

Synthetic approaches to 1-(2-chlorophenyl)isoquinoline-3-carboxylic acid

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In connection with our research of new antitumor compounds, previously undescribed approaches to the 1-(2-chlorophenyl)isoquinoline-3-carboxylic acid **9** are reported here. Two related accesses from phenylethylamine or amphetamine were investigated and were found to be successful. A more robust synthesis, using Suzuki's cross-coupling between 2-chlorophenylboronic acid **15** and the previously unreported methyl-1-bromoisoquinoline-3-carboxylate **14** was also developed. This synthetic route provides the ground for a combinatorial approach to the core structure of new potential peripheral benzodiazepine receptor ligands.

Introduction

In connection with our interest¹⁻⁴ in peripheral benzodiazepine receptor ligands such as PK 11195 **1**^{5,6} and Ro 5-4864 **2** (Fig. 1) we have investigated the synthesis of the 1-(2-chloro-

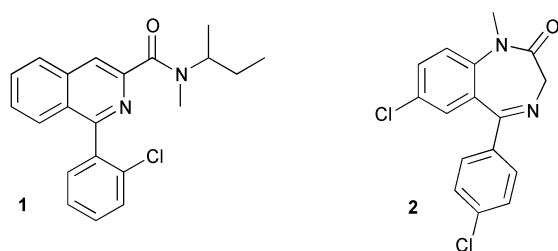


Fig. 1 Structures of PK 11195 and Ro 5-4864.

phenyl)isoquinoline structure of **1**. No preparation of this structure has yet been published⁷ and therefore we wish to report here our contribution to the chemistry of functionalised isoquinolines.

Results and discussion

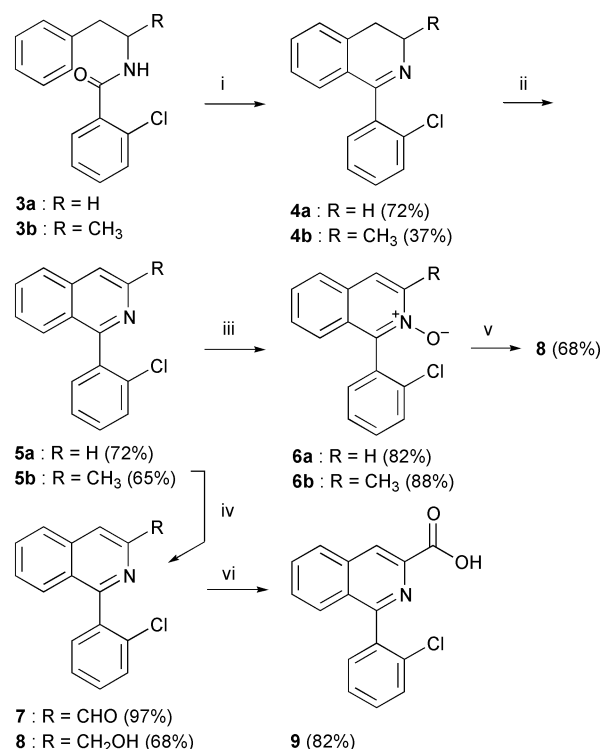
We began this work with two related approaches starting with phenylethylamine or amphetamine. † From these two amines, *ortho*-chlorobenzamides **3a, b** were prepared and the isoquinoline nucleus was formed using phosphorus oxychloride in boiling acetonitrile. Surprisingly, if dihydroisoquinoline **4a** was obtained in 72% yield, its methyl homologue **4b** was only obtained in 37% yield along with 2-chlorobenzonitrile resulting from a fragmentation reaction (*i.e.* a retro-Ritter reaction⁸). Aromatization of **4a** into **5a** was achieved in only 25% yield using sulfur in boiling decalin, ‡ but in 72% yield when an excess of manganese oxide was repeatedly added in boiling benzene over a four day period. On the other hand, a 65% yield of **5b** was obtained using sulfur in boiling decalin⁹ whereas no compound could be isolated in the course of trials with dichlorodicyanoquinone in boiling dioxane. The corresponding *N*-oxides **6a, b** were obtained using 3-chloroperoxybenzoic acid in dichloromethane.

† The IUPAC name for amphetamine is α -methylphenethylamine.

‡ The IUPAC name for decalin is decahydronaphthalene.

Introduction of a cyanide moiety on position 3 of compound **6a** was attempted using known procedures: either with diethylcyanophosphonate¹⁰ or trimethylsilyl cyanide.¹¹ No cyanation took place whereas a slow reduction of the *N*-oxide **6a** into **5a** was observed in both types of trial. Such a reduction has already been reported in the cases of nitropyridine *N*-oxide¹² and 1-methylisoquinoline-2-oxide.¹⁰

Two methods of methyl oxidation were applied on **5b**. (a) The radical-based bromination¹³ (or chlorination) of **5b** resulted in a very low yield of the polyhalogenated derivative along with extensive decomposition. (b) A much more efficient preparation of the aldehyde **7** from **5b** (97% yield) was achieved with selenium oxide in boiling 1,2-dichlorobenzene (iv on Scheme 1).

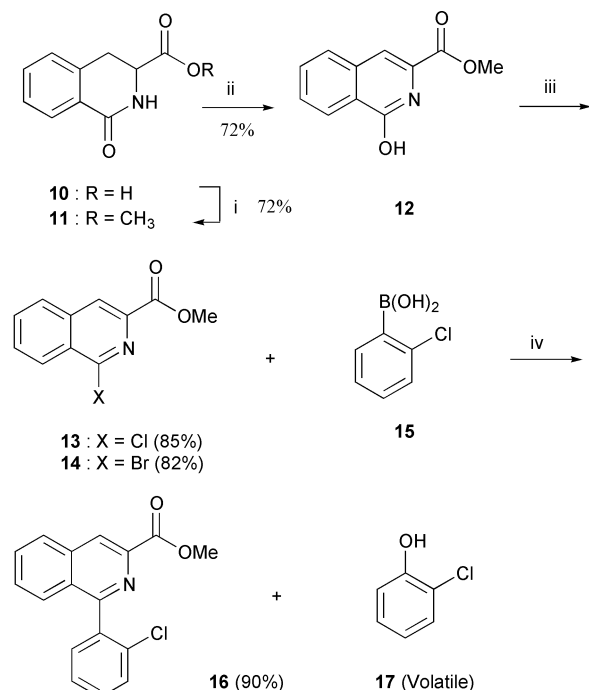


Scheme 1 i: POCl₃-MeCN, reflux. ii: S₈-decalin, reflux or MnO₂-benzene, reflux. iii: MCPBA-CH₂Cl₂. iv: SeO₂, 180 °C. v: (CF₃CO)₂O, 180 °C. vi: AgNO₃, NaOH-EtOH-H₂O 1 : 1.

It is noteworthy that very little oxidation was observed with selenium oxide in boiling dioxane and none if manganese oxide was used instead.

Another previously unreported method developed here, is based on the known rearrangement of 2-alkylpyridine *N*-oxides.¹⁴ Boiling *N*-oxide **6b** with an excess of trifluoroacetic anhydride in 1,2-dichlorobenzene, followed by hydrolysis, gave the alcohol **8** in 68% yield. In contrast to pyridine chemistry,¹⁵ no reaction took place in dichloromethane and little in boiling acetonitrile. This last method does provide an alternative to the use of toxic selenium oxide which is often detrimental to biological studies. Further oxidation of aldehyde **7** (or alcohol **8**), into the target acid **9** was then achieved using silver nitrate under basic conditions.¹³

The final approach was investigated independently from a recently published work.¹⁶ We started from the readily available¹⁷ dihydroisoquinoline carboxylic acid **10**. Its esterification into **11**,¹⁸ followed by an aromatization using palladium over charcoal in boiling diphenyl ether, provided an access to the isoquinolinone **12** in 67% overall yield (Scheme 2). Another



Scheme 2 i: MeOH, H₂SO₄, reflux. ii Pd/C, (C₆H₅)₂O, 259 °C. iii: POX₃, K₂CO₃-MeCN, reflux. iv: K₃PO₄, Pd(PPh₃)₄-DMF, 80 °C.

preparation of **12** was recently published¹⁶ and an even more direct approach to **12** has also been reported.¹⁹ The use of phosphorus oxychloride to prepare compound **12** was sometimes fraught with side reactions. Although a very efficient procedure has been recently reported,¹⁶ we developed a robust method, also using phosphorus oxychloride or bromide, but in the presence of potassium carbonate in boiling acetonitrile. Thus the troublesome hydrolysis of the reaction mixture takes place under neutral conditions, without heat evolution, and avoids unwanted decomposition. The 1-halogenated derivatives **13** or **14** were thus routinely prepared in 82–85% yields. Suzuki^{20,21} coupling reaction trials in DMF using potassium phosphate and 2-chlorophenylboronic acid **15** showed that yields, starting with the chlorinated derivative **13**, were never better than 50% and that the separation of **13** and ester **16** was quite difficult. This result is very similar to the 50% yield reported for the cross-coupling of compound **13** and a hindered 1-naphthylboronic derivative.¹⁶ Moreover, side reactions and catalyst deactivation took place when additions of arylboronic acid **15** and potassium phosphate were repeated. Analysis of the reaction mixture showed the formation of some volatile

2-chlorophenol **17** (resulting from a concurrent oxidative dehydroboration^{22,23}) and of a small amount of a mixture of unidentified polyaryl compounds.²⁴ On the other hand, the coupling reaction of compound **15** (using only 3 mol% of tetrakis(triphenylphosphine)palladium) with the brominated derivative **14** led to the ester **16** in 90% isolated yield, if 2 equivalents of arylboronic acid **15** and potassium phosphate were added in two portions over 16 hours. It is noteworthy that a complete ester hydrolysis has been reported if the palladium-catalysed coupling of compound **13** and 1-naphthylboronic derivative is made in the presence of potassium carbonate in DME.¹⁶ In our case we had to proceed to a subsequent basic hydrolysis of the ester **16** to obtain the target acid **9** in 95% yield.

Conclusion

This work indicates that, compared to pyridine, isoquinoline chemistry benefits from quite drastic heating increase for (i) the selenium oxide oxidation of compound **5b** or (ii) the rearrangement of *N*-oxide **6b**. Our preparation of the 1-chloroisoquinoline derivatives **13** and, more crucially the 1-bromoisoquinoline **14**, allowed the study of the Suzuki palladium-catalysed aryl cross-coupling reaction. Starting from compound **14**, this remarkable reaction proceeds with 90% yield, without any ester hydrolysis, and thus provides a new efficient access to 1-phenylisoquinolines such as **9**. This last synthetic route will hopefully lead to a combinatorial approach in the preparation of new potential peripheral benzodiazepine receptor ligands.

Experimental

General

¹H and ¹³C NMR spectra were recorded on a Bruker Avance-300 spectrometer. Unless otherwise stated, CDCl₃ was the solvent used. Shifts are given in ppm (δ) with respect to the TMS signal and coupling constants (*J*) are given in Hertz. Low and high resolution mass spectra were obtained by Mrs Nicole Morin (Ecole Normale Supérieure, 24 rue Lhomond F-75231 Paris) on a MS 700 JEOL using methane as the ionization vector. Column chromatography was performed on Merck silica gel 60/35–70 μm. Solvents were usually dried using activated²⁵ 3 Å or 4 Å molecular sieve.

Amides **3a**, **b**

Phenylethylamine or amphetamine (28.5 mmol) and 2-chlorobenzoyl chloride (5 g, 28.5 mmol) in dry acetonitrile (100 ml) were cooled to 0 °C. Dry triethylamine (4.4 ml, 31.4 mmol) was added and the suspension was allowed to warm up for 2 hours. This mixture was concentrated to dryness, dispersed in dichloromethane, washed with water and the organic phase was dried over magnesium sulfate prior to concentration to dryness. The oily residues obtained were in both cases used in the next step without further purification.

2-Chloro-*N*-phenylethylbenzamide 3a. ν_{\max} (KBr)/cm⁻¹ 3273, 2337, 1786, 1641, 1555; ¹H: 2.99 (t, 2H, *J* = 7.0, CH₂), 3.79 (m, 2H, CH₂), 6.21 (m, 1H, NH), 7.21–7.39 (m, 8H), 7.64 (m, 1H); ¹³C: 32.3, 41.1, 126.4, 126.8, 128.5, 128.7, 129.7, 130.0, 130.5, 131.0, 135.0, 138.6, 165.5; *m/z* 260.0837 (M⁺ + H, C₁₅H₁₄NOCl requires 260.0842).

***N*-(2-Chlorobenzoyl)amphetamine 3b.** ν_{\max} (KBr)/cm⁻¹ 3290, 3029, 2968, 1641, 1536; ¹H: 1.22 (d, 3H, *J* = 6.6, CH₃), 2.86 (m, 2H, CH₂), 4.46 (s, 1H, NH), 7.29 (m, 8H), 7.54 (m, 1H); ¹³C: 19.8, 42.3, 47.0, 126.4, 126.9, 128.3, 129.4, 130.0, 130.5, 131.0, 133.3, 137.7, 165.8; *m/z* 274.0996 (M⁺ + H, C₁₆H₁₇NOCl requires 274.0998).

3,4-Dihydroisoquinolines 4a, b

The crude product **3a** or **3b** (78 mmol) and phosphorus oxychloride (22 ml, 235 mmol) were refluxed in dry acetonitrile (300 ml) for 3 hours. The solution was cautiously poured on 600 ml of cold water. The resulting mixture was stirred for one hour. The solution was made basic with sodium hydroxide pellets and stirred while cooling. This was extracted with dichloromethane, the organic phase was washed with water, dried over magnesium sulfate and concentrated to dryness. The crude residue was chromatographed over silica gel eluting with dichloromethane–ethanol 99 : 1 in the case of **4a** or heptane–ethyl acetate 7 : 3 in the case of **4b**.

1-(2-Chlorophenyl)-3,4-dihydroisoquinoline 4a. This compound was obtained in 72% yield (from phenylethylamine) as a wax. ν_{\max} (KBr)/ cm^{-1} 3186, 2897, 2847, 2661, 1615; ^1H : 2.79 (m, 4H, CH_2), 6.83 (d, 1H, $J = 7.5$), 7.14 (m, 2H), 7.30 (m, 5H); ^{13}C : 26.3, 48.1, 127.36, 127.37, 127.9, 129.3, 130.0, 130.3, 130.5, 130.8, 131.4, 133.0, 137.6, 138.6, 166.7; m/z 242.0746 ($\text{M}^+ + \text{H}$, $\text{C}_{15}\text{H}_{13}\text{NCl}$ requires 242.0737).

1-(2-Chlorophenyl)-3-methyl-3,4-dihydroisoquinoline 4b. Obtained in 37% yield (from amphetamine) as an oil. The first chromatography fraction yielded the known 2-chlorobenzonitrile (46%). The NMR spectra of compound **4b** indicates the existence of several conformations with half lives in the range of NMR time measurement. This does complicate the carbon spectrum. ν_{\max} (KBr)/ cm^{-1} 3493, 2959, 2937, 1615; ^1H : 1.52 (s (br), 3H, CH_3), 2.73 (m, 1H, $\frac{1}{2}\text{CH}_2$), 2.89 (m, 1H, $\frac{1}{2}\text{CH}_2$), 3.7 (m (br), 1H, CH), 6.92 (d, 1H, $J = 7.8$), 7.14–7.45 (m, 7H); ^{13}C : 23.0 (br), 34.4 (br), 54.2 (br), 127.7, 128.0, 128.2, 128.8, 129.6, 129.8, 129.9, 130.7, 130.8, 130.9, 131.1, 131.3, 131.6, 131.8, 132.1, 132.3, 133.9, 138.0 (br), 139.6, 166.3 (br); m/z 256.0904 ($\text{M}^+ + \text{H}$, $\text{C}_{16}\text{H}_{15}\text{NCl}$ requires 256.0893).

1-(2-Chlorophenyl)isoquinoline 5a

In a Dean–Stark apparatus, the compound **4a** (6 g, 24.8 mmol) and manganese(IV) oxide (10 g, 124 mmol) were refluxed in benzene (500 ml) for four days in the course of which three more portions of manganese oxide were added and reaction samples were monitored by NMR. After removal of the solvent, the crude residue was chromatographed over silica gel (dichloromethane–ethanol 98 : 2) yielding compound **5a** (4.32 g, 72%) as an oil. ν_{\max} (KBr)/ cm^{-1} 3051, 1622, 1584, 1558; ^1H : 7.32–7.47 (m, 5H), 7.55 (d, 1H, $J = 9.0$), 7.58–7.64 (m, 2H), 7.81 (d, 1H, $J = 8.3$), 8.54 (d, 1H, $J = 5.9$); ^{13}C : 118.9, 125.1, 125.2, 125.5, 125.7, 127.52, 127.9, 128.1, 128.5, 129.5, 131.6, 134.6, 136.5, 140.3, 157.0; m/z 240.0574 ($\text{M}^+ + \text{H}$, $\text{C}_{15}\text{H}_{11}\text{NCl}$ requires 240.0579).

1-(2-Chlorophenyl)-3-methylisoquinoline 5b

Compound **4b** (5.7 g, 22.3 mmol) and sulfur (3.5 g, 111 mmol) in decalin (150 ml) were refluxed for 8 hours. After removal of the solvent, the crude residue was chromatographed over silica gel (dichloromethane) yielding compound **5b** (3.71 g, 65%) as a wax. ν_{\max} (KBr)/ cm^{-1} 3069, 3052, 1766, 1738, 1717; ^1H : 2.73 (s, 3H, CH_3), 7.36–7.56 (m, 8H), 7.77 (d, 1H, $J = 9.1$); ^{13}C : 23.9, 118.3, 125.0, 125.9, 126.0, 126.5, 126.7, 129.3, 129.35, 129.7, 130.9, 133.0, 136.6, 138.1, 150.4, 157.8; m/z 254.0745 ($\text{M}^+ + \text{H}$, $\text{C}_{16}\text{H}_{13}\text{NCl}$ requires 254.0737).

3,4-Dihydroisoquinoline N-oxides 6a, b

To a solution of 3,4-dihydroisoquinolines **5a** or **5b** (4.2 mmol) in dichloromethane (150 ml) was added 70% 2-chloroperoxybenzoic acid (2.1 g, 8.51 mmol). The solution was stirred overnight, and washed with a 1 M sodium hydroxide solution and water. The resulting organic phase was dried over magnesium sulfate and concentrated to dryness. The residue was chromato-

graphed over silica gel (dichloromethane–ethanol 97 : 3) to give the *N*-oxides **6a, b**.

1-(2-Chlorophenyl)isoquinoline N-oxide 6a. Obtained as a wax (82%). ν_{\max} (KBr)/ cm^{-1} 3327, 2361, 1324, 1223; ^1H : 7.31–7.56 (m, 7H), 7.66 (d, 1H, $J = 7.2$), 7.76 (d, 1H, $J = 8.5$), 8.23 (d, 1H, $J = 7.2$); ^{13}C : 123.7, 124.6, 126.8, 127.1, 128.2, 128.6, 129.2, 129.9 (2 signals ?), 130.3, 130.7, 131.2, 134.3, 137.0, 143.9; m/z 240.0573 ($\text{M}^+ + \text{H} - \text{O}$, $\text{C}_{15}\text{H}_{11}\text{NCl}$ requires 240.0580, the molecular peak was too small for an HRMS).

1-(2-Chlorophenyl)-3-methylisoquinoline N-oxide 6b. Obtained as an oil (88%). ν_{\max} (KBr)/ cm^{-1} 3056, 2922, 1360, 1334, 1295; ^1H : 2.57 (m, 3H, CH_3), 7.11 (d, 1H, $J = 8.8$), 7.25–7.50 (m, 5H), 7.61 (s, 1H), 7.62 (d, 1H, $J = 9.2$); ^{13}C : 18.4, 123.4, 124.8, 126.6, 127.7, 128.6, 129.1, 130.3, 131.0, 131.7, 131.8, 134.8, 144.5, 146.4; m/z 270.0690 ($\text{M}^+ + \text{H}$, $\text{C}_{16}\text{H}_{12}\text{NOCl}$ requires 270.0686).

1-(2-Chlorophenyl)isoquinoline-3-carboxaldehyde 7

Compound **5b** (1.15 g, 4.42 mmol) and selenium oxide (1.62 g, 13.2 mmol) were refluxed in 1,2-dichlorobenzene for 6 hours. The suspension was concentrated to dryness, dispersed in dichloromethane and filtered. The filtrate was concentrated again and the residue chromatographed over silica gel (heptane–ethyl acetate 2 : 8) to give the aldehyde **7** (1.15 g, 97%) as a solid which was used without further purification. ν_{\max} (KBr)/ cm^{-1} 3357, 2843, 2363, 1707; ^1H : 7.45 (m, 3H), 7.54 (m, 1H), 7.68 (m, 2H), 7.78 (m, 1H), 8.07 (d, 1H, $J = 8.1$), 8.44 (s, 1H, H-4), 10.24 (s, 1H, CHO); ^{13}C : 121.5, 127.5, 127.9, 129.5, 129.8, 130.4, 130.6, 130.7, 131.6, 131.63, 133.7, 136.2, 137.9, 146.5, 160.1, 194.0; m/z 268.0541 ($\text{M}^+ + \text{H}$, $\text{C}_{16}\text{H}_{11}\text{NOCl}$ requires 268.0529).

1-(2-Chlorophenyl)-3-hydroxymethylisoquinoline 8

Compound **6b** (0.25 g, 0.92 mmol) and trifluoroacetic anhydride (1.96 ml, 13.9 mmol) were refluxed in 1,2-dichlorobenzene for 2 hours. This was concentrated to dryness, treated with a mixture of ethanol (20 ml) and 1 M sodium hydroxide (20 ml) for 30 minutes. The resulting solution was extracted with dichloromethane, the organic phase was washed with water dried over magnesium sulfate and concentrated to dryness. The residue was chromatographed over silica gel (dichloromethane–ethanol 99 : 1) to give alcohol **8** (0.17 g, 68%) as a wax. ν_{\max} (KBr)/ cm^{-1} 3200, 3058, 1626, 1594, 1562; ^1H : 4.84 (s, 2H, CH_2), 7.29–7.45 (m, 5H), 7.51–7.62 (m, 3H), 7.76 (d, 1H, $J = 8.2$); ^{13}C : 66.7, 118.6, 128.2, 128.6, 128.8, 129.1, 131.7, 132.3, 133.1, 135.1, 138.7, 139.8, 154.0, 160.1; m/z 268.0529 ($\text{M}^+ - \text{H}$, $\text{C}_{16}\text{H}_{11}\text{NOCl}$ requires 268.0530).

1-(2-Chlorophenyl)isoquinoline-3-carboxylic acid 9

Aldehyde **7** (0.6 g, 2.24 mmol), silver nitrate (0.95 g, 5.61 mmol) and sodium hydroxide (0.72 g, 17.9 mmol) were stirred in a mixture of ethanol (40 ml) and water (40 ml) for 2 days. The ethanol was removed *in vacuo*, the resulting aqueous phase was made acidic with 1 M hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water and concentrated to dryness. The residue was recrystallized in heptane to yield acid **9** (0.52 g, 82%). Starting from alcohol **8**, using twice the amount of reagents, a similar yield of acid **9** was obtained. This acid was also obtained in 95% yield from ester **16** which was treated in boiling 50% aqueous ethanol with 4 equivalents of sodium hydroxide for one hour followed by the work up described above. Mp = 191 °C. ν_{\max} (KBr)/ cm^{-1} 3509, 2618, 2364, 1700; ^1H : 7.39–7.78 (m, 7H), 8.05 (d, 1H, $J = 8.2$), 8.67 (s, 1H); ^{13}C : 123.2, 127.3, 128.1, 129.2, 129.4, 130.4, 130.6, 131.0, 131.7, 132.1, 133.7, 137.0, 137.1, 139.0, 158.3, 165.3; m/z (C.I.) 284–286; Anal. ($\text{C}_{16}\text{H}_{10}\text{NClO}_2$): Calc: C: 67.74, H: 3.55, N: 4.94, found: C: 67.77, H: 3.68, N: 4.70%.

1-Hydroxy-3,4-dihydroisoquinoline-3-carboxylic acid methyl ester **11**

Acid **10**¹⁷ (1.5 g, 7.7 mmol) and one drop of concentrated sulfuric acid were heated in methanol (100 ml) for 8 hours. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane. This organic phase was washed with water, dried over magnesium sulfate, then concentrated to dryness to provide ester **11** as a solid which was used without further purification (1.5 g, 93%). ν_{\max} (KBr)/ cm^{-1} 3210, 1748, 1667; ^1H : 3.21 (dd, 1H, $J = 9.2, 15.6, \frac{1}{2}\text{CH}_2$), 3.34 (dd, 1H, $J = 5.1, 15.6, \frac{1}{2}\text{CH}_2$), 3.83 (s, 3H, OCH_3), 4.42 (m, 1H, CH), 6.48 (s (br), 1H, NH), 7.23 (d, 1H, $J = 7.9$), 7.38 (m, 1H), 7.48 (m, 1H), 8.08 (d, 1H, $J = 7.8$); ^{13}C : 31.0, 52.8, 52.9, 127.3, 127.4, 128.0, 128.3, 132.4, 136.1, 162.2, 170.9; m/z 206.0817 ($\text{M}^+ + \text{H}$, $\text{C}_{11}\text{H}_{11}\text{NO}_3$ requires 206.0817).

1-Hydroxyisoquinoline-3-carboxylic acid methyl ester **12**

Ester **11** (6 g, 29.2 mmol) and palladium over charcoal (10%, 1.55 g, 1.4 mmol) were refluxed in diphenyl ether (150 ml) overnight. After concentration to dryness (care should be taken as compound **12** will sublime if the last remnant of diphenyl ether is removed), the residue was chromatographed over silica gel (dichloromethane–ethanol 99 : 1) to afford ester **12** (4.3 g, 72%). Mp = 163 °C (ethyl acetate–heptane) (Lit.²⁶ = 161–162 °C); ν_{\max} (KBr)/ cm^{-1} 3172, 3087, 1728, 1666, 1605; ^1H and ^{13}C spectra were identical with the reported¹⁶ data.

Preparation of 1-halogeno derivatives **13** and **14**

Compound **12** (2.05 g, 10.1 mmol), potassium carbonate (4.2 g, 30.3 mmol) and the corresponding trihalogenated phosphorus oxide (30.3 mmol) were heated to reflux in dry acetonitrile (150 ml). The reaction went to completion in 90 minutes in the case of **14**, whereas another portion of phosphorus oxychloride (20.2 mmol) and potassium carbonate (20.2 mmol) had to be added after 10 hours, and the reflux resumed for an additional 4 hours to complete the preparation of **13**. The resulting suspension was then concentrated to dryness, the residue was cautiously dispersed in water and the insoluble material was filtered off, washed with water, dried and recrystallized in cyclohexane to yield compound **13** or **14**.

1-Chloroisoquinoline-3-carboxylic acid methyl ester **13**. (85% yield). Mp = 114 °C (Lit.¹⁶ = 118–119 °C); ν_{\max} (KBr)/ cm^{-1} 3224, 2508, 1714, 1255; ^1H and ^{13}C spectra were identical with the reported¹⁶ data; Anal. ($\text{C}_{11}\text{H}_8\text{NClO}_2$): Calc: C: 59.61, H: 3.64, N: 6.32, Cl: 16.00, found: C: 59.78, H: 3.64, N: 6.38, Cl: 16.19%.

1-Bromoisoquinoline-3-carboxylic acid methyl ester **14**. (82% yield). Mp = 125 °C; ν_{\max} (KBr)/ cm^{-1} 3510, 2357, 1717, 1251; ^1H : 4.02 (s, 3H, OCH_3), 7.81 (m, 2H), 7.96 (m, 1H), 8.37 (m, 1H), 8.52 (s, 1H, CH-4); ^{13}C : 52.9, 124.4, 128.4, 129.0, 130.3, 130.9, 131.9, 136.7, 140.9, 145.3, 164.9; Anal. ($\text{C}_{11}\text{H}_8\text{NBBrO}_2$): Calc: C: 49.65, H: 3.03, N: 5.26, found: C: 49.81, H: 3.08, N: 5.32%.

1-(2-Chlorophenyl)isoquinoline-3-carboxylic acid methyl ester **16**

Compound **14** (0.25 g, 0.93 mmol), potassium phosphate (0.26 g, 1.22 mmol), tetrakis(triphenylphosphine)palladium (0.03 g, 0.028 mmol) and 2-chlorophenylboronic acid **15** (0.19 g, 1.22 mmol) in dry DMF (20 ml) were heated at 80 °C overnight under an argon atmosphere. Supplementary portions

of potassium phosphate (0.13 g, 0.61 mmol) and 2-chlorophenylboronic acid (0.095 g, 0.61 mmol) were added and the heating was continued for 5 hours (^1H NMR monitoring of the reaction samples was used to insure its completion). The suspension was then concentrated to dryness and dispersed in water. This was extracted with dichloromethane, the organic phase was washed with water, dried over magnesium sulfate and concentrated to dryness. The residue was chromatographed over silica gel eluting first with dichloromethane to remove some unidentified polyarylated compounds and volatile 2-chlorophenol **17**, and then dichloromethane–ethanol 99 : 1 to provide **16** (0.25 g, 90%). Mp = 167 °C (heptane); ν_{\max} (KBr)/ cm^{-1} 3339, 1715; ^1H : 4.04 (s, 3H, OCH_3), 7.40–7.46 (m, 4H), 7.63–7.66 (m, 2H), 7.77 (m, 1H), 8.03 (d, 1H, $J = 8.2$), 8.66 (s, 1H); ^{13}C : 52.9, 124.2, 126.9, 127.5, 128.3, 128.7, 129.6, 130.1, 130.9, 131.5, 133.4, 135.9, 137.7, 140.9, 159.2, 166.4; Anal. ($\text{C}_{17}\text{H}_{12}\text{NClO}_2$): Calc: C: 68.58, H: 4.06, N: 4.7, Cl: 11.91, found: C: 68.48, H: 4.04, N: 4.70, Cl: 11.90%.

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