A Facile Synthesis of 2-Chloro-5,7-dihydro-pyrrolo[3,4-b]pyridine-6-carboxamidine, an Annulated Nicotinoid

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The chloropyridine moiety confers high potency to several types of analgesics and insecticides acting at nicotinic acetylcholine receptors (nAChRs). This includes (-)-epibatidine 1, isolated from the skin of Ecuadorian poison frog Epipedobates tricolor. The pharmacological profiles of 1 show the exceptionally strong analgesic activity and the high affinity for nAChR. Recent advances in the search for nAChR ligands include the discovery of ABT-594 2, currently in development for the treatment of Parkinson's and Alzheimer's disease. Whereas, imidacloprid 3, one of the most important synthetic insecticides, acts selectively at the insect versus the mammalian nAChR, ligands. Thus, we designed an annulated nicotinoid, which have a chloropyridinyl nitrogen and a cationic moiety suitably placed on dihydropyrrolopyridine skeleton in order to potentially interact with the receptor sites through hydrogen bonding and electrostatic interaction, respectively. Here, we wish to report a facile synthesis of 2-chloro-5,7-dihydro-pyrrolo[3,4-b]pyridine-6-carboxamidine 12 from 2-chloroquinoline 4. In our best knowledge, a synthesis of 2-chloro-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine 10 has not been reported previously.

It is envisioned that a facile synthesis of 6-chloro-pyridine-2,3-dicarboxylic acid 5 would offer the most concise synthetic route to the target molecule, as shown in Scheme 1. Despite a numerous advances in the dihydropyrrolopyridine chemistry, the synthesis of halide-containing one is quite rare, presumably, due to the lack of availability of halide-containing quinolinic and cinchomeronic acid precursors. Although there are some methods for the preparation of halide-containing pyridine dicarboxylic acids, a facile and reliable preparation of such compounds is poorly documented.

It is well known that the ruthenium-catalyzed oxidation of aromatic rings would offer a very efficient and simple route to carboxylic acid. Thus, 2-chloroquinoline 4 was reacted with ruthenium tetroxide, generated in situ from RuCl₃ and H₂O₂, in a biphasic conditions (CCL₄, CH₂CN, H₂O). Next, the acid 5 was treated with methyl iodide and cesium carbonate in DMF to give the ester 6. Surprisingly, a problem was encountered in the reduction of 6. In spite of many precedences, an attempted reduction of 6 with BH₃·THF or of 5 with LiAlH₄ was unsuccessful. In both reduction conditions, the reaction mixtures turned reddish and the starting materials were completely decomposed. After several trials, we found in situ generated calcium borohydride reduction of 6 cleanly afforded the diol 7 in 88% yield. The remaining steps were quite straightforward. By adding of thionyl chloride, 7 was readily converted to the halide 8 in 85% yield, and subsequent substitution of 8 with p-toluenesulfonylamine and sodium hydride in DMF furnished the tosylate 9 in 57% yield. Finally, the deprotection of 9 was accomplished with hydrogen bromide (30 wt.% solution in acetic acid) in the presence of phenol to afford 2-chloro-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine 10 in nearly quantitative yield.

In a recent report, Goodman et al. introduced N,N-di-Boc-
Notes

Scheme 1. (a) RuCl₃, H₂O, MeCN-CCl₃-H₂O; (b) Mel, Cs₂CO₃, DMF; (c) NaH, CsCl, EtOH; (d) SOCl₂; (e) p-TsNH₂, NaH, DMF; (f) 30% HBr-ÁOH, PhOH; (g) N,N'-di-Boc-N'-trihyguanidine, Et₃N, CH₂Cl₂; (h) TFA, EtSiH.

N'-triflyguanidine¹¹ which was utilized to guanidinate primary and secondary amines, and alcohols. Thus, the reaction of 10 with N,N'-di-Boc-N'-triflyguanidine produced N,N'-di-Boc-N'-guanidine 11, which was easily converted to the target compound 12 with trifluoroacetic acid in the presence of triethylsilane. The guanidine moiety has a strongly basic character which fully protonated under physiological conditions. Thereby, we reasoned the positive charge imposed on the molecule has a chance to form a π-cation interaction between the ligand and nAChR.

In conclusion, a highly efficient synthesis of 2-chloro-5,7-dihydropyrrolo[3,4-α]pyridine-6-carboxamidine 12, an annulated nicotinoid, has been accomplished starting from 2-chloroquinoline 4. It is noteworthy that the title compound contains chloropyridinyl nitrogen and a cationic moiety suitably placed on dihydropyrrolopyridine skeleton in order to potentially interact with nAChR. This work may offer a substantial method for the synthesis of halide-containing 6,7-dihydropyrazolo[3,4-b]pyridine and 2,3-dihydropyridine[3,4-c]pyridine, which were difficult to obtain. Currently, we are investigating the binding affinity of a series of annulated nicotinoids to nAChR and the result will be reported in due course.

Experimental Section

6-Chloro-pyridine-2,3-dicarboxylic acid dimethyl ester (6). Methyl iodide (24.2 g, 170.6 mmol) and cesium carbonate (27.79 g, 85.5 mmol) were added to a solution of 5 (5.73 g, 28.4 mmol) in DMF (100 mL) and the reaction mixture was allowed to stir for overnight. The mixture was diluted with ethyl acetate. The combined organic layers were washed successively with water, dried over magnesium sulfate, and evaporated under reduced pressure to give an oily residue. The residue was purified by flash chromatography on silica gel with ethyl acetate/hexane (1:7) as the eluent to give 5.28 g (81%) of 6 as a solid, mp 46-47 °C; 1H NMR (CDCl₃) δ 8.14 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H); 13C NMR (CDCl₃) δ 165.1, 164.2, 153.8, 151.3, 140.1, 125.5, 124.0, 52.9, 52.8; EIMS m/z (rel intensity) 231 (M⁺, 1), 229 (M⁺, 4), 198 (34), 140 (35), 102 (100), 76 (88); Anal. Calc'd for C₇H₆ClNO: C, 47.08; H, 3.51; N, 6.10. Found: C, 47.12; H, 3.49; N, 6.02.

6-Chloro-2-hydroxymethyl-pyridin-3(2H)-methanol (7). Calcium chloride (1.73 g, 15.6 mmol) and sodium borohydride (1.18 g, 31.2 mmol) were stirred in THF (30 mL) at room temperature for 1 h. A solution of 6 (1.79 g, 7.82 mmol) in THF (5 mL) was added dropwise to this hydride suspension. The reaction mixture was allowed to stir for 13 h at room temperature. The excess hydride was quenched with methanol and potassium carbonate was added to this residue. The organic layer was decanted and the residual solid washed repeatedly with THF. The combined organic layer was dried over sodium sulfate and concentrated to yield an oily residue. The residue was purified by flash chromatography on silica gel with ethyl acetate/hexane (1:7) as the eluent to give 1.2 g (88%) of 7 as a solid, mp 37-39 °C; 1H NMR (CDCl₃) δ 7.70 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 4.67 (d, J = 13.8 Hz, 4H); 13C NMR (CDCl₃) δ 157.4, 149.2, 139.0, 132.3, 123.1, 62.3, 60.5; EIMS m/z (rel intensity) 172 (3), 155 (100), 127 (83), 91 (40).

6-Chloro-2,3-bis-chloromethyl-pyridine (8). Thionyl chloride (5 mL, 68.8 mmol) was slowly added to a solution of 7 (1.10 g, 6.36 mmol) in dichloromethane (10 mL) at 0 °C for 30 min and the reaction mixture was allowed to stir at room temperature for overnight. The mixture was concentrated under reduced pressure to give an oily residue. The mixture was...
residue was purified by flash chromatography on silica gel with ethyl acetate/hexane (1:3) as the eluent to give 37 mg (85%) of 8. 1H NMR (CDCl3) δ 7.65 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 4.68 (s, 2H), 4.65 (s, 2H), 1.3 NMR (CDCl3) δ 155.4, 150.7, 141.1, 131.2, 124.8, 43.6, 41.0, EIMS m/z (rel intensity) 215 (M+ 2), 209 (M+ 3), 174 (3%); 13C NMR (CDCl3) δ 155.1, 151.0, 132.7, 128.0, 126.4, 122.7, 76.9, 54.0, 52.2, 27.8. EIMS m/z (rel intensity) 396 (M+ 2), 250 (10), 230 (28), 153 (47), 57 (100).

2-Chloro-5,7-dihydro-pyrrrol-3,4-b]pyridine-6-carboxylic acid (12). To a solution of 11 (226 mg, 0.57 mmol) in trifluoroacetic acid (4 mL) was added a few drops of triethylsilane. The reaction mixture was heated for 2 h and the solution was evaporated to dryness to give a residual solid. The solid was collected by filtration, washed with diethyl ether, and dried in vacuo to yield 86.4 mg (77%) of 12. mp 240-242°C; 1H NMR (CDCl3) δ 7.92 (s, 2H), 7.81 (d, J = 6.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.16 (s, 1H), 4.80 (d, J = 10.4 Hz, 4H); 13C NMR (CDCl3) δ 156.1, 151.5, 150.4, 133.9, 127.9, 123.0, 52.4, 50.8; EIMS m/z (rel intensity) 196 (M+ 40), 153 (100), 117 (35), 69 (30).

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References