyanomethyl groups on the C-2 position of the quinoline ring. Ethoxycarbonylmethyl-N-methoxycarbonyldihydroquinolines have previously been obtained by treating ethyl(tributylstannyl) acetate with quinoline and methyl chloroformate.[1] However, organostannyl reagents are often difficult to eliminate and are toxic and polluting. Moreover, this process seems to be limited to quinolines activated by alkyl chloroformate, whereas we needed an alkyl group on the nitrogen atom. In the case of 1-methylquinoliniums, Fukuzumi *et al.*[2] obtained the C-2 alkoxycarbonylmethylene adduct as the only product or in a mixture with the C-4 regioisomer when using a large excess of ketene silyl acetal. Reaction of ethyl bromoacetate with Reissert compounds[3] has also been said to lead to 1-ethoxycarbonylmethyl-1-cyano-2-carbophenyl-1,2-dihydroisoquinoline, but in low yields. Concerning the cyanoalkyl dihydroquinoline derivatives, the C-4 (α-cyanobenzyl) adduct was obtained by treating quinolinium methiodide with phenylacetonitrile and sodium ethoxide.[4] In contrast, there is no reference in the literature related to the introduction of cyanoalkyl groups on the C-2 position of quinolines. We report here a new regioselective route to ethoxycarbonylmethyl- and cyanomethyl-1,2-dihydro-*N*-methyl-quinolines and -isoquinolines starting from methyl-quinolinium or -isoquinolinium iodides (**1**, **2**) and commercially available trimethylsilyl reagents.

Results and Discussion

Nucleophilic addition to quinolinium salts is well known for the functionalization of the quinoline ring.[5] However, the regiochemistry of the addition is reported to be dependent on substituent effects as well as on the nature of the nucleophilic reagent, leading to a competition between C-2 and C-4 additions.[5,6] We have recently demonstrated that sonochemical activation allows regiospecific C-2 addition of anions to quinolinium iodides in good to quantitative yields.[7] In particular, the C-2 addition of the acetonyl anion, prepared *in situ* from acetone and sodium hydroxide, was systematically obtained when treating with *N*-methylquinolinium iodides.[7a] From these results we first tried to generate ethoxycarbonylmethyl or cyanomethyl moieties using sodium hydroxide and ethyl acetate or acetonitrile. All our attempts to functionalize **1** in this way failed, and the 1-methyl-2-qinolone **3** was systematically obtained as the only product (68–75% yield). In contrast with the behaviour of methyl ketones,[7a] and despite the sonochemical activation, the pK_a of ethyl acetate or acetonitrile (24–25 compared to 20 in the case of methyl ketones[8]) does not allow the proton abstraction leading to the anion to compete with the addition of the hydroxide anion to the methiodide (Scheme 1).



Scheme 1 *Reagents and conditions*: i, CH_3Y, NaOH, CH_3CN, ultrasound; ii, Me_3SiCH_2Y, CsF, CH_3CN, reflux or sonochemical activation

This led us to use trimethylsilyl reagents. As expected, trimethylsilyl acetate (ETSA) alone did not react with compound **1**.[9] The same reaction conducted with 1 equivalent of sodium hydroxide led to **4a**, but in only 8% yield along with **3** (34%). In order to avoid the quinoline formation, we decided to replace sodium hydroxide by fluoride. Indeed, the formation of a Si–F bond (142 kcal mol^{-1}) is usually a highly exothermic process, which provides the driving force for a number of useful synthetic reactions.[10] This is the case of active-methylene silylated compounds like ETSA or trimethylsilylacetonitrile (TMSAN), which are well known to add to the carbonyl double bond in the presence of fluoride leading to silyl-Reformatsky products.[11]

When quinolinium methiodide **1** was treated with ETSA or TMSAN in the presence of dried alkali metal flouride in acetonitrile solution the nucleophilic addition of the methylene anion was systematically observed (Scheme 1). As expected on the basis of their respective nucleophilic power, caesium fluoride led to better yields than potassium fluoride (86 and 40% respectively). Attempts to replace acetonitrile by methylene chloride or THF and alkali metal fluoride by tetrabutylammonium fluoride were unsuccessful. These observations are consistent with a charge-controlled process. The reactions were also conducted with **2**, leading to the C-1 adducts **5a**, **5b**. Examination of Table 1 shows that yields are better with ETSA than with TMSAN, and with quinoline compared to isoquinoline. From a mechanistic point of view, these results are consistent with formation of the methylene anion by nucleophilic attack at the silicon, and its addition to the *ortho* position *versus* nitrogen, which is the most electrophilic site. It can be suggested that the process

*To receive any correspondence (*e-mail:* m.grignon@lcoo.u-bordeaux.fr).

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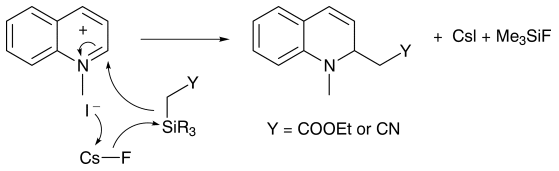

Scheme 2

is concerted and takes place in close proximity to the quinolinium iodide as depicted in Scheme 2.

Compounds **4b**, **5a**, **5b** are original. Compound **4a** had been previously isolated by Fukuzumi *et al.*[2] when treating **1** with the ketene triethylsilyl acetal of ethyl acetate and Bu_4NF. Only the NMR yield was reported (100%), and the experimental protocol was not described. Moreover, it appears that 10 equivalents of the silyl reagent were necessary for the reaction to occur. Our process, which is easy to handle and only needs 1 equivalent of commercially available silyl reagents, constitutes a real improvement for synthesizing **4a**.

Experimental

Flash column chromatography techniques (30 × 2 cm column) were employed to purify crude products using 70–230 mesh alumina (activity II-III, CH_2Cl_2) under positive air pressure. Ultrasound-promoted reactions were carried out in a common ultrasonic laboratory cleaner filled with thermostatted water at 0–5 °C.

Synthesis grade acetonitrile (Aldrich) was dried on molecular sieves. Commercial caesium and potassium fluorides (Aldrich, reagent ACS) were dried prior to use in a domestic microwave oven. Methiodides **1**, **2** were prepared according to literature procedures[12] by alkylation of quinoline or isoquinoline with methyl iodide in acetone solution.

To a stirred solution of quinolinium iodide (2.02 g, 7.4 mmol) in acetonitrile (20 mL) was added fluoride (KF or CsF, 8.1 mmol) and the trimethylsilyl reagent (Me_3SiCH_2Y, 8.1 mmol). The mixture was then stirred at reflux or sonicated at 0–5 °C until the starting material completely reacted as monitored by TLC (SiO_2, MeOH–Me_2CO, 10:90). The reaction mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was taken up with cyclohexane (R = CH_2COOEt, 100 mL) or dichloromethane (R = CH_2CN, 100 mL) and insoluble materials, if present, were removed by filtration and analysed separately. The solution was evaporated to dryness leading to an oil, which was chromatographed eluting typically with CH_2Cl_2 (Al_2O_3, activity II-III, 70–230 mesh).

2-*Ethoxycarbonylmethyl*-1-*methyl*-1,2-*dihydroquinoline* **4a**.—δ_H (250 MHz, $CDCl_3$) 1.22 (3 H, t, *J* 7.1 CH_2CH_3), 2.44 (1 H, dd, *J* 14.4, 7.6, CH_2CO), 2.56 (1 H, dd, *J* 14.4, 5.3, CH_2CO), 2.91 (3 H, s, NCH_3), 4.05 and 4.12 (2 H, dq, *J* 10.7 and 7.1, CH_3CH_2), 4.47 (1 H, ddd, *J* 7.6, 5.5 and 5.3, H-2), 5.78 (1 H, dd, *J* 9.5 and 5.5, H-3), 6.44 (1 H, d, *J* 9.5, H-4), 6.48 (1 H, d, *J* 8.1, H-8), 6.66 (1 H, dd, *J* 7.3 and 7.2, H-6), 6.93 (1 H, dd, *J* 7.2, and 1.5, H-5), 7.12 (1 H, ddd, *J* 8.1, 7.3 and 1.5 Hz, H-7); δ_C (62.89 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 36.5 (NCH_3), 38.0 ($COCH_2$), 57.6 (C-2), 60.6 (CH_3CH_2), 111.0 (C-8), 117.1 (C-6), 123.8 (C-3), 126.3 (C-4), 126.9 (C-5), 129.2 (C-7), 121.8, 144.2 (C), 171.4 (CO); *m*/*z* 231 (M^+, 6.4), 144 ($M - CH_2COOEt$, 100%); IR (neat) $\tilde{\nu}_{max}/cm^{-1}$ 1630 (C=C), 1725 (C=O) (Found: C, 72.45; H, 7.52; N, 6.0; O, 14.01. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06; O, 13.83%).

2-*Cyanomethyl*-1-*methyl*-1,2-*dihydroquinoline* **4b**.—δ_H (250 MHz, $CDCl_3$) 2.37 (1 H, dd, *J* 16.3, 6.8, CH_2CN), 2.47 (1 H, dd, *J* 16.3 and 5.5, CH_2CN), 3.01 (3 H, s, NCH_3), 4.40 (1 H, ddd, *J* 6.8, 5.6 and 5.5, H-2), 5.82 (1 H, dd, *J* 9.6 and 5.6, H-3), 6.56 (1 H, d, *J* 9.5, H-4), 6.56 (1 H, d, *J* 7.6, H-8), 6.74 (1 H, dd, *J* 7.5 and 7.4, H-6), 7.00 (1 H, dd, *J* 7.4, and 1.4, H-5), 7.18 (1 H, ddd, *J* 7.6, 7.5 and 1.4 Hz, H-7); δ_C (62.89 MHz, $CDCl_3$) 21.1 ($CNCH_2$), 37.1 (NCH_3), 57.5 (C-2), 111.4 (C-8), 117.9 (C-6), 121.3 (C-3), 127.4 (C-5), 127.7 (C-4), 129.8 (C-7), 122.0, 143.1 (C) 117.7 (C≡N); *m*/*z* 184 (M^+, 5.8), 144 ($M - CH_2CN$, 100%); IR (neat) $\tilde{\nu}_{max}/cm^{-1}$ 1640 (C=C), 2240 (C≡N) (Found: C, 78.48; H, 6.51; N, 14.99. $C_{12}H_{12}N_2$ requires C, 78.22; H, 6.57; N, 15.21%).

1-*Ethoxycarbonylmethyl*-2-*methyl*-1,2-*dihydroisoquinoline* **5a**.—δ_H (250 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7.1, CH_2CH_3), 2.50 (1 H, dd, *J* 14.1 and 7.1, CH_2CO), 2.71 (1 H, *J* 14.1, 6.2, CH_2CO), 2.94 (3 H, s, NCH_3), 4.04 (2 H, q, *J* 7.1), 4.80 (1 H, ddd, *J* 7.1, 6.2 and 1.1, H-1), 5.35 (1 H, d, *J* 7.3 H-3), 6.03 (1 H, dd, *J* 7.3 and 1.3, H-4), 6.80–6.96 (2 H, m), 6.98 (1 H, ddd, *J* 7.5, 7.2 and 1.3), 7.10 (1 H, ddd, *J* 7.3, 7.2, and 1.8 Hz); δ_C (62.89 MHz, $CDCl_3$) 14.1 (CH_2CH_3), 36.3 ($COCH_2$), 40.5 (NCH_3), 59.3 (C-1), 60.5 (CH_3CH_2), 97.6, 122.7, 124.7, 125.6, 127.6, 136.1 (6 CH), 128.1, 132.4 (C), 171.7 (CO); *m*/*z* 231 (M^+, 7.6), 144 ($M - CH_2COOEt$, 100%); IR (neat) $\tilde{\nu}_{max}/cm^{-1}$ 1610 (C=C), 1725 (C=O) (Found: C, 72.61; H, 7.43; N, 6.12; O, 13.63. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06; O, 13.83%).

1-*Cyanomethyl*-2-*methyl*-1,2-*dihydroisoquinoline* **5b**.—δ_H (250 MHz, $CDCl_3$) 2.46 (1 H, dd, *J* 16.4, 6.7, CH_2CN), 2.63 (1 H, dd, *J* 16.4, 6.7, CH_2CN), 3.02 (3 H, s, NCH_3), 4.69 (1 H, dd, *J* 6.7 and 6.1, H-1), 5.40 (1 H, d, *J* 7.3, H-3), 6.04 (1 H, d, *J* 7.3 Hz, H-4), 6.90–7.40 (4 H, m); δ_C (62.89 MHz, $CDCl_3$) 19.2 ($CNCH_2$), 40.9 (NCH_3), 59.4 (C-1), 98.3, 125.3, 126.0, 126.2, 132.0, 135.2 (6 CH), 126.9, 132.1 (C), 118.7 (C≡N); *m*/*z* 184 (M^+, 8.9), 144 ($M - CH_2CN$, 100); IR (neat) $\tilde{\nu}_{max}/cm^{-1}$ 1625 (C=C), 2320 (C≡N) (Found: C, 78.29; H, 6.49; N, 14.89. $C_{12}H_{12}N_2$ requires C, 78.22; H, 6.57; N, 15.21%).

Table 1 Condensation of $Me_3SiCH_2Y/CsF/CH_3CN$ with compounds **1** and **2**

Substrate	Reagent Y	Conditions	Product yield (%)
1	COOEt	2 h,))))	**4a** : 86
1	COOEt	2 h, reflux	**4a** : 84
1	CN	2 h,))))	**4b** : 43
1	CN	3.5 h, reflux	**4b** : 27
2	COOEt	2 h,))))	**5a** : 56
2	COOEt	2 h, reflux	**5a** : 77
2	CN	3 h,))))	**5b** : 48
2	CN	3 h, reflux	**5b** : 51

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