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Tetrahedron 61 (2005) 1407–1411

A new approach to 3-hydroxyquinoline-2-carboxylic acid

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Received 29 October 2004; revised 3 December 2004; accepted 6 December 2004

Available online 22 December 2004

Abstract—Quinoline-2-carboxylic acid derivatives cap the N-terminal of several natural cyclic peptides with antitumoral activity. A new and convenient route for the preparation of 3-hydroxyquinoline-2-carboxylic acid is discussed. The preparation of the title compound is accomplished by a four-step procedure from 3-hydroxyquinoline via MOM protection of the hydroxyl group, followed by a 1,2-addition of methyllithium to the quinoline ring with concomitant oxidation, and, finally, a two-step oxidation procedure for the transformation of the methyl group to the carboxylic acid along with removal of the MOM group. Furthermore, different attempts to its preparation led to other interesting quinolines, such as 2-chloro-3-hydroxyquinoline-4-carboxylic acid and a protected 3,3′-dihydroxy-2,2′-biquinoline.

1. Introduction

3-Hydroxyquinoline-2-carboxylic acid **1** is a key element in the synthesis of 2-fold symmetric bicyclic natural depsipeptides such as SW-163C, SW-163E,[1] sandramycin,[2] and thiocoraline,[3] and is incorporated into the peptide chain at the N-terminal through an amide bond. The heterocyclic chromophore plays a significant role in the DNA binding properties of these compounds; hence it is crucial to their biological activity.[4]

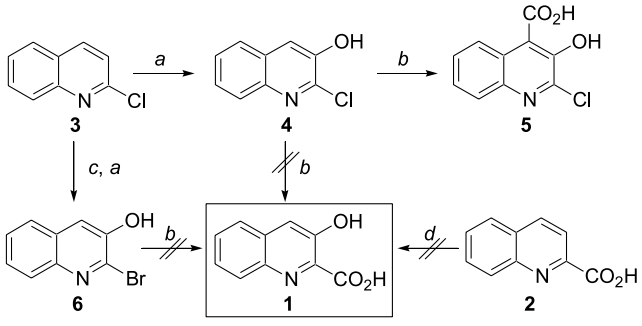
To the best of our knowledge, the only direct synthesis of partially protected 3-hydroxyquinoline-2-carboxylic acid derivatives has been described by Boger and Chen.[5] These authors used a modified Friedlander condensation of 2-aminobenzaldehyde with the *O*-methyloxime of ethyl 3-(benzyloxy)pyruvate to afford methyl 3-(benzyloxy)-quinoline-2-carboxylate. The difficulty of the ring construction, as it was exemplified in the aforementioned publication,[5] prompted us to study the preparation of 3-hydroxyquinoline-2-carboxylic acid **1** from commercially available quinoline derivatives through the introduction of suitable functional groups onto the ring.

2. Results and discussion

2.1. Preliminary studies

Due to the high value of metalation processes of quinolines for the preparation of polyfunctionalized quinolines,[6] it was decided to study these reactions in commercially available quinolines.

Based on the work of Quéguiner et al. who described directed lithiation of quinoline-2-carboxylic acid **2** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) at C-3,[7] the



Scheme 1. Initial attempts at the preparation of **1**. Reagents: (a) (i) LTMP, THF, −78 °C, 1 h; (ii) $B(OMe)_3$, −78 °C, 2 h; (iii) H_2O_2, NH_4Cl aq, Et_2O. (b) (i) MOMCl, NaOH, Adogen, CH_2Cl_2; (ii) BuLi, THF, −78 °C, 2 h; (iii) CO_2, −78 °C→rt, 0.5 h; (iv) 2 N HCl (**5**: 75%). (c) $POBr_3$, 105 °C, 4 h. (d) (i) LTMP, THF, −25 °C, 0.5 h; (ii) $B(OR)_3$ (R=Me, ^{i}Pr).

Keywords: Heterocycle; Biquinoline; *ortho*-Litiation; MOM; Cyclic peptides.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.12.011

introduction of an electrophile that could be transformed into an alcohol function, such as a trialkylborate, in that position was attempted. However, starting material was recovered from several conditions tested (Scheme 1).[8]

The strategy was then changed and carbon dioxide was chosen as electrophile with a lithiated hydroxyquinoline. The first quinoline used was 2-chloro-3-hydroxyquinoline **4** (Scheme 1), readily prepared from 2-chloroquinoline **3**,[9] in order to achieve a chloro-metal exchange. Methoxymethyl ether (MOM) was used as protecting group of the oxygenated function of **4** because it could be easily removed under acidic conditions. After the hydroxyl protection of **4**, the chloroquinoline was treated with *n*-butyllithium at −78 °C for 2 h followed by bubbling in carbon dioxide. However, the reaction product was 2-chloro-3-hydroxyquinoline-4-carboxylic acid **5** (Scheme 1), which was obtained in good yield (75% from **4**) and originated from the direct metalation at C-4 and deprotection of the hydroxyl group during work up. It is remarkable that compound **5** was isolated as the sole product in this process despite the use of BuLi as base, which can be added to quinolines, as later described in this paper.

Compound **5** could be useful as precursor to non-peptide antagonists for the human neurokinin-3 receptor, such as (*S*)-*N*-(1-phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide.[10]

The next route explored involved the preparation of 2-bromo-3-hydroxyquinoline **6** (Scheme 1), which could undergo bromo-metal exchange more easily. Thus, **3** was treated with phosphorous oxybromide, affording 2-bromoquinoline which was transformed into hydroxyquinoline **6** by *ortho*-lithiation by LTMP, following the procedure described for **4**.[9] However, the halogen–metal interchange and carboxylation failed, resulting in a complex mixture. This could be due to the competition of directed metalation at C-4, reduction of the C–Br bond, and addition of BuLi to the quinoline ring.[11]

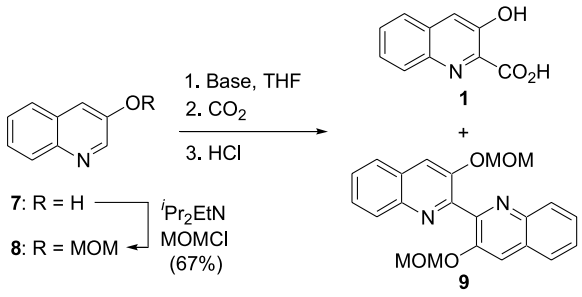
To avoid competing reactions produced in the halogen–metal exchange from **4** and **6**, *ortho*-metalation in a protected 3-hydroxyquinoline which, to the best of our knowledge, has not been used in *ortho*-directing processes, was then studied.

2.2. *ortho*-Metalation studies in 3-hydroxyquinoline 7

3-Hydroxyquinoline **7** was prepared from commercially available 3-aminoquinoline by the Bucherer reaction.[12] Although only a few examples of metalation of methoxymethoxy derivatives have been reported in the literature,[13] the MOM group was chosen as hydroxyl protecting owing to its facile introduction and elimination.

Thus, lithiation of 3-(methoxymethoxy)quinoline **8** was examined under different conditions by trapping the anion with carbon dioxide (Scheme 2).

The bases used were the well-known lithium diisopropylamide (LDA) and LTMP, as well as *t*-BuLi and the basic reagent composed of *n*-butyllithium and lithium



Scheme 2. Directed lithiation of 3-(methoxymethoxy)quinoline **8**.

dimethylaminoethoxide (BuLi-LiDMAE), which induces a regioselective C-α lithiation of pyridine derivatives.[14]

The results obtained are summarized in Table 1. At low temperature, neither LDA (entry 1) or BuLi-LiDMAE (entry 2) or *t*-BuLi (entry 3) worked in the *ortho*-lithiation process because starting material was recovered in the first case, and the corresponding 2-alkyl-3-(methoxymethoxy)-quinolines[15,16] were isolated when an alkyllithium was used as base.

Table 1. Directed lithiation of 3-(methoxymethoxy)quinoline **8**

Entry	Conditions	Ratio **1**:**9**:**8**[a]
1	LDA (3 equiv), −78 °C, 2 h	0:0:1
2	BuLi-LiDMAE (3 equiv), −78 °C, 2 h[b]	—[c]
3	*t*-BuLi (3 equiv), −78 °C, 2 h	—[d]
4	LTMP (2 equiv), −78 °C, 2 h	1.4:1:4.3
5	LTMP (3 equiv), −78 °C, 2 h	1.3:1:3.1
6	LTMP (3 equiv), −78 °C, 5 h	—[e]
7	LTMP (2 equiv), −40 °C, 1 h	0:1:5
8	LTMP (2 equiv), 25 °C, 6 h	0:15:1
9	LDA (2 equiv), 25 °C, 6 h	0:14:1

[a] Ratio determined by 400 MHz ^{1}H NMR analysis of the crude reaction.
[b] The solvent used was a mixture of hexane/THF 2:1.
[c] The reaction product was 2-butyl-3-(methoxymethoxy)quinoline produced by 1,2-addition of butyllithium to the quinoline ring with concomitant oxidation.
[d] The reaction product was 2-*tert*-butyl-3-(methoxymethoxy)quinoline coming from the 1,2-addition of *t*-butyllithium to the quinoline ring with concomitant oxidation.
[e] A complex reaction mixture was isolated, but starting material was detected by 400 MHz ^{1}H NMR analysis.

When LTMP was used at −78 °C (entry 4), the target compound was obtained in low yield (21%). The starting material as well as 2,2′-biquinoline **9** were also recovered. Formation of **9** could be explained by addition of the 2-lithio derivative to **8** and subsequent air oxidation.[17] This result was not substantially improved using more equivalents of base (entry 5, 24% yield) or longer reaction time (entry 6). At higher temperatures, the ratio of **9** increased (entries 7–8) and no formation of **1** was observed.

Other electrophiles, such as D_2O, MeI, $ClCO_2Me$, and DMF, were tested under the best carboxylation conditions (entry 5). The major reaction product was the starting material and 2,2′-biquinoline **9** was also isolated in similar ratios as before.

The low yield in the preparation of **1** by *ortho*-lithiation of 3-(methoxymethoxy)quinoline **8** could be due to the low reactivity of this quinoline versus lithium dialkylamides as

well as the fast formation of the 2,2′-biquinoline **9** previous to the total metalation of the starting material, even at low temperature.

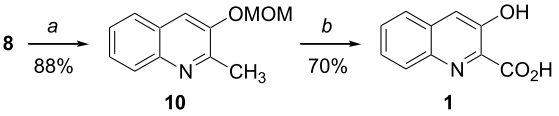
Another important conclusion of all of these experiments relates to the selectivity of the lithiation. The formation of 2,2′-biquinoline and 3-hydroxyquinoline-2-carboxylic acid demonstrates that lithiation occurred exclusively at C-2. In the literature, metalation of 3-(methoxymethoxy)pyridine was reported at C-4.[13c,d]

Despite the formation of **9** and the presence of the starting material, 3-hydroxyquinoline-2-carboxylic acid **1** was isolated with high purity (93% by HPLC analysis) after a simple acid–base work up.

Otherwise, 3,3′-bis-(methoxymethoxy)-2,2′-biquinoline **9** was prepared in 70% yield when metalation of **8** was carried out with LTMP at room temperature for 6 h. Furthermore, **9** was also prepared with LDA under the same conditions in a similar rate (entry 9). This compound could be interesting as a ligand in metal complexes,[18] or in dye laser applications.[19]

2.3. Preparation of 3-hydroxy-2-quinolinecarboxylic acid 1

Since 1,2-addition to 3-(methoxymethoxy)quinoline **8** is an important side-reaction in the *ortho*-lithiation process, and taking into account that methyl aromatic compounds can be oxidized to the corresponding carboxylic acid, we decided to take advantage of that reactivity and follow a strategy starting from **8** and based on nucleophilic addition followed by oxidation to render the acid **1**. Thus, the introduction of methyl group was accomplished by addition of methyllithium to 3-(methoxymethoxy)quinoline **8** (Scheme 3), which produced a mixture of the corresponding intermediate 1,2-dihydroquinoline and 2-methylquinoline **10** (from the partial air oxidation of the dihydroquinoline). Subsequent treatment of the reaction mixture with ammonium cerium (IV) nitrate (CAN) led to **10** in high yield with total regioselectivity.



Scheme 3. Preparation of 3-hydroxyquinoline-2-carboxylic acid **1**. Reagents: (a) (i) MeLi, THF, 0 °C, 1 h; (ii) CAN, acetone, 30 min. (b) (i) SeO_2, 1,4-dioxane, reflux, 1.5 h; (ii) H_2O_2, HCO_2H, 0 °C, overnight.

To carry out the oxidation of the methyl group in **10**, a strong oxidant, such as $KMnO_4$, was tested due to the low reactivity of methylquinolines. Using these drastic conditions, a complex crude reaction was obtained, presumably since ring cleavage could also occur. This problem was overcome using a two-step procedure of oxidation of **10** to the corresponding aldehyde with selenium dioxide, followed by oxidation by hydrogen peroxide in formic acid. In these acidic conditions the MOM group was removed, and 3-hydroxy-2-quinolinecarboxylic acid **1** was isolated in 70% yield. It is noteworthy that the last oxidation step proceeded with high yield, despite the presence of an electron-donating substituent.[20] Moreover, the overall yield of **1** was 62% after three steps from the readily available 3-(methoxymethoxy)quinoline, and no purifications were required. The final product was isolated simply by filtration, a key advantage of this method when considering the poor solubility of the target compound in organic solvents.

3. Conclusion

In conclusion, we have described an alternative synthesis of 3-hydroxyquinoline-2-carboxylic acid from the commercially available 3-aminoquinoline with a better yield than that reported for the existing synthesis. This new route does not require any purification step and the target compound precipitates from the reaction mixture, simplifying its handling and isolation. These advantages should facilitate the preparation of compounds bearing the biologically important moiety. In addition, other functionalized quinolines, such as 2-chloro-3-hydroxyquinoline-4-carboxylic acid and a protected 3,3′-dihydroxy-2,2′-biquinoline, were prepared by *ortho*-metalation processes.

4. Experimental

4.1. General

All reagents were commercial products (Fluka, Aldrich or Acros) and used as received. THF was freshly distilled from sodium/benzophenone. Dichloromethane (99.99% anhydrous) and 1,4-dioxane (99.98% anhydrous) were purchased from SDS and used as received. Reactions involving air and/or moisture sensitive reagents were conducted under an atmosphere of argon. Melting points were recorded in a Büchi apparatus and are uncorrected. IR spectra were obtained using a Thermo Nicolet Nexus spectrophotometer. NMR spectra were acquired with Varian Gemini-300 (300 MHz) and Mercury-400 (400 MHz) spectrometers; data are given on the δ scale referenced to TMS. Mass spectra were measured in the electron impact (EI) mode with a Hewlett-Packard model 5989A spectrometer. High-resolution mass spectra were performed on an AutoSpec/VG by Unidad de Espectrometría de Masas de Santiago de Compostela (Spain). HPLC was carried out using a Waters 996 Photodiode Array Detector, a SYMMETRY C18 column (4.6×150 mm, 5 μm) with H_2O (0.045% TFA) and acetonitrile (0.036% TFA) as eluents. Analytical TLC was performed on SiO_2 (silica Gel 60 F254, Merck) and spots were visualized with UV light. Column chromatography was carried out on SiO_2 (silica Gel 60 SDS 0.035–0.070 mm).

4.1.1. 2-Chloro-3-hydroxyquinoline-4-carboxylic acid (5). To a suspension of 2-chloro-3-hydroxyquinoline **4** (100 mg, 0.56 mmol) in dichloromethane (4 mL) was added 2 N NaOH (1 mL), and Adogen (55 mg) at room temperature. After 30 min, MOMCl was added and the mixture was stirred for 45 min. Water (5 mL) was added, and the product was extracted with dichloromethane (3×5 mL). After concentration of organic layers, the residue was chromatographed on silica gel (5/1 hexane/ethyl acetate) to provide pure protected hydroxyquinoline in 86% yield.

n-Butyllithium (0.16 mL of 1.6 M solution in hexane, 0.25 mmol) was then added dropwise to a −78 °C stirred solution of protected quinoline (46.3 mg, 0.21 mmol) in dry THF (1 mL). The solution was stirred for 2 h at the same temperature. Carbon dioxide was bubbled for 2 min, and the reaction mixture was allowed to warm to room temperature. Stirring was continued for 0.5 h and 2 N HCl (1 mL) was then added. After usual work up, 2-chloro-3-hydroxyquinoline-4-carboxylic acid **5** was isolated in 87% yield: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.47 (1H, d, J=8.3 Hz), 7.86 (1H, d, J=7.8 Hz), 7.62–7.55 (2H, m); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.7 (C), 147.8 (C), 143.7 (C), 140.7 (C), 128.3 (CH), 128.2 (CH), 127.0 (CH), 125.0 (C), 124.3 (CH), 119.5 (C); MS, *m/z* 225 (M^++2, 19), 223 (M^+, 54), 207 (44), 205 (100), 179 (23), 177 (56), 151 (12), 149 (36), 114 (60); HRMS calcd for $C_{10}H_6ClNO_3$: 223.0036, found: 223.0040.

4.1.2. 3-(Methoxymethoxy)quinoline (8). Methoxymethyl chloride (0.80 mL, 10.6 mmol) was slowly added to a solution of 3-hydroxyquinoline **7** (1.02 g, 7.1 mmol) and diisopropyl ethylamine (1.4 mL, 8.5 mmol) in dry dichloromethane (4 mL) at 0 °C. The solution was warmed to room temperature overnight, and then water (5 mL) was added. The product was extracted with dichloromethane (3×10 mL), washed with 2 M sodium hydroxide (10 mL), and water (10 mL), and dried over Na_2SO_4. Removal of the solvent gave 0.86 g (67%) of a red oil, which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (1H, d, J=2.8 Hz), 8.05 (1H, dd, J=8.1, 1.5 Hz), 7.73 (1H, dd, J=8.2, 1.1 Hz), 7.68 (1H, d, J=2.8 Hz), 7.57 (1H, ddd, J=8.2, 7.0, 1.5 Hz), 7.50 (1H, ddd, J=8.1, 7.0, 1.1 Hz), 5.31 (2H, s), 3.53 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4 (C), 144.5 (CH), 144.0 (C), 129.0 (CH), 128.6 (C), 127.0 (CH), 126.9 (CH), 126.8 (CH), 116.5 (CH), 94.6 (CH_2), 56.2 (CH_3); MS, *m/z* 189 (M^+, 67), 159 (19), 128 (18), 116 (31), 101 (13), 89 (19), 63 (13), 45 (100); HRMS calcd for $C_{11}H_{11}NO_2$: 189.0790, found: 189.0793.

4.1.3. 3,3′-Bis-methoxymethoxy-2,2′-biquinoline (9). *n*-Butyllithium (0.27 mL of 1.6 M solution in hexane, 0.43 mmol) was added at 0 °C to a stirred solution of 2,2,6,6-tetramethylpiperidine (73 μL, 0.44 mmol) in dry THF (1.2 mL). After 10 min, a solution of **8** (55.2 mg, 0.29 mmol) in dry THF (0.5 mL) was added dropwise, and the reaction was stirred at room temperature for 6 h. Saturated aqueous solution of NH_4Cl (5 mL) was added and the aqueous layer was extracted with dichloromethane (3×10 mL). Removal of the solvent followed by purification by flash chromatography (3/1 hexane/ethyl acetate) provided pure compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (2H, dd, J=7.9, 1.5 Hz), 7.89 (2H, s), 7.81 (2H, dd, J=8.0, 1.3 Hz), 7.60 (2H, ddd, J=8.2, 8.0, 1.5 Hz), 7.54 (2H, ddd, J=8.2, 7.9, 1.3 Hz), 5.21 (4H, s), 3.40 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0 (C), 149.6 (C), 143.8 (C), 129.6 (CH), 129.1 (C), 127.3 (CH), 127.1 (CH), 126.7 (CH), 117.2 (CH), 95.0 (CH_2), 56.1 (CH_3); MS, *m/z* 376 (M^+, 16), 331 (100), 301 (25), 285 (40).

4.1.4. 3-Methoxymethoxy-2-methylquinoline (10). To a stirred solution of **8** (0.67 g, 3.6 mmol) in dry THF (10 mL) at 0 °C was added methyllithium (2.8 mL of 1.5 M solution in diethyl ether, 4.2 mmol) dropwise. After stirring at 0 °C for 1 h, the mixture was treated with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with dichloromethane (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in acetone (2 mL) and treated with an aqueous solution of ammonium cerium (IV) nitrate (3.89 g in 10 mL) for 30 min. The mixture was extracted with dichloromethane (3×15 mL) and dried over Na_2SO_4, and the filtrate was concentrated under reduced pressure to give 0.63 g (88%) of an orange syrup, which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, dd, J=8.2, 0.9 Hz), 7.68 (1H, dd, J=8.2, 1.2 Hz), 7.61 (1H, s), 7.54 (1H, ddd, J=8.2, 7.0, 1.2 Hz), 7.43 (1H, ddd, J=8.2, 7.0, 0.9 Hz), 5.33 (2H, s), 3.52 (3H, s), 2.68 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.3 (C), 149.8 (C), 134.8 (C), 131.5 (CH), 129.6 (CH), 128.2 (CH), 127.6 (CH), 123.8 (C), 121.7 (CH), 95.7 (CH_2), 57.2 (CH_3), 16.7 (CH_3); HRMS calcd for $C_{12}H_{13}NO_2$: 203.0946, found: 203.0943.

4.1.5. 3-Hydroxyquinoline-2-carboxylic acid (1). Selenium dioxide (0.36 g, 3.3 mmol) was added to a solution of **10** (0.63 g, 3.1 mmol) in dry 1,4-dioxane (30 mL). The reaction mixture was refluxed for 1 h and then cooled to room temperature and filtered through a pad of Celite. The filtrate was evaporated to give a residue which was dissolved in formic acid (1 mL) and cooled to 0 °C. Hydrogen peroxide (1.7 mL of 30% solution in water, 15.5 mmol) was slowly added and the mixture was allowed to stand overnight between 0 and 10 °C. A precipitate formed and was collected by filtration, washed with cold water, and dried to give 3-hydroxyquinaldic acid as a yellow solid (0.41 g, 70%): mp 187–190 °C (decomp.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (1H, dd, J=8.6, 1.2 Hz), 8.01 (1H, s), 7.83 (1H, dd, J=8.4, 1.6 Hz), 7.70 (1H, ddd, J=8.6, 7.0, 1.6 Hz), 7.64 (1H, ddd, J=8.4, 7.0, 1.2 Hz), 3.27 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.7 (C), 152.2 (C), 138.1 (C), 137.9 (C), 130.7 (C), 128.8 (CH), 128.4 (CH), 126.6 (CH), 126.2 (CH), 122.3 (CH); IR (KBr) 3449, 1681; MS, *m/z* 189 (M^+, 91), 171 (39), 145 (70), 143 (100), 117 (63), 115 (91), 89 (52); HRMS calcd for $C_{10}H_7NO_3$: 189.0426, found: 189.0428.

Acknowledgements

This work was partially supported by CICYT (BQU2003-0089) and Barcelona Scientific Park. The authors are grateful to Greg Qushair (University of Barcelona), Drs. Andrés Francesch and Juan José González (PharmaMar) for previous work carried out towards the preparation of 3-hydroxyquinoline-2-carboxylic acid. E. R. thanks to Principado de Asturias for a postdoctoral fellowship.

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15. *2-Butyl-3-(methoxymethoxy)quinoline*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (1H, d, J=8.2, 1.6 Hz), 7.69 (1H, dd, J=8.1, 1.2 Hz), 7.63 (1H, s), 7.54 (1H, ddd, J=8.1, 7.1, 1.6 Hz), 7.44 (1H, ddd, J=8.2, 7.1, 1.2 Hz), 5.34 (2H, s), 3.53 (3H, s), 3.03 (2H, t, J=7.9 Hz), 1.81–1.76 (2H, m), 1.49–1.43 (2H, m), 0.97 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6 (C), 149.2 (C), 143.2 (C), 128.3 (CH), 128.1 (C), 126.9 (CH), 126.5 (CH), 126.0 (CH), 115.2 (CH), 94.3 (CH_2), 56.1 (CH_3), 33.7 (CH_2), 30.8 (CH_2), 22.8 (CH_2), 14.0 (CH_3).
16. *2-tert-Butyl-3-(methoxymethoxy)quinoline*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (1H, d, J=8.3 Hz), 7.68 (1H, dd, J=8.4, 1.2 Hz), 7.66 (1H, s), 7.53 (1H, ddd, J=8.4, 7.1, 1.6 Hz), 7.43 (1H, ddd, J=8.3, 7.1, 1.2 Hz), 5.36 (2H, s), 3.54 (3H, s), 1.54 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5 (C), 150.1 (C), 145.5 (C), 129.1 (CH), 128.0 (C), 126.6 (CH), 126.1 (2(CH), 115.6 (CH), 94.0 (CH_2), 56.2 (CH_3), 38.9 (C), 28.7 (CH_3).
17. The addition adduct 1,2-dihydro-2,2′-biquinoline was detected by 400 MHz ^{1}H NMR in some reaction mixtures.
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