Worldwide Pharmaceutical Sciences

Molecules to Market

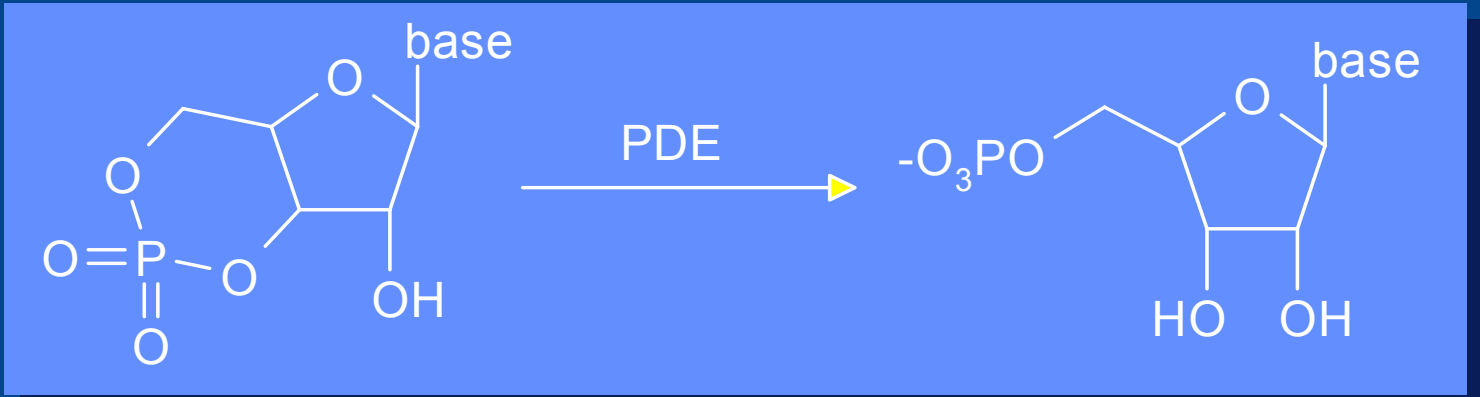
The Chemical Development of Tofimilast, a PDE4 Inhibitor for Asthma and COPD

Lorraine Murtagh

Chemical Research and Development, Pfizer, Sandwich, UK

The Role of Phosphodiesterases

- PDE (Phosphodiesterase) family:
- Intracellular enzymes that hydrolyse cyclic nucleotides (cAMP, cGMP) – important intracellular second messengers



PDE4

- Predominant PDE found in inflammatory cells and airway smooth muscle
  - Hydrolyses cAMP; inhibition of PDE4 - cAMP↑
  - Leads to broad-spectrum anti-inflammatory effects
    - e.g. airway smooth muscle relaxation, reduced inflammatory cell activation

PDE4 inhibitors for the Treatment of COPD and Asthma

Asthma

- Tightening of airways after contact with irritant (asthma trigger)
  - e.g. smoking, pollen, animals, house-dust mites
- Lining of airways becomes inflamed, build up of mucus
- Leads to further airway narrowing and breathing difficulty

- 5.2 m people in UK currently treated for asthma
  - includes 1.1 m children
- 1 in 5 UK households has an asthma sufferer

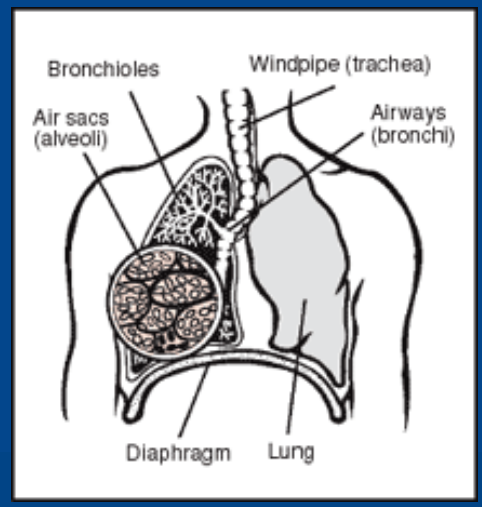
(source: www.asthma.org.uk)

- Asthma treatment: ICS are the gold std
- Still opportunities for new therapies – esp. pediatrics

PDE4 inhibitors for the Treatment of COPD and Asthma

COPD (Chronic Obstructive Pulmonary Disease)

- Accelerated, largely irreversible decline in lung function; includes:
  - Chronic bronchitis –inflammation of bronchi, mucus↑, cough
  - Emphysema – loss of alveolar elasticity, shortness of breath



- Some elements of inflammatory response insensitive to steroids
- Steroids less effective for COPD – critical need for new therapies

PDE4 inhibitors for the Treatment of COPD and Asthma

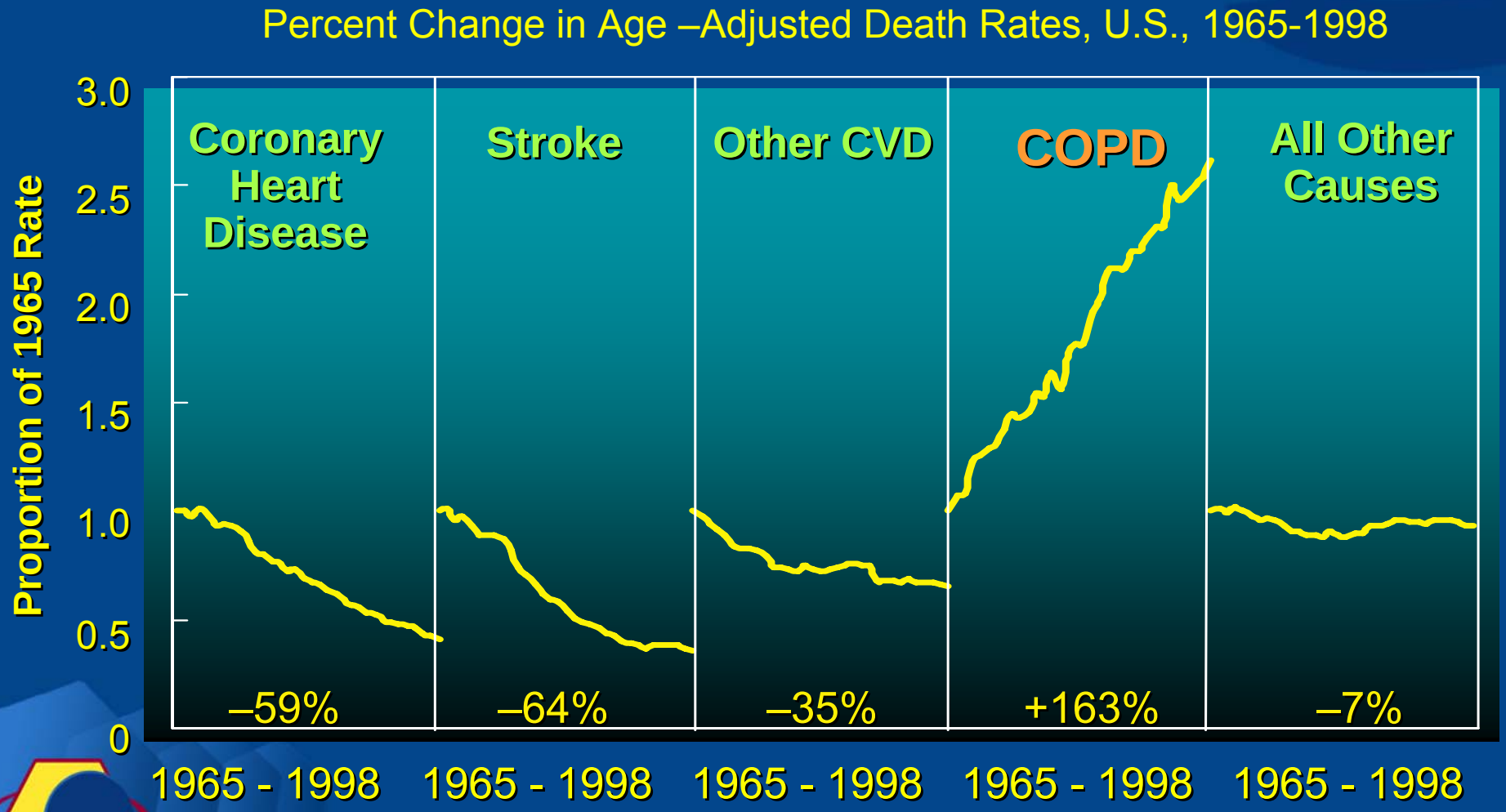
COPD (Chronic Obstructive Pulmonary Disease)

- Major cause smoking
- No cure but giving up slows progression of the disease

- Prevalence doubled in last 25-30yrs; Typically affects those >50yrs
- Affects ~ 4-6% of population in developed countries
- By 2020 (WHO prediction)
  - 3rd most common cause of death
  - 5th most prevalent disease worldwide

PDE4 inhibitors – potential new therapy for COPD & Asthma

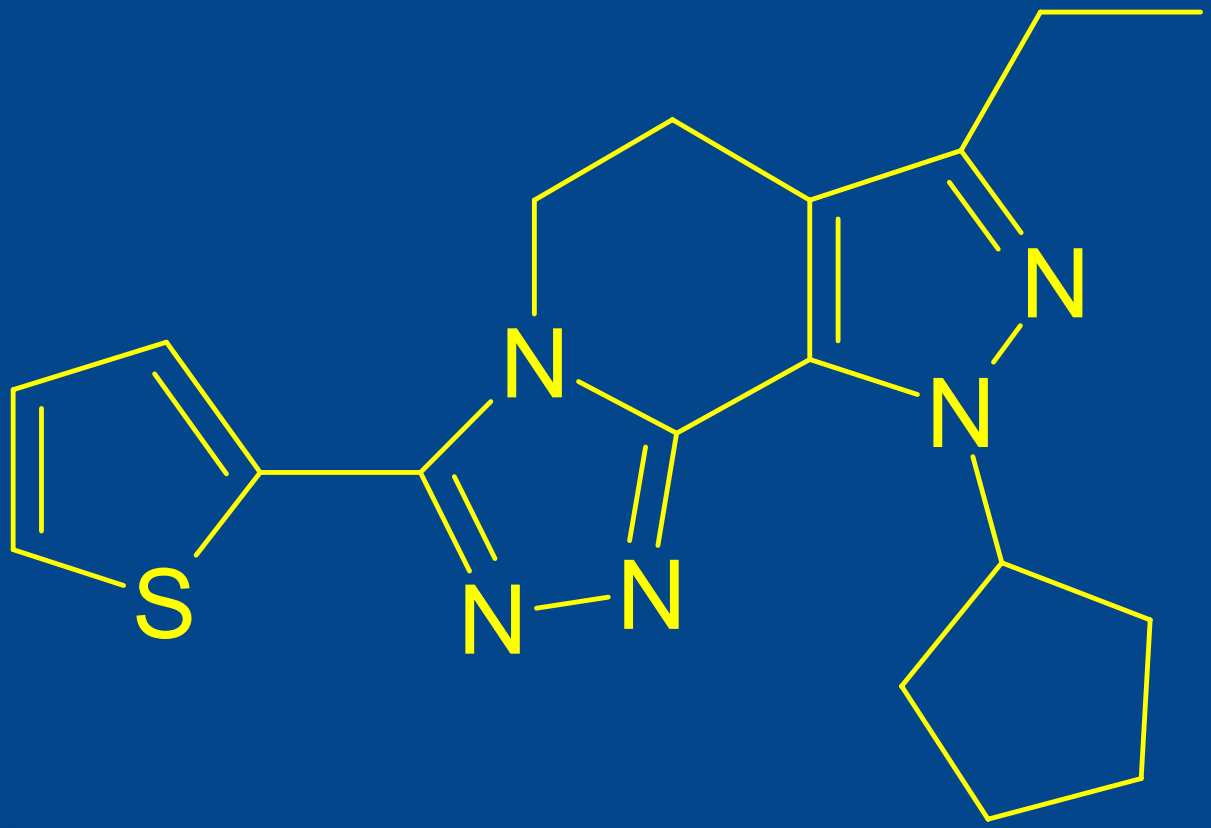
Disease Associated Death Rates in Developed World over past 3 decades



COPD – HIGH UNMET MEDICAL NEED

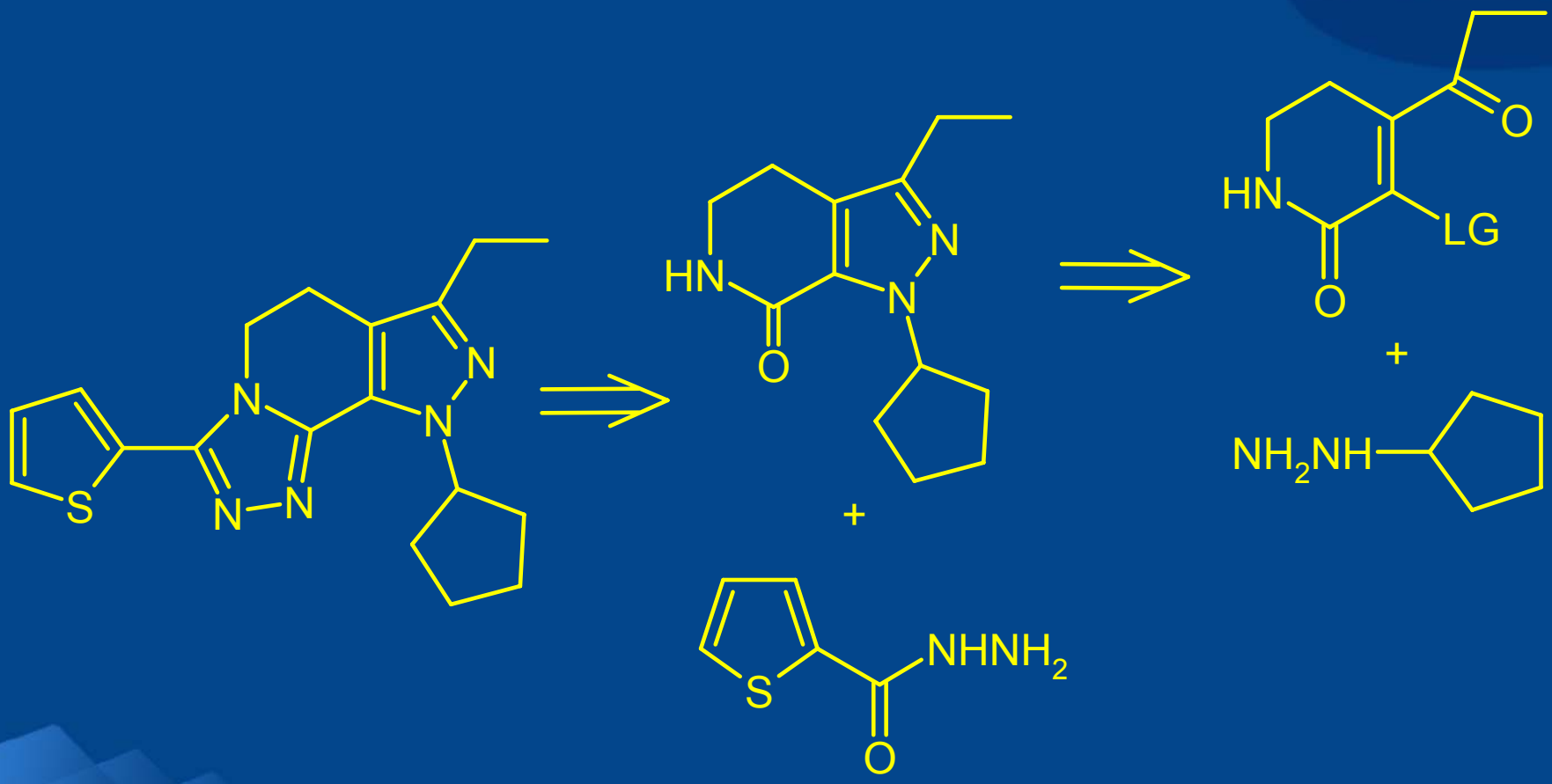
GOLD workshop report 2001

Tofimilast, an Inhaled PDE4 Inhibitor for the Treatment of COPD and Asthma

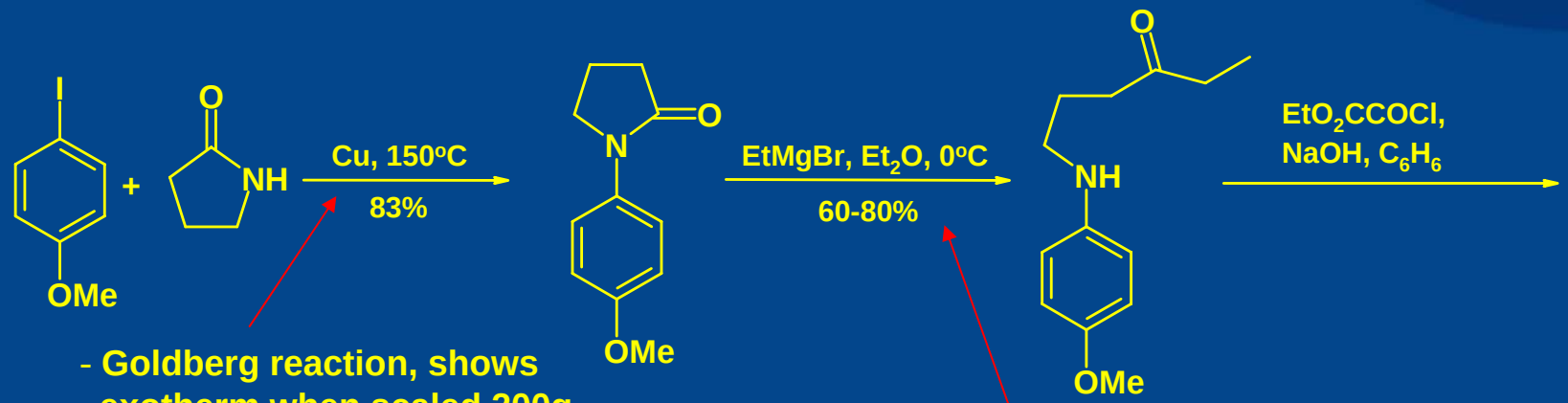


- Nominated for development in 1995

Tofimilast: Retrosynthesis

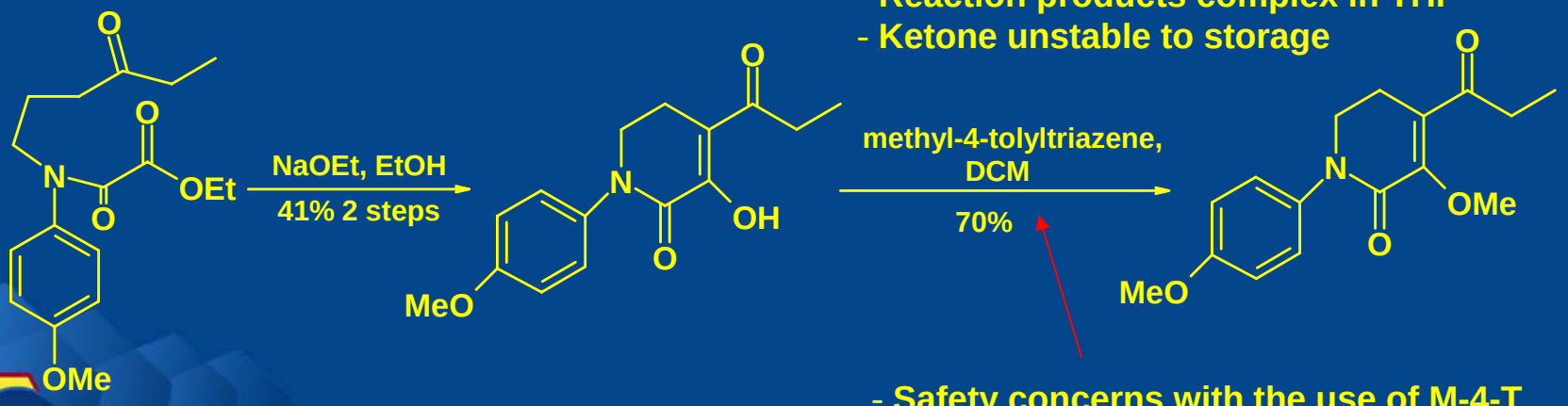


Discovery Chemistry Route



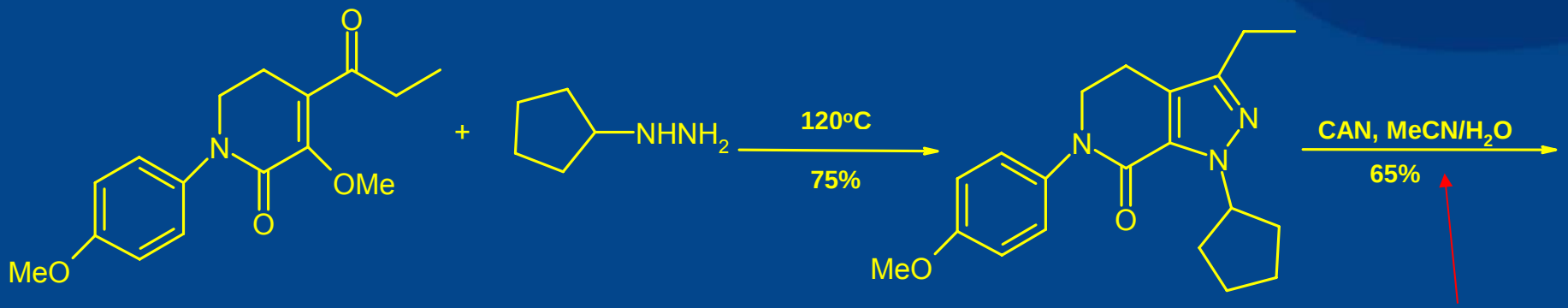
- Goldberg reaction, shows exotherm when scaled 200g

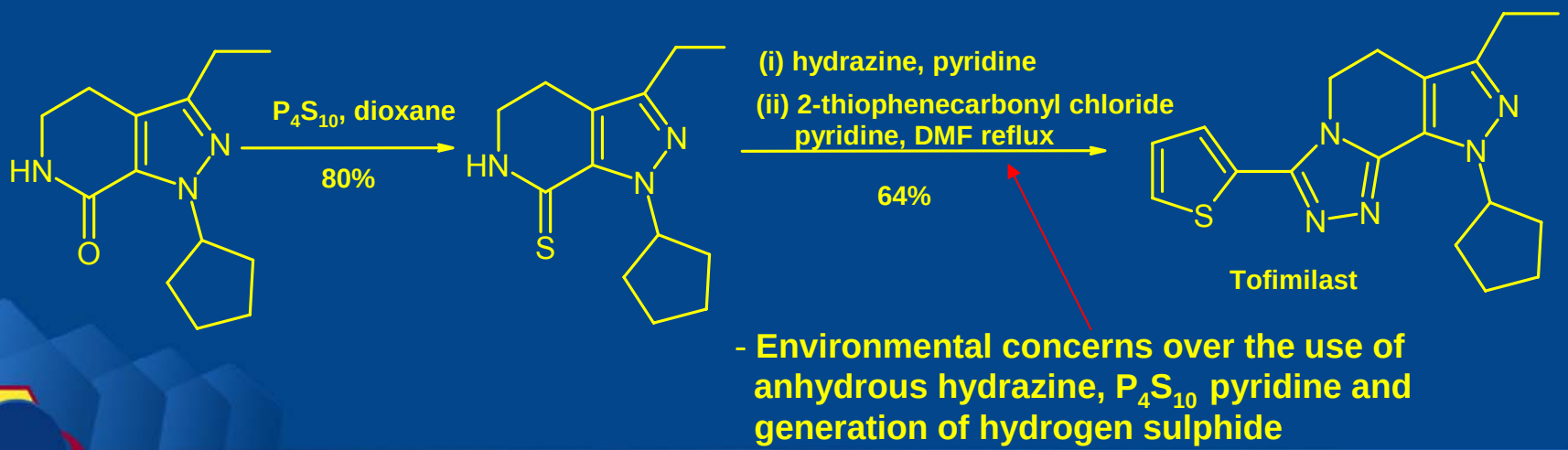
- Reaction products complex in THF
- Ketone unstable to storage



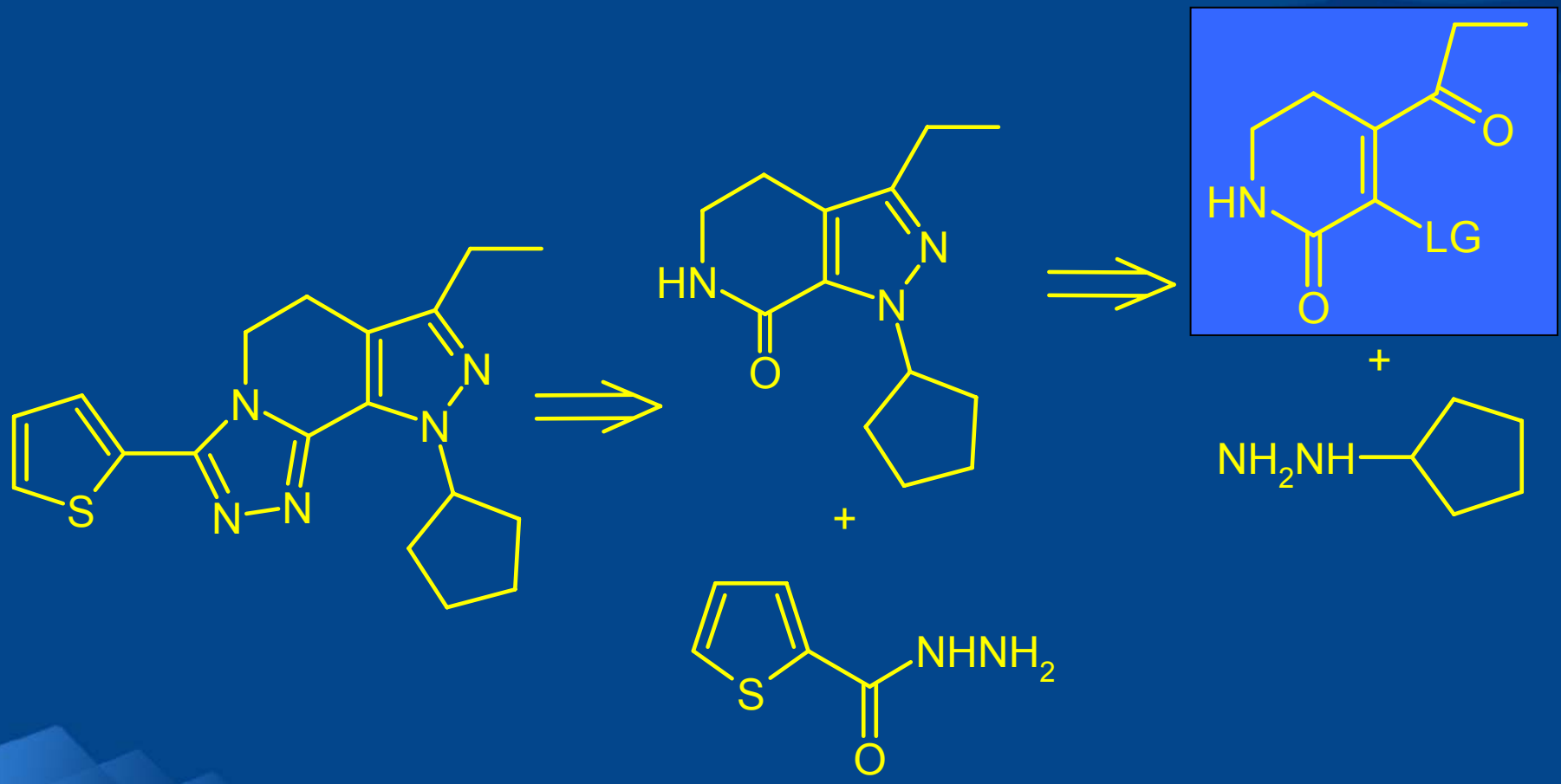
- Safety concerns with the use of M-4-T

Discovery Chemistry Route

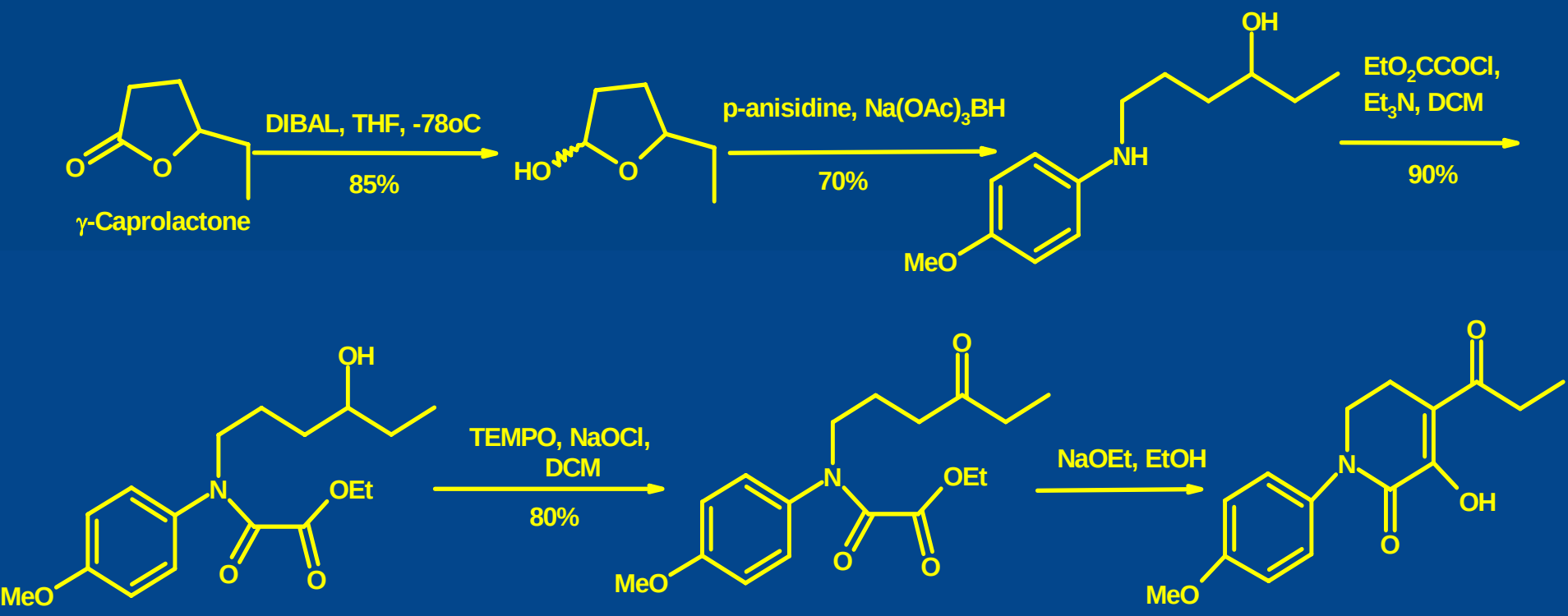




Target: Tetrahydropyridone Fragment

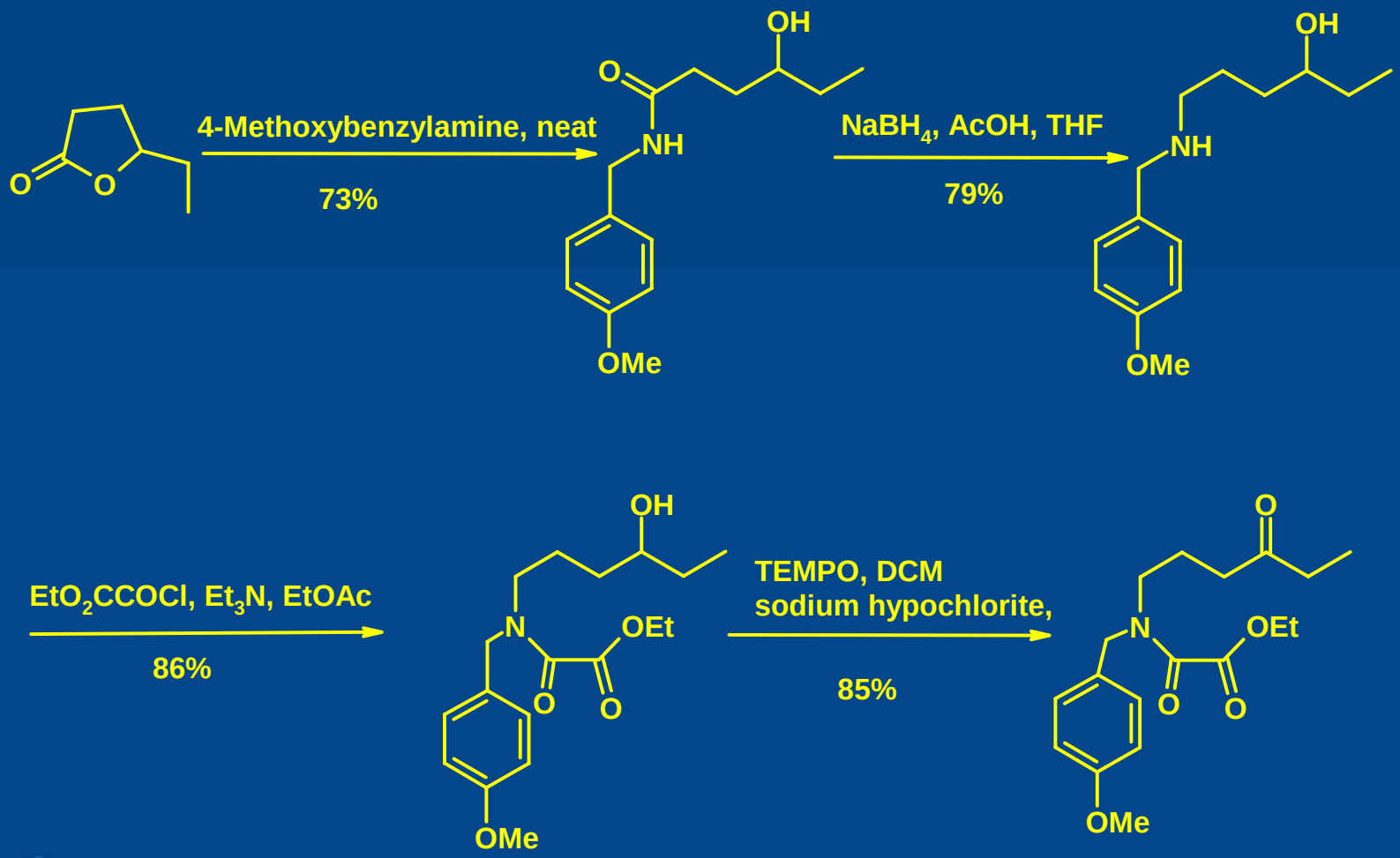


Tetrahydropyridone Synthesis (1)



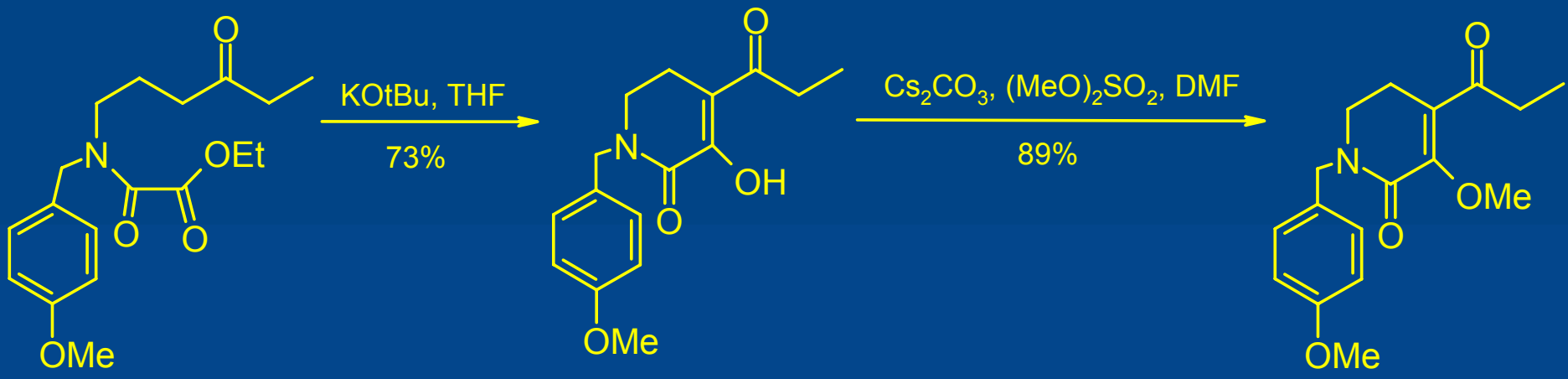
- Excellent yields on lab scale; BUT scale up problematic
  - Lactol unstable; reductive alkylation capricious
- Undesirable CAN deprotection of 4-methoxyphenyl group

Tetrahydropyridone Synthesis (2)



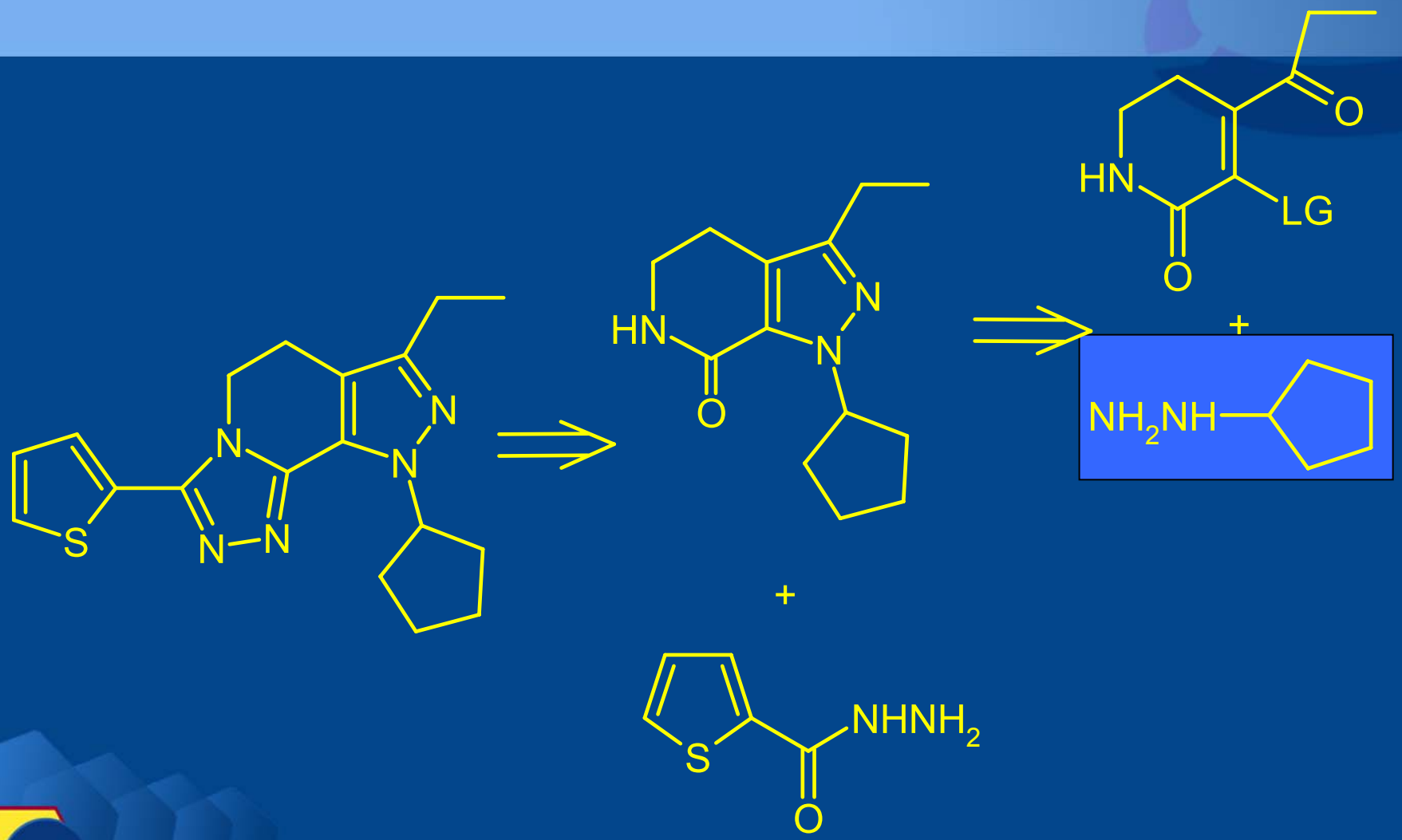
- Use of 4-Methoxybenzylamine:
  - Direct condensation & crystalline product
  - Increased options for deprotection

Tetrahydropyridone Synthesis (3)

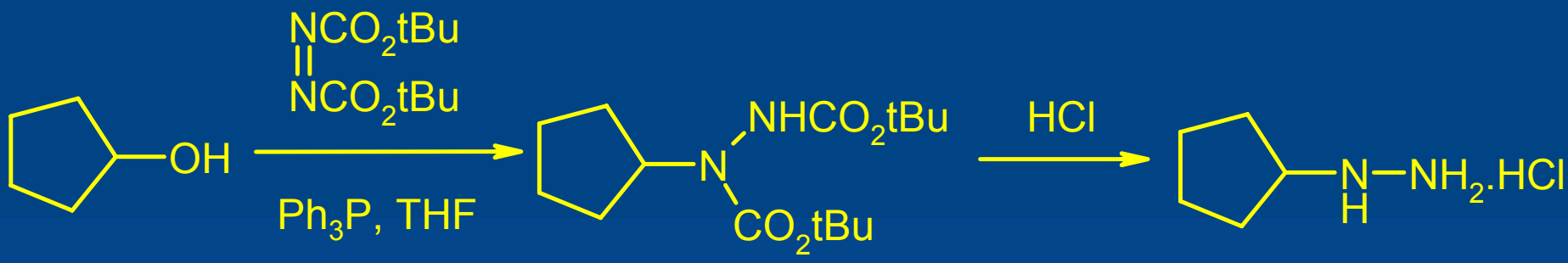


- Dieckmann cyclisation to lactam
  - Lactam isolated directly by addition of 6N HCl
- Original DC conditions utilised 3-Methyl-1-p-tolytriazene for O-methylation
  - Conditions identified to avoid competing C-alkylation
- MeI/K_2CO_3 gives mixture of O and C alkylation
- Screening identified alternative conditions for exclusive O alkylation
  - Dimethylsulphate, Cs_2CO_3, DMF

Target: Cyclopentylhydrazine Fragment

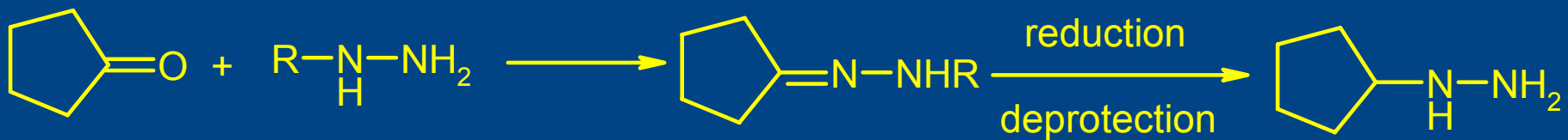


Cyclopentylhydrazine Formation



- Cyclopentyl hydrazine not commercially available
- One pot Mitsunobu procedure was developed for initial scale-up
  - 6N HCl added on completion of the Mitsunobu reaction
  - Cyclopentyl hydrochloride isolated directly from the reaction as a crystalline solid
- Process used for initial scale up to 7kg, 69%
- However concerns over the stability of di-*tert*-butyl azodicarboxylate
  - Approach abandoned

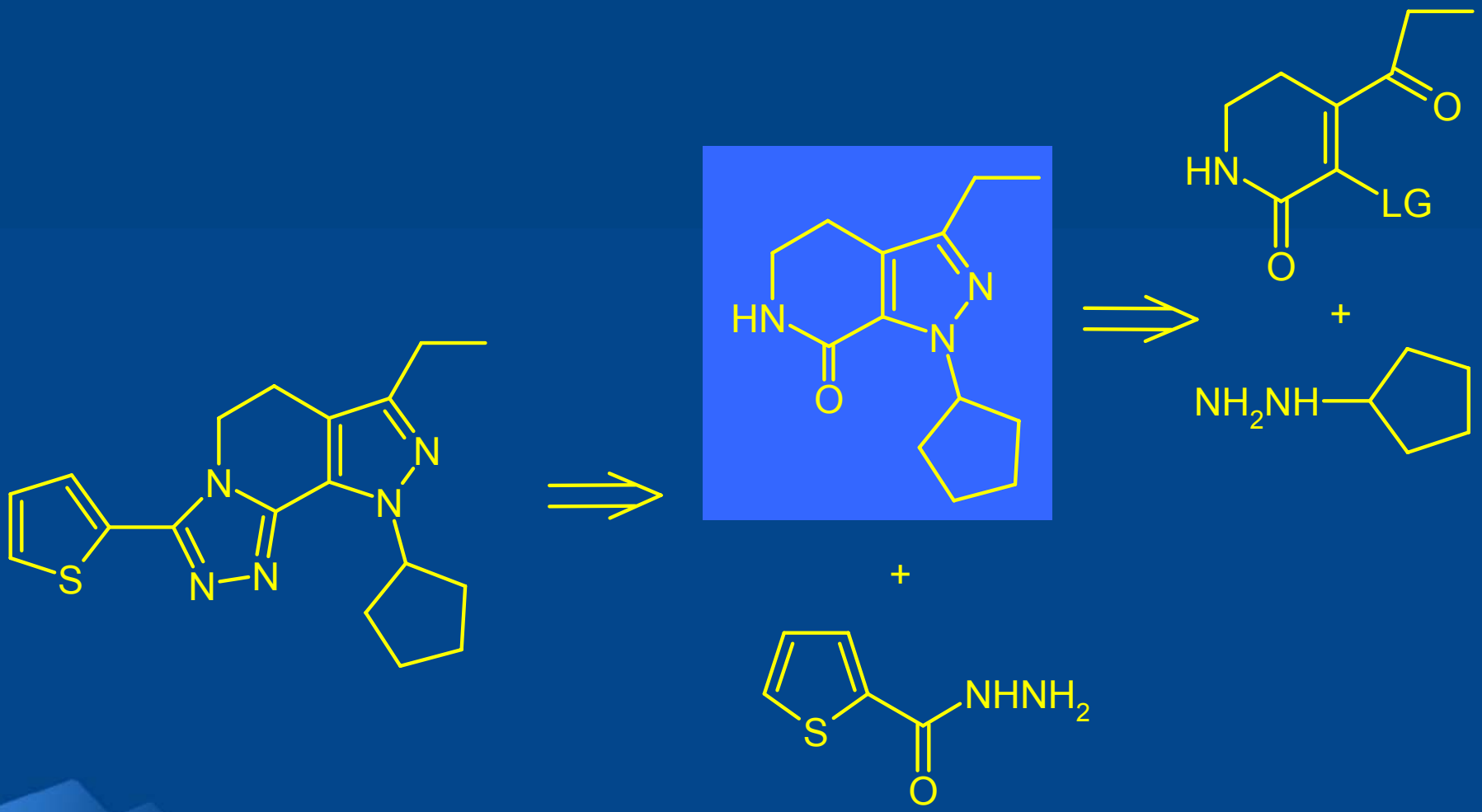
Cyclopentylhydrazine Formation



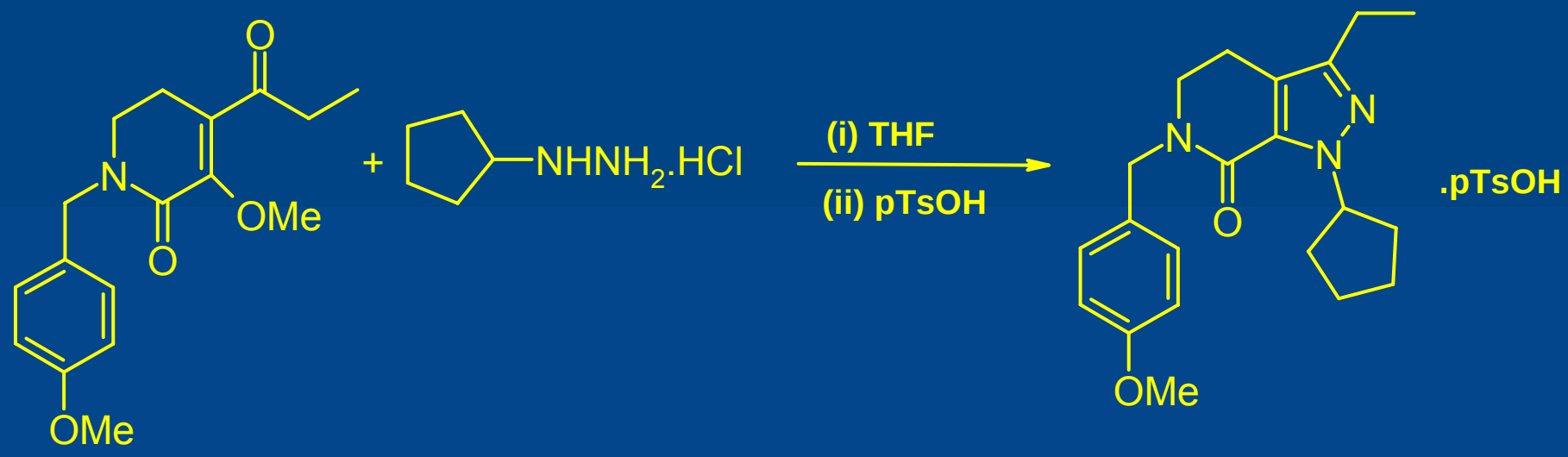
R=Acetyl
(^{t}BuO)CO
(MeO)CO

- Reduction of the hydrazones
  - Ra Ni caused significant hydrogenolysis of the N-N bond
  - Reduced cleanly borane /THF however significant contamination with boric acid
  - Pt/C clean high yielding selective reaction
- Deprotection to the hydrazine
  - N-BOC selected, 93% yield of cyclopentylhydrazine hydrochloride
  - Cyclopentyl hydrazine unstable under basic conditions or as the anhydrous form
  - Hydrochloride salt stable to storage

Pyrazole Ring Formation

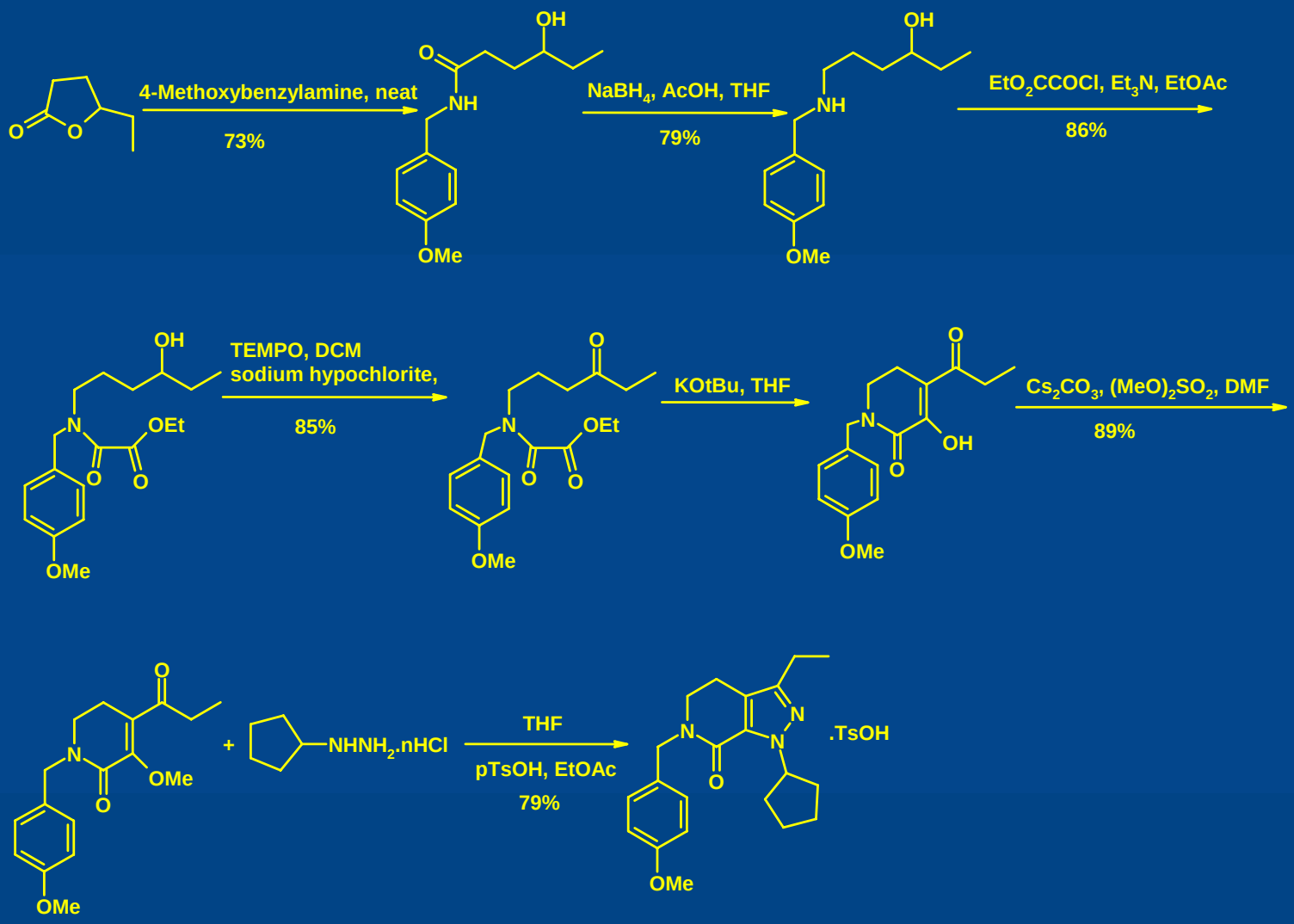


Pyrazole Ring Formation



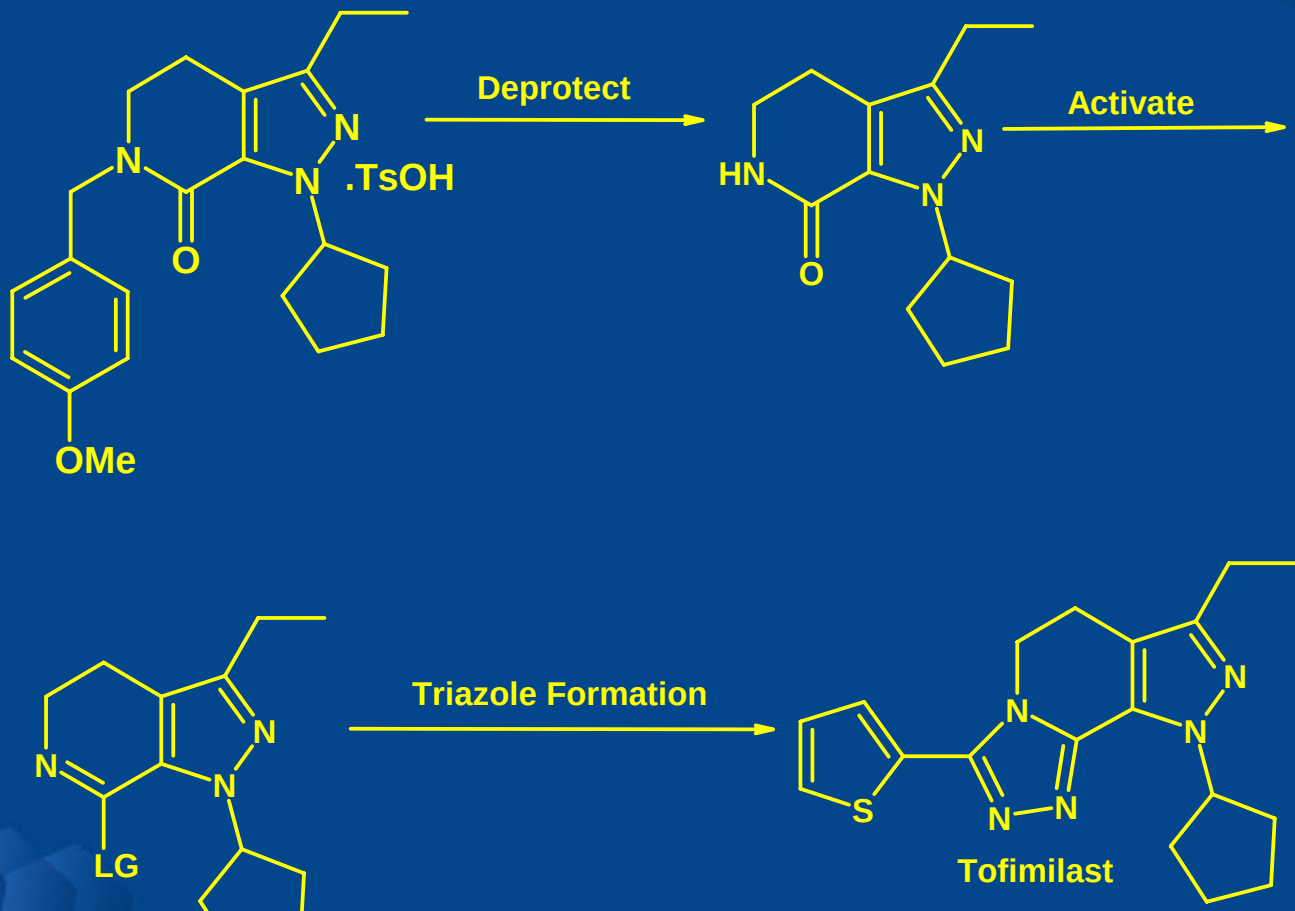
- DC conditions: 120˚C melt → mix of regioisomers, 54% desired after chromatography
- CRD: THF added, 85-90˚C; solvent distilled off as reaction progressed
  - MeOH and HCl swept into caustic scrubber
  - DCM extraction
- Product a low melting solid; initial development → used directly in PMB deprotection
- Salt screening identified TsOH and besylate salts as high mpt crystalline solids
  - Single regiosomer, TsOH salt isolated directly from EtOAc, 79% yield

Synthesis of the Pyrazolopyridone

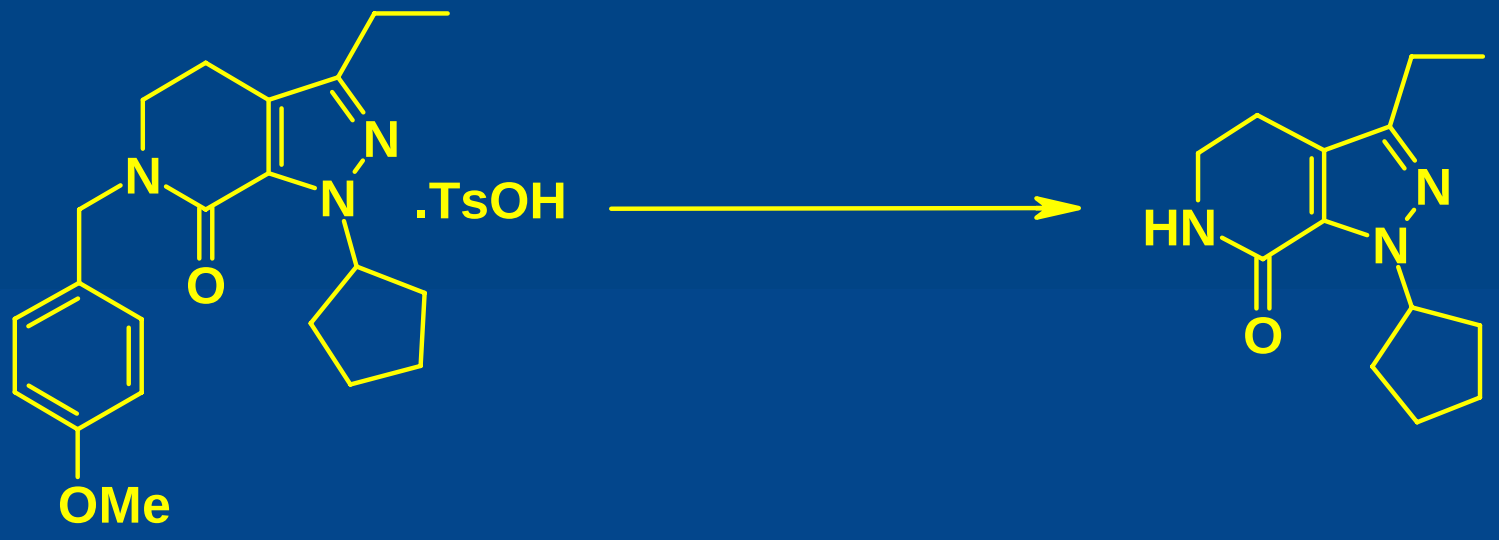


- 7 steps from γ-caprolactone yield 13.5% vs 2.5% DC, 45 kg largest scale
- Currently outsourced

End Game: Pyrazolopyridone to Tofimilast

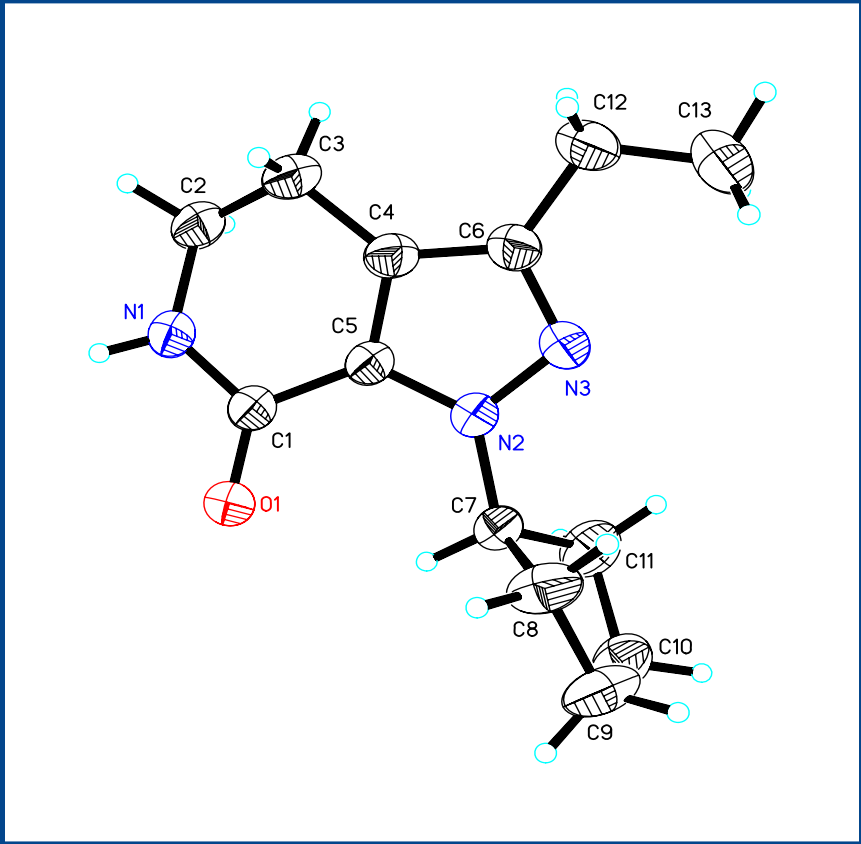


PMB Deprotection

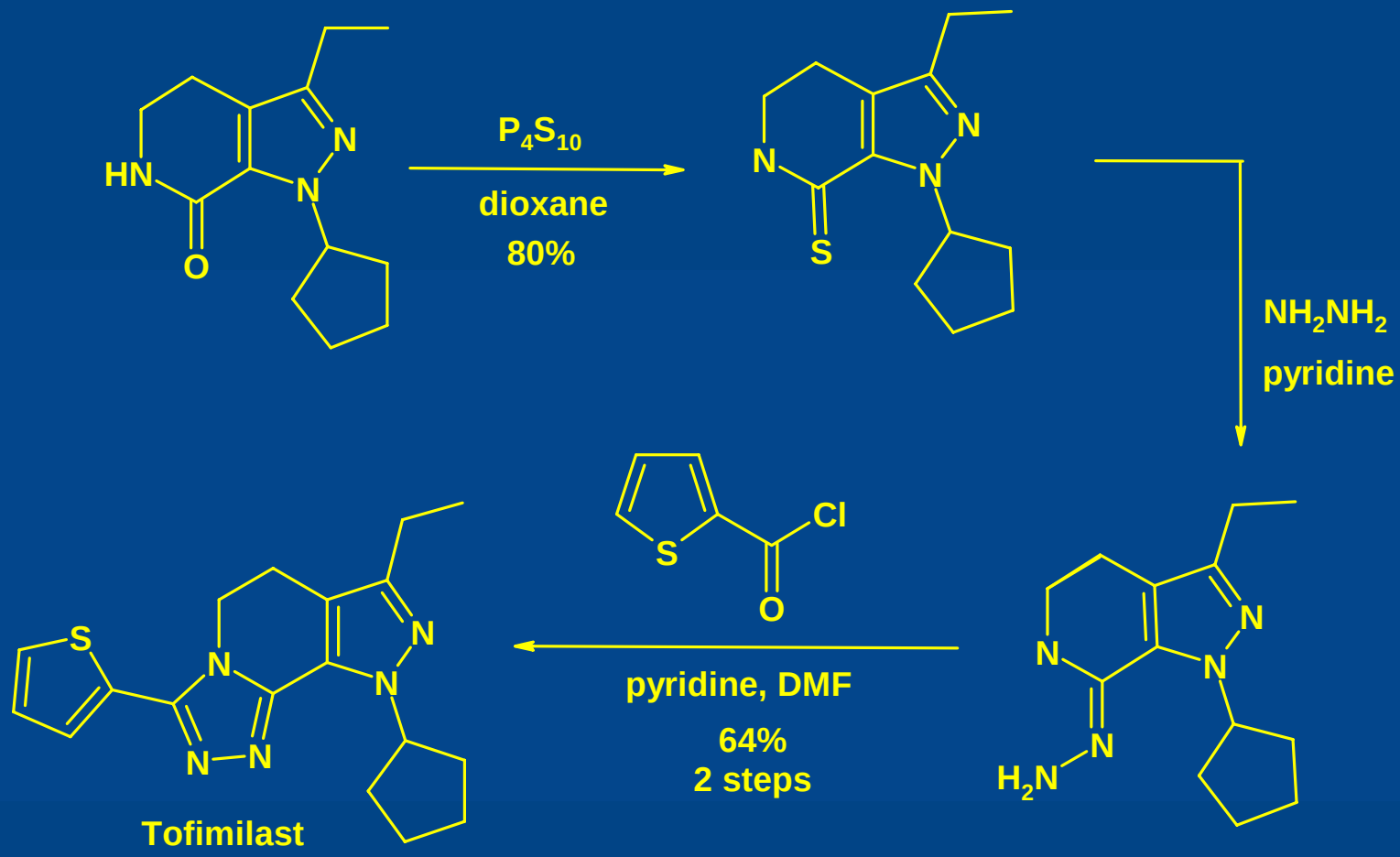


- Initial cleavage H_2SO_4/acetic acid
  - Anisole (10eq) added to prevent polymeric byproduct formation
  - BUT difficult to remove anisole from product and significant losses
- Switch H_2SO_4/toluene - allows direct drop process
  - Yield at scale (45kg) 80%, purity 99.6%
- Interestingly product isolated as the freebase - no neutralisation
  - Freebase identified by NMR, elemental and X-ray analysis

PMB Deprotection

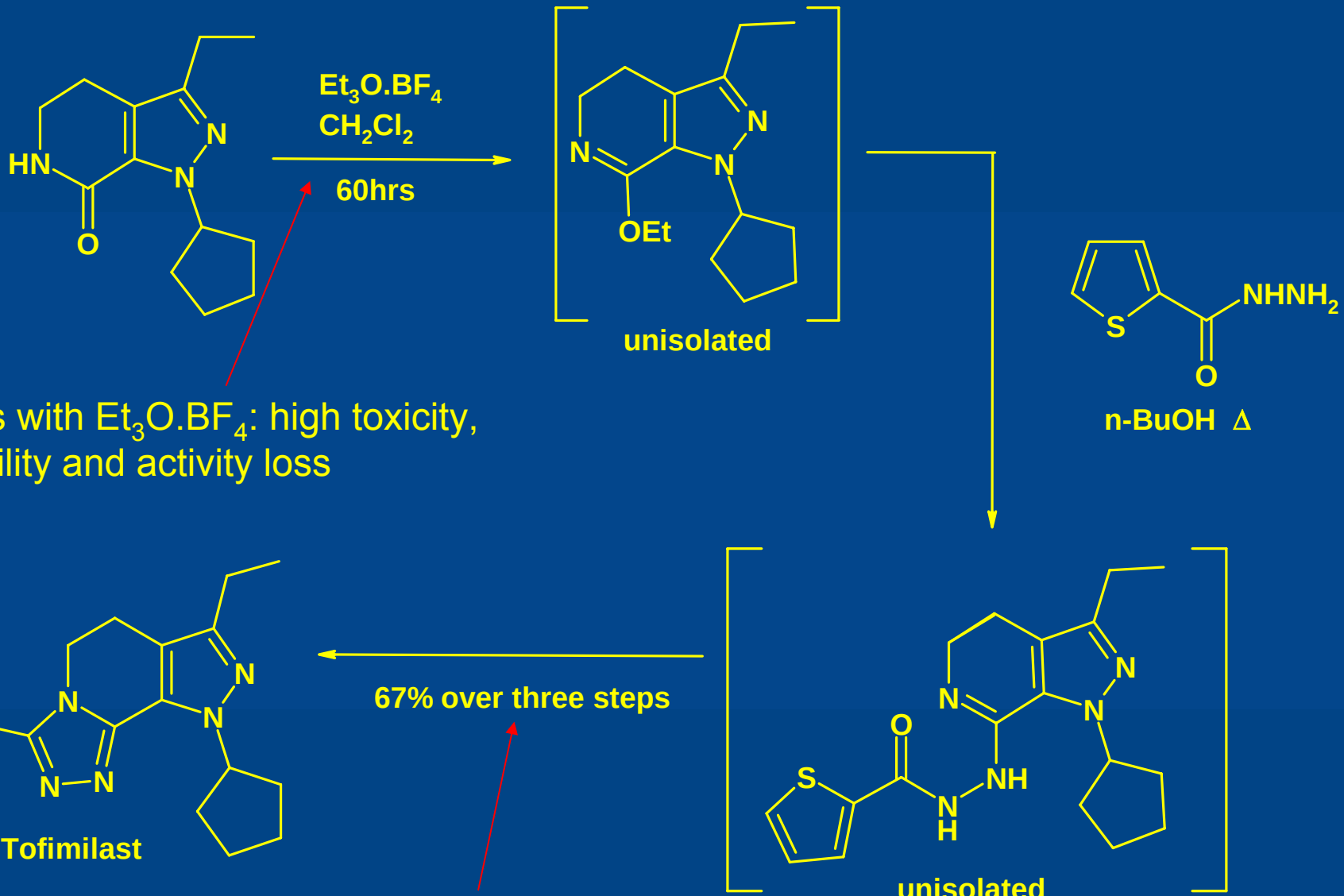


Lactam Activation and Triazole Formation
Original DC Conditions



- Unsuitable for scale-up, concerns about P_4S_{10}, hydrazine (anh), pyridine & H_2S
- Initial attempts using imidoyl chloride disappointing: best yield Tofimilast ~20%, PCl_5

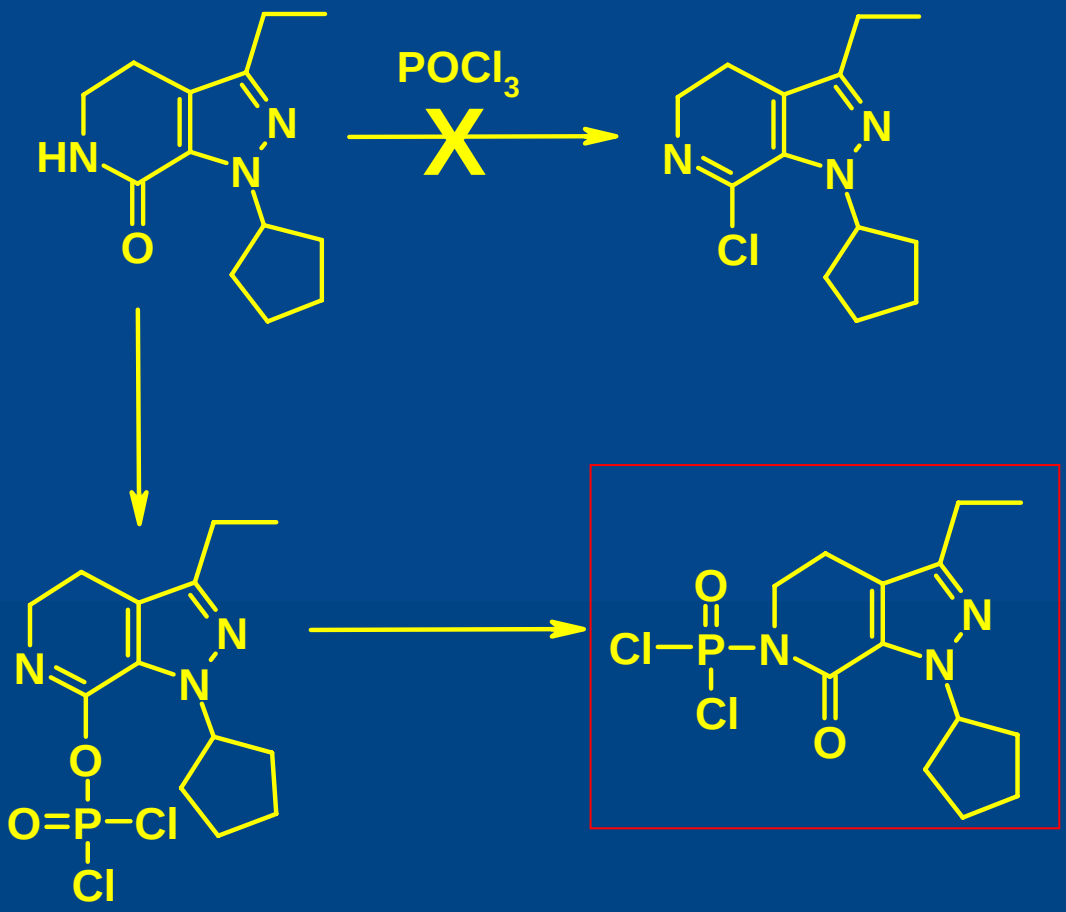
Lactam Activation via Imidate



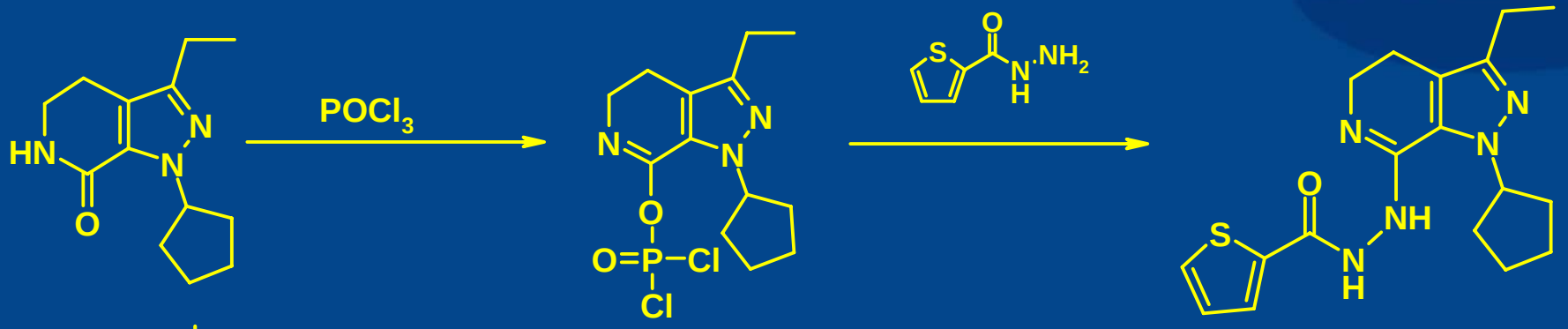
- Issues with $Et_3O.BF_4$: high toxicity, instability and activity loss
- Multiple solvents, nBuOH, DCM, IPA

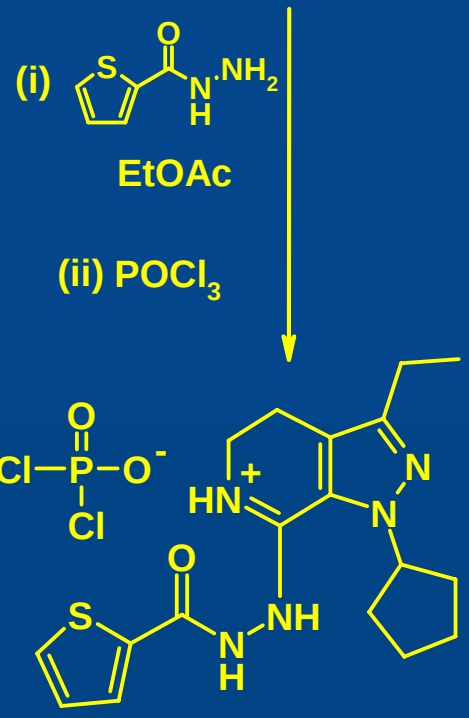
Alternative Lactam Activation ?

- Rescreened activating groups; PCl_5, $POCl_3$ again identified, but low yields of Tofimilast
- Pyridone/$POCl_3$ product isolated + characterised (NMR)
  - Unable to identify formation of imidoyl chloride during the course of the reaction



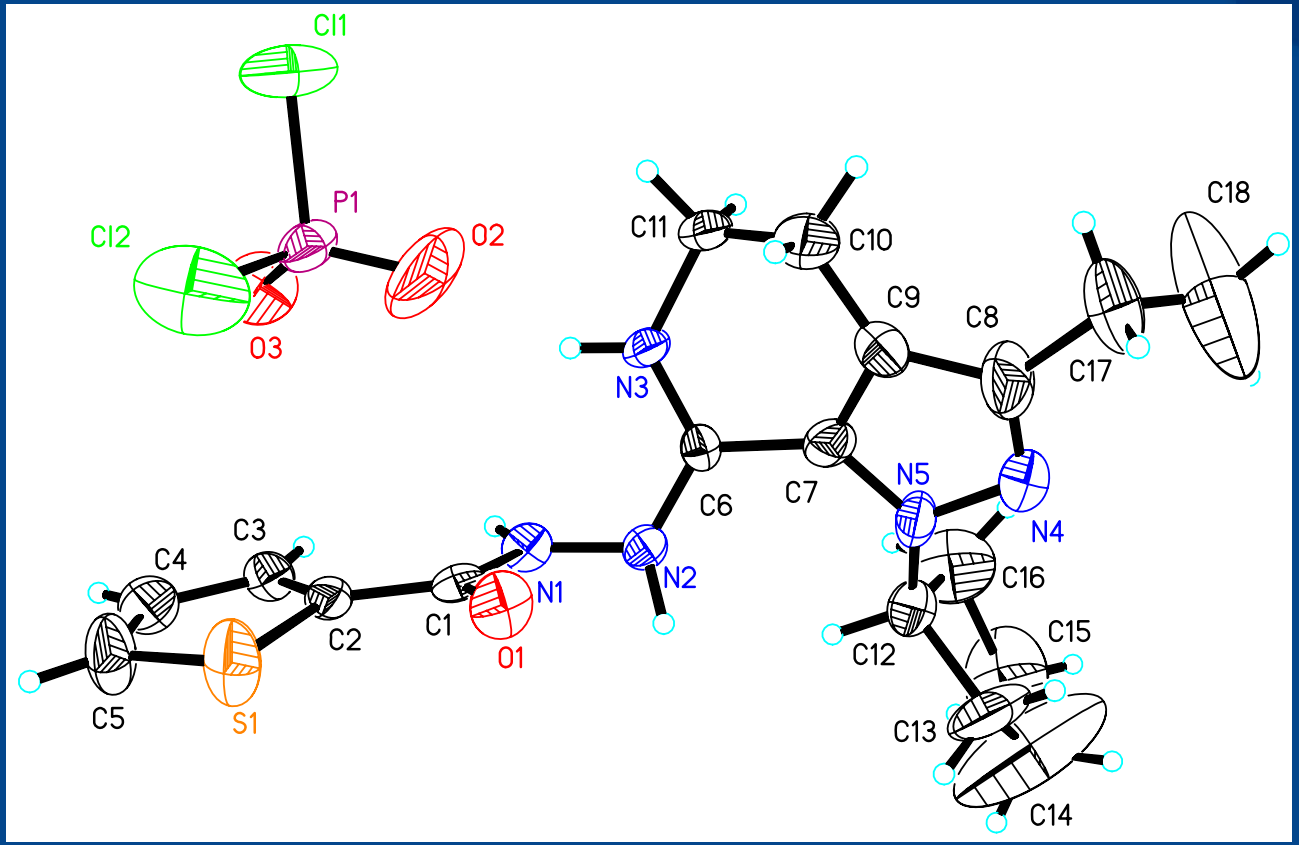
Process Optimisation



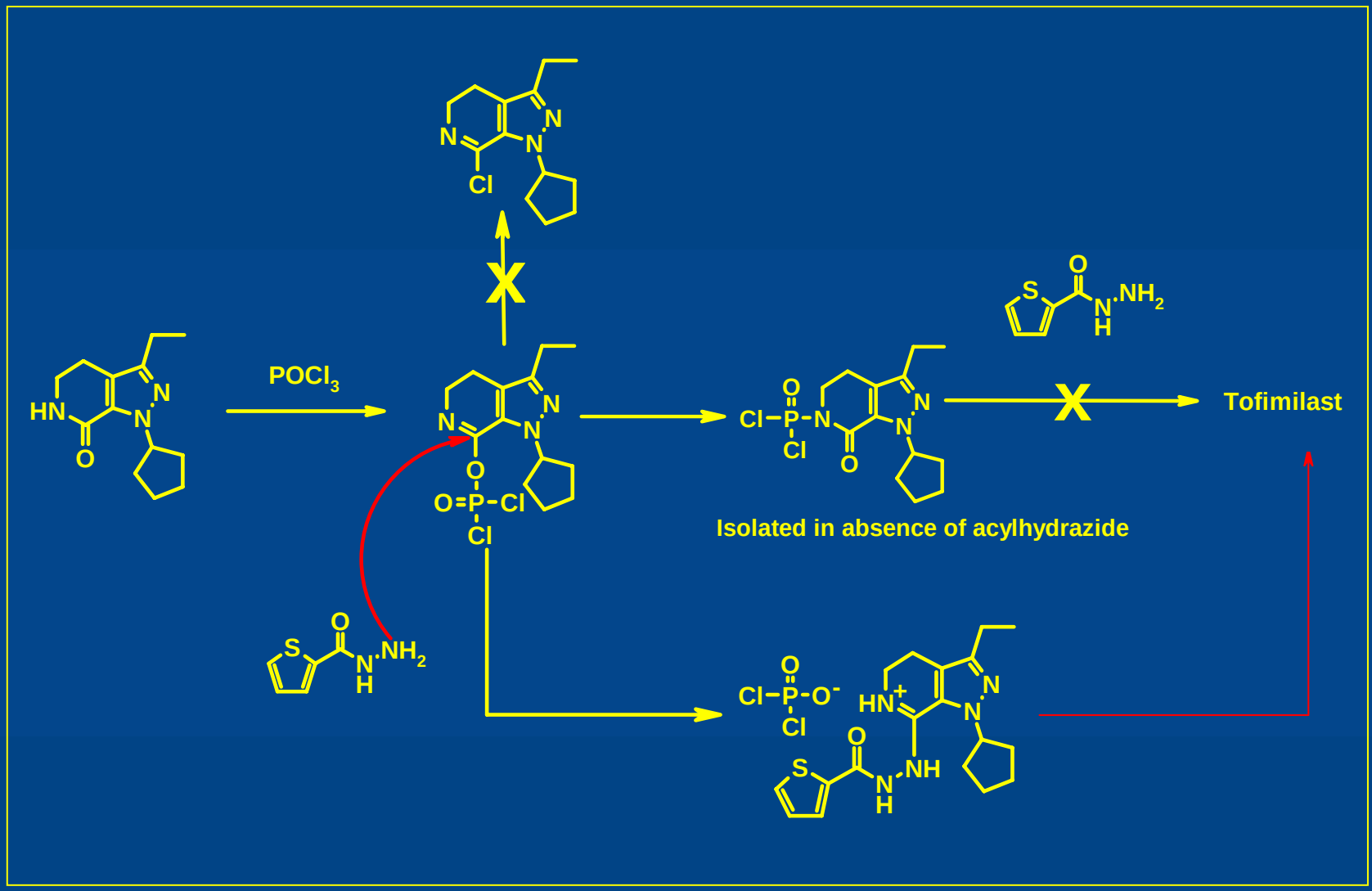


- Poor conversion to intermediate acyl amidrazone
- Process improvement:
  - Pre-mix 1eq amide & 1eq acyl hydrazide:then add 2.1eq $POCl_3$
  - EtOAc, 50°C optimal
  - Intermediate precipitates from reaction
  - Characterised as acyl amidrazone dichlorophosphate salt (x-ray)
  - Scale-up Dichlorophosphate salt, 18kg, 66%, 99.6% purity

Acyl Amidrazone Dichlorophosphate Salt



Potential Mechanism



Remaining Issues

- Reaction mechanism still not completely understood

  - First Pilot plant reaction stalled on initial run at ~ 56% conversion to salt

    - Reaction does not progress with further $POCl_3$, heat, extended reaction time

    - An additional charge acylhydrazide required

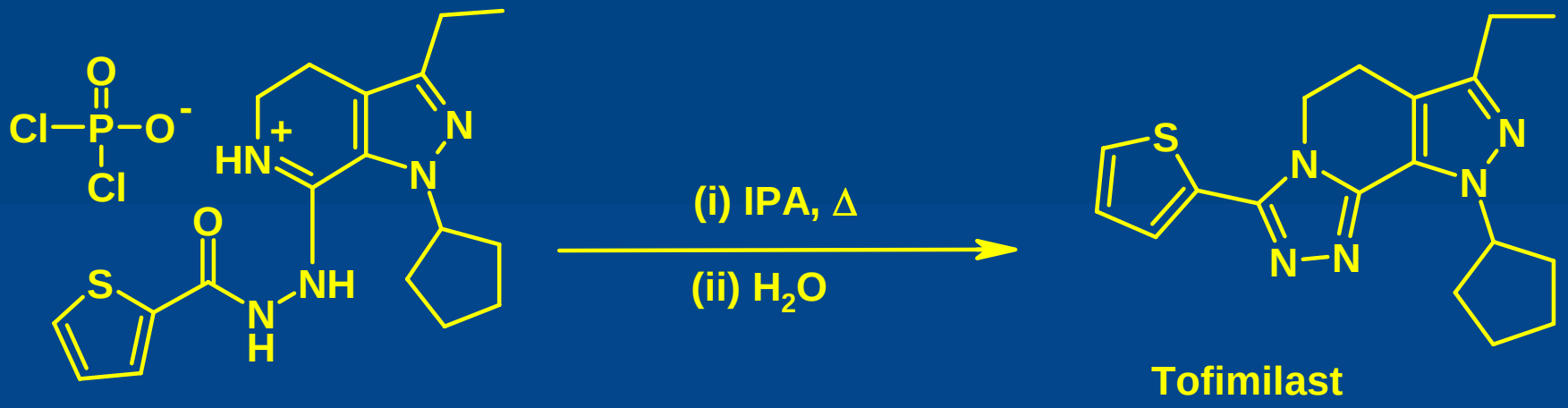
  - Second pilot plant batch 1eq acylhydrazide charged as two separate portions

    - Improved product conversion ~70%

  - Acylhydrazide reacts with $POCl_3$

    - Nature of the species formed has been hard to identify

Cyclisation to Tofimilast



- Cyclisation in IPA
  - Dichlorophosphate salt breaks during cyclization to give Tofimilast as free base
  - Water addition solubilizes dichlorophosphate by-products.
  - Product isolated directly from 50:50 mixture (4ml/g) of IPA and water

Crude Tofimilast is isolated in 70% yield, purity 96.0% (18kg scale)

Summary

- Developed an efficient nine step synthesis of Tofimilast
- Starting from γ-caprolactone avoids capricious Grignard addition
- Fused triazole formation via lactam activation with $POCl_3$
  - Novel dichlorophosphate acyl amidrazone intermediate
  - Replacement of thiolactam chemistry and unstable $Et_3O.BF_4$
- Final process minimises the environmental concerns with the original synthesis
- Successfully scaled to provide Tofimilast
  - Overall yield 5%

Acknowledgements

CRD

Tetrahydropyridone

- Frank. J. Urban
- Bruce Anderson
- Sue Orrill
- Peter Daniels
- Clive Mason

Fused triazole

- Niamh Willis
- Garry O'Connor
- Sam Prior
- John Matthews

- ***Groton and Sandwich CRD teams 1995-2005***

Crystal Engineering

- Ivan Marziano
- Neil McDowall
- Terry Kougoulos

ARD

- Karen Weaver - ARD
- Aurelia Maulny - ARD

SC

- Derek East - Pilot Plant
- Jon Blunt - Kilo Lab

Discovery Chemistry

- Allen Duplantier
- Elisabeth Bachert
- John Cheng
- Victoria Cohan
- Teresa Jenkins
- Kenneth Kraus
- Michael McKeehney
- Joann Pillar
- John Watson

- Ana Codina – Structural Elucidation group
- Neil Feeder – Mat Sci
- Steven Fussell - Process Automation
- Mike Hawksworth – PSREL

Potential Reactions