Oxidation of 2- and 3-Halogenated Quinolines: An Easy Access to 5- and 6-Halogenopyridine-2,3-dicarboxylic Acids

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Abstract: Pyridine-2,3-dicarboxylic acids bearing an halogen in the position α or β to the nitrogen atom were synthesized by oxidation of the corresponding quinolines. Two methods, using either ozone followed by hydrogen peroxide or ruthenium tetroxide under catalytic conditions were used. Diacids 1b,c and 2a-c substituted in 6-position by a chlorine or bromine and in 5-position by a fluorine, chloride or bromine, respectively, were isolated in yields ranging from 46–71%. Yields of 6-fluoro and 6- or 5-iodo diacids 1a,d and 2d did not exceed 30%.

Key words: oxidation, quinolines, pyridine-2,3-dicarboxylic acids, halogens, ozonolysis, ruthenium tetroxide

Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) are two powerful imaging techniques for clinical research and diagnosis, and also for in vivo biochemistry and pharmacology studies in animals and human.1 PET is a quantitative and very sensitive method but it requires high cost facilities due to the use of radiotracers labelled with cyclotron produced short half-life positron emitter (carbon-11, t1/2 = 20.4 min; fluor-18, t1/2 = 109.7 min). SPECT has coarser spatial and temporal resolution, reduced sensitivity and less quantification capability. However, it has the advantage of convenience with easily available gamma emitter radionuclides of longer half-lives (iodine-123, t1/2 = 13.2 h; technetium-99m, t1/2 = 6 h), and it is routinely used in all nuclear medicine centers. Therefore, the search for unique tracers capable of labelling with a positron or a gamma emitter could allow biological studies by PET that could validate further developments in SPECT.

Neurokinin (NK) antagonists have been involved in a wide range of pathological conditions such as asthma, pain, migraine, emesis and psychiatric disorders.2 With the aim of visualizing in vivo NK receptors in the central nervous system by both PET and SPECT, we have envisaged the synthesis of halogenated analogs3 of the antagonist EP 006522184 (Scheme 1). Recent studies4 showed that this naphthyridone derivative exhibits a subnanomolar affinity (IC50 = 0.21nM, in vitro inhibition of 125I-BH-SP binding in human IM-9 cells) towards the NK receptors, and that structural modifications on the pyridine ring have a relatively small influence on this value. Our synthesis strategy was based on the reaction scheme described for the preparation of EP-00652218.5 For this purpose, we required an efficient synthesis of the halogenated diacids 1 and 2.

Like pyridine-2,3-dicarboxylic acids which are building blocks used in the preparation of pharmaceuticals, herbicides and dyes,5 their halogeno derivatives are also very attractive polyfunctional tools. Indeed, they can be involved in a large variety of transformations including cross-coupling6 and metatation7 reactions. Surprisingly, the preparation of such compounds is poorly documented compared to alkyl substituted analogs. The described methods involved oxidation of quinolines. Hydrogen peroxide under acidic catalytic conditions8 was claimed to oxidize any halogenoquinolines although no yields and analytical data were given. Potassium permanganate9 and ruthenium tetroxide10 were both used in a single example.

Scheme 1
respectively, for the preparation of 4- and 6-chloropyridine-2,3-dicarboxylic acids from 4- and 6-chloroquinolines. Yields did not exceed 39%. To our knowledge, the more reliable synthesis of halogenopyridinedicarboxylic acids is based on electrolysis of the corresponding quinolines. However, the yields of diacids were strongly dependent on the nature and the position of the halogen (yields range from 0% to 73%) and this method was restricted to the oxidation of 3-chloro and 3-bromoquinolines. Dehalogenation and polymerization occurred with other quinolines. All these syntheses suffer from several drawbacks: moderate yield, no large scope, and need for a special equipment. Herein we report a reproducible and easily manipulative preparation of 6- or 5-halogenopyridine-2,3-dicarboxylic acids 1 and 2 by oxidation of their corresponding quinolines 3 and 4 (Scheme 2).

Preliminary comparative studies were performed on the commercially available 2-chloro- (3b) and 3-bromoquinolines (4c). Attempts to use the reported methods failed. H2O2 in the presence of catalytic amount of Fe(NO3)3 under acidic conditions (H2SO4 or HNO3) did not allow any formation of the 6-chlorodicarboxylic acid 1b from 2-chloroquinoline (3b). Oxidation of 3-bromoquinoline (4c) to the corresponding diacid 2c was carried out in 28% yield only. The difficult control of the addition rate of H2O2 could explain these poor results. Potassium permanganate did not give better results, complexation of pyridine with manganese derivatives led to loss of materials. 2-Chloroquinoline was not recovered and tars were obtained. Yields were not improved by changing either the concentrations and the addition rates of the oxidizing reagent.

Following the efficient oxidation of alkyl substituted quinolines to their corresponding diacids by ozone following the method (A or B) was used, and only a crude product was obtained. Yields were not improved by changing either the concentrations or the addition rates of the oxidizing reagent.

Scheme 2

Oxidation of iodoquinolines 3a,c,d and 4a,b,d was difficult and did occur in low yields (<30%, entries 7, 8 and 15, 16). It was observed that ozonolysis was the reaction of choice for the preparation of 2d (entry 15). When RuO2/NaOCl was used (entry 16), iodine was lost and 6-hydroxypyrindine-2,3-dicarboxylic acid (2e) was isolated in 50% yield. Deiodination was also observed during the electrolytic oxidation of 4d. Extraction of the diacid 1d from the reaction medium and its purification were tricky whatever the method (A or B) was used, and only a crude product was obtained.

In conclusion, the transformation of halogenoquinolines 3 and 4 into halogenopyridine-2,3-dicarboxylic acids 1 and 2 could be achieved using ozonolysis or ruthenium catalyzed oxidation. These oxidation procedures were efficient except for quinolines substituted in the 2 position by a fluorne or iodine atom, and superior to the described methods. They were also less sensitive to the substitution than the electrolytic method previously reported. The diacids 1 and 2 were easily purified and have been used for the preparation of new tracers of NK1 receptors labelled with positron or gamma emitters.

1H (200 MHz), 13C (62.8 MHz) and 19F (235.36 MHz) NMR spectra were recorded on a Bruker DPX 300 instrument. IR spectra were obtained on a Perkin Elmer 684 spectrophotometer. Mass spectra were recorded on a Nermag R 10 spectrometer at 70 eV. HRMS were recorded on a Jeol Gcmate instrument. Elementary analyses were performed using a ThermoQuest analyser CHNS-O. Melting points were determined using Kofler bank and are uncorrected.
Oxidation of 2- and 3-Halogenated Quinolines 3, 4; General Procedure (Method A)

**Warning**: Caution should be taken during ozonolysis and H₂O₂ oxidations. Absence of peroxide before distillation of CH₂Cl₂ has to be controlled.

A stream of ozonized oxygen (0.5 mmol/min) was bubbled through a solution of quinolines 3a or 4 (24 mmol) in CH₂Cl₂ (250 mL) for 4 h at 0°C. After purging for 5 min with O₂, then for 5 min with N₂, aqueous solutions of NaOH (10%, 60 mL) and H₂O₂ (30%, 528 mmol, 60 mL) were added. CH₂Cl₂ was distilled off and the residual mixture was refluxed for 1 h and then acidified with 37% HCl to pH 1. H₂O was evaporated until precipitation of the acid started. The mixture was allowed to crystallize at r.t. and the precipitate was filtered to give pyridine-2,3-dicarboxylic acids 1a or 2a as solid. Further purifications were carried out by recrystallization from H₂O.

**Table Oxidation of Quinolines 3, 4 into Diacids 1 and 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Quinoline</th>
<th>Method</th>
<th>Diacid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>A</td>
<td>1a</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>B</td>
<td>2a</td>
<td>20%</td>
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<tr>
<td>3</td>
<td>3c</td>
<td>A</td>
<td>1b</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>B</td>
<td>2b</td>
<td>64%</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>A</td>
<td>1c</td>
<td>59%</td>
</tr>
<tr>
<td>6</td>
<td>3d</td>
<td>B</td>
<td>2c</td>
<td>46%</td>
</tr>
<tr>
<td>7</td>
<td>3d</td>
<td>A</td>
<td>1d</td>
<td>19%</td>
</tr>
<tr>
<td>8</td>
<td>3d</td>
<td>B</td>
<td>2d</td>
<td>20%</td>
</tr>
<tr>
<td>9</td>
<td>3d</td>
<td>A</td>
<td>1e</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3d</td>
<td>B</td>
<td>2e</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4a</td>
<td>A</td>
<td>1a</td>
<td>68%</td>
</tr>
<tr>
<td>12</td>
<td>4a</td>
<td>B</td>
<td>2a</td>
<td>71%</td>
</tr>
<tr>
<td>13</td>
<td>4a</td>
<td>A</td>
<td>1c</td>
<td>55%</td>
</tr>
<tr>
<td>14</td>
<td>4a</td>
<td>B</td>
<td>2c</td>
<td>49%</td>
</tr>
<tr>
<td>15</td>
<td>4a</td>
<td>A</td>
<td>1d</td>
<td>30%</td>
</tr>
<tr>
<td>16</td>
<td>4a</td>
<td>B</td>
<td>2d</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Method A: O₃ (5 equiv, 0.5 mmol/min), CH₂Cl₂, 0°C, then H₂O₂ (22 equiv), NaOH, 100°C, 1 h; Method B: RuO₂ (0.025 equiv), NaOCl (130 equiv added in 3 portions), CCl₄, r.t.

**Oxidation of 2- and 3-Halogenated Quinolines 3, 4 with Ruthenium Tetroxide; General Procedure (Method B)**

To a mixture of CCl₄ (200 mL) and NaOCl (commercial bleach, 1.8 mol, 90 mL diluted with 400 mL of H₂O) was added RuO₂ (0.06 g, 0.46 mmol) under vigorous stirring at r.t. When the reaction mixture was yellow, quinolines 3b or 4 (18.36 mmol) was added. After stirring at r.t. for 2 h, the mixture became black. TLC analysis (CH₂Cl₂–MeOH, 95:5) showed that the conversion was not complete and an additional amount of NaOCl (0.6 mol, 30 mL) was added. This operation was repeated 4 h later. After 6.5 h, the conversion was complete. The aqueous phase was separated, washed with Et₂O (2×100 mL) and acidified to pH 1–2 with 37% HCl. Evaporation of the aqueous mixture gave the crude product as a yellow solid. This solid was desalinated by chromatography on a C-18 column (washing with H₂O and elution with MeOH) to give a brown oil. Crystallization from H₂O gave pyridine 2,3-dicarboxylic acid 1 or 2 as crystals. Further purifications were carried out by recrystallization from H₂O.

Ozonolysis were carried out with an ozone generator BMT 802. Reverse phase chromatography was performed using C-18 silica gel Macherey-Nagel PolygoPrep 60–50. All solvents (analytical grade), reagents and quinolines 3b and 4c were purchased from ACROS, Aldrich or Fluka and used without further purification. 2-Fluoroquinoline (3a), 2-bromoquinoline (3c), 2-iodoquinoline (3d), 3-fluoroquinoline (4a), and 3-iodoquinoline (4d) were prepared as previously described. 3-Chloroquinoline (4b) was obtained by reaction of 3-trimethylstannylquinoline with N-chlorosuccinimide.
6-Fluoropyridine-2,3-dicarboxylic Acid (1a)
Impure, see text.
IR (KBr): 1700, 1718 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 7.4\) (dd, \(J_{HH} = 8.2\) Hz, \(J_{HF} = 2.5\) Hz, 1 H), 8.4 (dd, \(J_{HH} = J_{HF} = 8.2\) Hz, 1 H).

\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta = 109.7\) (d, \(J_{CF} = 36.5\) Hz), 122.6 (d, \(J_{CF} = 3.8\) Hz), 142.9 (d, \(J_{CF} = 8.8\) Hz), 150.1 (d, \(J_{CF} = 15.1\) Hz), 161.9 (d, \(J_{CF} = 243.3\) Hz), 163.9, 164.9.

\(^3\)F NMR (DMSO-\(d_6\)): \(\delta = -64.7\).

EI-MS: \(m/z\) (\%): 186 (2, M\(^+\) + 1), 98 (26), 96 (43), 53 (26), 52 (35), 51 (79), 50 (100), 49 (74), 48 (45), 46 (29), 45 (99), 44 (99).

5-Chloropyridine-2,3-dicarboxylic Acid (2b)
White crystals; mp 152–154 °C.
IR (KBr): 1670, 1734 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 7.7\) (d, \(J = 8.3\) Hz, 1 H), 8.5 (d, \(J = 8.3\) Hz, 1 H).

\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta = 126.0\), 130.5, 145.0, 151.3, 151.8, 165.4, 166.0.

EI-MS: \(m/z\) (\%): 159 (33, M\(^+\)), 157 (80), 141 (36), 140 (42), 139 (100), 113 (42), 112 (27), 111 (44), 78 (34), 76 (74), 75 (38), 51 (35), 50 (24), 44 (23).

Anal. Calcd for C\(_7\)H\(_4\)ClNO\(_4\): C, 38.26; H, 2.73; N, 6.38. Found: C, 38.09; H, 2.84; N, 6.75.

6-Chloropyridine-2,3-dicarboxylic Acid (1b) (monohydrate)
White crystals; mp 152–154 °C.
IR (KBr): 1670, 1734 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 7.7\) (d, \(J = 8.3\) Hz, 1 H), 8.5 (d, \(J = 8.3\) Hz, 1 H).

\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta = 126.0\), 130.5, 145.0, 151.3, 151.8, 165.4, 166.0.

EI-MS: \(m/z\) (\%): 229 [M\(^+\) (C\(_6\)H\(_3\)NO\(_4\)-H\(_2\)O), 5], 227 [M\(^+\) (C\(_6\)H\(_3\)NO\(_4\)-H\(_2\)O), 5], 203 (18), 201 (25), 185 (39), 183 (26), 45 (100), 44 (50).

Anal. Calcd for C\(_6\)H\(_3\)BrNO\(_4\): C, 31.84; H, 2.29; N, 5.31. Found: C, 32.09; H, 2.36; N, 5.26.

5-Bromopyridine-2,3-dicarboxylic Acid (2c)
White solid; mp 152 °C.
IR (KBr): 1654, 1724 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 7.9\) (d, \(J = 8.5\) Hz, 1 H), 8.2 (d, \(J = 8.5\) Hz, 1 H).

\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta = 125.3\), 129.6, 141.1, 143.8, 153.4, 165.9, 166.6.

EI-MS: \(m/z\) (\%): 229 (M\(^+\) (C\(_6\)H\(_3\)BrNO\(_4\)-H\(_2\)O), 5), 227 [M\(^+\) (C\(_6\)H\(_3\)BrNO\(_4\)-H\(_2\)O), 5], 203 (18), 201 (25), 185 (39), 183 (26), 45 (100), 44 (50).

Anal. Calcd for C\(_6\)H\(_3\)BrNO\(_4\): C, 31.84; H, 2.29; N, 5.31. Found: C, 32.09; H, 2.36; N, 5.26.

6-Iodopyridine-2,3-dicarboxylic Acid (1d)
Impure, see text.
IR (KBr): 1604, 1638, 1672 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 6.5\) (d, \(J = 9.4\) Hz, 1 H), 7.9 (d, \(J = 9.4\) Hz, 1 H).

\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta = 109.9\), 119.1, 129.5, 141.6, 160.4, 161.4, 163.5.

EI-MS: \(m/z\) (\%): 184 (3, M\(^+\) + 1), 149 (48), 57 (44), 55 (40), 44 (100), 43 (88), 42 (21).

5-Hydroxy pyridine-2,3-dicarboxylic Acid (1e)
Beige crystals; mp 260 °C.
IR (KBr): 1638, 1724 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 8.3\) (d, \(J = 2.1\) Hz, 1 H), 8.8 (d, \(J = 2.1\) Hz, 1 H).

\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta = 128.6\), 132.8, 137.8, 150.8, 150.9, 166.1, 167.7.

EI-MS: \(m/z\) (\%): 183 (4, M\(^+\)), 139 (11), 50 (100).

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