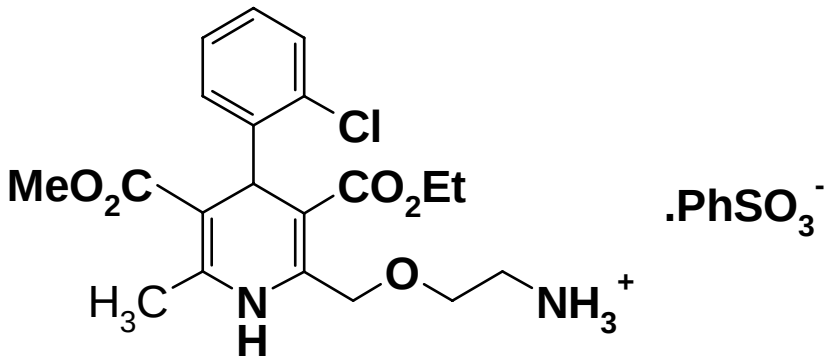
Removal of Azide Protection in the Identification and Development of a Manufacturing Process to Amlodipine

Alan Pettman

Pfizer Global Research and Development

Amlodipine besylate

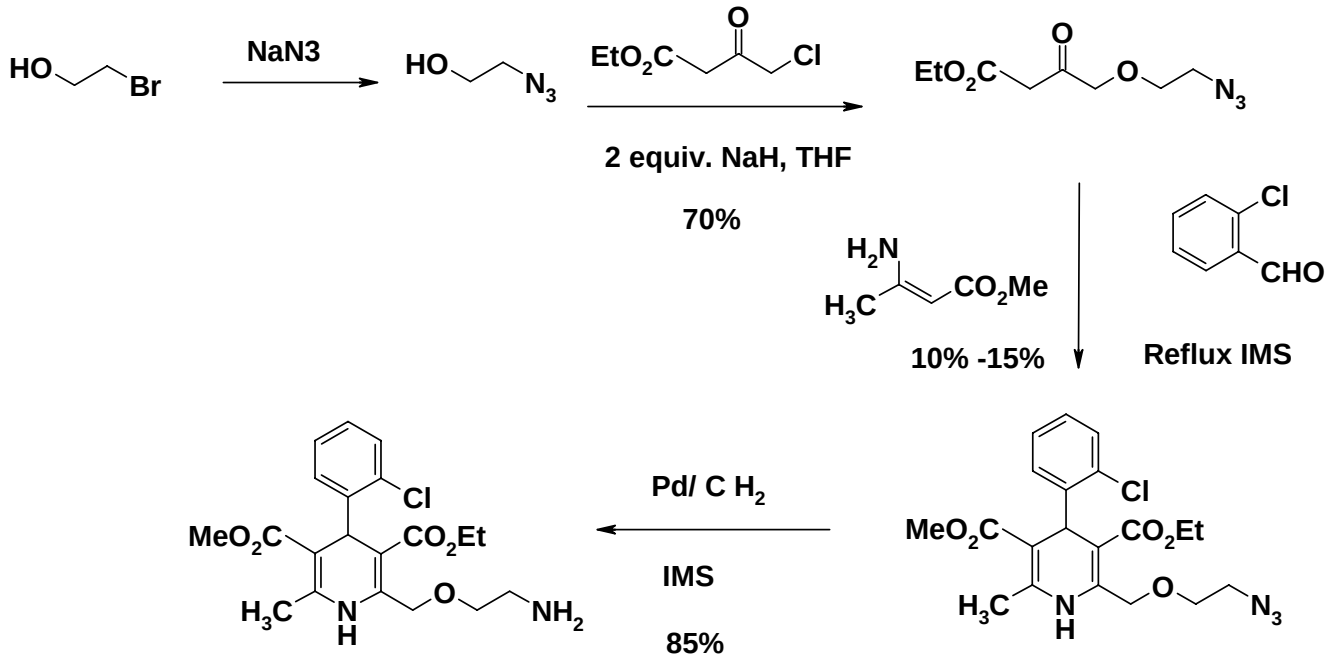


- Calcium Antagonist for the Treatment of Ischemic Heart Disease and Hypertension
- Gradual onset of action, once-a-day dosing regimen and exceptional patient acceptance
- Known as ISTIN™ in the U.K
- NORVASC® is the trademark in the rest of the world
- Marketed as the racemate

Some key data

- Discovered in the UK in 1982
- Development started in 1982
- Launched in the U.K. in 1989
- Third biggest selling drug in 2004 with worldwide sales for the treatment of angina and hypertension of $4.6 billion
  - Now ranked number 9

Discovery Synthesis – single pot Hanztsch

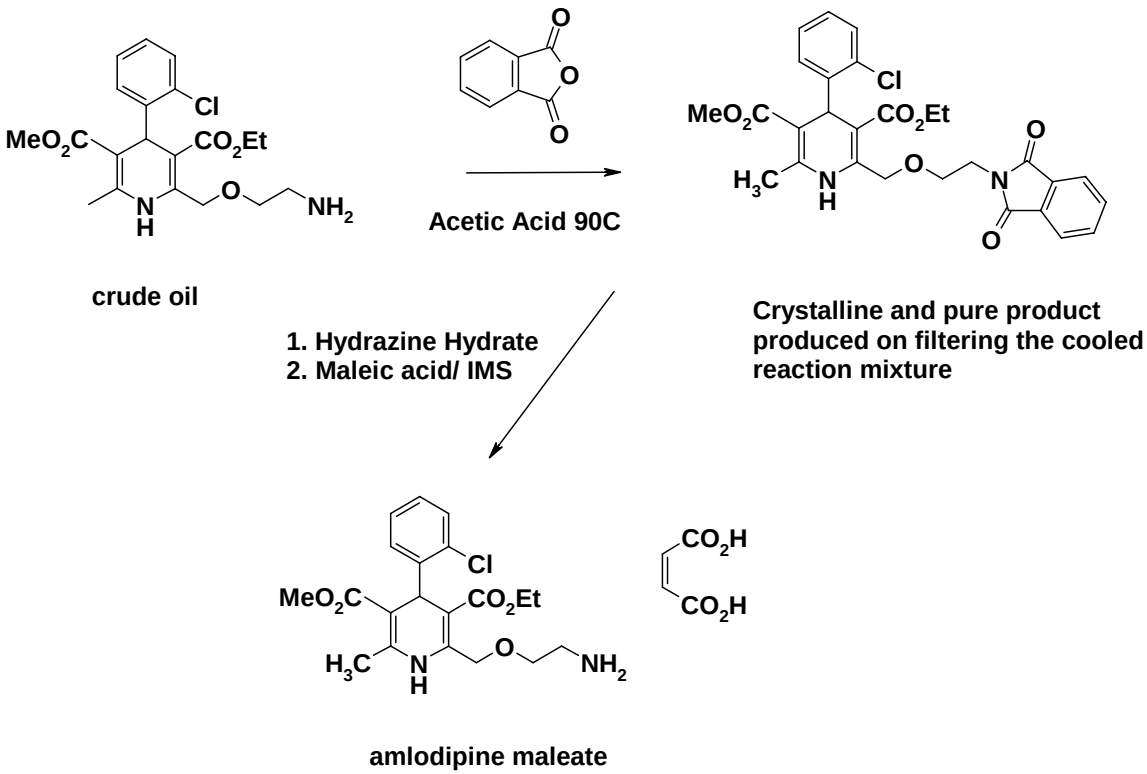


Issues

- Safety – Azido ethanol is a shock sensitive explosive*
- Efficiency – Very poor Hantzsch reaction with the product isolated by chromatography
- Robustness – Difficult to control de-chlorination in the azide reduction step
- Quality – Unable to achieve regulatory quality by chromatography and multiple crystallisations

* Appleby, I. C. Process Res. Dev. Dep., Pfizer Cent. Res., Sandwich/Kent, UK. Chemistry & Industry (London, United Kingdom) (1986), (10), 337.

Purification by derivative formation

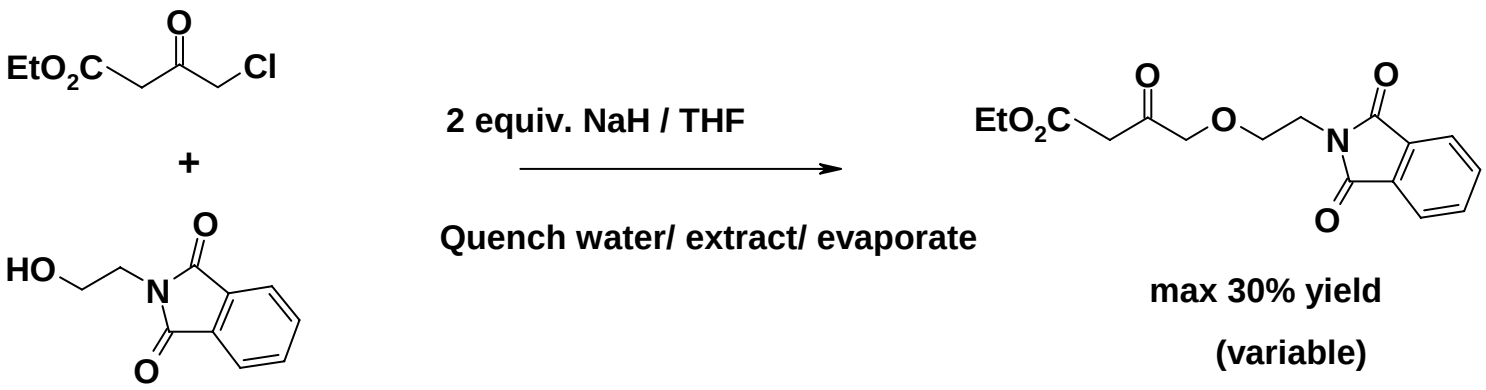


- Prepared material for pre clinical toxicity studies – 48gms!
- But introduced toxic hydrazine

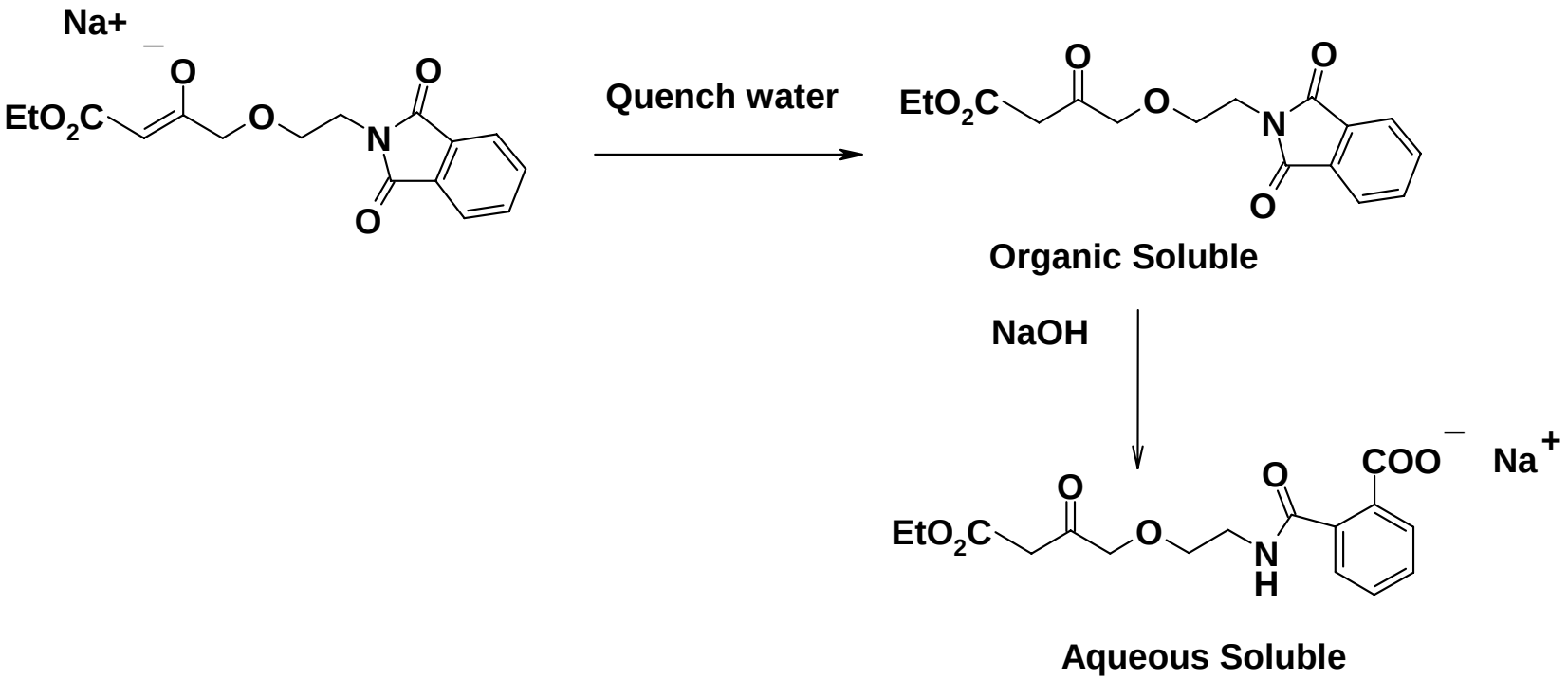
Towards a commercial synthesis

- Fundamentally locked into a Hantzsch synthesis

- Main focus was selection of the N-protecting group
  - A number of different protecting groups were tried but the phthalimide was selected for our main focus given its crystallinity and ease of purification
  - However the ether preparation was capricious in discovery

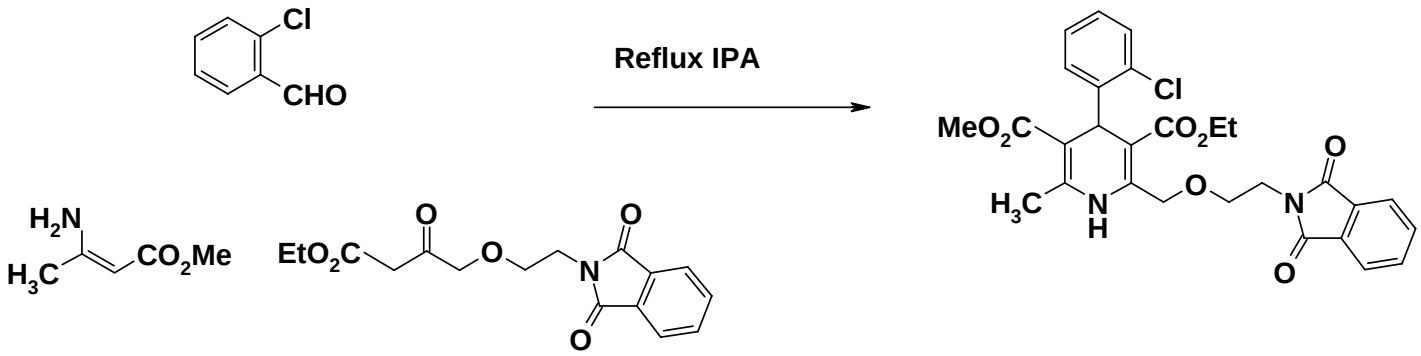


Understanding the mass balance

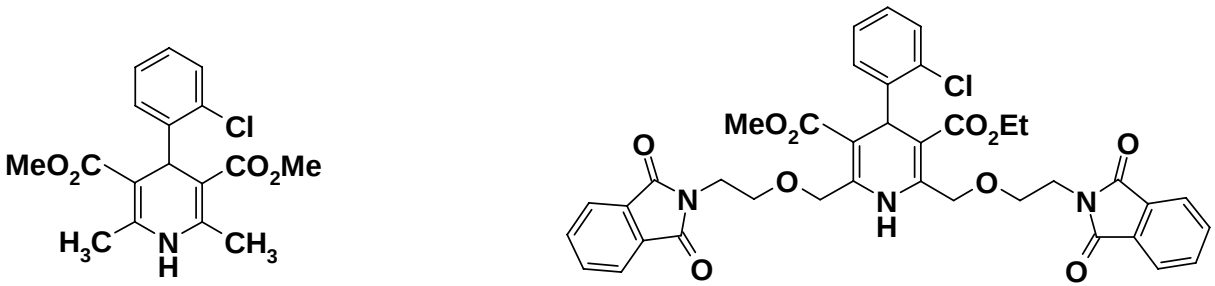


- Product of the reaction is the sodium salt and quenching directly into water produces hydrolysis to a water soluble by-product
- Quenching into 1N HCl then extraction produced product in 70% assayed yield
- Later changed to tBuOK/ toluene to avoid the use of NaH, with acetic acid neutralisation prior to aqueous workup
- Used as a crude oil directly in the Hantzsch reaction

Hantzsch reaction (single pot)

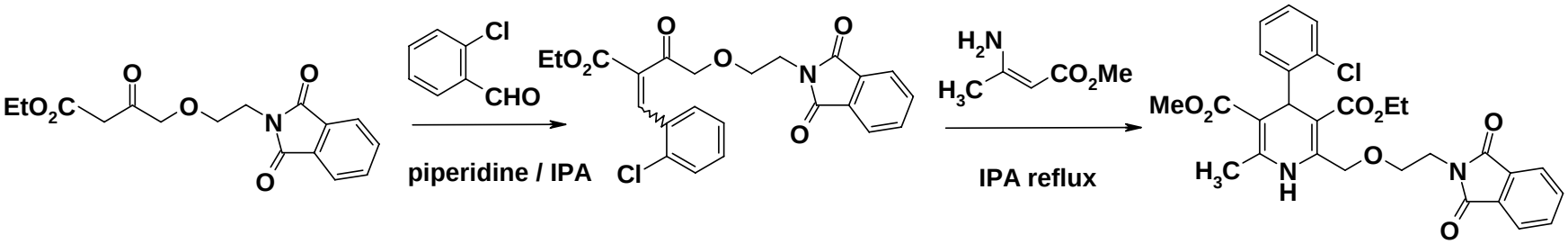


Product was isolated from IPA without chromatography in a disappointing 20% yield



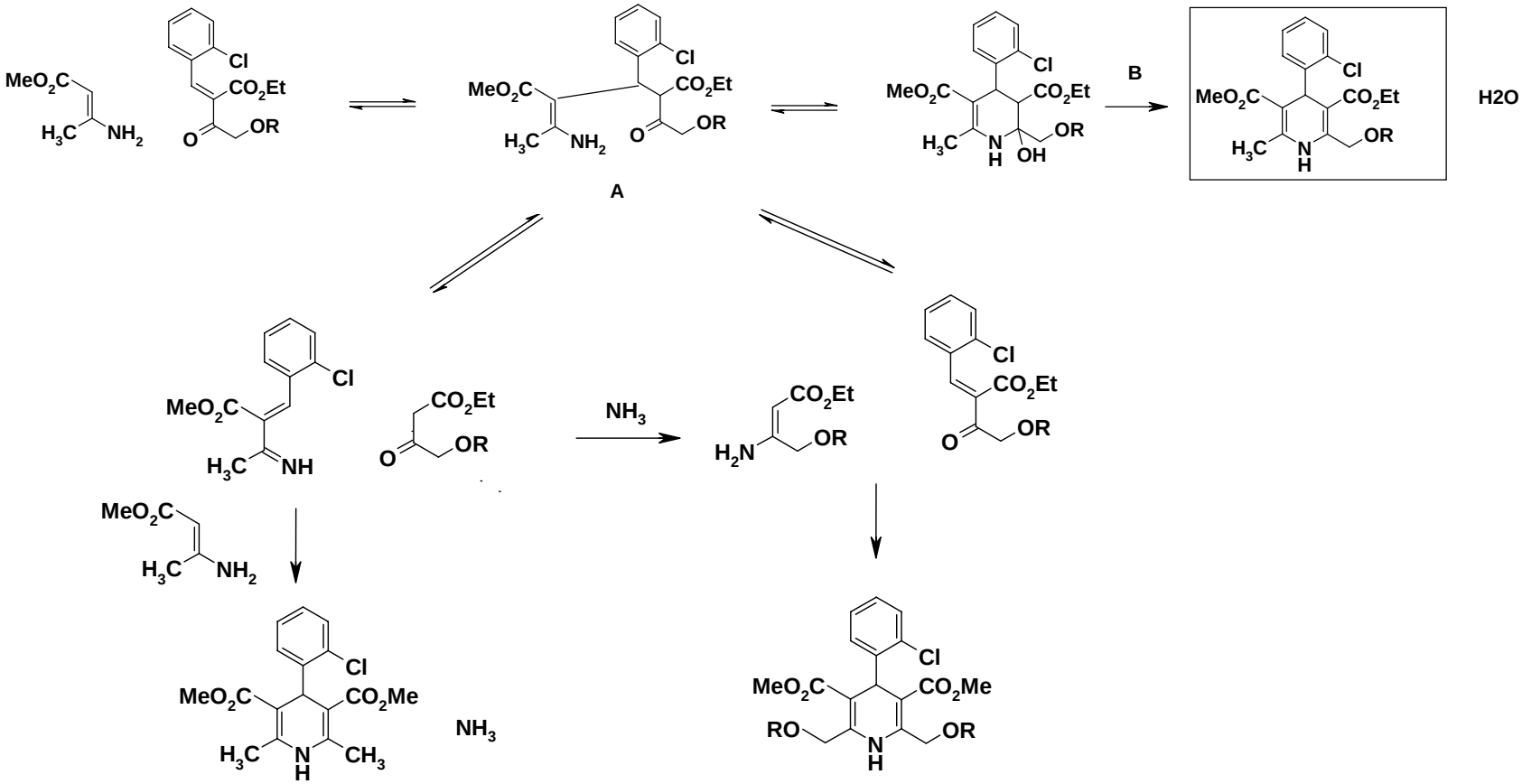
Main products were the symmetrical Hantzsch products

Two component Hantzch



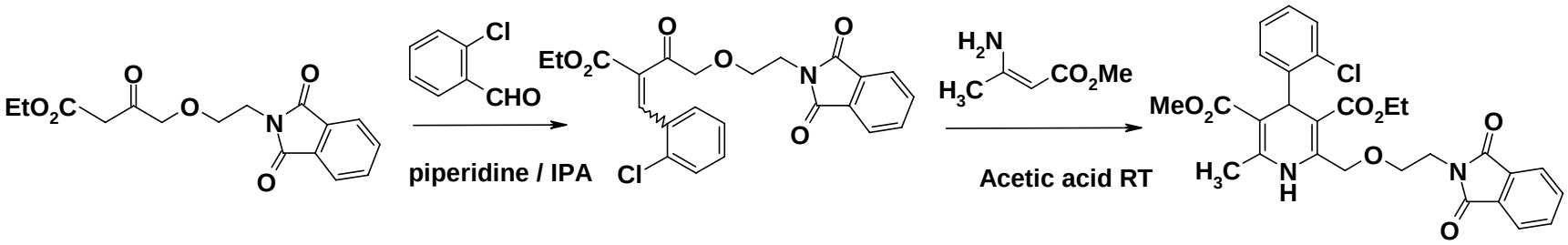
- Moved to a two stage Hantzsch reaction via the Knoevenagel product
- Product isolated in a modest 40% yield
- Symmetrical dihydropyridine products still formed suggesting some “scrambling” of the knoevenagel intermediate

Understanding the “scrambling” mechanism



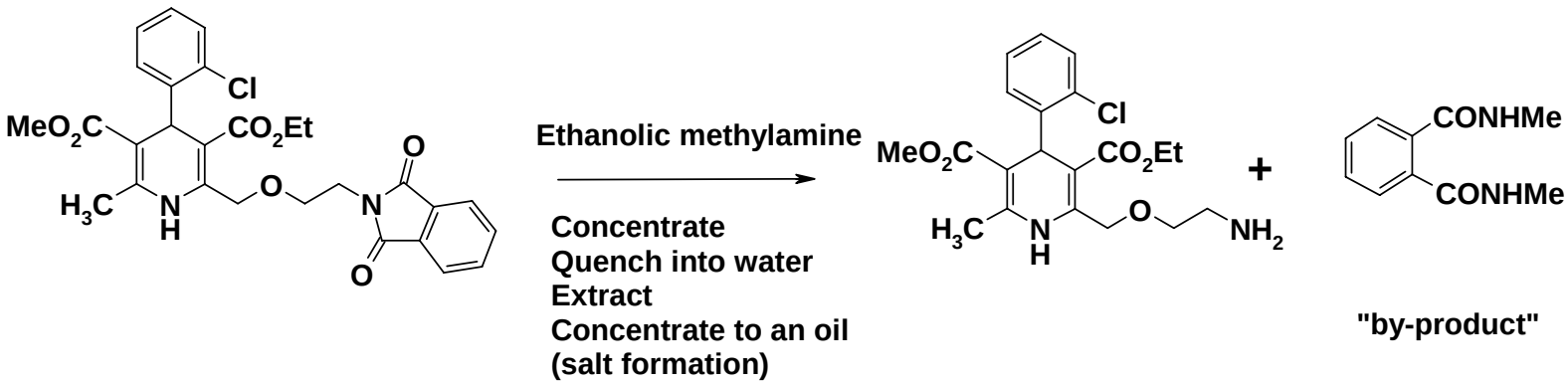
- Proposal that addition of acid would possibly decrease the equilibrium concentration of intermediate A by increasing the rate of the elimination step B
- Shown previously that acetic acid is a very good crystallisation solvent for the Hantzsch product
- What about acetic acid as the reaction solvent?

Hantzsch Reaction in acetic acid



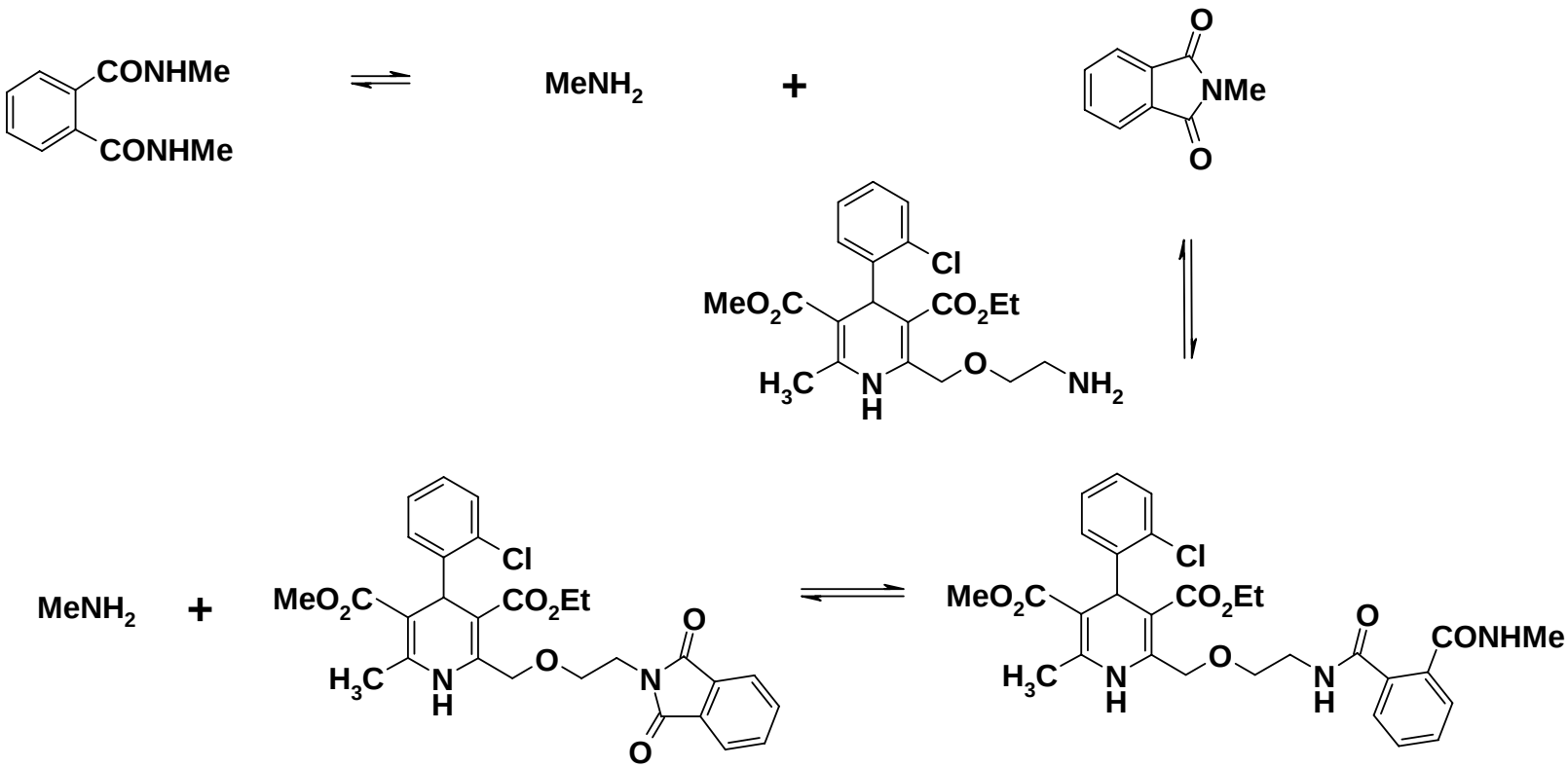
- Product was filtered from the acetic acid solution in 85-90% yield after reaction at RT

Phthalimide deprotection steps



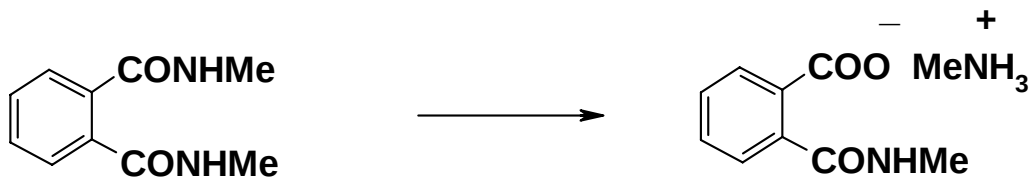
- Main objective was to find an alternative to hydrazine
- 33% ethanolic methylamine selected
- Chemistry worked well on small scale but yields and quality plummeted on scaleup with the formation of starting material
- Workup by concentration, quench with water, extraction and evaporation

Reversibility in the deprotection



- Reaction is reversible and needs excess methyl amine to be present
- Suggestion that on scale-up the methylamine distils off faster than small scale therefore effecting the equilibrium

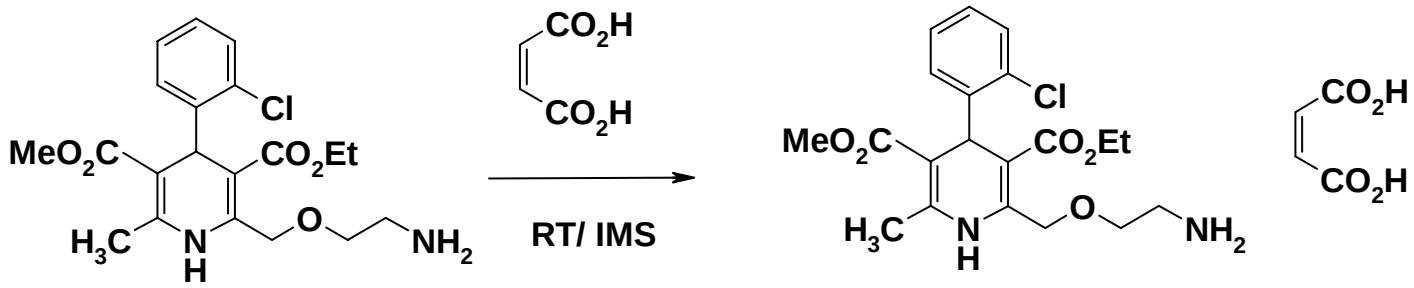
De-protection in aqueous methylamine



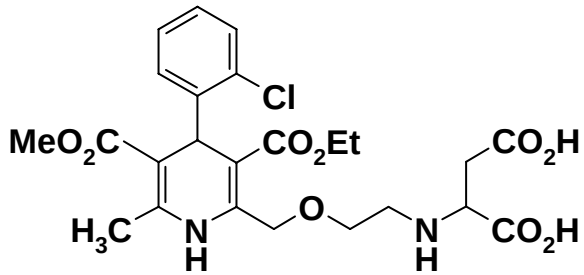
- Literature NMR study showed that the by-product of the deprotection, rapidly and irreversibly hydrolyses in water (neighbouring group participation)

- Simply stirring the phthalimide in 40% aqueous methylamine at room temperature overnight then filtering, produced amlodipine free base in 92-95% yield
  - First time amlodipine free base had been seen as solid after several years of development

Salt form

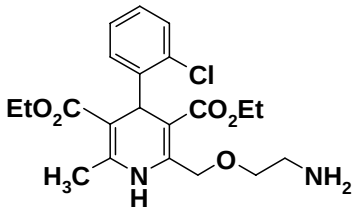


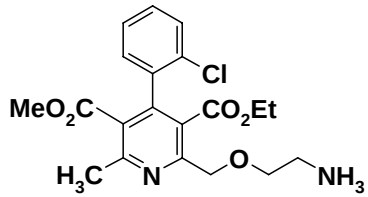
- Maleate salt form was used for early development but produced formulation problems, both stability and processing
- Also scaleup issues during the preparation and maleate salt recrystallisation resulting from “aspartic acid” formation (michael addition)
  - Also a formulation degradant



Amlodipine besylate and benzene sulphonic acid issues

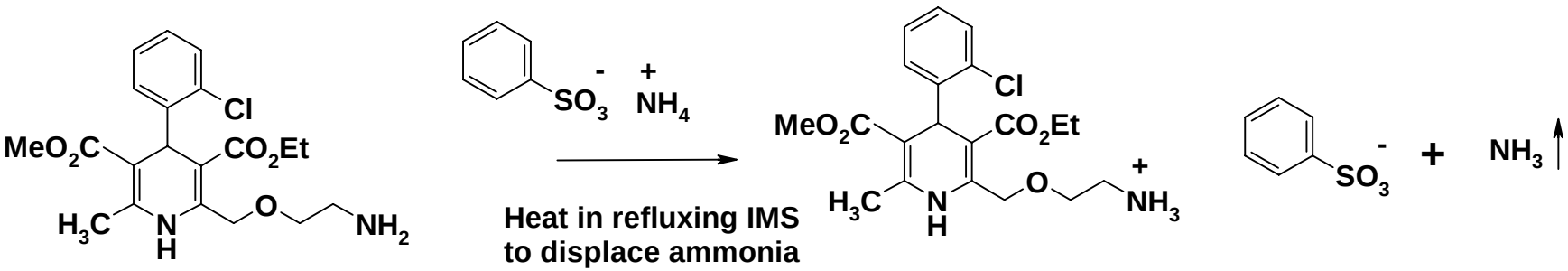
- After a detailed alternative salt screening program, the besylate salt was selected for further development on the basis of a number of unexpected performance characteristics
- Initially prepared by the addition of benzenesulphonic acid to amlodipine free base in IMS
- However, benzene sulphonic acid is a waxy impure solid which would be difficult to handle on large scale
- Commercial sources of benzene sulphonic acid were also impure containing benzene, sulphuric acid, and the sulphone
- During the salt formation, significant levels of the oxidised pyridine product were formed along with some of the diethyl ester derivate of amlodipine by transesterification





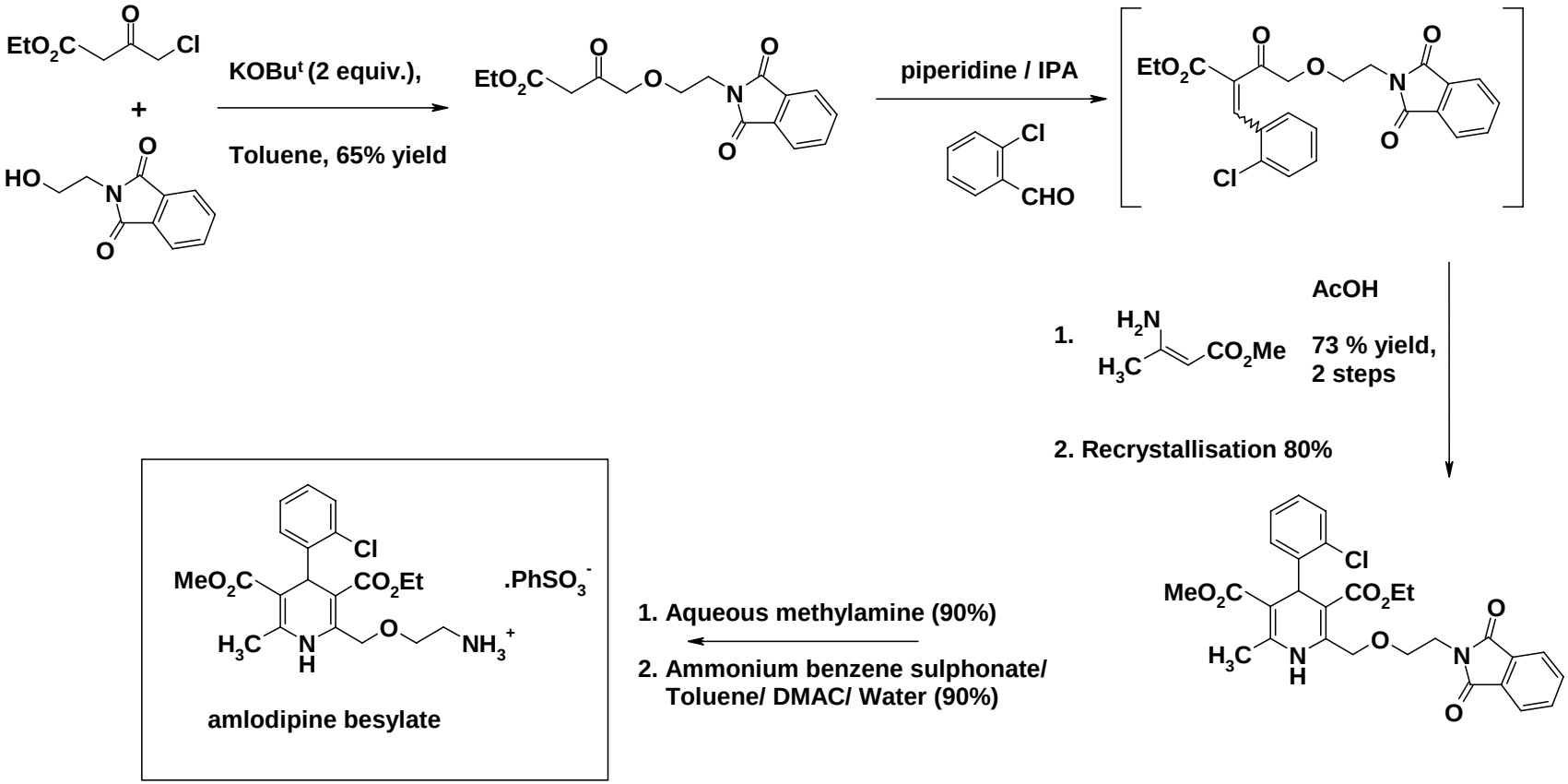
- There were also concerns about ethyl besylate formation
- Proposed than effectively buffering the salt formation would prevent impurity formation which were all thought to be acid catalysed
- So we decided to prepare and use the ammonium salt of benzene sulphonic acid which also helped purify the crude benzene sulphonic acid

Use of ammonium besylate



- Heating amlodipine free base in IMS with ammonium besylate then cooling and filtering produced product with minimal oxidation and transesterification in 90-95% yield
- No detectable ethyl besylate formation
- However, **<u>just before</u>** the NDA filing it was decided that we needed to rapidly identify and alternative process to prepare the besylate salt which did not have the potential to form ethyl besylate
- The process was rapidly changed to an ammonium besylate/ DMAC/ Toluene/ water system

Process Summary



Acknowledgements

Process R+D

- Arthur Bentley (Retired)
- Mark Glanfield (Retired)
- Ian Sinclair (Retired)
- Paul Higginson
- Alan Pettman

Analytical

- Peter Brewer (Retired)
- Anne Berry (Retired)

Pilot Plant

- Derrick Morgan (Retired)
- Dave Sims (Retired)