# Synthesis of intermediates useful for the preparation of Etripamil

*V. Pagliari, G. Lucca, S. Saponaro, E. Bernardi, R. Rossi, S. Mantegazza*

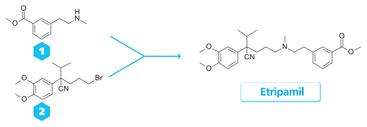
## Introduction

**Etripamil is a short-acting non-dihydropyridine L-type calcium-channel blocker and is currently in phase 3 clinical trial.** The main advantage of **Etripamil** consists in **the innovative method of administration**: the intranasal application. It has been formulated as a **nasal spray for self-administration by patients** who experience paroxysmal supraventricular tachycardia (PSVT) recurrences with a rapid onset of action without hospitalization [1].

**Etripamil**, as described in the patent application WO 2016/165014 [2], is currently synthesized through a convergent synthesis which ultimately involves a **reaction between compound 2 and compound 1**.

**This synthesis has several critical issues including:**

- **the use of toxic gases** (KCN, $Me_2SO_4$) which can only be handled by authorized personnel;
- **the lack of control of the stereocenter** requiring a final resolution step (only the (S) enantiomer of Etripamil shows the desired pharmacological activity);
- **the need to purify some intermediates** with a chromatographic column.

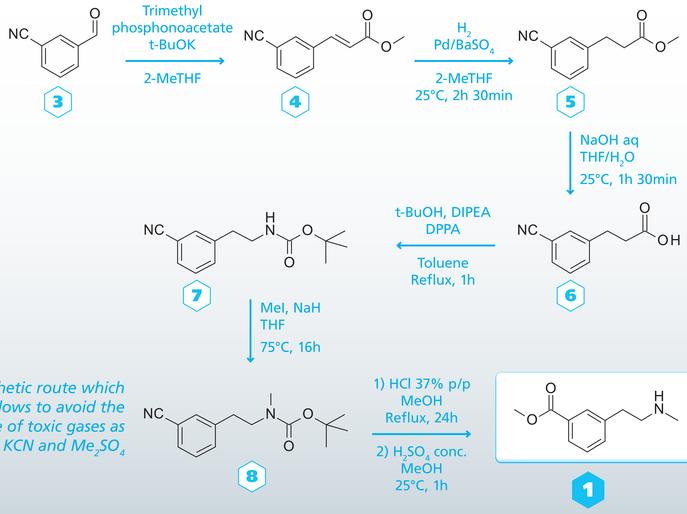



## Aim of the work

**In this work, possible synthetic alternatives** were evaluated compared to that reported in the Milestone Pharmaceuticals patent (WO 2016/165014) to obtain synthon 1. Subsequent coupling and reductive amination lead to the formation of **Etripamil**.

**The final aim was to produce a generic drug of Etripamil**, through an **economical, non-infringing and industrially scalable process**, which **avoids the use of toxic substances** such as KCN and $Me_2SO_4$ and with a control of the stereocenter.

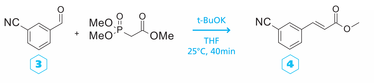
## Synthesis of compound 1




*Synthetic route which allows to avoid the use of toxic gases as KCN and $Me_2SO_4$*




## 1 Horner-Wadsworth-Emmons

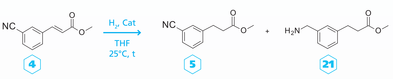



| Experiment | Eq | Volume THF | Acid (workup) | Yield* |
|---|---|---|---|---|
| 1 [4] | 2,17 | 45 | $NH_4Cl$ (saturated sol.) | 51% |
| 2 | 1,3 | 45 | $NH_4Cl$ (saturated sol.) | 83% |
| 3 | 1,3 | 45 | HCl 36%p/p | 84% |
| **4** | **1,3** | **18** | **HCl 36%w/w** | **90%** |

Exp.1: Procedure from literature
Exp.2,3,4: Optimization

**Yields calculated based on NMR assay*

## 2 Catalytic hydrogenation

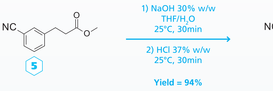



| Experiment | Catalyst | Pressure (bar) | Time (h) | Ratio** 30/31 |
|---|---|---|---|---|
| 1 | Pt/C 10% R/W | 10 | 16 | 1:1 |
| 2 | Pt/C 10% R/W | 1 | 1 | 6,6:1 |
| 3 | Pt/C 10% R/W | 1 | 3,4 | 4,5:1 |
| 4 | Pd /C 10% | 1 | 1 | 1:2,6 |
| 5 | $PtO_2$ | 1 | 4,3 | 10:1 |
| **6** | **$Pd/BaSO_4$ 5%** | **1** | **1,3** | **19.5:1** |
| **7** | **$Pd/CaCO_3$ 5%** | **1** | **2** | **18,4:1** |

Yield* > 90%

*** product: by-product ratio calculated using two significant signals from the NMR spectrum.*

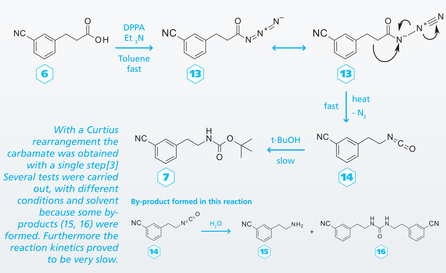
## 3 Saponification




**Yield = 94%**

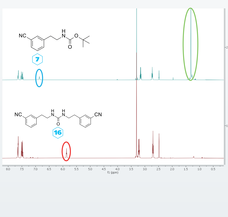
Total Yield:
HWE+ hydrogenation+ saponification = 83%

## 4 Curtius rearrangement

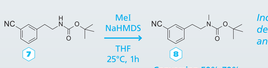



*With a Curtius rearrangement the carbamate was obtained with a single step[3] Several tests were carried out, with different conditions and solvent because some by-products (15, 16) were formed. Furthermore the reaction kinetics proved to be very slow.*

*$^1$H NMR spectra of product 7 and by-product 16.*



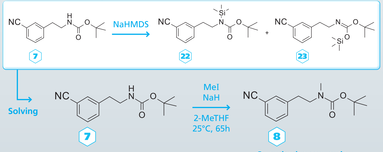

## 5 Carbamate methylation



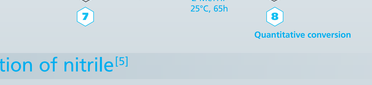

**Conversion 50%-70%**

*Incomplete conversion despite the excess base and methylating agent.*

**Possible cause of incomplete conversion**

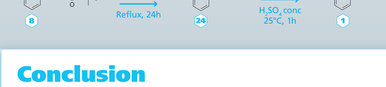



*Silylation of oxygen and/or nitrogen*
↓
*Hypothesis confirmed by $^1$H-NMR spectrum*




**Quantitative conversion**

## 6 Deprotection and esterification of nitrile[5]




## Conclusion

Alternative syntheses for compounds 1 were developed and optimized. **A patent application has been submitted.**

**REFERENCES**

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