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An alternative approach to synthesis of 2-*n*-butyl-5-nitrobenzofuran derivative: A key starting material for dronedarone hydrochloride

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Abstract. A practical synthesis of (2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxyphenyl)methanone, a key intermediate in the preparation of anti arrhythmic drug, is described. The commercially available 4-nitrophenol (**3**) is converted in five steps to 2-butyl-5-nitrobenzofuran (**9**) which upon Friedel–Crafts acylation with 4-methoxybenzoyl chloride followed by deprotection of methyl group gives (**2**).

Keywords. Fries rearrangement; selective α-bromination; cyclisation; Friedel–Crafts acylation.

1. Introduction

This report describes an alternative approach for the synthesis of (2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxyphenyl)methanone (**2**) (figure 1). This key functionalized scaffold is required for the preparation of dronedarone hydrochloride **1** (figure 1) which is anti arrhythmic drug. It is used for the treatment of atrial fibrillation and atrial flutter in patients whose hearts have either returned to normal rhythm or who undergo drug therapy or electric shock treatment to maintain normal rhythm.

There are several synthetic routes appeared in the literature for the preparation of **2**. Cambrex karlskoga *et al.*[1] (scheme 1) in 2009 reported for the preparation of **2** using 1-chloro-4-nitrobenzene and ethyl *N*-hydroxyacetimidate. Hydrolysis of ethyl *N*-4-nitrophenoxyacetimidate with HCl in acetonitrile gave *O*-(4-nitrophenyl)hydroxylamine, condensation and rearrangement of *O*-(4-nitrophenyl)hydroxylamine and 1-(4-hydroxyphenyl)heptane-1,3-dione afforded **2** in acetic acid via an *in situ* intermediate of 1-(4-hydroxyphenyl)-3-((4-nitrophenoxy)imino)heptan-1-one. Kretzschmar *et al.*[2] (scheme 2) in 2010 developed an alternative process commenced from 1-bromo-4-nitrobenzene and 1-(4-methoxyphenyl)ethanone oxime. 2-(2-hydroxy-5-nitrophenyl)-1-(4-methoxyphenyl)ethanone reacted with pentanoyl chloride gave 2-(2-(4-methoxyphenyl)-2-oxoethyl)-4-nitrophenyl pentanoate, cyclisation of 2-(2-(4-methoxyphenyl)-2-oxoethyl)-4-nitrophenyl pentanoate in the presence of tributylamine and unmodified molecular seives afforded (2-butyl-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone (**10**) and further deprotection of methyl group with tributylamine hydrochloride at 200°C furnished **2**. Gubin *et al.* (scheme 3) described another process in US5223510 patent. In this process, 4-nitrophenol was converted to 3-(bromomethyl)-4-nitrophenol in the presence of *para* formaldehyde, 50% aq. HBr and 36N H_2SO_4. Wittig reaction of 3-(bromomethyl)-4-nitrophenol with triphenylphosphine gave respective ylide and subsequent reaction with pentanoyl chloride in the presence of TEA produced 2-butyl-5-nitrobenzofuran (**9**). Acylation of 2-butyl-5-nitrobenzofuran with 4-methoxybenzoyl chloride using Lewis acid $SnCl_4$ afforded (2-butyl-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone (**10**) and demethylation of (2-butyl-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone with $AlCl_3$ gave **2**. All the above reported synthetic pathways presented certain draw backs such as usage of commercially not available reagents, vigorous conditions like deprotection at 200°C, preparation of moisture sensitive intermediate like ylide and expensive reagents usage such as $SnCl_4$. As a result of these limitations, an alternative approach to **2** was investigated to provide more rapid and convenient to access to this valuable synthetic intermediate[3–7], using inexpensive and commercially available raw materials.

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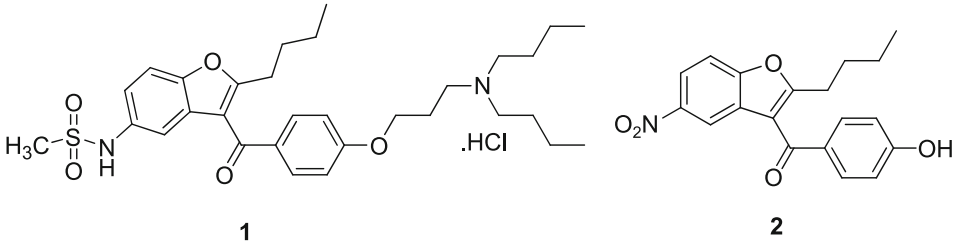
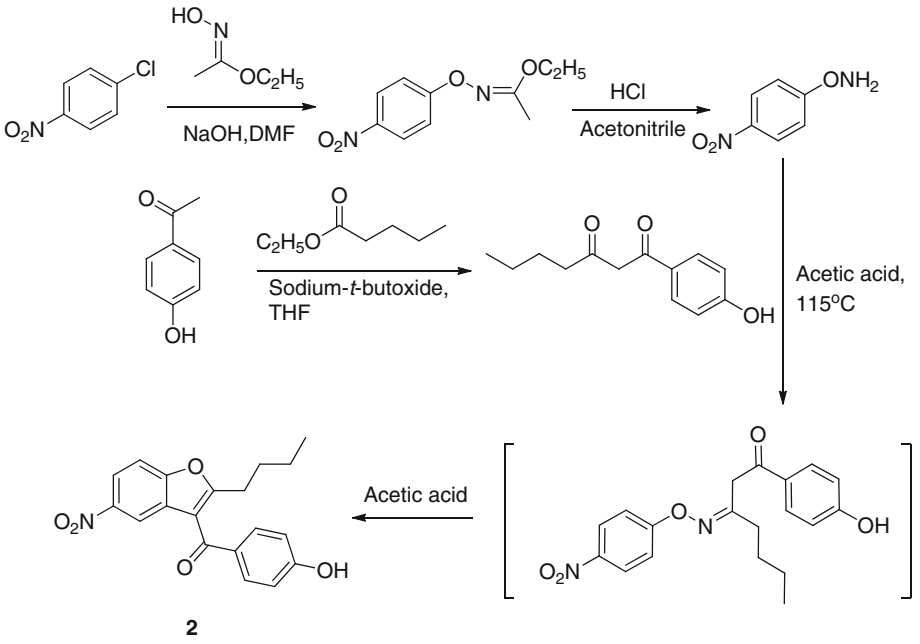
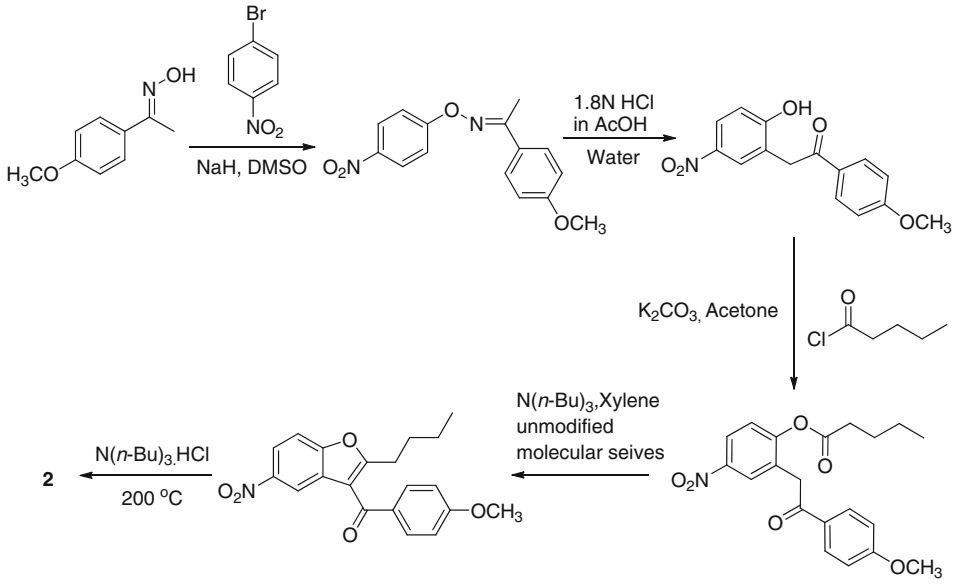


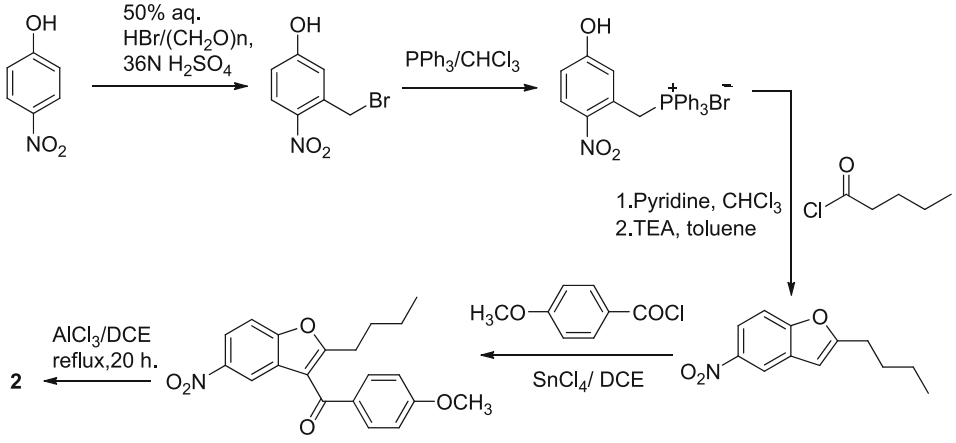
Figure 1. Structure of dronedarone hydrochloride **1** and key starting material **2**.



Scheme 1. Synthetic pathway reported by Cambrex Karlskoga *et al*.



Scheme 2. Synthetic pathway reported by Kretzschmar *et al.*



Scheme 3. Synthetic pathway reported by Gubin *et al.*

2. Experimental

The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-2000 at 400 and 500 MHz FT NMR spectrometer, the chemical shifts were reported in δ ppm relative to TMS. The FT–IR spectra were recorded in the solid state as KBr dispersion medium using Perkin Elimer 1650 FT-IR spectrophotometer. The mass analysis was performed on HP-5989A LC/MS spectrometer. Elemental analysis was performed using a Perkin-Elmer 2400 II CHN Analyzer. The solvents and reagents were used without further purification.

2.1 *4-nitrophenyl hexanoate* (**4**)

Hexanoyl chloride (106 g, 0.79 mol) was added dropwise to a stirred solution of 4-nitrophenol (**3**) (100 g, 0.72 mol), TEA (150 mL, 1.08 mol) in DCM (500 mL) at 0–5°C under nitrogen atmosphere maintained for 1 h. After completion of the reaction, water was added (500 mL), DCM (500 mL) and stirred for 15 min. Layers were separated and organic layer was washed with 5% aqueous HCl (400 mL) and water (100 mL). The obtained DCM layer was washed with 5% aqueous $NaHCO_3$ (400 mL) followed by 5% aqueous NaCl (100 mL). Separated organic layer was distilled at below 40°C under vacuum afforded **4**. Viscous oil, yield 95% (161.5 g). MS: m/z 296, (M^++ CH_3COOH); FT-IR (cm^{-1}): 1765 (O-C=O ester stretching), 1096 (aromatic–O-C stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24–8.28 (d, 2H), 7.23–7.29 (d, 2H), 2.58–2.61 (t, J = 8.5 Hz, 2H), 1.73–1.78 (m, 2H), 1.32–1.41 (m, 4H), 0.91–0.95 (t, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.1, 155.4, 145.0, 124.9, 122.3, 34.0, 31.0, 24.2, 22.1, 13.7; Anal. calcd. for $C_{12}H_{15}NO_4$: C,60.75; H, 6.37; N, 5.90, Found: C, 60.67; H, 6.28; N, 5.88%.

2.2 *1-(2-hydroxy-5-nitrophenyl)hexan-1-one* (**5**)

To a mixture of 4-nitrophenyl hexanoate (**4**) (100 g, 0.42 mol) in nitrobenzene (600 mL) was added anhydrous $AlCl_3$ (61.8 g, 0.46 mol), then contents were heated to 140°C and maintained for 5 h. After completion of the reaction, slowly poured into chilled aqueous 5% HCl (1000 mL) and stirred for 15 min, extracted the compound with DCM (200 mL) and washed the organic layer with water (300 mL). The obtained organic layer was distilled off at 40°C under vacuum until DCM traces evaporates, gave dark brown coloured liquid. Slowly added above liquid into chilled 15% aqueous NaOH (900 mL) at room temperature (rt) and stirred for 1 h at same temperature and precipitated solid was isolated by filtration and washed with water (200 mL). To the wet cake, hexane was added (200 mL) at room temperature, maintained for 30 min, filtered and washed with hexane (50 mL). To the crude material 5% aqueous HCl (100 mL) and hexane (200 mL) added, heated to 55–60°C and maintained for 20 min, separated the layers, repeated the extraction process with hexane (3 × 50 mL). The combined hexane layer was washed with water (50 mL) and distilled under vacuum at 50°C which afforded **5**. Off white colour solid, yield 45% (45.0 g). DSC: endothermic peak 64.7°C; MS: m/z 236 (M^+-H); FT-IR (KBr) cm^{-1}: 1644 (−C=O keto stretching); ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.02 (s, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.33–8.36 (dd, J = 9.5, 3.0 Hz, 1H), 7.08–7.1 (d, J = 9.5 Hz, 1H), 3.07–3.1 (t, J = 7.0 Hz, 2H), 1.77–1.8 (m, 2H), 1.39–1.42 (m, 4H), 0.93–0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR

(400 MHz, $CDCl_3$): δ 206.3, 167.2, 139.4, 130.7, 126.4, 119.5, 118.1, 38.2, 31.1, 23.6, 22.3, 13.8; Anal. calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90, Found: C, 60.73; H, 6.42; N, 5.88%.

2.3 *1-(2-methoxy-5-nitrophenyl)hexan-1-one* (**6**)

To a stirred mixture of 1-(2-hydroxy-5-nitrophenyl) hexan-1-one (**5**) (20 g, 0.084 mol), DBU (31.5 mL, 0.21 mol) in acetone (100 mL) was added methyl iodide (4 × 2.6 mL, 0.16 mol) in four portions with time intervals of 30 min and maintained at room temperature for 2 h. After completion of reaction, distilled off acetone under vacuum at below 50°C to obtain crude material. To the crude, the water was added (100 mL), DCM (100 mL) and stirred for 15–20 min, then separated two layers and extracted aqueous layer with DCM (50 mL). Combined organic layer was washed with 5% aqueous HCl (50 mL), followed by water (50 mL) and finally distilled off below 40°C which gave **6**. Off white colour solid, yield 83% (17.6 g). DSC: endothermic peak 47.5°C; MS: m/z 252.2 (M^++H); FT-IR (KBr) cm^{-1}: 1683 (−C=O keto stretching), 1011 (aromatic–O-CH_3 ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51–8.52 (d, J = 2.8 Hz, 1H), 8.31–8.34 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.07–7.09 (d, J = 9.2 Hz, 1H), 4.03 (s, 3H), 2.93–2.97 (t, J = 7.2 Hz, 2H), 1.65–1.73 (m, 2H), 1.31–1.35 (m, 4H), 0.89–0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 200.6, 162.4, 141.3, 128.9, 128.2, 126.0, 111.7, 56.4, 43.5, 31.3, 23.7, 22.4, 13.8; Anal. calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57, Found: C, 62.20; H, 6.76; N, 5.44%.

2.4 *2-bromo-1-(2-methoxy-5-nitrophenyl)hexan-1-one* (**7**)

To a stirred solution of 1-(2-methoxy-5-nitrophenyl)hexan-1-one (**6**) (20 g, 0.079 mol) in dichloromethane (20 mL) was added bromine (4.1 mL, 0.079 mol) at room temperature over a period of 10 min and maintained for 1 h. After completion of reaction added more dichloromethane (20 mL) and decolourized the unreacted bromine by washing with 10% aqueous sodium thiosulphate (20 mL). Evaporation of resultant organic layer afforded intermediate **7**. Off white colour solid, yield 93% (24.4 g). DSC: endothermic peak 60.1°C; MS: m/z 330.2 (M^++H), 332.2 (M^{+2}+H); FT-IR (KBr) cm^{-1}: 1670 (−C=O keto stretching), 1012 (aromatic–O−CH_3 ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57–8.58 (d, J = 2.8 Hz, 1H), 8.35–8.38 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.08–7.10 (d, J = 9.2 Hz, 1H), 5.25–5.28 (dd, J = 8.4 Hz, J = 6.4 Hz, 1H), 4.05 (s, 3H), 2.20–2.26 (m, 1H), 1.99–2.18 (m, 1H), 1.38–1.47 (m, 4H), 0.92–0.96 (t, J = 7.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.8, 161.9, 141.4, 128.8, 127.2, 126.5, 111.9, 56.7, 52.8, 32.7, 29.4, 22.1, 13.7; Anal. calcd. for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24, Found: C, 47.31; H, 4.71; N, 4.10%.

2.5 *2-Bromo-1-(2-hydroxy-5-nitrophenyl)hexan-1-one* (**8**)

To a stirred solution of 2-bromo-1-(2-methoxy-5-nitrophenyl)hexan-1-one (**7**) (15 g, 0.045 mol) in DCM (90 mL) was added slowly $AlCl_3$ (18.1 g, 0.14 mol) at 15–20°C then raised to room temperature and maintained for 1 h. After completion of the reaction poured the reaction mass in to chilled 5% aqueous HCl (150 mL) and stirred for 15 min. Separated DCM layer was washed with water (75 mL) followed by 5% aqueous $NaHCO_3$ (75 mL) and finally water (75 mL). Distillation of DCM layer under vacuum at 30°C gave **8**. Off white colour solid, yield 86% (12.3 g). DSC: endothermic peak 73.3°C; MS: m/z 314 (M^+-H), 316 (M^{+2}-H); FT-IR (KBr) cm^{-1}: 3409 (Aromatic-O-H stretching), 1648 (−C=O keto stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.51 (s, 1H), 8.76–8.77 (d, J = 4.0 Hz, 1H), 8.36–8.39 (dd, J = 9.6 Hz, J = 3.2 Hz, 1H), 7.13–7.15 (d, J = 9.2 Hz, 1H), 5.17–5.20 (t, J = 8.0 Hz, 1H), 2.12–2.27 (m, 2H), 1.40–1.59 (m, 4H), 0.99–1.03 (t, J = 7.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 198.3, 167.9, 139.5, 131.3, 126.3, 119.9, 115.9, 45.6, 32.4, 29.6, 22.1, 13.7; Anal. calcd. for $C_{12}H_{14}BrNO_4$: C, 45.59; H, 4.46; N, 4.43, Found: C, 45.51; H, 4.55; N, 4.36%.

2.6 *2-butyl-5-nitrobenzofuran* (**9**)

To a stirred clear solution of 2-bromo-1-(2-hydroxy-5-nitrophenyl)hexan-1-one (**8**) (15 g, 0.047 mol) in DCM (75 mL) was added TEA (13.2 mL, 0.094 mol) at room temperature and maintained for 2 h. After completion of reaction slowly water was added (50 mL), stirred for 15 min then layers were separated and washed organic layer with 5% aqueous HCl (50 mL), water (50 mL) and upon distillation of DCM under vacuum at 30°C afforded syrup material. Dissolved syrup compound in methanol (75 mL) and added a solution of $NaBH_4$ (2.4 g, 0.071 mol) in methanol (10 mL) over a period of 10–15 min at 0–5°C. The mixture was stirred at same temperature for 30 min then raised to room temperature and maintained for 1 h. After completion of reaction added 15% aqueous HCl (50 mL) and heated to 90–95°C, maintained the reaction at same temperature

for 5 h, after completion of reaction, the contents were cooled to room temperature, added toluene (90 mL) and stirred for 15 min. Separated aqueous and organic layer, extracted aqueous layer with toluene (45 mL). Combined organic layer was washed with water (2 × 25 mL), evaporation of resultant organic layer under vacuum afforded **9**. Viscous oil, yield 73% (7.6 g). MS: m/z 218 (M^+-H); FT-IR cm^{-1}: 1064 (aromatic–O–CH ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36–8.37 (d, J = 2.4 Hz, 1H), 8.10–8.13 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.42–7.44 (d, J = 8.8 Hz, 1H), 6.49–6.50 (d, J = 8.0 Hz, 1H), 2.77–2.81 (t, J = 7.6 Hz, 2H), 1.70–1.78 (m, 2H), 1.40–1.47 (m, 2H), 0.94–0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.3, 157.4, 143.7, 129.3, 118.9, 116.4, 110.7, 102.4,29.3, 28.0, 22.1, 13.6; Anal. calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39, Found: C, 65.59; H, 5.75; N, 6.45%.

2.7 *(2-Butyl-5-nitrobenzofuran-3yl)(4-methoxyphenyl)methanone* (**10**)

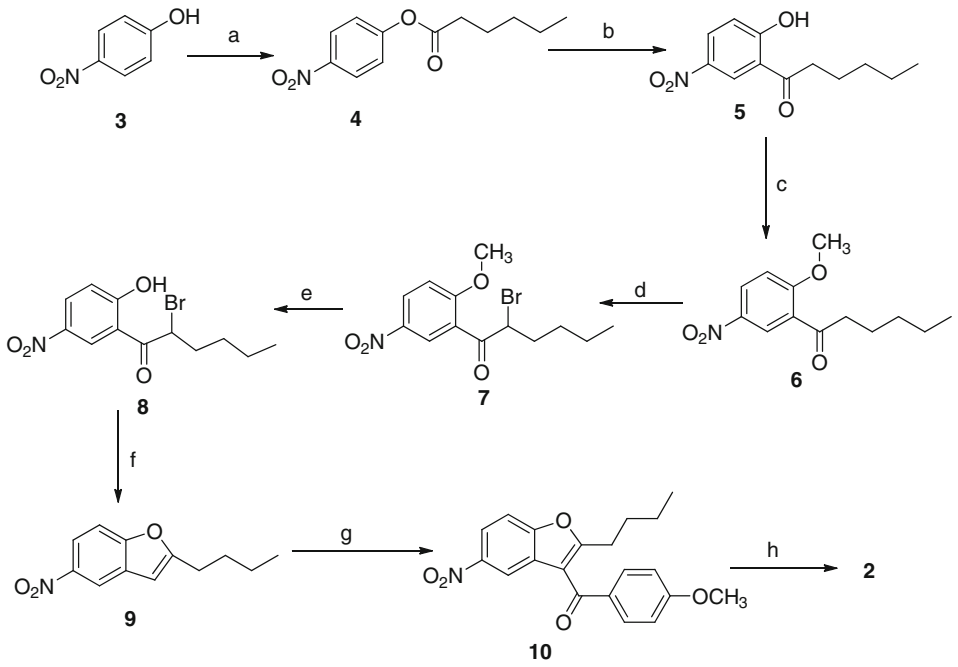
To a stirred solution of $AlCl_3$ (19.7 g, 0.14 mol) in DCM (250 mL) was added drop-wise 4-methoxybenzoyl chloride (21.3 g, 0.12 mol) over a period of 20 min at 0–5°C and maintained for 30 min. To the above contents, 2-butyl-5-nitrobenzofuran (**9**) (25 g, 0.11 mol) was added drop-wise over a period of 15 min, raised to room temperature and maintained for 4 h. After completion of reaction, poured the reaction mass in to chilled 5% HCl (250 mL) and stirred for 15 min. Separated DCM layer was washed with 5% aqueous $NaHCO_3$ (125 mL) followed by water (125 mL) and finally distillation of organic layer afforded crude **10**. Dissolved the crude **10** material in *i*-PrOH (75 mL), cooled to 0–5°C and maintained for 1 h, collected the solid by filtration and washed with chilled *i*-PrOH (12.5 mL) which gave pure **10**. Off white colour solid, yield 82% (33.0 g). DSC: endothermic peak 95.4°C MS: m/z 354.1 (M^++H); FT-IR (KBr) cm^{-1}: 1640 (−C=O keto stretching), 1165 (aromatic–O–CH ether stretching),1023 (aromatic–O–CH_3 ether stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 2.4 Hz, 1H), 8.20–8.23 (dd, J = 8.8 Hz, J = 2.4 Hz,1H), 7.81–7.85 (m, 2H), 7.55–7.57 (d, J = 8.8 Hz, 1H), 6.97–7.01 (m, 2H), 3.91 (s, 3H), 2.90–2.94 (t, J = 7.2 Hz, 2H), 1.72–1.80 (m, J = 7.2 Hz, 2H), 1.30–1.40 (m, J = 7.2 Hz, 2H), 0.87–0.91 (t, J = 7.2 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.9, 167.0, 163.9, 156.2, 144.5, 131.5, 130.8, 127.8, 120.1, 117.5, 117.1, 113.9, 111.2, 55.4, 29.8, 27.8, 22.2, 13.5; Anal. calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96, Found: C, 67.78; H, 5.58; N, 3.90%.

2.8 *(2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxyphenyl)methanone* (**2**)

To a stirred solution of $AlCl_3$ (20.3 g, 0.15 mol)) in chlorobenzene (140 mL) was added drop-wise a solution (2-butyl-5-nitrobenzofuran-3yl)(4-methoxyphenyl)methanone (**10**) (20 g, 0.056 mol) in chlorobenzene (40 mL) over a period of 10 min at room temperature, contents were heated to 75–80°C and maintained for 5 h. After completion of reaction poured the reaction mass into chilled 5% HCl (200 mL), DCM (80 mL) and stirred for 15 min. Separated aqueous layer was extracted with DCM (40 mL), combined organic layer was washed water (2 × 60 mL), finally distillation of organic layer at 75–80°C afforded the title compound **2** in crude form. Pure compound was isolated by dissolving the crude material **2** in chlorobenzene (40 mL) and heated to 75–80°C and maintained for 15 min, cooled to 0–5°C for 1 h and filtered. White colour solid, yield 85% (16.3 g). DSC: endothermic peak 131.2°C MS: m/z 338 (M^+-H); FT-IR (KBr) cm^{-1}: 3216 (aromatic–O–H stretching), 1599 (–C=O keto stretching), 1166 (aromatic–O–CH ether stretching); ^{1}H NMR ($CDCl_3$): δ 8.34 (d, J = 2.0 Hz, 1H), 8.20–8.23 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.77–7.80 (m, 2H), 7.55–7.58 (d, J = 9.2 Hz, 1H), 6.93–6.97 (m, 2H), 6.43 (s, 1H), 2.90–2.94 (t, J = 7.6 Hz, 2H), 1.72–1.80 (m, J = 7.6 Hz, 2H), 1.30–1.40 (m, J = 7.2 Hz, 2H), 0.87–0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.3, 167.6, 161.6, 156.3, 144.5, 132.1, 130.3, 127.7, 120.2, 117.5, 117.1, 115.8, 111.4 29.7, 27.9, 22.2, 13.5; Anal. calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13, Found: C, 67.17; H, 5.11; N, 4.20%.

3. Results and discussion

Our synthesis (scheme 4) of **2** commenced from commercially available 4-nitrophenol (**3**), which was reacted with hexanoyl chloride[8–11] in the presence of TEA to furnish 4-nitrophenyl hexanoate (**4**) in residue form with 90–95% yield. However, the obtained **4** was substantiated by IR spectrum, a strong absorption band observed in functional group region at 1765 cm^{-1} attributed to ester stretching. Further, Fries rearrangement[12–15] of **4** in nitrobenzene solvent at 140°C afforded 1-(2-hydroxy-5-nitrophenyl)hexan-1-one (**5**). The ^{1}H NMR spectrum of **5** depicted three non-equivalent sets of proton signals at δ 8.74, 8.33, 7.08 corresponding to aromatic region, which proved that the rearrangement could have occurred in **4**, the *para* position which is substituted by nitro group. Hence, coming acyl cation has to attack at *ortho* position of hydroxyl group. In



Scheme 4. Proposed synthetic scheme for the preparation of **2**.

order to optimize the temperature in this stage, reaction was carried out at lower temperature (<140°C), no product formation was observed in TLC. Removal of nitrobenzene was bottle neck in this step during the isolation of **5** and due to cumbersome workup procedure, the yield in this step was in range of 45–50%.

3.1 *Reagents and condition*

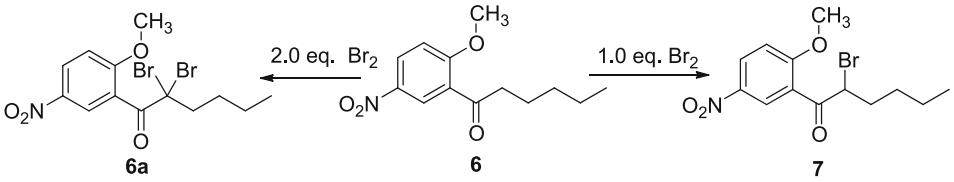
(a) Hexanoyl chloride, TEA, DCM, 0–5°C, 1 h; (b) $AlCl_3$, nitrobenzene, 140°C, 5 h; (c) CH_3I, DBU, acetone, 25–30°C, 2 h; (d) Br_2, DCM, 25–30°C, 1 h; (e) $AlCl_3$, DCM, 25–30°C, 1 h; (f) TEA, DCM, 25–30°C, then $NaBH_4$, 25–30°C, 30 min, 15% HCl, 90–95°C, 4–6 h; (g) 4-methoxybenzoyl chloride, $AlCl_3$, DCM, 25–30°C, 4–5 h; (h) $AlCl_3$, chlorobenzene, 75–80°C, 4–5 h.

Methylation of resultant **5** with methyl iodide[16–19] afforded 1-(2-methoxy-5-nitrophenyl)hexan-1-one (**6**), during the feasibility study incompletion of reaction was noticed using 2.0 equiv of methyl iodide in a single lot and for further completion of reaction added excess amount of reagent, even if we used excess equiv in a single lot, starting material still remains and at the end of the final process included the lot-wise addition of methyl iodide with 2.0 equiv. The isolated compound **6** exhibited upward signal in DEPT spectrum at δ 56.4, singlet in ^{1}H NMR at δ 4.03 attributed to O−CH_3. Compound **6** was treated with bromine[20–22] gave 2-bromo-1-(2-methoxy-5-nitrophenyl)hexan-1-one (**7**), exclusively desired α-brominated compound was isolated using 1.0 equiv of bromine with 80–85% yield and undesired dibromo compound **6a** was observed using 2.0 equiv of bromine solution (scheme 5). This reaction was favourable in diethyl ether, methyl *t*-butylether, dichloromethane solvents at room temperature. Mass spectrum of **7** substantiated the bromo abundance in 1:1 ratio, single proton signal in deshielding zone of ^{1}H NMR at δ 5.25 corresponding to bromo attached proton.

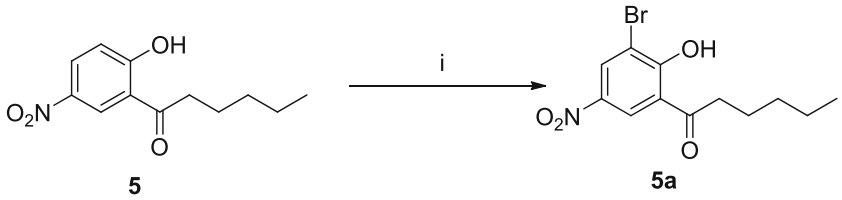
At earlier stages, we have targeted for the synthesis of **8** from compound **5**, enthusiastic results were not found using various brominating reagents such as Br_2, NBS, $NH_4Br/(NH_4)_2S_2O_8$[23,24] at different conditions.

^{1}H NMR of the obtained compound **5a** depicted the absence of proton at *ortho* position to hydroxy group (scheme 6). The keto group of **5** involving in resonance and exhibiting hydroxy character (scheme 7).

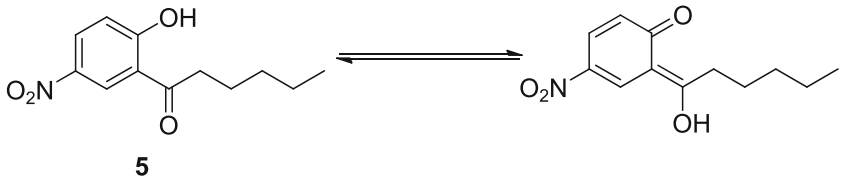
Compound **7** was further subjected to deprotection with $AlCl_3$[25] to give 2-bromo-1-(2-hydroxy-5-nitrophenyl)hexan-1-one **(8)**, confirmed the compound by ^{1}H NMR and observed that the absence of O−CH_3 protons at δ 4.03. Cyclization[26,27] of **8** (scheme 8) in the presence of TEA gave an 2-butyl-5-nitrobenzofuran-3(2H)-one (**8a**), further reduction with sodium borohydride[28] afforded an *in situ* intermediate of 2-butyl-5-nitro-2,3-dihydrobenzofuran-3-ol (**8b**) and dehydration of *in situ* substrate by 15% aqueous HCl[28] furnished 2-butyl-5-nitrobenzofuran (**9**) with 70–75% of yield. The obtained **9** was confirmed using ^{1}H NMR, single proton signal at δ 6.49 attributed to third position



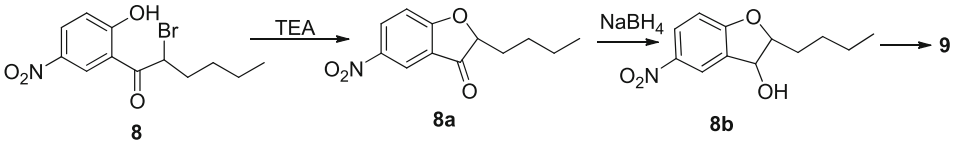
Scheme 5. Formation of dibromo compound using 2.0 equiv of bromine.



Scheme 6. Formation of aromatic brominated compound from **5** using brominating reagents (i) Br_2 or $NH_4Br/(NH_4)_2S_2O_8$ or NBS.



Scheme 7. Resonance structure of **5**.



Scheme 8. Intermediates during the conversion of **8** to **9**.

Table 1. Optimization of $AlCl_3$ mole ratio from **9** to **10** and performed at 25–30°C.

Entry	Mole ratio	Solvent	Purity[a] (area%)	9 (area%)	Yield[b] (%)
1	2.0	DCM	94.03	0.2	71.3
2	1.6	DCM	94.8	0.13	75.1
3	1.5	DCM	95.6	0.08	80.3
4	1.3	DCM	97.3	0.03	82.8
5	1.2	DCM	97.0	–	78.3
6	4.0	DCM	68.3[c]	21.9	–

[a,b]After *i*-PrOH purification, [c]Reaction performed at reflux temperature, HPLC purity was calculated before *i*-PrOH purification

Table 2. Screening of reagent, solvent and mole ratio of $AlCl_3$ for **10** to **2**.

Entry	Reagent	Mole ratio	Solvent	Temp (°C)	Purity[b] (area %)	10 (area %)	Yield[c] (%)
1	Aq. HCl	3.0	Acetonitrile	75–80	–	–	–
2	Aq. HBr	3.0	MIBK	110–115	–	–	–
3[a]	$AlCl_3$	2.5	DCM	42	–	–	–
4	$AlCl_3$	2.7	Toluene	105–110	–	–	35
5	$AlCl_3$	1.5	Chlorobenzene	75–80	66.8	26.2	53
6	$AlCl_3$	2.0	Chlorobenzene	75–80	78.4	9.5	68
7	$AlCl_3$	2.5	Chlorobenzene	75–80	99.2	0.3	83
8	$AlCl_3$	2.7	Chlorobenzene	75–80	99.5	0.15	85
9	$AlCl_3$	4.0	Chlorobenzene	75–80	98.3	0.03	73

[a]Compound was not isolated and monitored the reaction by TLC.
[b,c]After chlorobenzene purification

aromatic –CH of benzofuran moiety and it indicated that **8** was cyclised.

Existing literature[28] for preparation of **10** was involved Friedel–Crafts acylation of **9** with 4-methoxybenzoyl chloride in the presence of $SnCl_4$ which is one of the expensive reagents and replaced the reagent by $AlCl_3$ with significant yield and purity. IR spectrum of **10** depicted a strong absorption band at 1640 cm^{-1} corresponding to keto stretching, absence of δ 6.49 signal in ^1H NMR indicating that acyl cation attacked at third position of benzofuran moiety. To improve the yield, reaction was screened with different mole ratio of $AlCl_3$. Though the reaction completed using 1.6 and 2.0 equiv of $AlCl_3$, the yield of the product was moderate due to the formation of impurities, where as the reaction did not go for completion using 1.2 equiv. Finally, usage of 1.3 equiv of $AlCl_3$ led to true conversion of reaction to afford crude **10**, which was recrystallized in *i*-PrOH and gave 97% HPLC pure **10** with 82% yield (table 1).

Finally, demethylation of **10** with $AlCl_3$[28] afforded the white coloured target key starting material **2** and the substantiated spectral data of **2** is in congruence with the literature[2,29] reports. Demethylation was performed using different acidic reagents like aqueous HCl (table 2, entry 1), aqueous HBr (table 2, entry 2) at different conditions and conversion of **10** was not observed. Screened the solvents using $AlCl_3$, in dichloromethane (table 2, entry 3) rate of reaction was slow and in toluene (table 2, entry 4) lower yield obtained, finally chlorobenzene was selected for demethylation due to its high boiling point and polarity. Starting material was observed using 1.5 and 2.0 equiv (table 2, entry 5,6) of $AlCl_3$, where as with 4.0 equiv (table 2, entry 9) lower yield obtained due to impurities formation and by using 2.5 and 2.7 equiv (table 2, entry 7,8) better yield was isolated. At initial stages, we target for synthesis of **2** in a single pot (table 1, entry 6) from compound **9**, incompletion of reaction noticed during demethylation using dichloromethane solvent for both stages, by employing excess amount of $AlCl_3$ also did not give a good results. Purification of crude **2** in minimum amount of chlorobenzene afforded **2** with 99.0% HPLC purity.

4. Conclusion

In conclusion, we have developed an alternative process with inexpensive and commercially available raw materials for the preparation of 2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxyphenyl)methanone, a key intermediate of dronedarone hydrochloride.

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