Convergent Synthesis of Dronedarone, an Antiarrhythmic Agent

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We have developed a convergent synthesis of dronedarone, an antiarrhythmic agent. The key steps of the process are the construction of a benzofuran skeleton by iodocyclization and the carbonylative Suzuki–Miyaura cross-coupling for biaryl ketone formation. This synthetic route required only eight steps from 2-amino-4-nitrophenol in 23% overall yield.

Key words  dronedarone; antiarrhythmic agent; iodocyclization; drug synthesis; convergent process

Atrial fibrillation is one of the most common types of arrhythmia, and is a disease of irregular and rapid heart rhythm. As atrial fibrillation may induce the formation of a thrombus at the atrium, it increases the risk of cardiogenic cerebral embolism. To maintain normal sinus rhythm for the patients with atrial fibrillation, a controlled electric shock and drug therapy are used. Amiodarone (1; Fig. 1) is widely used as a class III antiarrhythmic agent and is an effective multichannel blocker. However, amiodarone has iodo-substituents and is lipophilic, it causes thyroid dysfunction and has a long lifetime up to 100 d that is accompanied by its accumulation in adipose tissue and other organs as non-cardiovascular adverse effects.1–3) Amiodarone (1) is a drug-discovery point of view, those processes lack the flexibility of the 2-position in benzo[b]furan because this position was defined at the first stage of the synthesis. Therefore, an alternative route toward 2 that contains the introduction of a variety of substituents at the 2-position on benzo[b]furan at later stage was needed.

We have already developed a versatile construction of 3-iodobenzo[b]furans by electrophilic iodocyclization of ethoxyethyl ethers to alkynes14–16) (Chart 2). Advantages of our synthetic method for benzo[b]furan are as follows: (1) ethoxyethyl ether serves as not only protecting group for the preparation of precursors, but also as a good leaving group for iodocyclization; (2) a wide variety of substituents such as aryl, alkyl, and amide groups at the 2-position on benzo[b]furans is allowed; (3) the iodine moiety after cyclization can be easily transformed to other substituents by transition metal-catalyzed cross-coupling reactions; and (4) this iodocyclization is completed within 10 min at room temperature. Therefore, we considered that our methodology could be adapted for the synthesis of dronedarone (2) having a 2-alkylbenzo[b]furan core. Our synthetic plan is shown in Chart 3; biaryl ketone of 2 would be formed at the last stage by carbynylative Suzuki–Miyaura cross-coupling17) with 3-iodobenzo[b]furan 6 and arylboronic acid 7 aiming for a convergent process, and 6 would be derived from alkyn 8 by our developed iodocyclization protocol. Aryl alkyn 8 would be formed by Sonogashira coupling of corresponding iodoarene 9 and 1-hexyne. The iodo moiety of 9 was expected to be accessible from inexpensive 4-nitro-2-aminophenol (10) by a formation of the aryldiazonium salt followed by iodination.

Fig. 1. Structures of Antiarrhythmic Agents

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Results and Discussion

Our synthetic procedure is shown in Chart 4. Aryldiazonium salt formation of 10 and subsequent iodination using potassium iodide afforded iodoarene 11.18,19 The conversion of nitrophenol 11 to 9 was accomplished by a three-step sequence of reduction, N-mesylation, and bis-acetal formation in good yield. Sonogashira cross-coupling of 9 with the terminal alkyne provided 8, a precursor of electrophilic cyclization. According to our iodocyclization protocol,14 exposure of alkyne 8 to the bis(2,4,6-collidine)iodonium hexafluorophosphate [(coll)2PF6]-BF3·OEt2 combination afforded benzo[b]furan 6 along with its N-ethoxyethyl product. The mixture was then directly treated with hydrochloric acid for hydrolysis to converge 6, a left building block of 2, as a sole product in 77% yield over two steps.

Arylboronic acid 7, a right segment of 2, was prepared by a four-step sequence: nucleophilic ring-opening reaction of oxetane 12 with dibutylamine formed aminoalcohol 13.20 The transformation of the resulting hydroxyl group to the chloro substituent by thionyl chloride provided 14, and nucleophilic substitution with p-bromophenol constructed alkyl aryl ether 15. Finally, a dihydroxyboryl group was introduced by halogen-lithium exchange reaction of 15 followed by boronic ester formation and subsequent hydrolysis to afford 7.

At the last stage, we studied the carbonylative Suzuki–Miyaura cross-coupling reaction of 6 and 7 for biaryl ketone formation aiming toward dronedarone (2). After several examinations, we have found that employing the classical reaction conditions produced 2 in 57% yield without forming a biaryl, a direct coupling product with 6 and 7.17 The 1H- and 13C-NMR spectra of synthetic 2 agreed with those of the reported data.21 Now, the synthesis of 2 was completed in a convergent manner, and our synthetic route of 2 required only linear eight steps from commercially available material 10 in 23% overall yield.

In summary, we have developed a convergent synthetic process of 2, that was characterized by iodocyclization and carbonylative Suzuki–Miyaura cross-coupling reaction as key steps. In our process, setting the substituent at the 2-position on benzo[b]furan occurred at a later stage than in the previously reported route of 2. Thus, a variety of analogous compounds of 2 whose substituent differed at this position would be easily prepared from 9 in four steps. In addition, this convergent synthesis was achieved in eight steps from 10 in 23% overall yield. Therefore, we envisage that this synthetic route for 2 will be useful for the research and development of new antiarrhythmic agents.

Experimental

General Remarks Melting points were measured by a Yanagimoto micro melting point apparatus. IR spectra were measured on a PerkinElmer Spectrum 100 FT-IR spectrom-
Reagents and conditions: (a) NaNO₂, 30% H₂SO₄, DMSO, 0°C, 1h; then KI, r.t., 12h, 77%; (b) i) SnCl₂, EtOH, 70°C, 15h; ii) MeCl, pyridine, CH₂Cl₂, r.t., 15h; (iii) ethyl vinyl ether, PPTS, CH₂Cl₂, r.t., 24h, 72% in 3 steps; (c) 1-bromobutane, PdCl₂, Ph₃P, CuI, Et₃N, CH₂CN, r.t., 23h, 95%; (d) i) t-BuLi, THF, -78°C, 45min then MeCl, r.t., 23h; then sat. NH₄Cl aq., r.t., 30min, 60%; (e) MsCl, CH₂Cl₂, r.t., 10min; (f) 10% HCl, THF, MeOH, 60°C, 30min, 77% in 2 steps; (g) Bu₂NI, THF, -78°C, 45 min; then Bi(O₂Pr)₃, r.t., 23h; then sat. NH₄Cl aq., r.t., 30min, 46%; (h) PdCl₂(PPh₃)₂, K₂CO₃, CO (1 atm), anisole, 80°C, 23h, 57%.

Chart 4. Synthesis of Dronedarone (2)

- 2-Iodo-4-nitrophenol (11) According to the modified procedures by Dai and Lai [9] and Zhu et al. [8] to a solution of 2-amino-4-nitrophenol (10) (14.8 g, 96.0 mmol) in 30% H₂SO₄ (500 mL) and dimethyl sulfoxide (DMSO) (500 mL) was added a solution of NaN₃ (9.94 g, 144 mmol) in water (50 mL) at 0°C. The reaction mixture was stirred at the same temperature for 1 h, after which a solution of HI (47.8 g, 288 mmol) in water (50 mL) at 0°C. After reaction was completed, the mixture was neutralized with 5% aqueous solution of Na₂CO₃ at 0°C. The mixture was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo to afford crude 4-aminoo-2-iodophenol (16.5 g), which was used for next reaction without further purification.

To a mixture of crude 4-aminoo-2-iodophenol (16.5 g) in pyridine (6.23 mL, 77.0 mmol) and CH₂Cl₂ (175 mL) was added MsCl (5.96 mL, 77.0 mmol) at 0°C, and the mixture was stirred at r.t. for 15 h. After reaction was completed, the mixture was quenched with aqueous 6 M NaOH (700 mL), and was extracted with EtOAc. The organic layer was then added with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo to obtain crude 4-(4-hydroxy-3-iodophenyl)methanesulfonylamine (22.0 g), which was used for next reaction without further purification.

To a mixture of crude N-(4-(4-hydroxy-3-iodophenyl))methanesulfonylamine (22.0 g) and pyridinium p-toluene sulfonate (PPTS) (1.76 g, 7.00 mmol) in dry CH₂Cl₂ (350 mL) was added ethyl vinyl ether (20.1 mL, 210 mmol) and stirred at r.t. for 24 h. After reaction was completed, the mixture was quenched with saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc=1:1 to give I (19.7 g, 77%) as yellow crystals. mp 84–86°C (hexane/EtOAc); IR νmax: 3479, 3020, 1602, 1524, 1341 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃): δ: 8.60 (d, J=2.4 Hz, 1H), 8.18 (dd, J=9.0, 2.7 Hz, 1H), 7.07 (d, J=9.0 Hz, 1H), 6.23 (brs, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ: 160.4, 141.9, 134.4, 126.1, 114.6, 84.5; HR-ESI-MS Calcd for C₁₃H₁₃NO₃ [M⁺H]⁺ 263.9163. Found 263.9164.
phy on silica gel eluting with hexane/EtOAc=3:1 to give 1:1 diastereomeric mixture of 9 (24.6 g, 72% in 3 steps) as a yellow oil. IR $\nu_{\text{max}}$ 2981, 1590, 1341, 1279, 1164 cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) δ: 7.78 (d, $J=2.4$ Hz, 1H), 7.30 (dd, $J=7.7$, 2.4 Hz, 1H), 7.04 (d, $J=8.7$ Hz, 1H), 5.52 (q, $J=6.0$ Hz, 1H), 5.47–5.40 (m, 1H), 3.87–3.52 (m, 4H), 2.98 (s, 3H), 1.58 (d, $J=5.1$ Hz, 3H), 1.30–1.16 (m, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ: 156.14, 156.12, 141.7, 141.6, 132.33, 132.28, 129.4, 115.3, 115.2, 100.6, 100.5, 87.52, 87.49, 84.9, 63.6, 63.1, 61.1, 39.7, 20.0, 19.9, 19.8, 15.1, 15.0; HR-ESI-MS Calcd for C$_9$H$_{17}$N$_2$O$_4$S [M+Na]$^+$ 480.3124. Found 480.3124.

$\text{N}$-(4-(1-Ethoxyethoxy)-3-(hex-1-yn-1-yl)phenyl)-N-(1-ethoxyethyl)methanesulfonamide (8) A mixture of 9 (2.29 g, 5.00 mmol), PdCl$_2$ (22.2 mg, 0.125 mmol), PPh$_3$ (0.656 mg, 0.250 mmol), CuI (34.3 mg, 0.180 mmol), Et$_2$N (2.09 mL, 15.0 mmol), and 1-hexyne (1.15 mL, 0.10 mmol) in dry CH$_2$CN (9.3 mL) was stirred at rt for 23 h. After reaction was completed, the mixture was quenched with aqueous 5% NH$_4$Cl. The residue was extracted with EtOAc, washed with brine, dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc=4:1 to give 1:1 diastereomeric mixture of 8 (1.95 g, 95%) as a brown oil. IR $\nu_{\text{max}}$ 2935, 2233, 1600, 1340, 1162 cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) δ: 7.36 (d, $J=2.4$ Hz, 1H), 7.21 (dd, $J=8.7$, 2.7 Hz, 1H), 7.03 (d, $J=8.7$ Hz, 1H), 5.53 (q, $J=6.0$ Hz, 1H), 5.46–5.40 (m, 1H), 3.90–3.53 (m, 4H), 2.97 (s, 3H), 2.45 (t, $J=6.9$ Hz, 2H), 1.64–1.44 (m, 7H), 1.29–1.15 (m, 9H), 0.95 (t, $J=7.2$ Hz, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ: 157.7, 157.6, 153.8, 135.7, 135.8, 131.83, 131.77, 128.4, 117.1, 117.0, 116.1, 100.7, 100.5, 95.3, 84.8, 76.0, 63.6, 61.4, 61.3, 39.7, 30.6, 21.8, 20.2, 20.1, 19.8, 19.3, 15.11, 15.08, 13.5; HR-ESI-MS Calcd for C$_9$H$_{17}$N$_2$O$_4$S [M+H]$^+$ 412.2152. Found 412.2148.

$\text{N}$-(2-Butyl-3-iodobenzofuran-5-yl)methanesulfonamide (6) To a mixture of 8 (0.823 g, 2.00 mmol) in dry CH$_2$Cl$_2$ (10.0 mL) was added [coll][PF$_6$] (0.206 g, 4.00 mmol) and BF$_3$·OEt$_2$ (0.494 mL, 4.00 mmol) at rt and was stirred for 10 min. After reaction was completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$ and saturated aqueous solution of Na$_2$SO$_4$. The mixture was extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo, which was used for next reaction without further purification.

This residue was solved in tetrahydrofuran (THF) (36 mL), MeOH (36 mL) and aqueous 10% HCl (36 mL), and the mixture was stirred at 60°C for 30 min. After reaction was completed, the mixture was extracted with EtOAc, washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc=3:1 to give 6 (0.606 g, 77% in 2 steps) as light green crystals. mp 101–102°C (hexane/EtOAc); IR $\nu_{\text{max}}$ 3371, 3255, 2960, 1619, 1583, 1342, 1152 cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) δ: 7.37 (d, $J=8.4$, 0.6 Hz, 1H), 7.25–7.19 (m, 2H), 7.06 (s, 1H), 3.02 (s, 3H), 2.85 (t, $J=7.8$ Hz, 2H), 1.78–1.67 (m, 2H), 1.40 (sxt, $J=7.5$, 2H), 0.96 (t, $J=7.5$ Hz, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$) δ: 160.9, 152.4, 132.14, 132.11, 119.9, 114.8, 111.8, 62.1, 38.9, 29.8, 27.7, 22.1, 13.7; HR-ESI-MS Calcd for C$_8$H$_{17}$I$_2$NO$_3$S [M+H]$^+$ 393.9968. Found 393.9975.

3-(Dibutylamino)propan-1-ol (13) According to the literature, 13 to a solution of oxetane (12) (4.88 mL, 75.0 mmol) and dibutylamine (25.5 mL, 150 mmol) in dry CH$_2$CN (75 mL) was added LiBF$_4$ (14.1 g, 150 mmol), and was stirred at r.t. for 4 h. After reaction was completed, the mixture was quenched with aqueous 36% NH$_4$Cl (300 mL). The mixture was extracted with EtOAc, washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo, and purified by distillation under reduced pressure (boiling point (bp) 97°C/24 mmHg) to give 13 (7.63 g, 54%) as a colorless oil. IR $\nu_{\text{max}}$ 2927, 2853 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) δ: 8.01–7.71
(brm, 2H), 6.82 (d, J=7.0 Hz, 2H), 3.93 (brs, 2H), 2.69 (brt, J=6.5 Hz, 2H), 2.48 (t, J=7.5 Hz, 4H), 1.94 (brquint, J=6.5 Hz, 4H), 1.47–1.40 (m, 4H), 1.25 (sext, J=7.5 Hz, 4H), 0.87 (t, J=7.5 Hz, 6H), 13C-NMR (125 MHz, CDCl3) δ: 160.9, 135.6, 129.4, 113.5, 65.6, 53.4, 52.8, 28.2, 26.1, 20.5, 13.9; HR-ESI-MS Calcd for C17H13BNNO3 [M+H]$: 308.2392. Found 308.2381.

N-(2-Butyl-3-(4-(3-(dibutylamino)propoxy)benzoyl)-benzofuran-5-yl)methanesulfonamide (Dronedarone, 2) According to the literature, a mixture of 6 (0.149 g, 0.380 mmol), 7 (0.128 g, 0.420 mmol), PdCl2(PPh3)2 (8.0 mg, 0.0114 mmol), and K2CO3 (0.158 g, 1.14 mmol) was filled with CO, and dry anisole (2.3 mL) was added. The mixture was vigorously stirred at 80°C for 23 h. After reaction was completed, the mixture was filtered through Celite. The filtrate was extracted with CH2Cl2 and CH3CN, washed with water followed by brine, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with CHCl3/MeOH=15:1 to give 2 (0.120 g, 57%) as a colorless oil. IR ν-max: 3369, 3257, 2960, 1725, 1639, 1600, 1572, 1538, 1460, 1401, 1339, 1255, 1156 cm$^{-1};$ 1H-NMR (300 MHz, CDCl3) δ: 7.81 (d, J=9.0 Hz, 2H), 7.48 (dd, J=8.4, 0.9 Hz, 1H), 7.30 (s, 1H), 7.29 (d, J=8.4 Hz, 1H), 6.95 (d, J=9.0 Hz, 2H), 4.10 (t, J=6.3 Hz, 2H), 2.92 (s, 3H), 2.85 (t, J=7.5 Hz, 2H), 2.62 (t, J=6.9 Hz, 2H), 2.44 (t, J=7.2 Hz, 4H), 1.96 (quint, J=6.9 Hz, 2H), 1.73 (quint, J=7.5 Hz, 2H), 1.48–1.23 (m, 10H), 0.89 (t, J=6.0 Hz, 6H), 0.87 (t, J=6.0 Hz, 3H), NH was not observed; 13C-NMR (75 MHz, CDCl3) δ: 190.3, 165.8, 163.2, 151.8, 132.4, 132.4, 131.2, 128.2, 120.2, 116.7, 115.5, 114.3, 111.8, 66.5, 53.9, 50.3, 39.0, 30.0, 29.1, 28.0, 26.9, 22.3, 20.7, 14.1, 13.6; HR-ESI-MS Calcd for C41H31BNO3 [M+H]$: 557.3044. Found 557.3026.

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Conflict of Interest The authors declare no conflict of interest.

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