# A short synthesis of Dronedarone

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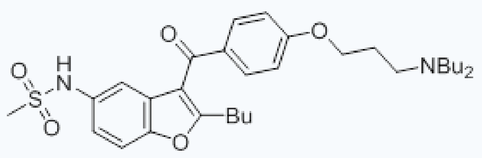
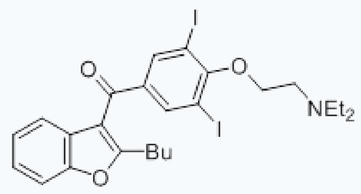
## INTRODUCTION

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]



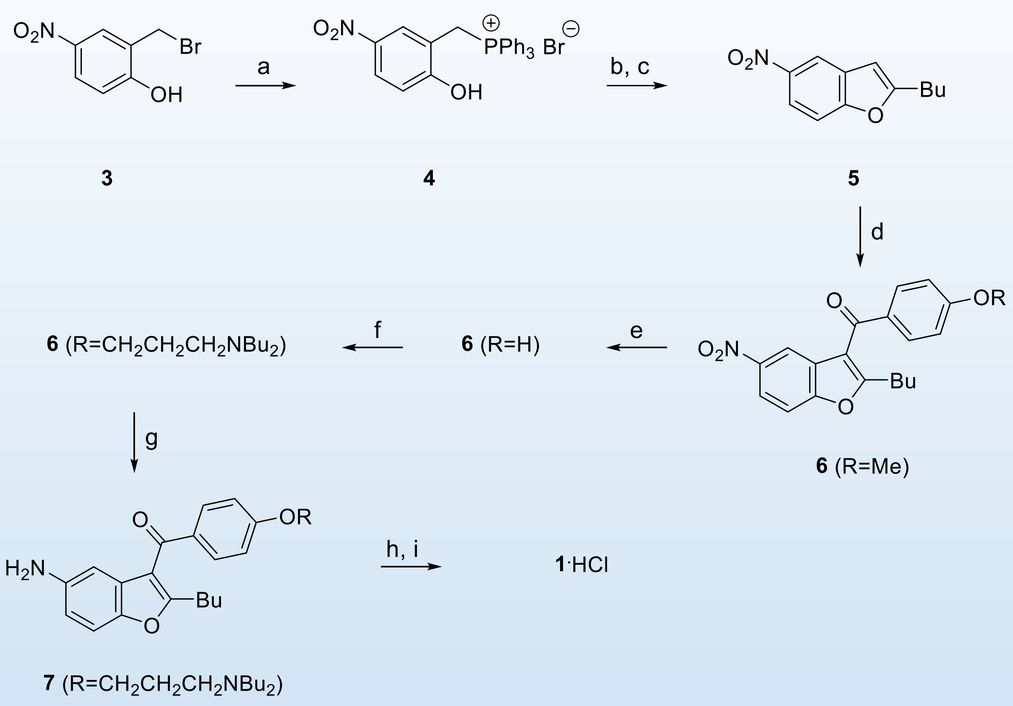
**1**



**2**

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 poster describes the development of a very short process leading to **1** and the outcome of our optimization efforts.

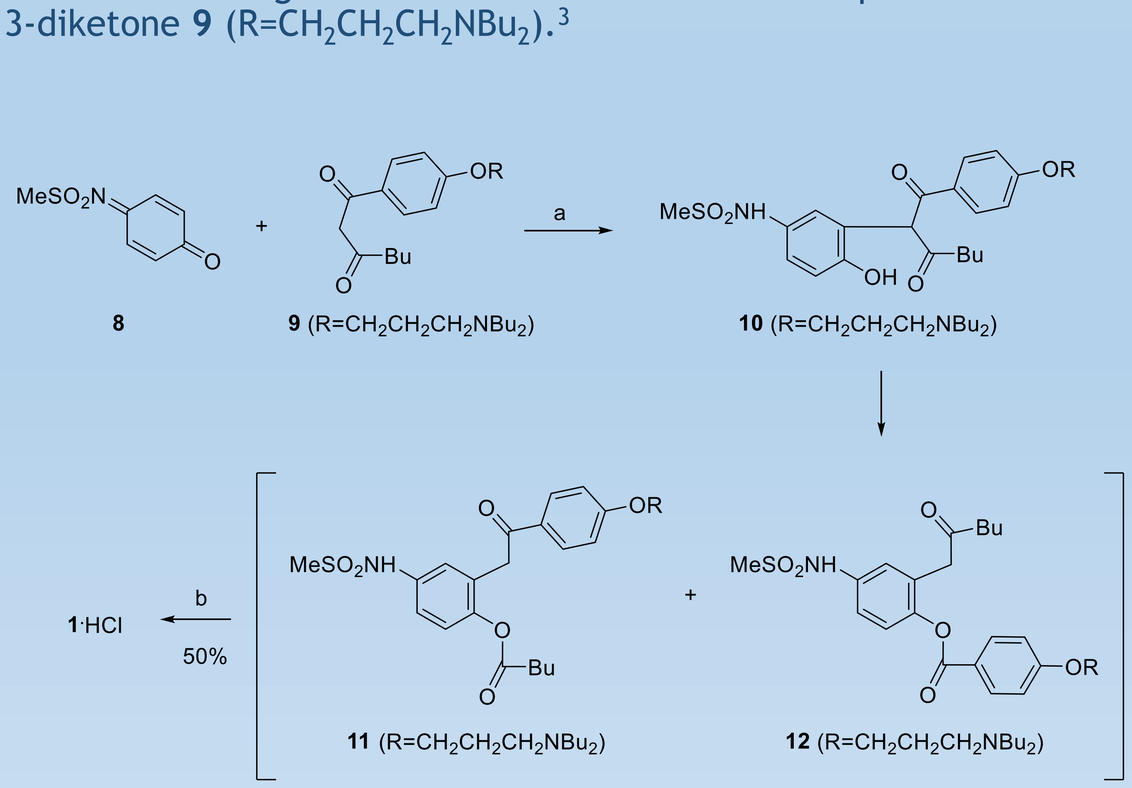
The original method patented over 25 years ago by Gubin *et al.*[2] was based on the construction of a 2,5-disubstituted benzofuran derivative **5** followed by its benzoylation with *p*-anisoyl chloride (Figure 1).




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

## A NEW SYNTHETIC ROUTE

Some of the newer approaches to Dronedarone (1·HCl) aimed at attaining the desired substitution pattern already at the stage of the benzofuran system formation, thus avoiding the Friedel-Crafts acylation (step d above). We decided to provide all the required substituents already at the stage of the cyclization reaction. We have achieved this using a Nenitzescu reaction between quinonimine **8** and 1,3-diketone **9** (R=$CH_2CH_2CH_2NBu_2$).[3]




a) $Et_3N$ b) $Et_3N$, $ZnCl_2$

## OPTIMIZATION RESULTS

Results of optimization of conditions to produce a mixture of **11**and **12** in dioxane are shown in Table 1 below

Table 1

| Run | Dioxane dried over MS | Base | Addition time [min] | Rxn time [h] | Final ratio 9: (11+12): 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 **11** and **12** were isolated

The mixture of **11** and **12** 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

| 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 **9**, 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

## DISCUSSION

Higher conversion was achieved with longer addition time (Table 1; 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 **11** and **12** had to be cleaned by column chromatography.

The type of amine did not seem to matter much (Table 2; 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.

## SUMMARY

A modification of the Nenitzescu reaction was used to obtain Dronedarone base from quinonimine **8** and 1,3-diketone **9** (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 **11** and **12**.

## REFERENCES

1. Laughlin, J. C.; Kowey, P. R. *J. Cardiovasc. Electrophysiol.* **2008**, *19*, 1220-1226.
2. Gubin, J.; Lucchetti, J.; Inion, H.; Chatelain, P.; Rosseels, G.; Kilenyi, S. EP471609 A1 1992.
3. Richter, F.; Schreiner, E.; Pirc, S.; Copar, A. WO2012062918 A1, 2012.