Synthesis of intermediates useful for the preparation of Etripamil

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

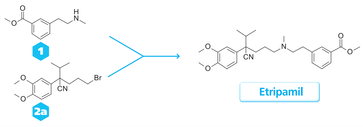
Introduction

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 2a 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.

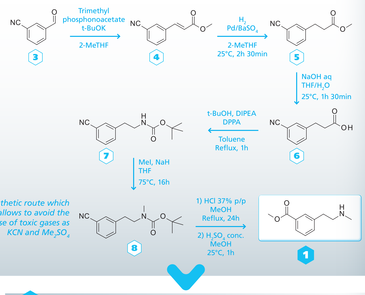


Aim of the work

In this work, possible synthetic alternatives were evaluated compared to that reported in the Milestone Pharmaceuticals patent (WO 2016/165014) to obtain synthon 1 and 2b. Subsequent coupling and reductive amination lead to the formation of **Etripamil**.

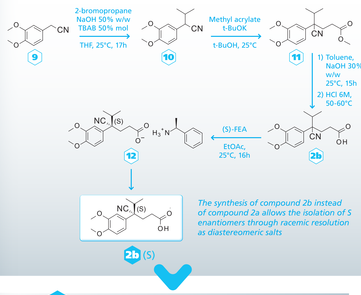
The final aim was to produce a generic drug of Etripamil, through an **economical, non-infringing and industrially scalable process**, which **avoids the use of toxic substances** such as KCN and Me_2SO_4 and with a control of the stereocenter.

Synthesis of compound 1



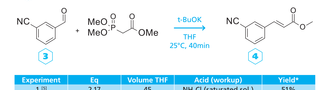
Synthetic route which allows to avoid the use of toxic gases as KCN and Me_2SO_4

Synthesis of compound 2b



The synthesis of compound 2b instead of compound 2a allows the isolation of S enantiomers through racemic resolution as diastereomeric salts

1 Horner-Wadsworth-Emmons

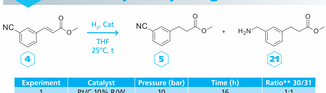


Experiment	Eq	Volume THF	Acid (workup)	Yield*
1 [1]	2,17	45	NH_4Cl (saturated sol.)	51%
2	1,3	45	NH_4Cl (saturated sol.)	83%
3	1,3	45	HCl 36%p/p	84%
4	**1,3**	**18**	**HCl 36%w/w**	**90%**

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	Pd/C	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%

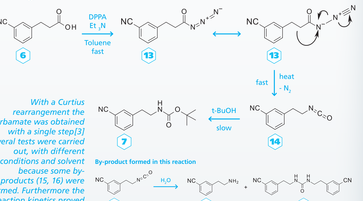
*** product: by-product ratio calculated using two significant signals from the NMR spectrum.*

3 Saponification

Yield = 94%

Total Yield:
HWE+ hydrogenation+ saponification = 83%

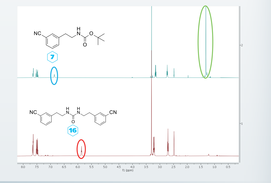
4 Curtius rearrangement



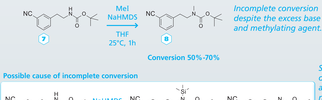
With a Curtius rearrangement the carbamate was obtained with a single step[3] Several tests were carried out, with different conditions and solvent because some by-products (15, 16) were formed. Furthermore the reaction kinetics proved to be very slow.

By-product formed in this reaction

^{1}H NMR spectra of product 7 and by-product 16.



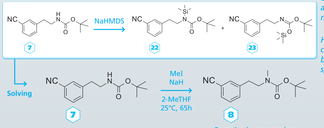
5 Carbamate methylation



Conversion 50%-70%

Incomplete conversion despite the excess base and methylating agent.

Possible cause of incomplete conversion

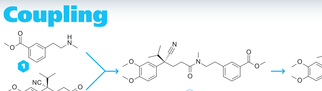


Silylation of oxygen and/or nitrogen

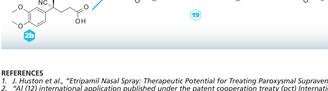
Hypothesis confirmed by ^{1}H-NMR spectrum

Quantitative conversion

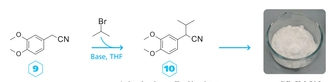
6 Deprotection and esterification of nitrile[6]



Coupling



1 Step 1



Isolated and crystallized in mixture MeOH H2O 4:2, T= 40°C

NOT SHOWN ON THE PATENT

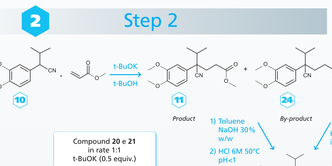
mp (°C): 53.0-54.3

Optimization	Base (1 eq.)	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)
1	LiHMDS 1.3M in THF	-20	4	~ 86	80.6
2	NaHMDS 1.9M in THF	-20	4	~ 94	82
3	NaHMDS 1.9M in THF	0	4	~ 88	78.2
4	**NaHMDS 1.9M in THF**	**20**	**2**	**~ 97**	**83**

Screening of Bases	Base	pKa	Reaction solvent	Yield (%)
1	**NaHMDS (1 equiv.)**	**26 [7]**	**THF**	**83**
2	LDA (1.3 equiv)	35,7 [8]	THF	68
3	t-BuOK (1 equiv.)	17	t-BuOH	tracce
4	NaOH 50% p/p	14 [9]	THF	64

Generation of LDA in Flow

LDA is a very useful and versatile strong base, widely utilized due to its good solubility in organic solvents and non-nucleophilic nature. Its thermal decomposition, to generate LiH, is well known [10] and its use in industrial manufacture may be undesidered or limited for safety concern. Generation and use in flow may overcome most of the safety issues and enable its use in process development.



	LDA generation time (min)	Yield (%)
Batch	120	65
Flow	65	62.7

Results:
Yields in step 1 of the two trials, batch and flow, are comparable

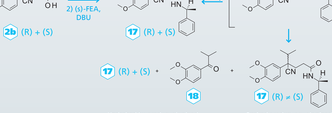
Compatible reaction conditions for the continuous generation of LDA at room temperature

2 Step 2

Compound **20** e **21** in rate 1:1 t-BuOK (0.5 equiv.)

Yield: 71,4%

3 Optical Resolution[11]



Yield: 28.3%

The optical resolution was accomplished by cristallization of diastereomeric salts. From the data obtained, the purity of the salt formed with the (S) enantiomer of verapamyl acid is approximately 98,4%. The purity can however be increased by providing a re-cristallization step.

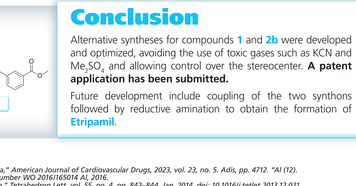
4 De-epimerization

Undesired by-product obtained

Desired product not obtained

Verapamilic acid enantiomers resolution through the synthesis of diastereomers with chiral pools like (R) or (S)-FEA. By adding a base, the retro-Michael addition can then take place and could drive the diastereomeric ratio in favor of the termodinamically more stable diastereoisomer. One diastereomer should be formed preferentially [4]. Several trials were conducted but none of them gave the expected results.

The diasteromeric ratio was monitored by the two NMR signals in the figure



Conclusion

Alternative syntheses for compounds **1** and **2b** were developed and optimized, avoiding the use of toxic gases such as KCN and Me_2SO_4 and allowing control over the stereocenter. **A patent application has been submitted.**

Future development include coupling of the two synthons followed by reductive amination to obtain the formation of **Etripamil**.

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