A convenient synthesis of cyclopenta[b]pyridin-2,5-dione as a non-glycosidic cardiotonic agent

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Dedicated to Professor Guy Quéguiner on the occasion of his 70th birthday

Abstract
A straightforward synthesis of cyclopenta[b]pyridin-2,5-dione is reported starting from the commercially available 2-bromo-6-methoxy pyridine. The overall route consists in a first sequence of regioselective ortholithiation and methoxycarbonylation followed by Heck vinylation, alkene reduction, cyclization and decarboxylation.

Keywords: Lithiation, Heck vinylation, pyridine, cyclopenta[b]pyridine-2,5-dione

Introduction
A recent pharmacological evaluation of various functionalized 2-pyridones as cardiotonic agents has revealed that the cyclopenta[b]pyridin-2,5-dione (1) displays a high activity rather similar to Milrinone (2) which is the most effective non glycosidic cardiotonic agent clinically used for the treatment of severe heart failure.1 Cyclopenta[b]pyridin-2,5-dione (1) constitutes also an interesting tensor of pharmaceutics exemplified by the antibacterial product 5 and a building-block for the access to 2-cyclopenta[b]pyridin-5-one (3) as seco analogues of 8-azasteroids (4).2

Results and Discussion
Despite the fact that the cyclopenta[b]pyridin-2,5-dione (1) is gaining interest as biologically active compounds and valuable building-blocks only two methods of preparation could be found in the literature. The first synthesis of cyclopenta[b]pyridin-2,5-dione (1) was first reported in 1954 (6 steps synthesis and a 13 % overall yield).3 Mosti and his team published in 2003 a novel
synthetic route based upon a one-pot and two-step construction of the 2-pyridone ring from the cyclopenta-1,3-dione.\(^1\) We recently described a novel synthesis of 6-methyl cyclopenta[b]pyridin-5-one (8) based on Heck vinylation of 2-bromo-6-methyl nicotinate (6) with methacrylate affording the pyridylacrylate intermediate 7, alkene reduction and Dieckmann condensation as depicted in Scheme 1.\(^4\) We wish to report here our results on the application of the latter method to the preparation of the cyclopenta[b]pyridin-2,5-dione (1). Our retrosynthetic analysis suggests that 2-bromo-6-methoxynicotinate (10) could be a valuable precursor for this purpose (scheme 1). The pyridylacrylate 9 could be first prepared by Heck vinylation of bromopyridine 10. The expected cyclopenta[b]pyridin-2,5-dione (1) would be then obtained by reduction of the alkene followed by a cyclization-decarboxylation sequence. The success of this novel approach mainly depends on the access to the unknown 2-bromo-6-methoxynicotinate 10. Two possible routes could be designed: (i) the regioselective displacement of a bromine atom at position 2 of the methyl 2,6-dibromonicotinate (11) which could be readily prepared in two steps from the 2,6-dichloronicotinic acid by bromination and esterification\(^7\) or (ii), the regioselective methoxycarbonylation of the commercially available 2-bromo-6-methoxypyridine (12).

\[ \begin{align*} 
1 & \quad \text{Cyclopenta[b]pyridin-2,5-dione} \\
2 & \quad \text{Milrinone} \\
3 & \\
4 & \\
5 & \\
\end{align*} \]

Figure 1
Scheme 1. Previously reported synthesis of 6-methylcyclopenta[b]pyridine-5-one (8) and retrosynthetic analysis of cyclopenta[b]pyridin-2,5-dione (1).

We first attempted to displace the bromine atom at position 2 of ethyl 2,6-dibromonicotinate (11) with sodium methoxide. Treatment of 11 with 1.5 equivalent of sodium methoxide was carried out in refluxing MeOH for 24h following the Hirokawa’s protocol. A complete conversion of the starting material was observed and a mixture of 2- and 6-monosubstituted products 10 and 14 in a 7:3 ratio (1H NMR) could be obtained in 75% yield. Unfortunately, the two regioisomers 10 and 14 could not be separated by chromatography. Moreover, replacement of sodium methoxide by potassium methoxide also led to a 1:1 mixture regioisomers 10 and 14.

Scheme 2. Reagents and conditions: (i) MeONa (1 equiv.), MeOH, reflux, 24h, 75%.

We then shifted to the second route based on the regioselective methoxycarbonylation at position 3 of 2-bromo-6-methoxy pyridine (12). To this purpose, we first examined the lithiation of 2-bromo-6-methoxy pyridine (12) by treatment with hard bases such as lithium amides in THF before quenching the lithio intermediates with D_{2}O (Table 1). A first set of lithiation experiments was achieved using 2,2',6,6'-tetramethylpiperidinyl-lithium (LTMP) at -78 °C (entries 1-3).
Table 1. Assays of regioselective lithiation of 12 with lithium amides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equiv.</th>
<th>T (°C)</th>
<th>15a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>15b (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>1</td>
<td>-78°C</td>
<td>-</td>
<td>-</td>
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<tr>
<td>2</td>
<td>LTMP</td>
<td>2</td>
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<td>4</td>
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<td>-78</td>
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<td>5</td>
<td>LDA</td>
<td>3</td>
<td>°C</td>
<td>15</td>
<td>-</td>
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<td>6</td>
<td>2</td>
<td>-50</td>
<td>22</td>
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<td>3</td>
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<td>-50°C</td>
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<sup>a</sup>The ratio was determined by <sup>1</sup>H NMR spectroscopy

No deuterated product was obtained using 1 equivalent of LTMP whereas the 5-deuterated compound 15b was selectively formed in 64% yield using 2 equivalents of LTMP. The starting material conversion could be significantly improved employing 3 equivalents of LTMP leading to a mixture of 3- and 5-deuterated products (15a, 15b) in 2:8 ratio in favor of the 15b isomer. The less hard lithium diisopropylamine (LDA) was also checked (entries 4-7). Treatment of 12 with 2 equivalents of LDA followed by D2O trapping specifically provided the 3-deuterated product 15a in 15% yield (entry 4). This result could be related to the higher acidity of the proton at position 3. Surprisingly, we observed that the yield of 3-deuterated compound 15a was not improved using 3 equivalents of LDA at the same temperature (entry 5). Moreover warming the 3-lithio anion from -78°C to -50 °C before trapping with D2O afforded a mixture of 15a and 15b (entries 6, 7).

Scheme 3. Reagents and conditions: (i) (a) LDA (2 equiv.), -78°C, THF, 1h, (b) solid carbon dioxide, (c) HCl (2M), 13%; (ii) (a) (COCl)<sub>2</sub>, DMFcat., (b) MeOH, 92%.
The 3-lithio anion formed by treatment of 12 with 2 equivalents of LDA at -78°C in THF (table 1-entry 4) did not react with methyl cyanoformate but could be trapped by carbon dioxide to give the 3-bromo-6-methoxynicotinic acid (16) after acidic treatment. Acid (16) was isolated in 13 % yield but the unreacted starting material 12 could be was readily recovered and re-used. Finally 16 was obtained in 41 % overall yield after five lithiation–carboxylation sequences. Esterification of 16 gave the expected methyl 2-bromo-6-methoxy nicotinate (10) in 92 % yield.

Heck vinylation of 10 with methyl acrylate using the η3-allylpalladium chloride dimer with P(o-Tol)3 complex as catalyst in toluene and dimethylacetamide (DMA) as co-solvent provided the β-2-pyridyl acrylate 9 in an excellent 82% yield. The use of DMA is a crucial parameter as the vinylation of 10 failed without this co-solvent. Reduction of the alkene under soft conditions provided diester 17 which could be cyclized by a Dieckmann condensation with sodium methoxide to methyl cyclopenta[b]pyridine-5-one-6-carboxylate (18) in 70% overall yield. Finally, treatment with hydrochloric acid allows hydrolysis, decarboxylation and demethylation of 18 to give cyclopenta[c]pyridine-2,5-dione (1) in 84 % yield.

**Scheme 4.** Reagents and conditions: (i) methyl acrylate (2.5 equiv.), Pd2[allyl2Cl2], P(o-Tol)3, NaOAc (3 equiv.), toluene: DMA (3:1), 92%; (ii) H2 (1 atm), Pd/C (10 mol %), MeOH, r.t., 2h, 93%; (iii) NaOMe, THF, reflux, 2h, 75%; (iv) HCl (5 M), reflux, 3h, 84%.

**Conclusions**

A convenient route to cyclopenta[b]pyridin-2,5-dione (1) is reported starting from methyl 2-bromo-6-methoxynicotinate (10) through a 4 steps synthesis, vinylation, alkene reduction and cyclization-decarboxylation, in 48% overall yield. Two routes were studied for the previous preparation of the parent methyl 2-bromo-6-methoxynicotinate (10). Regioselective displacement of the bromine atom of methyl 2,6-dibromonicotinate (11) by the sodium or potassium methoxide could not be applied leading to a mixture of regioisomers which could not be separated by chromatography. The second approach was based upon the regioselective
carboxylation of the commercially available 2-bromo-6-methoxypyridine (12) at position 3 of the pyridine nucleus. The regioselective lithiation-carboxylation and esterification of 12 at position 3 was achieved using LDA at -78°C in THF to give the expected methyl 2-bromo-6-methoxynicotinate (10) in 12 % yield in two steps.

**Experimental Section**

**General Procedures.** Tetrahydrofuran (THF), ether (Et₂O) were pre-dried with pellets of KOH and distilled over sodium benzophenone ketyl under Ar before use. CH₂Cl₂, NEt₃ and toluene were distilled from CaH₂. Methanol and ethanol were distilled from magnesium turnings; dimethylacetamide was distilled over 4 Å molecular sieves. For Flash chromatography, Merck silica gel (70-230 mesh) was used. The melting points were measured on a Kofler melting points apparatus and were not corrected. The ¹H NMR and ¹³C NMR spectra were recorded with a Bruker Avance-300 spectrometer operating at 300 MHz. Commercially available starting materials were used without further purification. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1650 spectrophotometer. Elemental analysis of compounds was carried out on a Carlo Erba 1160. Mass spectra were recorded on a JEOL JMS AX-500 spectrometer, in electronic impact (EI). The starting compound 12 is commercially available.

**Preparation of 6-methoxy-2-bromonicotinate (10)**

**Methyl 2,6-dibromonicotinate (11).** To a stirred solution of 2,6-dibromonicotinic acid⁷ (500 mg, 1.8 mmol) and 3 drops of DMF in dry CH₂Cl₂ (10 ml) was slowly added oxalyl chloride (172 µL, 2.0 mmol) at 0°C. The mixture was stirred at room temperature for 1h and solvents were removed in vacuo. To the crude product was added dry methanol (10 ml) at 0 °C and the resulting solution was stirred for 2 h at room temperature. Methanol was removed in vacuo and the crude solid was dissolved in CH₂Cl₂ (10 ml). The pH of the aqueous layer was then adjusted to 7 by adding aq. K₂CO₃ (2M). The separated organic layer was washed three times with water, dried (MgSO₄) and concentrated in vacuo to give 11 (488 mg, 92 % yield) as beige powder, mp = 51-52 °C; IR (KBr) ν 3093, 2957, 1728, 1567, 1416; ¹H NMR (CDCl₃) δ 3.93 (s 3H), 7.52 (d, 1H, J = 8.1 Hz), 7.93 (d, 1H, J = 8.1 Hz; ¹³C NMR (CDCl₃) δ 53.5, 127.3, 128.7, 140.4, 141.7, 143.9, 165.0; Anal. Calcd for C₇H₅Br₂NO₂ (294.9): C, 28.51; H, 1.71; N, 4.75. Found: C, 29.01; H, 1.67; N, 4.71 %.

**Procedure for nucleophilic substitution using sodium methoxide.** To a stirred solution of methyl 2,6-dibromonicotinate (11, 1.5 g, 5.0 mmol) in dry MeOH (20 ml) was added NaOMe (270 mg, 5.0 mmol). The mixture was refluxed for 24 h and then poured into cold aq. NaHCO₃ (5 %, 50 ml) and the product was extracted with ether (3x20 mL). The separated organic phase was separated and concentrated in vacuo. Ether (40 mL) was added to the crude liquid and the organic phase was washed with brine (40 mL), dried (MgSO₄) and concentrated in vacuo. The
crude product was purified by chromatography on silica gel (CH$_2$Cl$_2$) to give a (7:3) mixture of 10 and 14 (923 mg, 75 %).

**2-Bromo-6-methoxypyridine (12).** To a stirred solution of 2,6-dibromopyridine (20 g, 84 mmol) in dry MeOH (50 mL) was added NaOMe (8g, 148 mmol). The mixture was refluxed for 25 h and then poured into a cold aq. soln. of NaHCO$_3$ (5%, 50 mL). The product was extracted with ether (3x30 ml) and the combined organic layers were washed with brine (40 ml) and concentrated in vacuo. The crude product was purified by chromatography on silica gel (EtOAc/Petrol 9:1) to give 12 (13 g, 83 %) as a liquid; bp=206-207°C; IR (KBr) υ 2953, 1596, 1582, 1558, 1525, 1472, 1329, 1298, 1022, 857; 1H NMR (CDCl$_3$) δ 3.93 (s 3H), 6.69 (t, 1H, J = 7.7 Hz), 7.06 (d, 1H, J = 7.7 Hz), 7.40 (d, 1H, J = 7.7 Hz).

**2-Bromo-6-methoxynicotinic acid (16).** To a stirred solution of LDA (106 mmol) in dry THF (50 mL) was added dropwise under N$_2$ at –78°C a solution of 2-bromo-6-methoxypyridine 12 (10 g, 53 mmol) in dry THF (50 ml). After stirring 1 h. at the same temperature, the mixture was poured on an excess of carbonic dry ice. Solvents were removed in vacuo and the crude residue was dissolved in water (30 ml). The separated aqueous layer was washed with CH$_2$Cl$_2$ (3x15 ml) and pH was adjusted to 4 by adding aq. HCl (2M). The product was extracted with CH$_2$Cl$_2$ (3x15 ml) and the combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated in vacuo to give 16 (1.6 g, 13 %) as a beige solid; mp= 212-213°C; IR (KBr) υ 3418, 2959; 1H NMR (CDCl$_3$) δ 3.89 (s, 3H), 6.91 (d, 1H, J = 8.4 Hz), 8.10 (d, 1H, J = 8.4 Hz); 13C NMR (CDCl$_3$) δ 54.8, 109.4, 122.8, 137.9, 142.7, 163.7, 165.8. Anal. Calcd for C$_7$H$_6$BrNO$_3$ (232.0): C, 36.26; H, 2.61; N, 6.04. Found: C, 36.23; H, 2.67; N, 6.21 %.

**Methyl 2-bromo-6-methoxynicotinate (10).** To a stirred solution of 2-bromo-6-methoxynicotinic acid 16 (1 g, 4.3 mmol) and 3 drops of DMF in dry CH$_2$Cl$_2$ (20 ml) was slowly added oxalyl chloride (462 µL, 5.4 mmol) at 0°C. The mixture was stirred at room temperature for 1 h and solvents were removed in vacuo. Dry methanol (30 ml) was then added at 0°C and the resulting mixture was stirred for 2 h at room temperature. Methanol was removed in vacuo and CH$_2$Cl$_2$ (30 ml) was added. The organic phase was washed with water (3x15 ml), dried (MgSO$_4$) and concentrated in vacuo to give the ester 10 (973 mg, 92 %) as white solid, mp= 54-55 °C; IR (KBr) υ 1247, 1586, 1724, 2952; 1H NMR (CDCl$_3$) δ 3.85 (s, 3H), 3.93 (s, 3H), 6.93 (d, 1H, J = 8.5 Hz), 7.99 (d, 1H, J = 8.5 Hz); 13C NMR (CDCl$_3$) δ 42.5, 54.7, 109.3, 121.1, 139.7, 142.4, 164.5, 165.1. Anal. Calcd for C$_8$H$_8$BrNO$_3$ (246.0): C, 39.05; H, 3.28; N, 5.69. Found: C, 39.11; H, 3.32; N, 5.71 %.

**Preparation of the cyclopenta[b]pyridin-2,5-dione (1) (E)-Methyl 6-methoxy-2-(3-methoxy-3-oxoprop-1-enyl)nicotinate (9).** A degassed mixture of methyl 2-bromo-6-methoxynicotinate (10, 0.30 g, 1.2 mmol), methyl acrylate (293 µl, 3.3 mmol), allylpalladium chloride dimer Pd$_2$(allyl)$_2$Cl$_2$ (24 mg, 0.065 mmol), P(o-Tol)$_3$ (40 mg, 0.13 mmol), Na$_2$CO$_3$ (320 mg, 3.0 mmol), toluene (2.53 ml) and dimethyl acetamide DMA (0.84 ml) was heated in a sealed tube at 115°C for 5 h. The reaction mixture was filtrated though Celite and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc /
Petrol 3:7) to give 9 (296 mg, 82%) as a yellow solid, mp= 112-113°C; IR (KBr) ν 1132, 1243, 1482, 1589, 1737, 2961, 3012, 3097; 1H NMR (CDCl3) δ 3.81 (s, 3H), 3.90 (s, 3H), 3.99 (s, 3H), 6.72 (d, 1H, J = 8.6 Hz), 7.11 (d, 1H, J = 15.2 Hz), 8.11 (d, 1H, J = 8.1 Hz), 8.57 (d, 1H, J=15.2 Hz); 13C NMR (CDCl3) δ 52.2, 52.8, 54.2, 112.4, 119.7, 125.2, 140.9, 141.8, 152.8, 164.9, 166.5, 167.6; Anal. Calcd for C12H13NO5 (251.2): C, 57.37; H, 5.22; N, 5.58. Found: C, 57.43; H, 5.34; N, 5.61 %.

Methyl 6-methoxy-2-(3-methoxy-3-oxopropyl)nicotinate (17). A degassed suspension of 10 % Pd/C (60 mg, 0.06 mmol) in a solution of 9 (150 mg, 0.6 mmol) in MeOH (10 ml) was vigorously stirred for 3 h at room temperature under H2 (1 bar). The reaction mixture was filtered though a short pad of Celite and concentrated in vacuo to give 17 (141 mg, 93 %) as a yellow liquid; IR (KBr) ν 1021, 1248, 1595, 1723, 2962; 1H NMR (CDCl3) δ 2.77 (t, 2H, J = 7.0 Hz), 3.47 (t, 2H, J = 7.0 Hz), 3.63 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 6.53 (d, 1H, J = 8.7 Hz), 8.06 (d, 1H, J = 8.7 Hz); 13C NMR (CDCl3) δ 30.2, 30.7, 50.4, 52.6, 106.9, 116.6, 140.4, 159.9? 163.8, 165.5, 172.9; Anal. Calcd for C12H15NO5 (253.2): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.75; H, 6.04; N, 5.66 %.

Methyl 2-methoxy-5-oxo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (18). Sodium methoxide (81 mg, 1.5 mmol) in THF (5 ml) was added to a solution of 17 (250 mg, 1 mmol) in dry THF (8 ml) under N2 and the mixture was refluxed for 2 h. The pH was then adjusted to 5 by adding aq. Na2CO3 (10%, 5 ml), sat. aq. NH4Cl (5 ml), dried (MgSO4) and concentrated in vacuo. The crude product was purified by chromatography on silica gel (EtOAc / petrol 3:7) to give 18 (166 mg, 75 %) as a beige solid, mp= 81-82 °C; IR (KBr) ν 1021, 1250, 1439, 1595, 1736, 2960; 1H NMR (CDCl3) δ 3.29-3.31 (m, 1H), 3.45-3.50 (m, 1H), 3.70-3.74 (m, 1H), 3.73 (s, 3H), 4.00 (s, 3H), 6.68 (d, 1H, J = 8.7 Hz), 7.82 (d, 1H, J= 8.7 Hz); 13C NMR (CDCl3) δ 33.3, 53.1, 53.2, 54.9, 112.2, 123.3, 135.1, 169.7, 169.8, 175.1, 196.5.

6,7-Dihydro-1H-cyclopenta[b]pyridine-2,5-dione (1). A solution of 18 (100 mg, 0.45 mmol) in aq. HCl (5 M, 2 ml) was refluxed for 3 h. The mixture was cooled to room temperature and the pH was adjusted to 5 by adding aq. K2CO3 (2 M). The product was extracted with EtOAc (5x15mL). The combined organic layers were dried (MgSO4), concentrated in vacuo to give 1 (56 mg, 84 %) as a beige solid, mp> 260°C; IR (KBr) ν 3085, 2924, 1675-1653, 1427, 1105; 1H NMR (DMSO) δ 2.56 (m, 2H), 2.94 (t, 2H, J = 5.1 Hz), 6.31 (d, 1H, J = 9.4 Hz), 7.58 (d, 1H, J = 9.4 Hz), 12.6 (s, 1H); 13C NMR (DMSO) δ 24.5, 34.7, 116.3, 119.2, 134.1, 164.1, 169.5, 199.3; Anal. Calcd for C8H7NO2 (149.1): C, 64.43; H, 4.73; N, 9.39. Found: C, 64.42; H, 4.83; N, 9.23 %.
References and Notes

1. Fossa, P.; Menozzi, G.; Dorigo, P.; Floreani, M.; Mosti, L. *Bioorg. Med. Chem.* **2003**, *11*, 4749. The authors reported that cyclopenta[b]pyridin-2,5-dione is able to increase atrial contractility to an extent which is significantly higher than of Milrinone. Cyclopenta[b]pyridin-2,5-dione is similar to Milrinone in its pharmacological action and in its activity. The positive inotropic effect exerted is related to an increase of cAMP levels obtained through inhibition of cGMP-inhibited cAMP phosphodiesterase (PDE) called Type 3 (PDE3). The maximal inhibition of cyclopenta[b]pyridin-2,5-dione against PDE3 being 81.93±0.29% versus 100% of Milrinone.


5. Hirokawa and co-workers (Hirokawa, Y.; Horijawa, T.; Kato, S. *Chem. Pharm. Bull.* **2000**, *48*, 1847-1853 previously reported that the regioselective displacement of a chlorine from methyl 2,6-dichloronicotinate with sodium methoxide is more effective using MeOH as solvent leading to methyl 2-chloro-6-methoxychloroniconinate as the major isomer (7:3 ratio).

6. Above -50°C the C-3 lithio-anion was degraded.