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A Facile and Efficient Synthesis of Dronedarone Hydrochloride

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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 CO_2 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, CO_2 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 **2** (Figure 1).[1-5] Although marked advances in the synthesis of **1** in the last 20 years have been achieved,[6-23] the synthetic strategy developed by the Sanofi company,[6] *via* the intermediate 2-butyl-3-(4-methoxybenzoyl)-5-nitrobenzofuran, is still utilized with minor improvements, for large scale syntheses. However, the mutagenic property of the intermediate negates all of its advantages.[8] In addition, another serious limitation in this procedure is the formation of considerable amount of aluminum hydroxide in the Friedel-Craft acylation. Very recently, Richter *et al*.[22] and our group[23] independently reported an efficient process to **1** through a key intermediate 3-carbonylated benzofuran **9** which avoided the use of the mutagenic intermediate. However, the limitations of this procedure for large-scale preparation include (1) the use of expensive 3-oxoheptanoate in the construction of **9**, (2) the pollution of aluminum hydroxide in the Friedel-Craft acylation, and (3) the difficulty in the purification of **10**, *etc*. As part of our continuous program on the development of synthesis of **1**, herein we report an efficient and convenient approach towards **1** by using a sequential cyclization-carboxylation of 2-ethynylphenol **6** followed by CO_2 fixation at the 3-position of the benzofuran ring to form 3-carbonylated benzofuran **7** mediated by potassium carbonate without the addition of any transition metal catalyst as a key step.

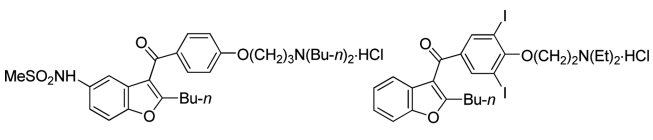

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Figure 1. The structures of dronedarone (**1**) and amiodarone (**2**).

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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, using tetramethylsilane (TMS) and $CDCl_3$ (^{13}C δ 77.0) 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 Na_2SO_4 and evaporated *in vacuo*. The residue was purified by chromatography on a silica gel column (AcOEt/PE = 1/10) to afford **12** (1.14 g, 98%) as a white solid. mp 68.2-68.4 °C (lit.[24] mp 68 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.26 (d, J = 8.8 Hz, 1H), 8.24 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 8.70 (d, J = 2.8 Hz, 1H).

Preparation of 2-(Hex-1-yn-1-yl)-4-nitrophenyl Acetate (5). To a solution of **4** (0.65 mmol, 0.20 g) and Et_3N (4.2 mmol, 0.6 mL) in anhydrous THF (6 mL) was added $Pd(PPh_3)_4$ (0.01 mmol, 0.012 g) and 1-hexyne (0.98 mmol, 0.08 g) at room temperature. After being stirred for 10 min, CuI (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 H_2O (10 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined

organic phase was washed with brine, dried over Na_2SO_4 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H) , 8.30 (d, J = 2.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.54, 19.18, 20.76, 21.90, 30.44, 73.91, 98.60, 119.80, 123.11, 123.63, 128.46, 145.34, 156.05, 167.89. HRMS-ESI: *m/z* $[M\text{-}CH_3CO]^-$ calcd. for $C_{12}H_{12}NO_3$: 218.0817; found: 218.0818.

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. ^{1}H NMR (400 MHz, $CDCl_3$) 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, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H) , 8.39 (d, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) 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, 157.56. HRMS-ESI: *m/z* $[M\text{-}H]^-$ calcd for $C_{12}H_{13}NO_3$: 219.0895; 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 K_2CO_3 (3.7 mmol, 0.5 g) in DMF (5 mL) was stirred under 10 kg/cm^2 pressure of CO_2 at 65 °C for 24 h. After the reaction was completed, the reaction mixture was added 2 M HCl (15 mL) and extracted with AcOEt. The combined organic phase was washed with brine, dried over Na_2SO_4 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 206.2-206.8 °C (lit.[25] mp 207 °C). ^{1}H NMR (400 MHz, DMSO-d_6) 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, J_1 = 2.4 Hz, J_2 = 9 Hz, 1H), 8.70 (d, J = 2.4 Hz, 1H).

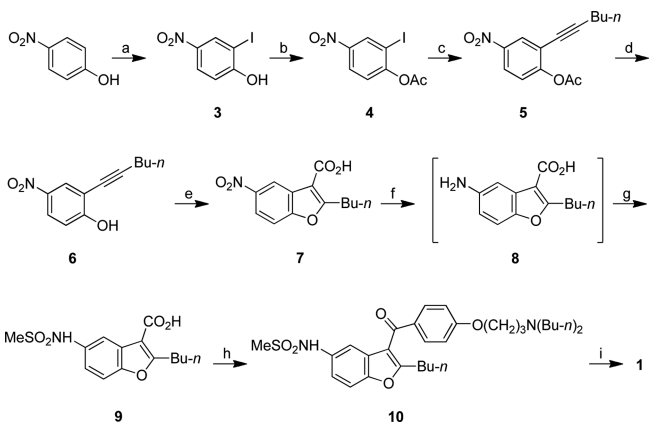
Preparation of 2-Butyl-5-(methylsulfonamido)benzofuran-3-carboxylic Acid (9). A mixture of **7** (2.4 mmol, 0.5 g) and 50 mg of 10% Pd/C in 2-methyl tetrahydrofuran (15 mL) was stirred under 5 kg/m^2 pressure of hydrogen at room temperature for 5 h. The mixture was filtered and the filtrate was used 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 Na_2SO_4 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 °C (lit.[22] mp 251.9-252.2 °C). ^{1}H NMR (400 MHz, DMSO-d_6) 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)propoxy)benzoyl)benzofuran-5-yl)methanesulfonamide (10). To a solution of **9** (5.0 mmol, 1.55 g) in trifluoroacetic anhydride (100 mmol, 21.0 g) was added *N*-(3-phenoxypropyl)-*N*-butylbutan-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 CH_2Cl_2 (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 CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4 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 °C (lit.[6] mp 65.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 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-iodo-4-nitrophenol (**3**),[26] 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 $Pd(PPh_3)_4$/CuI/Et_3N 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



Scheme 1. *Reagents and conditions*: (a) I_2, KI, $NH_3{\cdot}H_2O$, H_2O, 20% HCl, 0 to 5 °C, 24 h, 98%. (b) Ac_2O, Pyridine, THF, 0 to 25 °C, 4 h, 98%. (c) $Pd(PPh_3)_4$, CuI, Et_3N, 1-hexyne, THF, 25 °C, 7 h, 81%. (d) $NH_2NH_2{\cdot}H_2O$, MeOH, 25 °C, 30 min, 89%. (e) K_2CO_3, CO_2, DMF, 65 °C, 24 h, 63%. (f) 10% Pd/C, H_2, 2-MeTHF, 25 °C, 5 h. (g) MsCl, pyridine, 2-MeTHF, 0 °C, 5 h, 69% (from 7 to 9). (h) $PhO(CH_2)_3N(n\text{-}Bu)_2$, PPA, $(CF_3CO)_2O$, reflux, 15 h, 82%. (i) $HCl{\cdot}Et_2O$, acetone, –20 °C, 1 h, 89%.

Table 1. Optimization of reaction conditions of **6a**

Entry	Base (eq)	Temp (°C)	CO_2 (kg/cm^2)	Solvent	Yield (%)[b]
1	K_2CO_3 (10)	65	10	DMF	63
2	K_2CO_3 (10)	65	20	DMF	64
3	K_2CO_3 (10)	65	5	DMF	25
4	K_2CO_3 (10)	80	10	DMF	62
5	K_2CO_3 (10)	50	10	DMF	22
6	K_2CO_3 (20)	65	10	DMF	63
7	K_2CO_3 (5)	65	10	DMF	31
8	K_2CO_3 (10)	65	10	1,4-dioxane	0
9	K_2CO_3 (10)	65	10	MeCN	0
10	K_2CO_3 (10)	65	10	toluene	0
11	NaH (10)	65	10	DMF	53
12	*t*-BuONa (10)	65	10	DMF	42

[a]All reactions were carried out in the presence of a base under the CO_2 atmosphere for 24 h. [b]Isolation yields.

3-carbonylated benzofuran **7**, a key precursor to **1**. The benzofuran ring can be constructed by ring closing reaction of 2-ethynylphenol 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/cm^2 pressure of CO_2 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 CO_2) were thoroughly screened. Increasing the pressure of CO_2 to 20 kg/cm^2 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 CO_2 to 5 kg/cm^2 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 *t*-butoxide exhibited lower yields compared to the reaction with potassium carbonate (entries 11, 12).

The reduction of **7** was performed by using 10% palladium over carbon as catalyst under 5 kg/cm^2 pressure of hydrogen in 2-methyl tetrahydrofuran at 65 °C for 5 h. After the catalyst was filtered off, the filtrate obtained was directly used for the next reaction, thereby circumventing a tedious work-up process and isolation step. Transformation of the resulting **8** into the mesylated product **9** was accomplished in 69% overall yield (from **7** to **9**) with methanesulfonyl chloride in the presence of pyridine at 0 °C for 5 h. The Friedel-Craft acylation of **9** with *N*-(3-phenoxypropyl)-*N*-butylbutan-1-amine gave the desired dronedarone free base **10** with an increase in the yield from 70% to 82% according to a modification of the known procedure.[23] After the completion of the reaction, dronedarone was readily converted into its hydrochloric acid salt **1**.[22]

Conclusion

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-cabonylated benzofuran from 2-ethynylphenol 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.

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