A Facile and Efficient Synthesis of Dronedarone Hydrochloride

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Received November 15, 2013, Accepted March 7, 2014

A facile and efficient synthesis of dronedarone hydrochloride starting from commercially available 4-nitrophenol is described. This approach features a tandem-type synthesis of 3-carbonylated benzofuran involving cyclization of 2-ethynylphenol followed by CO₂ fixation at the 3-position of the benzofuran ring mediated by potassium carbonate without the addition of any transition metal catalyst.

Key Words : Dronedarone, Tandem-type synthesis, Cyclization, CO₂ fixation

Introduction

Since its discovery in 1990, dronedarone 1, a modified analogue of amiodarone 2 which is used as an antiarrhythmic drug, has attracted wide attention because of its superiorities in safety and tolerance compared with hyprotic drug, has attracted wide attention because of its

A facile and efficient synthesis of dronedarone hydrochloride starting from commercially available 4-nitrophenol is described. This approach features a tandem-type synthesis of 3-carbonylated benzofuran involving cyclization of 2-ethynylphenol followed by CO₂ fixation at the 3-position of the benzofuran ring mediated by potassium carbonate without the addition of any transition metal catalyst.

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Experimental

Materials and Methods. THF and 2-methyl tetrahydrofuran were distilled from sodium/benzophenone and DMF from calcium hydride under reduced pressure. Other reagents were obtained from commercial sources and were used as received. All melting points were measured on a WRS-1B digital melting-point apparatus and were uncorrected. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer in CDCl₃, using tetramethylsilane (TMS) and CDCl₃ (δ 7.26 ppm) as internal standards. J values were given in Hertz. Mass spectra was recorded on a Waters Quattro Micromass instrument using electrospray ionization techniques.

Preparation of 2-Iodo-4-nitrophenyl Acetate (4). A solution of acetic anhydride (4.2 mmol, 0.43 g) containing catalytic amount of pyridine were added dropwise to a solution of 3 (3.8 mmol, 1.0 g) in anhydrous THF (25 mL) at 0 °C. After being stirred for 4 h at room temperature, the solvent was removed under reduced pressure. The residue was diluted with AcOEt (25 mL) and the water (25 mL) was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic phase was washed with brine, dried over Na₂SO₄ and evaporated in vacuo.

Preparation of 2-(Hex-1-yn-1-yl)-4-nitrophenyl Acetate (5). To a solution of 4 (0.65 mmol, 0.20 g) and Et₃N (4.2 mmol, 0.6 mL) in anhydrous THF (6 mL) was added Pd(PPh₃)₄ (0.01 mmol, 0.012 g) and 1-hexyne (0.98 mmol, 0.08 g) at room temperature. After being stirred for 10 min, Cul (0.02 mmol, 0.04 g) was added and the resulting mixture was stirred for 7 h at 25 °C. To the mixture was added AcOEt (10 mL) and H₂O (10 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined

Figure 1. The structures of dronedarone (1) and amiodarone (2).
organic phase was washed with brine, dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by chromatography on a silica gel column (AcOEt/PE = 1/10) to afford 5 (0.14 g, 81%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 0.94 (t, J = 7.2 Hz, 3H), 1.45-1.51 (m, 2H), 1.58-1.61 (m, 2H), 2.36 (s, 3H), 2.43 (t, J = 7.2 Hz, 2H), 7.22 (d, J = 8.8 Hz, 1H), 8.12 (dd, JJ = 2.8 Hz, J₂ = 8.8 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 13.54, 19.18, 20.76, 21.90, 30.44, 73.91, 98.60, 119.80, 123.13, 123.63, 128.46, 145.34, 156.05, 167.89. HRMS-ESI: m/z calcd. for C₁₃H₁₂NO₃·H₂O: 218.0895; found: 218.0898.

Preparation of 2-(Hex-1-yn-1-yl)-4-nitrophenol (6). To a solution of 5 (0.46 mmol, 0.12 g) in MeOH (14 mL) was added hydrazine monohydrate (0.68 mmol, 0.032 mL). After being stirred for 10 min, the mixture was adjusted pH to 7 with dilute HCl. After evaporating the solvent, the residue was purified by chromatography on a silica gel column (AcOEt/PE = 1/5) to afford 6 (0.086 g, 85%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 0.95 (t, J = 7.6 Hz, 3H), 1.40-1.46 (m, 2H), 1.71-1.78 (m, 2H), 2.78 (t, J = 7.6 Hz, 3H), 6.51 (bs, 1H), 7.44 (d, J = 9.2 Hz, 1H), 8.12 (dd, J₁ = 2.4 Hz, J₂ = 8.8 Hz, 1H), 8.39 (d, J = 2.4 Hz, 1H). ¹³C NMR (CDCl₃) δ 13.72, 19.18, 22.23, 28.15, 29.46, 65.55, 102.63, 110.88, 116.61, 119.16, 129.42, 143.98, 157.98. HRMS-ESI: m/z calcd. for C₁₂H₁₀NO₃: 218.0895; found: 219.0898.

Preparation of 2-Butyl-5-nitrobenzofuran-3-carboxylic Acid (7). A mixture of 6 (0.37 mmol, 0.08 g) and anhydrous K₂CO₃ (3.7 mmol, 0.5 g) in DMF (5 mL) was stirred under 10 kg/cm² pressure of CO₂ at 65 °C for 24 h. After the reaction was completed, the reaction mixture was added 2 M aqueous HCl followed by water. The organic phase was washed with brine, dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by chromatography on a silica gel column (AcOEt/MeOH = 5/1) to afford 7 (0.10 g, 63%) as a white solid. mp 251.6-252.3 °C (lit.¹ mp 206.2-206.8 °C). ¹H NMR (400 MHz, DMSO-d₆) δ 0.89 (t, J = 7.6 Hz, 3H), 1.30-1.34 (m, 2H), 1.70-1.75 (m, 2H), 3.13 (t, J = 7.6 Hz, 2H), 7.85 (d, J = 9 Hz, 1H), 8.24 (dd, J₁ = 2.4 Hz, J₂ = 9 Hz, 1H), 8.70 (d, J = 2.4 Hz, 1H).

Preparation of 2-Butyl-5-(methylsulfonylamido)benzo-furan-3-carboxylic Acid (9). A mixture of 7 (2.4 mmol, 0.5 g) and 50 mg of 10% Pd/C in 2-methyl tetrahydrofuran (15 mL) was stirred under 5 kg/m² pressure of hydrogen at room temperature for 5 h. The mixture was filtered and the filtrate was used directly for the next mesylation reaction. Pyridine (0.22 g, 2.8 mmol) and methanesulfonyl chloride (2.3 mmol, 0.26 g) were added successively to the filtrate at 0 °C. The reaction mixture was stirred for 5 h at 0 °C. After completion of the reaction, the reaction mass was washed with a 10% aqueous HCl followed by water. The organic phase was dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (AcOEt/MeOH = 5/1) to afford 9 (0.40 g, 69%) as a white solid. mp 251.6-252.5 °C (lit.² mp 251.9-252.2 °C). ¹H NMR (400 MHz, DMSO-d₆) δ 0.87 (t, J = 7.6 Hz, 3H), 1.30-1.35 (m, 2H), 1.66-1.70 (m, 2H), 2.91 (s, 3H), 3.12 (t, J = 7.6 Hz, 2H), 7.18-7.21 (m, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 2.4 Hz, 1H), 9.61 (s, 1H), 12.98 (s, 1H).

Preparation of N-(2-Butyl-3-(4-(3-(dibutylamino)prop- oxy)benzoyl)benzofuran-5-yl)methanesulfonyamide (10). To a solution of 9 (5.0 mmol, 1.55 g) in trifluoroacetic anhydride (100 mmol, 21.0 g) was added N-(3-phenoxypyrrolyl)-N-butyrobutan-1-amine (5.0 mmol, 1.32 g) and polyphosphoric acid (5.0 mmol, 1.69 g). The mixture was refluxed for 15 h and then the solvents were evaporated. The residue was dissolved in CH₂Cl₂ (20 mL), and then the mixture was adjusted pH to 5 with 2 M aqueous NaOH. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic phase was washed with brine, dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by chromatography on a silica gel column (AcOEt/PE = 1/2) to afford 10 (2.27 g, 82%) as a white solid. mp 65.5-66.6 °C (lit.6 mp 65.3 °C). ¹H NMR (400 MHz, CDCl₃) δ 0.86-0.90 (m, 9H), 1.27-1.31 (m, 6H), 1.42-1.47 (m, 4H), 1.69-1.73 (m, 2H), 1.93-1.96 (m, 2H), 2.44 (t, J = 7.2 Hz, 4H), 2.64 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.90 (s, 3H), 4.07 (t, J = 5.6 Hz, 2H), 7.05-7.78 (m, 7H).

Results and Discussion

Our synthetic route to 1 starting from 4-nitrophenol was outlined in Scheme 1. The iodination of 4-nitrophenol gave 2-ido-4-nitrophenol (3), which was subjected to esterification with acetic anhydride to afford phenyl acetate 4 in almost quantitative yield. The Sonogashira coupling of 4 and 1-hexyne worked well at 25 °C for 7 h in anhydrous THF in the presence of Pd(PPh₃)₄/Cul/Et₃N in 81% yield. The subsequent hydrolysis of the coupling product 5 with hydrazine monohydrate in methanol gave the desired 2-ethynylphenol 6 in 89% yield.²⁷

With 6 in hand, the next task is to prepare the intermediate
3-carbonylated benzofuran 7, a key precursor to 1. The benzofuran ring can be constructed by ring closing reaction of 2-ethylphenol derivatives, but subsequent functionalization at the 3-position of the benzofuran ring is generally realized in the presence of transition metal catalyst. Gratifyingly, the sequential cyclization-carboxylation of 6 was carried out following Inamoto’s procedure to give the expected 7 in 63% yield by using 10 eq of anhydrous potassium carbonate under 10 kg/cm² pressure of CO₂ at 65 °C for 24 h (Table 1, entries 1).²⁸ To enhance the yield of this reaction, the reaction conditions (base, solvent, temperature and the pressure of CO₂) were thoroughly screened. Increasing the pressure of CO₂ to 20 kg/cm² or raising the reaction temperature from 65 °C to 80 °C had little effect on the reaction efficiency (entries 2, 4). However, decreasing the pressure of CO₂ to 5 kg/cm² or the reaction temperature to 50 °C resulted in much decreased yield of 7 (entries 3, 5). No significant improvement in yield was observed by utilizing an increased amount of potassium carbonate (entries 6), but use of a decreased amount of potassium carbonate caused a significant drop in yield (entries 7). We also screened solvents systems. No expected product was obtained with 1,4-dioxane, acetonitrile or toluene (entries 8-10). We subsequently observed that the cyclization in the presence of sodium hydride or sodium tert-butoxide exhibited lower yields compared to the reaction with potassium carbonate (entries 11, 12).

Table 1. Optimization of reaction conditions of 6a

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<th>Entry</th>
<th>Base (eq)</th>
<th>Temp (°C)</th>
<th>CO₂ kg/cm²</th>
<th>Solvent</th>
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</table>

All reactions were carried out in the presence of a base under the CO₂ atmosphere for 24 h. Isolation yields.

In conclusion, we have developed an efficient approach towards dronedarone hydrochloride (1) starting from commercially available 4-nitrophenol by using a sequential cyclization-carboxylation to form 3-carbonylated benzofuran from 2-ethylphenol mediated by potassium carbonate without the addition of any transition metal catalyst as the key step. This route could be applied in large scale synthesis of 1 and its analogs.

Acknowledgments. Publication cost of this paper was supported by the Korean Chemical Society.

References