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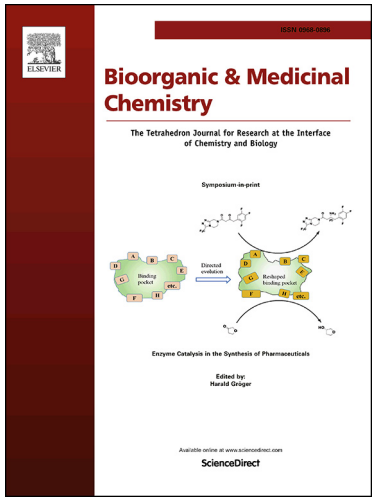

A short synthesis of Dronedarone

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Graphical Abstract

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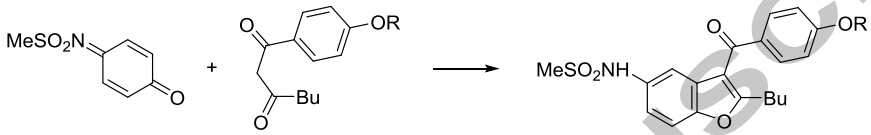

Dronedarone (R=$CH_2CH_2CH_2NBu_2$)

A short synthesis of Dronedarone

Barbara Piotrkowska [a], Sven Nerdinger[b*], Erwin Schreiner[b], Lovro Selič[c], and Piotr P. Graczyk[a]

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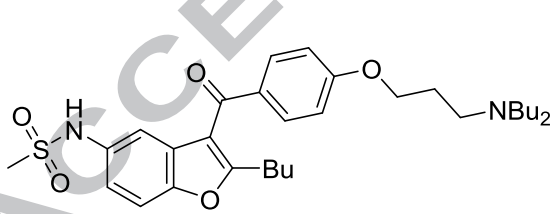
ABSTRACT

A modification of the Nenitzescu reaction was used to obtain Dronedarone from quinonimine **15** and 1,3-diketone **18** (R=$CH_2CH_2CH_2NBu_2$) in a two-stage process in almost 55% overall yield. Our results represent significant improvement over other state-of-the-art methods as no extra steps for the decoration of the benzofuran core are required.

Keywords: Dronedarone; optimization; Nenitzescu; quinonimine

1. Introduction

Dronedarone (**1**) is a drug structurally related to amiodarone (**2**) and developed by Sanofi Pharma for the treatment of atrial fibrillation and atrial flutter[1].



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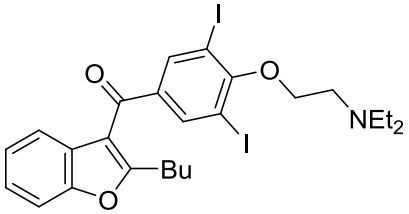

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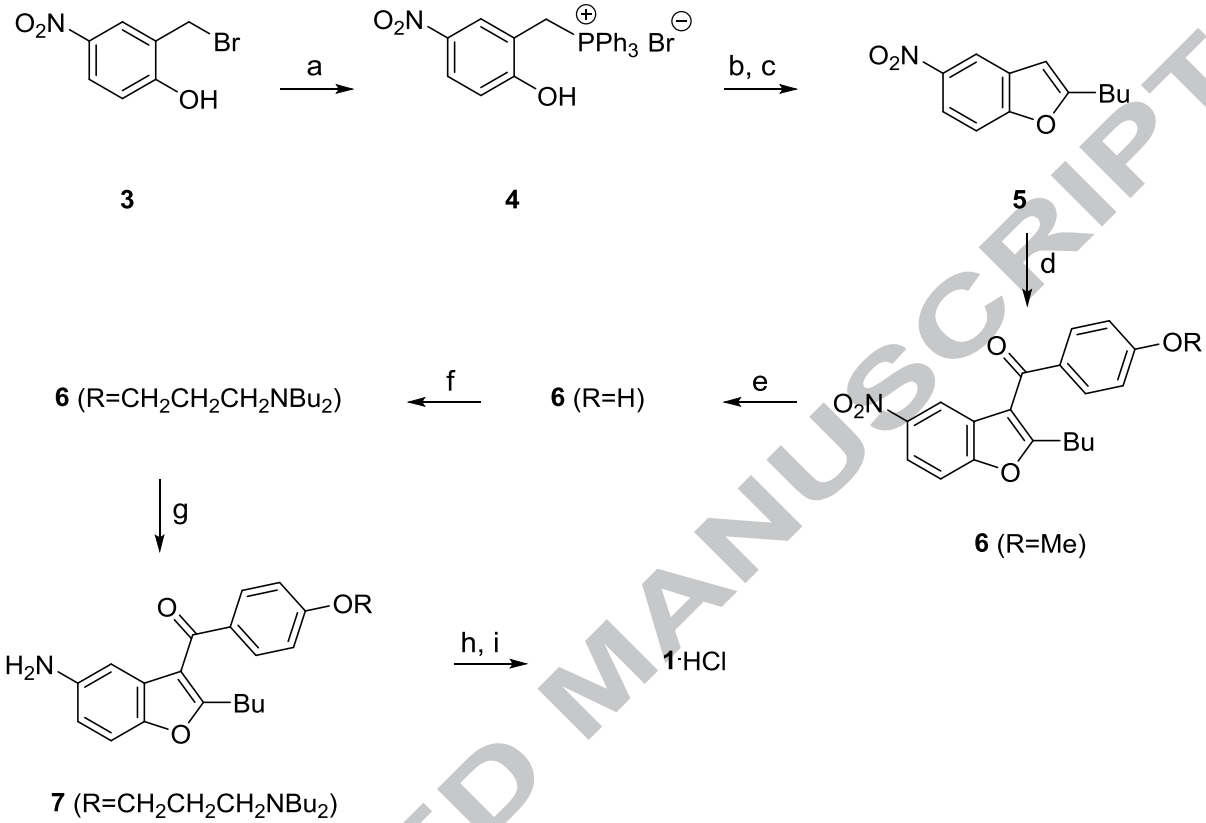
Thanks to its efficacy and only minimal side effects as compared with **2** there has been constant interest in discovering better synthetic routes to this molecule. This paper describes the development of a very short process leading to **1** and the outcome of our optimization efforts.

2. Background

The original method patented over 25 years ago by Gubin et al.[2] was based on the construction of a 2,5-disubstituted benzofuran derivative **5** followed by its benzoylation with *p*-anisoyl chloride (Figure 1).



a) PPh_3 b) $C_4H_9C(O)Cl$, pyridine c) Et_3N d) p-$MeOC_6H_4C(O)Cl$, $SnCl_4$ e) $AlCl_3$ f) $ClCH_2CH_2CH_2NBu_2$, K_2CO_3 g) H_2/PtO_2 h) MsCl, Et_3N i) HCl

Figure 1. The original synthesis of Dronedarone hydrochloride (**1**·HCl)

The target Dronedarone was obtained as hydrochloride salt **1**-HCl in almost 40% overall yield.

While the yield was acceptable, the synthesis was relatively long (8 steps) and had several shortcomings, one of which was the formation of large amounts of $Ph_3P=O$ during cyclization to form the key intermediate **5**. Alternative approaches to **5**, not involving phosphorus chemistry, were later proposed by others[3,4,5,6,7,8,9] and are schematically shown in Figure 2.

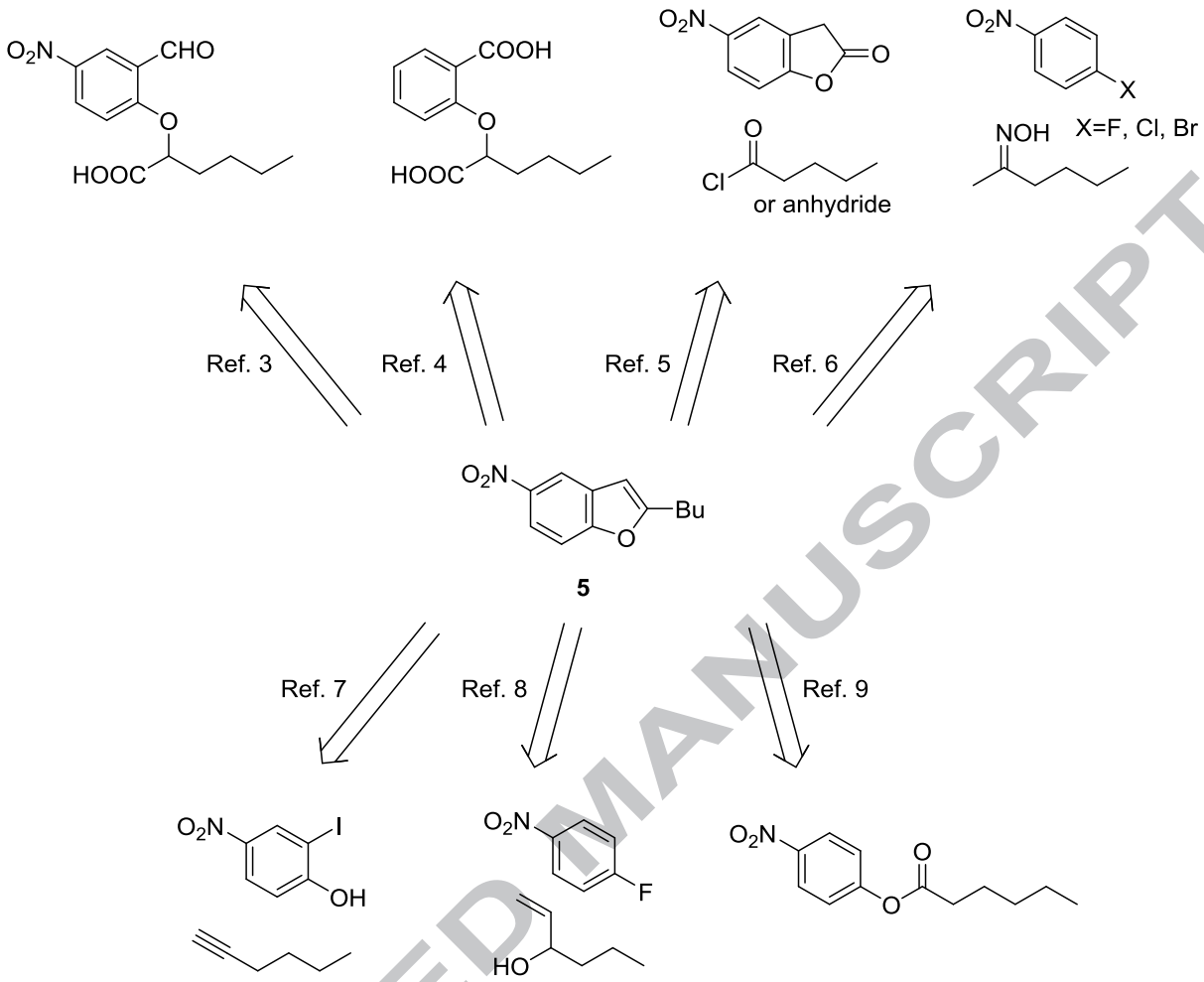


Figure 2. Alternative synthetic approaches to **5** not involving phosphorus chemistry.

Other methods could also potentially be used for this purpose.[10]

Most of the earlier synthetic approaches to Dronedarone had to have the central benzofuran system benzoylated. Originally, the key intermediate benzofuran **5** was benzoylated in the presence of $SnCl_4$. Soon, a couple of alternative ways to perform benzoylation of **5** to produce **6** (R=Me or R=$CH_2CH_2CH_2NBu_2$) have been reported (Figure 3). The use of a milder Lewis acid, $FeCl_3$ (yield 98%) was proposed by Biard (R= $CH_2CH_2CH_2NBu_2$)[11] and $AlCl_3$ (yield 88%) by Mohanarangam *et al.* (R=Me).[12]

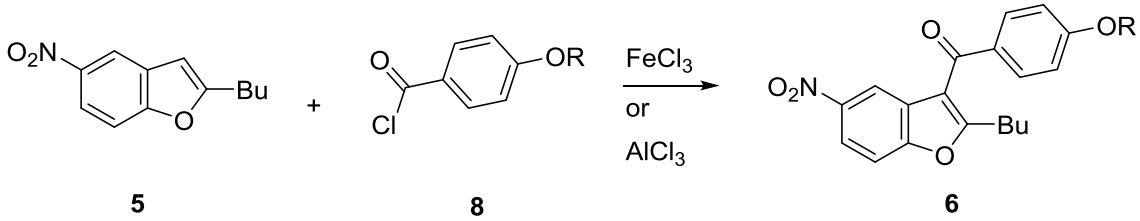
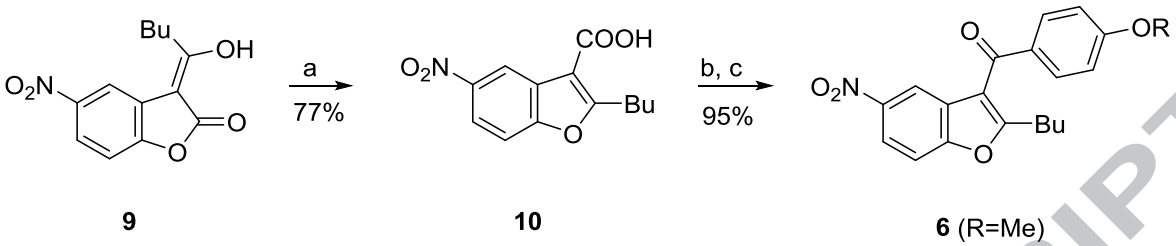


Figure 3. Alternative ways to benzoylate **5**

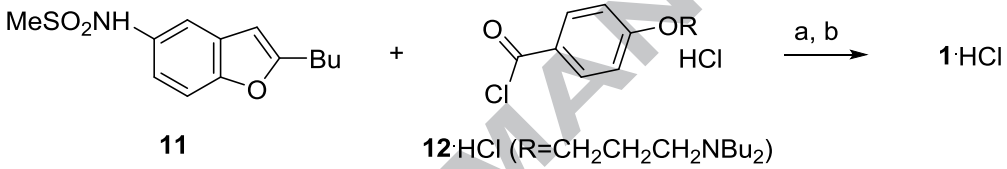
The Friedel-Crafts acylation leading to **6** could also be performed in a highly regioselective manner (less than 5% of *o*-acylation) with the functionalities inverted as shown in Figure 4[13].



a) H_2SO_4, AcOH b) $SOCl_2$ c) p-anisole, $AlCl_3$

Figure 4. Preparation of **6** through acylation with functionalities inverted

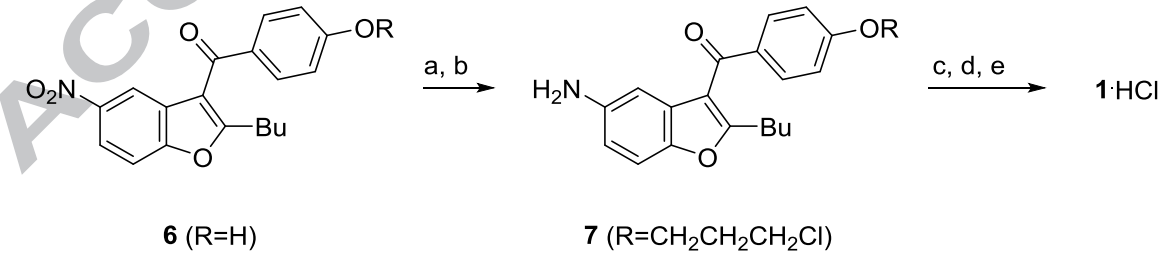
Benzoylation of sulfonamide **11** (Figure 5) using either $FeCl_3$ (yield 86% of **1**)[14] or $SnCl_4$ (yield 65.9% of **1**)[15] made the process a little more convergent.



a) $FeCl_3$ or $SnCl_4$ b) HCl

Figure 5. Benzoylation of sulfonamide **11**

While in the original route phenolic OH in **6** (R=H) underwent etherification with dibutylaminochloropropane (Figure 1, step f), in some of the newer approaches the introduction of the amino group was carried out stepwise. Figure 6 shows the process developed by Mohanarangam *et al.*[12]. Phenolic OH in **6** (R=H) was alkylated with 1-bromo-3-chloropropane. Following reduction of the nitro group and formation of sulfonamide, the chloro derivative was subjected to the reaction with dibutylamine.

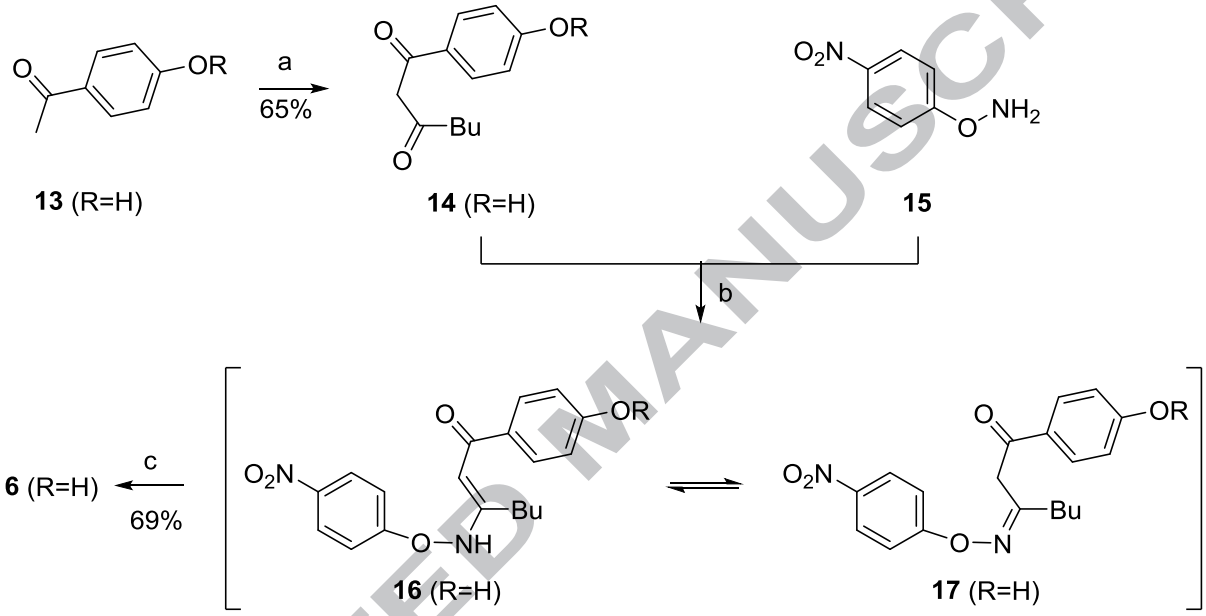


a) 1-bromo-3-chloropropane, K_2CO_3 b) $HCOONH_4$, Pd/C c) MsCl, $NaHCO_3$ d) Bu_2NH e) HCl

Figure 6. Stepwise installation of amino groups in **6** (R=H).

An alternative method[16] used 3-chloro-1-propanol instead of 1-bromo-3-chloropropane as the alkylating agent. Subsequent reaction of **7** (R=$CH_2CH_2CH_2OH$) with mesyl chloride formed sulfonamide at C(5) and converted the hydroxyl into mesylate, which then could be reacted with dibutylamine giving **1**.

In contrast to the syntheses presented above, some of the newer approaches to Dronedarone (**1**·HCl) aimed at achieving the desired substitution pattern already at the stage of the benzofuran system formation, thus avoiding the Friedel-Crafts acylation. A classic example of such strategy is based on an oxo variant of the Fisher indole synthesis and involves the reaction between diketone **14** (R=H) and hydroxylamine derivative **15** (Figure 7).[17]

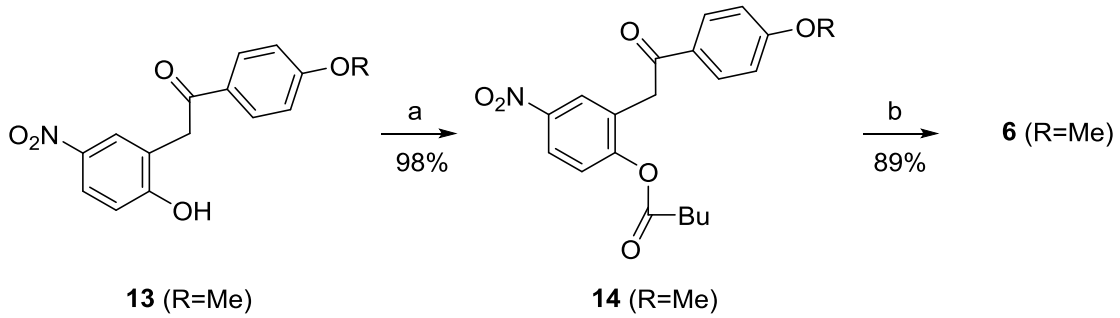


a) BuCOOEt, MeONa b) AcOH, 70-100 °C c) AcOH, water, 70 °C

Figure 7. An oxo variant of the Fisher indole synthesis *en route* to **6** (R=H)

Tautomer **16** (R=H) was then converted into **6** (R=H) by heating in water – acetic acid mixture.

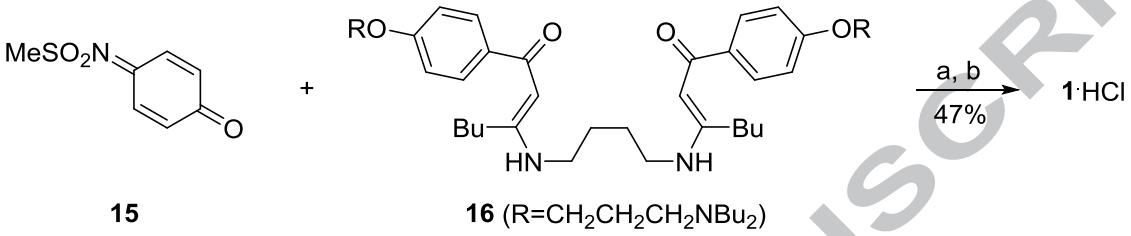
Intermediate **6** (R=Me) was obtained by researchers from Sanofi[18] through cyclization of ketoester **14** (Figure 8).



a) $CH_3(CH_2)_3C(O)Cl$, K_2CO_3 b) Bu_3N, molecular sieves

Figure 8. Benzofuran **6** (R=Me) through cyclization of ketoester **14**

While additional derivatization of **6** (Figure 8, R=Me) was required to obtain **1**·HCl, some of the more recent methods have focused on providing all the required substituents already at the stage of the cyclization reaction. An example of such approach based on a Nenitzescu reaction between quinonimine **15** and enaminone **16** ($R=CH_2CH_2CH_2NBu_2$) was developed by Sanofi-Aventis and is shown in Figure 9.[19]

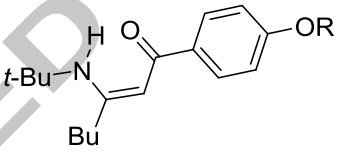


15 **16** ($R=CH_2CH_2CH_2NBu_2$)

a) Glacial AcOH b) HCl

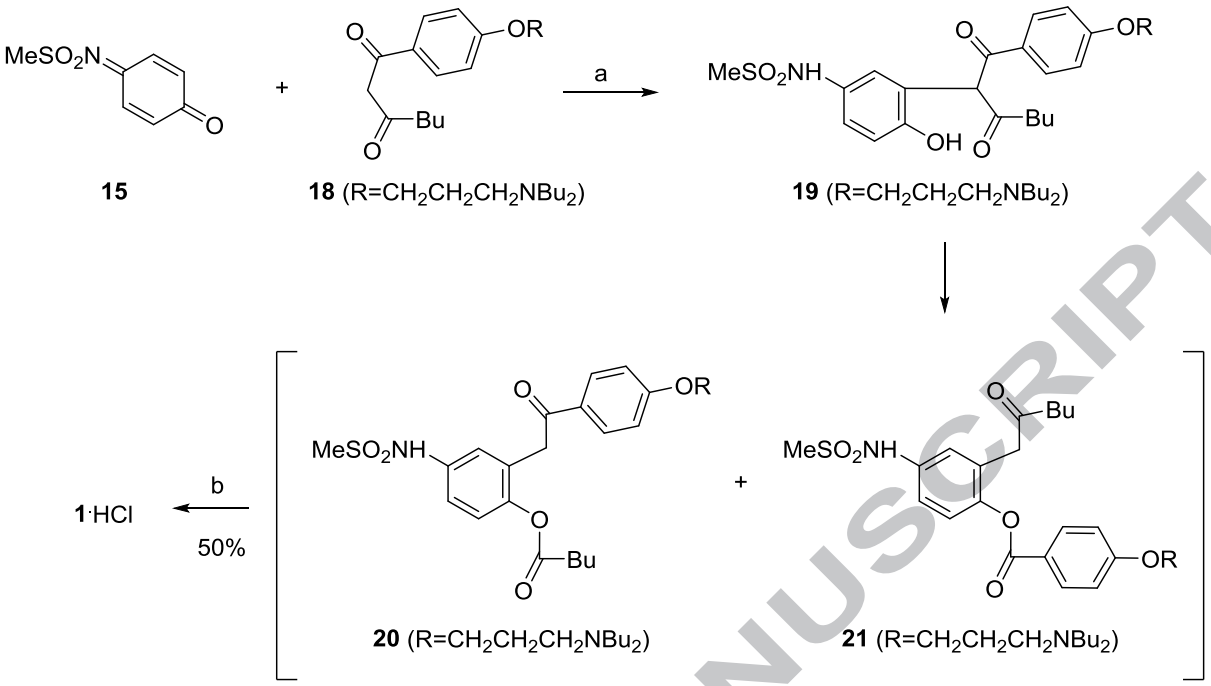
Figure 9. Nenitzescu reaction between quinonimine **15** and enaminone **16**

Instead of **16** ($R=CH_2CH_2CH_2NBu_2$), enaminone **17** ($R=CH_2CH_2CH_2NBu_2$) could also be used (yield 73%).[19]



17 ($R=CH_2CH_2CH_2NBu_2$)

A team from Sandoz and Lek demonstrated that instead of preparing the relevant enaminone, one could further simplify the process by making use of the parent 1,3-diketone **18** ($R=CH_2CH_2CH_2NBu_2$) instead (Figure 10).[20]



a) Et_3N b) Et_3N, $ZnCl_2$

Figure 10. Nenitzescu-like reaction between quinonimine **15** and 1,3-diketone **18**

A mixture of retro-Claisen products **20** and **21** was then converted in the presence of Et_3N and $ZnCl_2$ into the final product in 50% yield, which could serve as an elegant proof-of-concept for such a convergent process.

3. Results and discussion

Recently, our efforts focused on further improvement in the purity and yield of the product. Initially, the stage of formation of a mixture of retro-Claisen products **20** and **21** was investigated. Reaction was carried out in dioxane using 1 equivalent of organic base. The influence of several parameters was checked, among them the quality (dryness) of solvent, the type of base, reaction time, etc. The results are presented in Table 1.

Table 1. Results of optimization of conditions to produce a mixture of **20** and **21**

Run	Dioxane dried over MS	Base	Addition time [min]	Rxn time [h]	Final ratio **18**: (**20**+**21**): **1**
1	no	Et_3N	8	1	13.8: 80.3: 5.5
2	no	Et_3N	10	2	7.2: 81.9: 9.1
3	no	Et_3N	20	2	4.9: 84.3: 9.6
4	no	Et_3N	15	3	2.8: 83.3: 10.9
5	yes	Et_3N	15	2	2.3: 89.4: 1.0
6	yes	Et_3N	15	2	2.8: 93.1: 1.6
7	yes	DIPEA	12	2.5	5.9: 84.9: 1.9
8	yes	DIPEA	17	3	97.3[a]
9	yes	Et_3N	16	3	98.3[a]

[a] no other compounds except **20** and **21** were isolated

Higher conversion was achieved with longer addition time (runs 3, 8, 9) and longer reaction time (runs 8 and 9). A high level of conversion (>97%) could be obtained with either base (DIPEA or Et_3N; runs 8 and 9). Unfortunately, in order to achieve purity required for the next step (formation of **1**) the mixture of **20** and **21** had to be cleaned by column chromatography.

The mixture of **20** and **21** was then subjected to the reaction with varying amounts of $ZnCl_2$ in the presence of tertiary amine such as Et_3N or Bu_3N in various solvents over periods from 1 to 68 h. The results are shown in Table 2.

Table 2. Results of optimization of conditions to produce Dronedarone from a mixture of **20** and **21**

Run	Solvent	Et_3N [eq]	$ZnCl_2$ [eq]	Reflux time [h]	Purity [%]	Yield of **1** [%][a]
1	dioxane	1.5	1.1	18.5	89	88
2	dioxane	1.5	1.2	23	64	80
3	toluene	1.5[b]	[c]	1	[d]	19[e]
4	toluene	1.5	1.1	19	78	quant
5	p-xylene	1.5[b]	[c]	21	[d]	76[e]
6	dioxane	2	0.3	20, 45, 68	[d]	63, 79, 81[e]
7	dioxane	1.5	0.3[f]	24, 44	[d]	79, 95[e]
8	dioxane	1.5	0.27[f]	45	99.3%	75%[g]

[a] Yield based on starting diketone **18**, unless stated otherwise [b] Bu_3N used instead of Et_3N [c] molecular sieves used instead of $ZnCl_2$ [d] product not isolated [e] respectively, conversion rate based on HPLC [f] as 1.0 M solution in Et_2O [g] as hydrochloride **1**·HCl

The type of amine did not seem to matter much (runs 2 and 5). It was not necessary to use more than 1 equivalent of $ZnCl_2$, just 0.3 eq. or less was sufficient (runs 6, 7, 8), preferably in the form of a 1.0 M solution in Et_2O (runs 7, 8). A dehydrating agent such as molecular sieves instead of Lewis acid did not work well (runs 3, 5). To achieve high conversion rates long reflux time was required (runs 7, 8). Run 8 represents optimized set of conditions for the process.

4. Summary and conclusions

A modification of the Nenitzescu reaction was used to obtain Dronedarone base from quinonimine **15** and 1,3-diketone **18** ($R=CH_2CH_2CH_2NBu_2$) in a two-stage process in almost 55% overall yield. Additional work is underway to further simplify the process, in particular to avoid chromatographic purification of **20** and **21**.

5. Experimental

All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. Moisture- or air-sensitive reactions were conducted under nitrogen atmosphere in oven-dried (120 °C) glass apparatus. The solvents were removed under reduced pressure using standard rotary evaporators. Purity of the final compounds was examined by LCMS using Waters Symmetry, C18, 3.9 x 150 mm, 5 µm analytical reverse phase C18 column with 0.1 % HCOOH-water solution, and 0.1%HCOOH-acetonitrile solution gradient and Dionex 3000RS chromatograph with Ultimate DAD-3000 detector at 254 nm. ^{1}H NMR analysis was performed on Varian UnityPlus 200 MHz in $CDCl_3$ or CD_3OD as solvent. Compounds **15** and **18** were synthesized as published by us earlier.[20]

5.1. Mixture of **20** and **21**

To a solution of 1,3-diketone **18** ($R=CH_2CH_2CH_2NBu_2$) (1.0 g, 2.57 mmol) in anh. dioxane (dried over molecular sieves), Et_3N (0. 356 ml, 2.57 mmol) was added followed by dropwise addition of the solution of **15** (0.48 g, 2.57 mmol) in dioxane (5 mL) within 16 min. After addition was completed the brown reaction mixture was stirred for 3 h at RT. The solvent was evaporated (water bath 40 °C) to provide the crude mixture of **20** and **21** as a brown oil. It was purified by column chromatography using hexane : ethyl acetate : Et_3N (1:1:0.15; v/v/v) as eluent (product R_f = 0.5). Fractions containing the desired products were combined to provide a mixture of **20** and **21** as light yellow viscous oil (1.06 g, 72%; purity 98.3%). The mixture was used directly in the next step.

5.2. Dronedarone base (**1**)

The mixture of **20** and **21** (1.05 g, 1.83 mmol) was dissolved in anh. dioxane (15 mL). Triethylamine (0.382 ml, 2.74 mmol) was added followed by 0.5 M solution of $ZnCl_2$ in THF (1.0 mL, 0.50 mmol). The reaction mixture was then refluxed for 45 h, cooled to RT and filtered through a pad of Celite. The charcoal was added to the filtrate and the mixture was stirred for 1 h at 50 °C. Solids were filtered off on a pad of silica and Celite and the cake was washed with dioxane until all product was eluted. The filtrate was concentrated to provide **1** (0.76 g, 1.365 mmol, 75%, HPLC purity 99.3%) as a yellow oil. ^{1}H NMR (ppm, $CDCl_3$): 7.80 (d, 2H), 7.43 (d, 1H), 7.36 (d, 1H), 7.28 (m, 1H), 6.95 (d, 2H), 4.10 (t, 2H), 2.91 (s, 3H), 2.83 (t, 2H), 2.61 (t, 2H), 2.43 (t, 4H), 1.95 (m, 2H), 1.72 (m, 2H), 1.42 (m, 4H), 1.30 (m, 6H), 0.89 (m, 9H).

5.3. Dronedarone hydrochloride (**1**·HCl)

The base **1** (0.76 g, 1.365 mmol) converted to hydrochloride by dissolution in EtOAc (10 mL) followed by dropwise addition of a 2.25 M solution of HCl in Et_2O (0.604 ml, 1.36 mmol) over 5 min. A suspension formed was stirred for 1 h at RT, 1 h at 0 °C. The solid was filtered off and dried to provide **1**·HCl (0.79 g, 98%) as off-white solid, m.p. 142 °C, purity 100%. ^{1}H NMR (CD_3OD, ppm): 7.81 (d, 2H), 7.52 (d, 1H), 7.32 (s, 1H), 7.23 (dd, 1H), 7.10 (d, 2H), 4.26 (t, 2H), 3.43 (m, 2H), 3.23 (m, 4H), 2.90 (m, 5H), 2,30 (m, 2H), 1,79 – 1,71 (m, 6H), 1.50 – 1.42 (m, 4H), 1.37 – 1.30 (m, 2H), 1.03 (t, 6H), 0.89 (t, 3H).

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