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An Improved Scalable Route to Pure Dronedarone Hydrochloride

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Supporting Information

ABSTRACT: An efficient scalable synthesis for dronedarone hydrochloride (**2**) via Friedel–Craft acylation of 2-(-2-butyl-1-benzofuran-5-yl)-1*H*-isoindole-1,3(2*H*)dione (**12**) with 4-(3-chloropropoxy) benzoic acid (**13**) in good yield and high purity has been developed by using Eaton's reagent instead of hazardous and toxic metal halide catalyst like $AlCl_3$ or $SnCl_4$.

INTRODUCTION

Atrial fibrillation (AF) is the most common of the serious cardiac rhythm disturbance and is responsible for substantial morbidity and mortality, requiring hospitalization. Amiodarone (**1**; Figure 1) is a highly effective multichannel blocker and

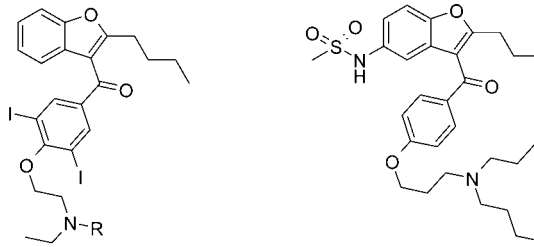
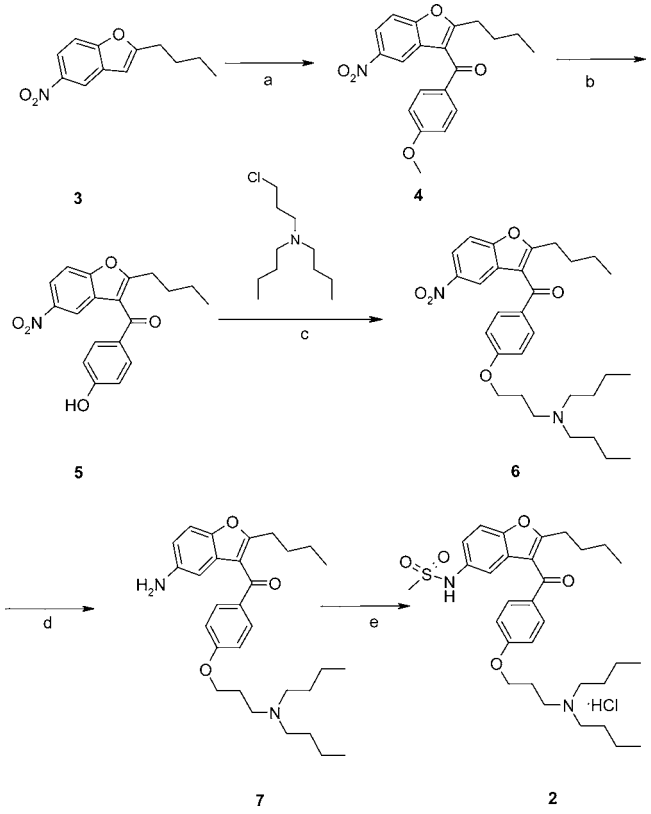


Figure 1. Amiodarone and dronedarone hydrochloride.

most widely used as antiarrhythmic drug; however, chronic use of **1** and its active metabolite desethyl-amiodarone can cause adverse effects on thyroid such as hypothyroidism or thyrotoxicosis.[1] Amiodarone is an iodinated benzofuran derivative (as seen in **1**), due to the presence of the iodo-substituent; **1** is lipophilic and has a long half-life up to 100 days; and causes thyroid dysfunction and accumulation in adipose tissue and other organs such as liver, lung, cornea, and skin.[2,3] Dronedarone (**2**) is a modified synthetic analogue of amiodarone[4] with two molecular changes; that is, it lacks the iodine functionality of amiodarone, but has an additional sulfonamide group placed on the benzofuran ring which decreases lipophilicity, resulting in a shorter lifetime and lower tissue accumulation. Dronedarone is a potent blocker of multiple ion currents and U.S. FDA has approved dronedarone hydrochloride for atrial fibrillation on July 2, 2009.

Out of the several reported processes[5a−e] of dronedarone hydrochloride (**2**), a couple of relevant schemes are shown in Schemes 1[5a] and 2.[5b] In the first process, nitrobenzofuran **3** is benzoylated with *p*-anisoyl chloride followed by demethylation and subsequent alkylation with *N*-(3-chloropropyl)-dibutylamine which results in nitro compound **6**. Catalytic reduction of nitro compound **6** followed by sulphonamide formation affords the target compound dronedarone hydrochloride (**2**). A serious problem associated with this route is that the nitro intermediate **5** is mutagenic[5c] and hazardous to humans and the environment.

Scheme 1. Reported synthesis as prepatent US 5,223,510[a]



[a]Reagents (a) *p*-anisoyl chloride, $SnCl_4$; (b) $AlCl_3$, 1,2- dichloro-ethane, reflux 20 h; (c) K_2CO_3, MEK; (d) H_2/PtO_2, EtOH; (e) CH_3SO_2Cl, TEA.

In the second synthetic route (Scheme 2), N-alkylation of di-*n*-butylamine with methyl-4-(3-bromopropoxy)benzoate was followed by hydrolysis of methyl ester and conversion of the resulting acid to the corresponding acid chloride **9**. Amino

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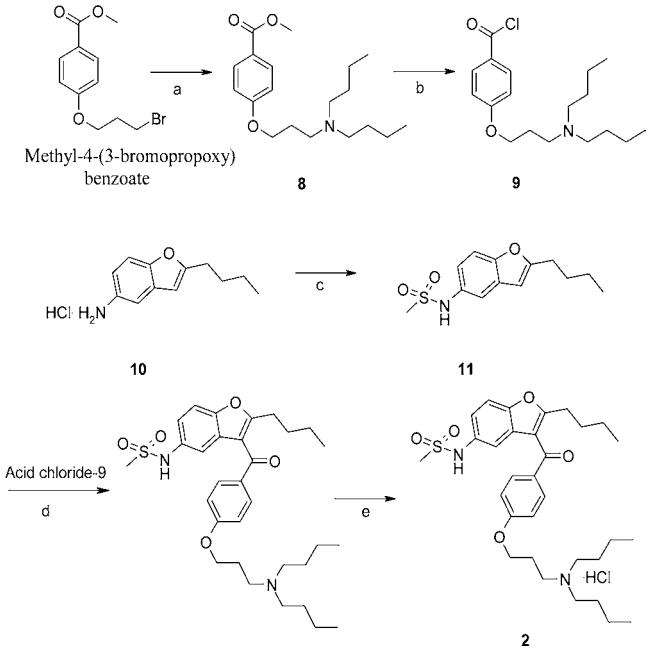
Scheme 2. Reported synthesis as prepatent US 7,312,345[a]



[a]Reagents (a) dibutyl amine; (b) (i) HCl , (ii) $SOCl_2$; (c) CH_3SO_2Cl, base; (d) $SnCl_4$, DCM; (e) 10% HCl in ethyl acetate.

benzofuran **10** under treatment with methanesulfonyl chloride provides sulfonamide **11**. Friedel–Crafts acylation of sulfonamide **11** with acid chloride **9** using $SnCl_4$ provides dronedarone hydrochloride (**2**) in low to moderate yield. Key Fridel–Craft reaction is not a clean conversion and product formation occurs along with impurities which require column purification of the free base and subsequent salt formation. Moreover, the Friedel–Crafts acylation is the final step which is catalyzed by Lewis acids like $SnCl_4$ or $AlCl_3$ and there is always a possibility of heavy metal contamination in the finished product.

An efficient, economic, scalable route with environment friendly reagents is highly required for commercial scale synthesis of API grade dronedarone hydrochloride. Herein, we describe an improved scale-up synthesis of **2**, which can be utilized for manufacturing on commercial scale. In an attempt to overcome the low yielding Friedel–Crafts acylation reaction, we thought to use a suitable protecting group for the amino functionality of benzofuran derivative **10** during the key Friedel–Crafts acylation reaction with benzoic acid derivative **13**. Amination followed by deprotection of phthalimido group and final sulfonation with mesyl chloride would give us the free base.

RESULT AND DISCUSSION

As mentioned in scheme 2, the Friedel–Crafts acylation on sulfonamide **11** with acid chloride **9** was low yielding and accompanied by several impurities. In an attempt to overcome these difficulties, we protected the amino group of benzofuran **10** as its corresponding phthalimido derivative which would be stable for a wide verity of reaction conditions.[6,7] Moreover, deprotection of the phthalimido group can be achieved under very mild condition using $MeNH_2$.[8] With this intention, amino benzofuran **10** was treated with phthalic anhydride in the presence of triethylamine to provide the phthalimido derivative **12**. For the condensation of compound **13** with phthalimido compound **12** (Scheme 3), we tried several Lewis acids including traditional metal halides; the results are summarized in Table 1.

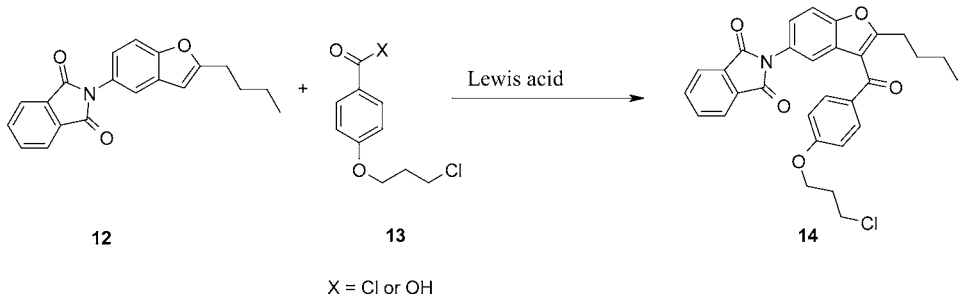
Table 1. Results of Friedel–Crafts acylation using various reagent and conditions

sr. no.	–X	Lewis acid	condition	result	ref
1	–Cl	$AlCl_3$	DCM, –20 °C, 1 h	68%[a]	9
2	–Cl	$SnCl_4$	DCM, 0 to 25 °C 1 h	80%[a]	9
3	–Cl	$FeCl_3$	DCM, reflux 6 h	-[b]	9
4	–OH	$ZnCl_2$–Al_2O_3	DCM reflux 5 h	-[b]	10
5	–Cl	ZnO	DCM, 25 °C, 24 h	-[b]	11
6	–OH	P_2O_5–Al_2O_3	1,2 dichloroethane, reflux, 24 h	-[b]	12
7	–OH	P_2O_5–SiO_2	1,2 dichloroethane, reflux, 24 h	-[b]	13
8	–Cl	$Zn(OTf)_2{\cdot}6H_2O$	CH_3NO_2, 25 °C, 24 h	-[b]	14
9	–OH	PPA-P_2O_5	60 °C, 2.5 h	60%[a]	15
10	–OH	MsOH-P_2O_5	35 °C 1 h	75%[a]	16–20

[a] Isolated yields. [b]No product formation was observed by TLC.

From the series of metal halide catalysts used, $SnCl_4$ (Table 1, entry 2) worked well and yielded the desired intermediate which was subsequently converted to dronedarone hydrochloride with high yield and good purity. Even though the final isolated product was completely devoid of any metal contamination (tin content below detection limit), but because of the risk involved in industrial scale handling of $SnCl_4$ and the resulting large excess of toxic tin waste, we intended to eliminate the use of $SnCl_4$ in our commercial manufacturing process of dronedarone hydrochloride.

Scheme 3. Friedel–Crafts acylation of phthalimido compound 12



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The second most suitable reagent for this step was Eaton's reagent. We used commercially available Eaton's reagent [7.7% (w/w) of P_2O_5 in MsOH] to optimize the reaction condition and found that carrying out the coupling reaction using 2.5 equiv of this reagent at 35 °C produced good yield (75%). To reduce the volume of MsOH, we used 15% (w/w) P_2O_5 in MsOH (which reduces the volume of MsOH) and results were reproduced with good yield (76%). One of the major advantages of our route was the use of the acid (**13**), instead of its acid chloride. Eaton's reagent was a safe and commercial viable replacement of hazardous $SnCl_4$.

Amination of chloroderivative **14** using di-*n*-butylamine proceeded smoothly to furnish the amino derivative **15** in excellent yield. At this stage, the phthalimido group was removed using 40% aqueous methylamine solution, and the resulting amine was isolated as its dioxalate salt **16**. The dioxalate salt formation actually made the isolation much easier and provided a stable intermediate. Finally, sulfonamide formation was effected with mesyl chloride. The major problem of this step is the formation of disulfonamide, which is well documented.[21] To control this impurity during reaction, separately, we have synthesized the disulfonamide impurity using excess methane sulfonyl chloride (2.5 equiv) in DCM. We have screened various solvents such as DCM, THF, ethyl acetate, acetone, and toluene, and organic base such as TEA, DIPEA, pyridine, and *N*-methyl morpholine at various temperatures from 0 to 50 °C to elucidate the best condition to minimize the disulfonamide formation. In chlorinated solvents like DCM or chloroform, impurity formation was observed from the beginning of the reaction, but in the case of solvents like acetone, ethyl acetate, and THF, after major product formation, a much better reaction profile was observed. From all our efforts, we concluded that adding 1.05 equiv of methane sulfonyl chloride dropwise in presence of TEA in toluene at −5 to 5 °C gives the best result with negligible impurity formation and high yield of free base. The synthesis was completed by converting the free base into the desired hydrochloride salt using 10% (v/v) aq HCl in DCM followed by purification from acetone which provided dronedarone hydrochloride (**2**) in good overall yield. The final isolated product was highly pure and complies with ICH guidelines for impurity profile. The final optimized conditions and route are depicted in Scheme 4.

Our synthetic route has several advantages: the phthalimido protection of amino benzofuran **10** ensures less impurity formation during the critical Friedel−Crafts acylation, and use of isolation of precursor amine **16** as stable dioxalate salt with high purity makes this process highly efficient.

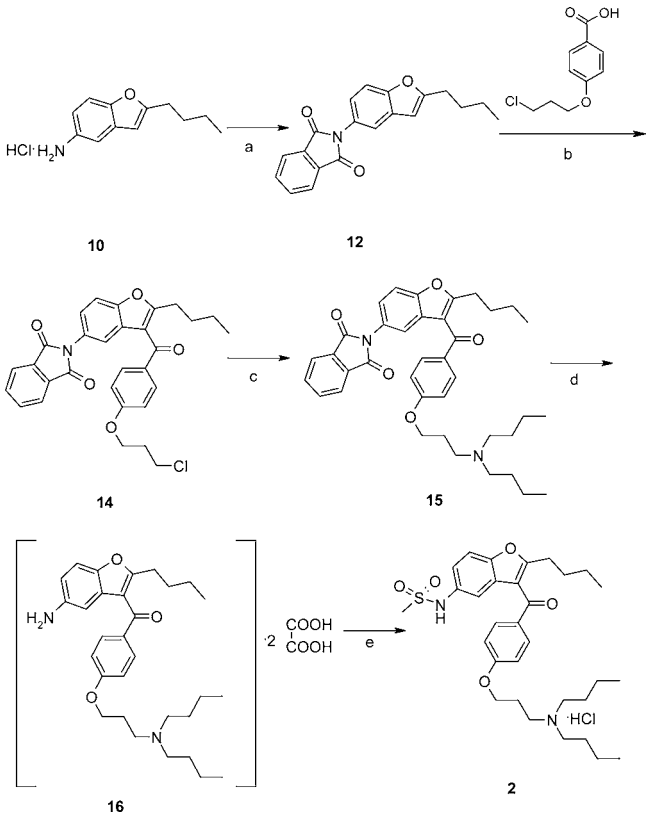
CONCLUSION

In conclusion, we have developed an efficient, plant-friendly, and high yielding process for the preparation of dronedarone hydrochloride (**2**) substantially free from all known and unknown impurities. This improved process has been successfully demonstrated on kilogram scale and is now being adopted for the manufacturing of dronedarone hydrochloride (**2**) on a commercial scale.

EXPERIMENTAL SECTION

All chemical were purchased from commercial suppliers. Melting points were determined by DSC on Mettler Toledo. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ and CD_3OD, on a Varian 400 MHz, and mass spectra were determined on an API 2000LC/MS/MS mass spectrometer, Applied Biosciences.

Scheme 4. Synthesis of dronedarone hydrochloride[a]



[a]Reagents and conditions: (a) phthalic anhydride, TEA, toluene, reflux 1.5 h; (b) P_2O_5-MsOH, 35 °C, 60 min; (c) di-*n*-butyl amine, KI, TBAB, DMF, 85 °C, 14 h; (d) mono methylamine 40% aq sol^n, oxalic acid dihydrate, IPA, 75 °C, 60 min; (e) (i) $NaHCO_3$, DCM, CH_3SO_2Cl, TEA, toluene, −5 to 5 °C, 30 min, (ii) aq HCl, DCM.

Preparation of 2-(-2-Butyl-1-benzofuran-5-yl)-1*H*-isoindole-1,3(2*H*)dione (12). Amino benzofuran **10** (2.0 kg, 8.86 mol) was slowly added to a stirred mixture of sodium bicarbonate (1.0 kg, 11.90 mol), water (6.0 L), and toluene (3.0 L) with controlled frothing. After 30 min, the layers were separated and the organic layer was washed with water (2.0 L). Phthalic anhydride (1.32 kg, 8.91 mol) and triethyl amine (90 g, 0.88 mol) were sequentially added to the organic layer containing the free amine and the reaction mass was refluxed for 1.5 h with azeotropeic removal of water. The reaction mixture was allowed to cool to 75 °C, whereupon cyclohexane (6.0 L) was added and the mixture was cooled down to 20 °C and stirred for 1 h. The precipitated solids were filtered, washed with cyclohexane (2.0 L), and dried at 50 °C to afford phthalimido compound **12** (2.64 kg, 93%).

Mp: 152 °C; *m/z*: 320.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.4 Hz, 3H), 1.38−1.47 (m 2H), 1.70−1.78 (m, 2H), 2.79 (t, J = 7.4 Hz, 2H), 6.42 (s, 1H), 7.20 (dd, J = 8.6 Hz, 2.1 Hz, 1H), 7.49−7.52 (m, 2H), 7.76−7.80 (m, 2H), 7.93−7.97 (m 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.69, 22.13, 28.04, 29.60, 102.06, 111.10, 118.90, 121.88, 123.54, 126.07, 129.64, 131.76, 134.18, 153.85, 161.15, 167.62. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.29. Found: C, 75.40; H, 5.20; N, 4.25.

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Preparation of 3-[4-(3-Chloro propoxy)benzoyl] 2-*n*-Butyl Benzofuran-5-yl-1*H*-isoindole-1,3 (2*H*) Dione (14). Eaton's reagent was prepared by adding P_2O_5 (2.78 kg 19.58 mol) portionwise to methane sulfonic acid (10.6 L) under nitrogen atmosphere and stirred for 30 min at 25 to 35 °C. To this intermediate, **13** (1.76 kg 8.22 mol) was added and allowed to stir for 15 min, then phthalimido derivative **12** (2.5 kg, 7.83 mol) was charged and stirred for 1 h at 35 °C. After complete consumption of the starting material, the reaction was quenched by pouring reaction mass into a mixture of water (25.0 L) and DCM (5.0 L) below 15 °C and layers were separated. The organic layer was washed twice with 5% sodium bicarbonate solution (10.0 L), followed by a water wash (10.0 L). DCM was distilled off, the residue was slurred with methanol (20.0 L), and the solids were filtered, washed with methanol (5.0 L), and dried at below 45 °C to furnish chloro compound **14** (3.07 kg, 76%).

Mp: 109 °C; *m*/*z*: 516.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.4 Hz, 3H), 1.32−1.41 (m, 2H), 1.73−1.80 (m, 2H), 2.24−2.29 (m, 2H), 2.95 (t, J = 7.5 Hz, 2H), 3.75 (t, J = 6.3 Hz, 2H), 4.20 (t, J = 5.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.29 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.76−7.78 (m, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.86−7.94 (m, 2H). ^{13}C NMR(100 MHz, $CDCl_3$):13.55, 22.16, 27.70, 29.93, 31.88, 41.15, 64.38, 111.40, 114.15, 116.75, 120.11, 123.15, 123.47, 126.98, 127.66, 131.49, 131.57, 134.15, 152.65, 162.47, 165.90, 167.22, 189.46. Anal. Calcd for $C_{30}H_{26}ClNO_5$: C, 69.83; H, 5.08; N, 2.71. Found: C, 70.08; H, 5.09; N, 2.72.

Preparation of 5-Amino-3-[4-(3-di-*n*-butyl amino propoxy)benzoyl] 2-*n*-Butyl Benzofuran Dioxalate (16). Chloro compound **14** (3.0 kg, 5.81 mol), potassium iodide (0.97 kg, 5.84 mol), tetra *n*-butyl ammonium bromide (150 g, 0.46 mol), di-*n*-butyl amine (1.5 kg, 11.63 mol), and dimethyl formamide (4.5 L) were heated to 85 °C for 14 h. The reaction mixture was cooled to 25 °C, and water (18.0 L) and DCM (6.0 L) were added. Layers were separated, and the organic layer was sequentially washed with 2.0 N hydrochloric acid (6.0 L) and water (2 × 15.0 L) followed by saturated sodium bicarbonate solution (7.5 L). DCM was distilled completely to afford amine **15** as oil. Isopropyl alcohol (12.0 L) followed by methylamine 40% aqueous solution (3.0 L) was added and the mixture was heated for 1 h at 75 °C. The reaction mixture was concentrated under vacuum. The residue was diluted with isopropyl alcohol (15.0 L) and oxalic acid dihydrate (1.47 kg, 11.63 mol) was added and stirred at 65 °C for 30 min. The reaction mixture was cooled to 5 °C and stirred for 1 h. The precipitated solids were filtered and washed with isopropyl alcohol (3.0 L) followed by acetone (3.0 L) and dried at 50 °C to furnish dioxalate salt **16** (3.15 kg, 82%).

Mp: 170 °C; *m*/*z*: 479.3 $(M + H)^+$; ^{1}H NMR (400 MHz, DMSO-*d*6): δ 0.79 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 6H), 1.19−1.24 (m, 2H), 1.28−1.37 (m, 4H), 1.57−1.65 (m, 6H), 2.12−2.18 (m, 2H), 2.72 (t, J = 7.5 Hz, 2H), 3.04−3.09 (m, 4H), 3.20−3.24 (m, 2H), 4.17 (t, J = 5.9 Hz, 2H), 6.53 (d, J = 2.0 Hz, 1H), 6.59 (dd, J = 8.7 Hz, 2.2 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H); ^{13}C NMR(100 MHz, DMSO_d6): 13.63, 13.73, 19.64, 21.85, 23.16, 25.17, 27.44, 29.75, 49.07, 52.05, 65.39, 107.01, 111.55, 114.73, 116.46, 127.61, 131.59, 131.65, 141.06, 148.03, 162.35, 163.68, 164.22, 190.10. Anal. Calcd for $C_{34}H_{46}N_2O_{11}$: C, 61.99; H, 7.04; N, 4.25. Found: C, 61.91; H, 7.15; N, 4.41.

Preparation of Dronedarone Hydrochloride (2). Dioxalate salt **16** (3.0 kg, 4.55 mol) was added portionwise into the stirred mixture of water (9.0 L), DCM (9.0 L), and sodium bicarbonate (1.7 kg, 20.24 mol). The suspension was stirred for 30 min. Inorganic solids were filtered and layers were separated. The organic layer containing precursor free amine was washed with water (2 × 6.0 L). DCM was distilled out. To this crude residue, toluene (9.0 L) was added, followed by triethyl amine (690 g, 6.83 mol), and cooled to −5 °C. Methane sulfonyl chloride (548 g, 4.78 mol) was added dropwise at −5 to 5 °C and stirred for 30 min. Reaction mass was quenched by adding 5.0% aqueous sodium bicarbonate solution (9.0 L) and layers were separated and washed with water (6.0 L). Toluene was distilled out and the residue was stirred with a mixture of DCM (9.0 L), concentrated hydrochloric acid (1 L) ,and water (9.0 L) for 30 min. After layer separation, the organic layer was washed with water (2 × 6.0 L). DCM was distilled out and to the residue mixture of ethyl acetate and isopropyl alcohol (30.0 L, 9:1) was added and stirred at 25 °C for 4 h. The reaction mixture was cooled to 5 °C and stirred for 2 h. The precipitated solids were filtered to afford dronedarone hydrochloride crude (2.0 kg, 75%). Recrystallisation of crude dronedarone hydrochloride from acetone results in pure dronedarone hydrochloride with purity more than 99.5% by HPLC and any individual impurity less than 0.10% (1.62 kg, 60%).

Mp: 143 °C; *m*/*z*: 557.3 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.3 Hz, 6H), 1.34−1.45 (m, 6H), 1.72−1.84 (m, 6H), 2.38−2.45 (m, 2H), 2.91 (s, 3H), 2.96 (t, J = 7.7 Hz, 2H), 3.03−3.07 (m, 4H), 3.22−3.27 (m, 2H), 4.24 (t, J = 5.4 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 2.1 Hz, 8.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H) 7.78 (d, J = 8.8 Hz, 2H), 11.93 (s, 1H); ^{13}C NMR(100 MHz, $CDCl_3$): 13.23, 13.35, 19.70, 21.95, 23.32, 24.75, 27.57, 29.67, 38.15, 49.84, 52.08, 64.72, 111.12, 113.99, 115.18, 116.38, 119.75, 127.42, 131.30, 131.50, 133.06, 151.14, 161.77, 165.55, 189.79. Anal. Calcd for $C_{31}H_{45}ClNO_5S$: C, 62.77; H, 7.56; N, 4.72; S, 5.40. Found: C, 62.83; H, 7.46; N, 4.91; S, 5.60.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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