Evaluation of Flow Technology at AstraZeneca

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Objectives

- Background
- Vision
  - Link between C1-C2 and beyond
- Flow Chemistry in AZ
  - Examples
- Summary

Background

Conventional Batch Technology

- As Chemists, we understand concept of batch technology
  - RMs in – Process steps – product out
- Unchanged for ~100 years
- Excellent all-rounder; however there are limitations
  - Mass Transfer
  - Heat Transfer and dissipation
  - Limits of pressure / temperature
  - Cycle Times
  - Asset costs / maintenance

Why choose Flow?

- Business drivers of cost, speed, and quality by:
  - **Less development** associated with scale up "*leave the tap running*" from LI/LO/C1 to C2

- **Cheaper API production** – cheaper processes or routes
  - Access to hazardous chemistry
    - a lower inventory & better control within the reactor
  - Access to chemistry that cannot be scaled in batch
    - Microwave chemistry
    - Unstable intermediates/products
    - Mixing sensitive reactions → Improved selectivity/purity

- Biggest impact of the "*leave the tap open*" principle:
  - On average a C1 campaign will cost £100,000
  - On average a C2 campaign will cost £750,000

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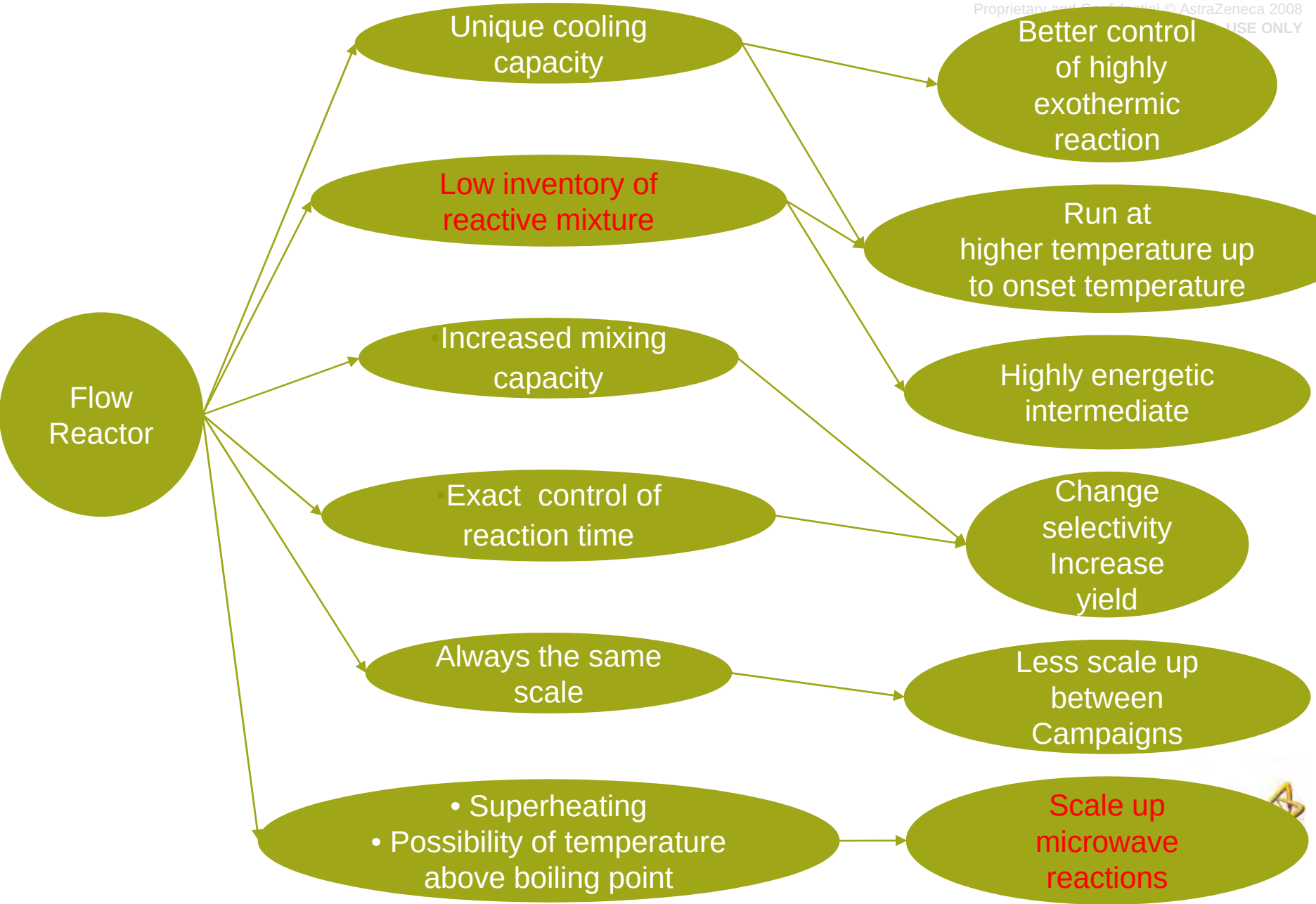
Benefits of a Flow Reactor



Technology Evaluation in Discovery Chemistry

- 2006 Alderley Park Chemistry Automation Team (APCAT) was a co-ordination hub for gathering and sharing information on chemical technologies, best practices and new ways of working
- The uptake of microwaves in discovery labs complemented flow technology
- APCAT considered flow a viable ‘new technology’.
- Initially limited commercial equipment available therefore a watching brief was kept.
- Syrris Africa system was trialled but considered over complicated and high cost.
- Other AZ sites were also evaluating flow equipment (syringe pumps, chip reactors, Alfa Laval, FRX, CYTOS etc).
- Early 2008 Uniqsis FlowSyn and Vapourtec R2/R4 models became available.

The AZ Vision for CP

Global Continuous Processing Vision

- Coordinated efforts
  - Interested parties from all sites / functions
  - Developed direction for Pharm Dev.
    - Global Flow Network

1) Focus on C1-C2 to deliver CP as a core capability
   - Key interaction with Med Chem
     - Develop once and scale
     - Minimise development from C1

2) Expand beyond C2 as experience / projects progress

3) Develop Flow capabilities
   - Work-up and Isolation (crystallisation)
   - Multi phase systems (reactions – gassing / slurries / suspensions)

Leaving the Tap Open

Initial objective

from 'Faster Development of C2 methods' C2 Paradigm project

- Save development time from RSL (<1 kg) to Med Eval. (3-5 kg), C1 to C2

Microwave → FlowSyn/Alfa Laval (lab) → Alfa Laval (LSL)

- Same conditions (T, P, conc.)
- Minimal Development

- Broaden the window for scale-up of late stage Medicinal Chemistry routes

How do we Approach Flow Chemistry in AZ?

Thinking in a flow mindset

Challenges	Solution
Precipitations	
• Slurry reactions cannot be pumped into the reactor • Small amounts of precipitations might be allowed, when formed during the reaction	Solubility test: • Concentration • Different solvent (mixture of solvent) • Temperature
Kinetics	
• Reaction must have a **satisfactory** conversion within **45-60 min** • Stability of the resulting product after the reaction	• Temperature (can be raised in the flow reactor) • Equivalent of reagents (an excess can be used, exact control of reaction time)
Proof of concept	
Run in flow reactor	• Run the reaction in a microwave • Use a chip

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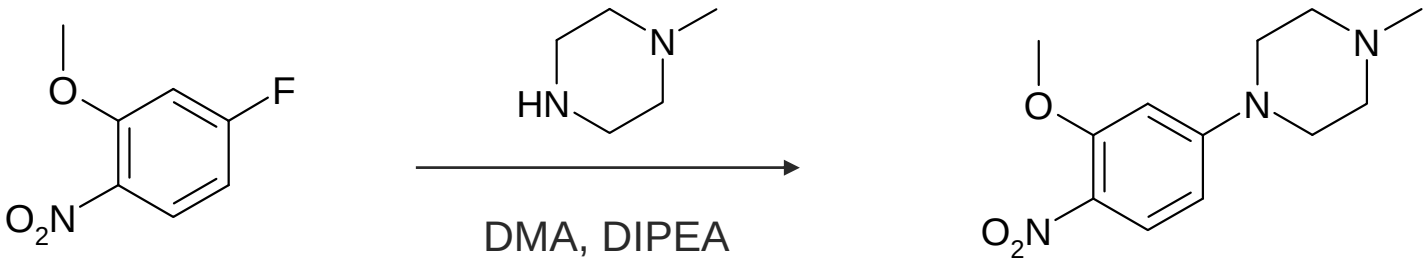
Early Successes - SNAr Chemistry



Initial Conditions: 80 °C, overnight

Yield: 83%

Microwave Conditions: 9 reactions investigated reaction temperature (80 – 140 °C), time (5 and 10 min) and stoichiometry (1.1 and 1.5 eq piperazine).

⇨ 1.5 eq piperazine, 120 °C, 10 min – 85% complete by LCMS

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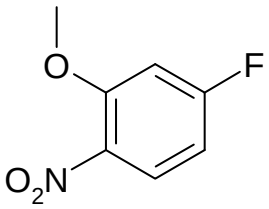
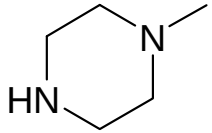
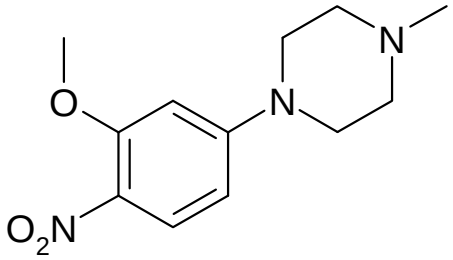


DMA, DIPEA



DMA, DIPEA



Conditions

Concentration: 0.9 M

Coil: 20 mL SS

Temp: 150 °C

Residence Time: 10 m

Flow rate: 2 mL/min

Work Up:

Crude reaction mixture used directly in the next step (transfer hydrogenation of nitro- to aniline)

Output:

Ca. 14.5 g (100%UV by LCMS)

Run Time: 30 minutes

(Yield for the 2 steps = 73%)

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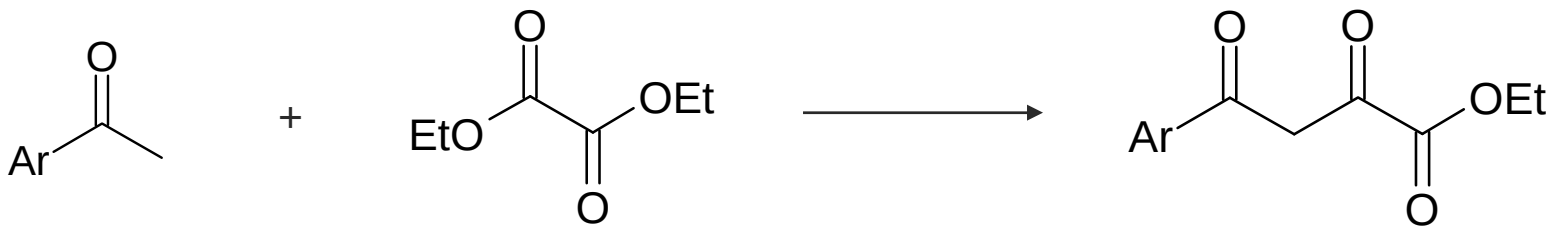
Early Successes - Claisen Condensation



Initial Conditions: NaH, toluene

Modified Conditions: NaOEt, EtOH, THF, room temp, 45 min

Work Up: Acidify (2 N HCl), filter precipitate and dry

Yield = 96%

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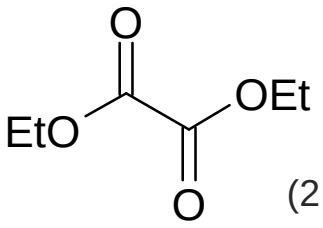

(2 eq)

THF

2.2 eq. NaOEt

EtOH

<u>Conditions</u>:

Concentration: 0.32 M

Coil: 20 mL SS

Temp: 60 ^{o}C

Residence Time: 5 min

Flow rate: 4 mL/min

<u>Work Up:</u>

Add 2 N aq. HCl

Filter precipitate

Wash with isohexane

and dry

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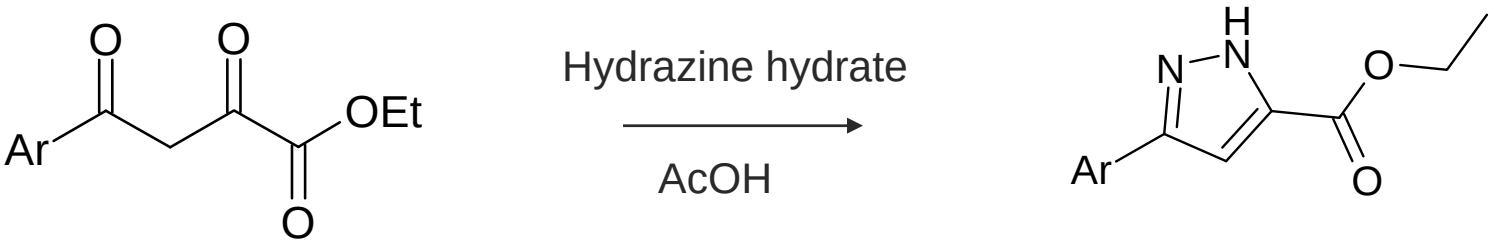
Early Successes - Pyrazole formation



Initial Conditions: Hydrazine hydrate, AcOH (suspension), rt, 4 h

Modified conditions: Hydrazine.HCl, THF, EtOH, reflux, 45 min, suspension

Work Up: Basify (sat. NaHCO3), dilute with water, filter and dry product

Yield = 82%

Addition of water to the reaction mixture gave a solution without impeding the reaction

No Flow!

Move to hydrazine hydrate, 2 N aq. HCl, DMF….

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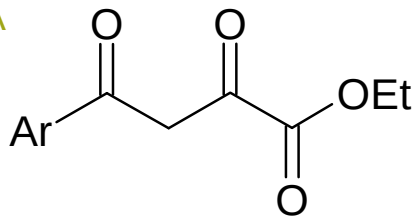
Early Successes - Pyrazole formation

Pump A

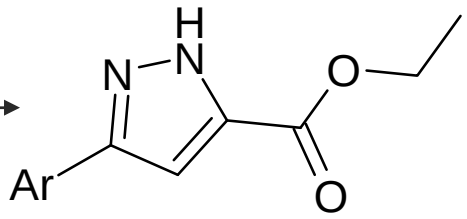


DMF

Pump B

Hydrazine hydrate

2 N aq. HCl, DMF



Conditions:

Concentration: 0.23 M

Coil: 14 mL HT Teflon

Temp: 100 °C

Residence Time: 5 min

Flow rate: 2.8 mL/min

Work Up:

Basify (sat. aq. $NaHCO_3$)

Dilute with water

Filter and dry

Output:

1.969 g (79% yield, 100% purity)

Run Time: 15 minutes

Theoretical Throughput

/Min	0.64 mmol	0.17 g
/Hour	38.6 mmol	10.2 g
/Day	**0.31 mol**	**81.6 g**

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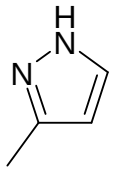
Nitration Chemistry at AZ Reims

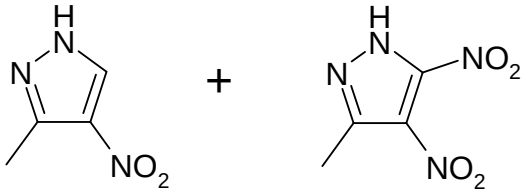
Pump A



c.H_2SO_4 (15eq)

Pump B

c.HNO_3 (13eq)



Conditions:

Concentration: 3 M

Coil: SS18 mL

Temp: 65 °C

Residence Time: 90 min

Flow rate: 0.2 mL/min

Work Up:

Basify (aq. K_2CO_3)

Extract with EtOAc

Evaporate

Output:

0.82 g/h (88% yield, 100% purity)

J.Pelleter and F.Renaud, *OPRD*, 2009, **13** (4), 698

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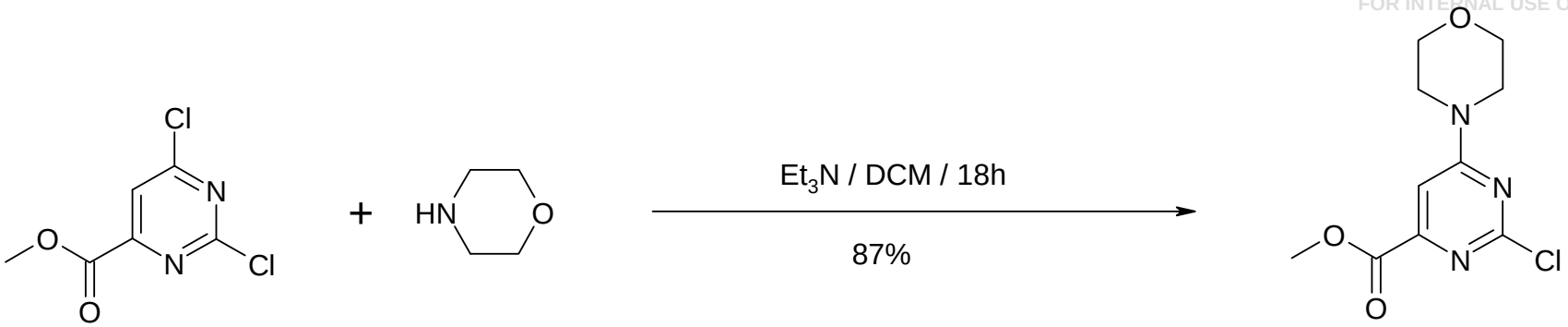
Speed is not always the essence



Initial Conditions: Morpholine (1.0eq), Triethylamine (slurry), rt,18 h

Work Up: dilute with water, dry/evaporate organic layer and triturate

Modified conditions: Morpholine (1.0 eq), DIPEA, MeCN, rt, 30 secs

Overall yield 46%, material had to be purified to remove impurity

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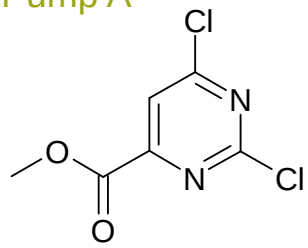
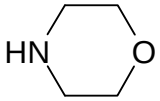
Speed is not always the essence

Pump A

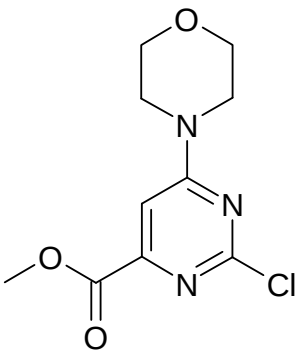


MeCN, DIPEA

Pump B



MeCN



Conditions

Concentration: 0.2 M

Coil: 2.5 mL PTFE

Temp: 20 °C

Residence Time: 0.5 min

Flow rate: 5 mL/min

Work Up:

Solvent swap, aqueous work up then chromatography.

Output: 2g, 46% yield.

Run Time: 30 minutes

Conclusion: Batch is better

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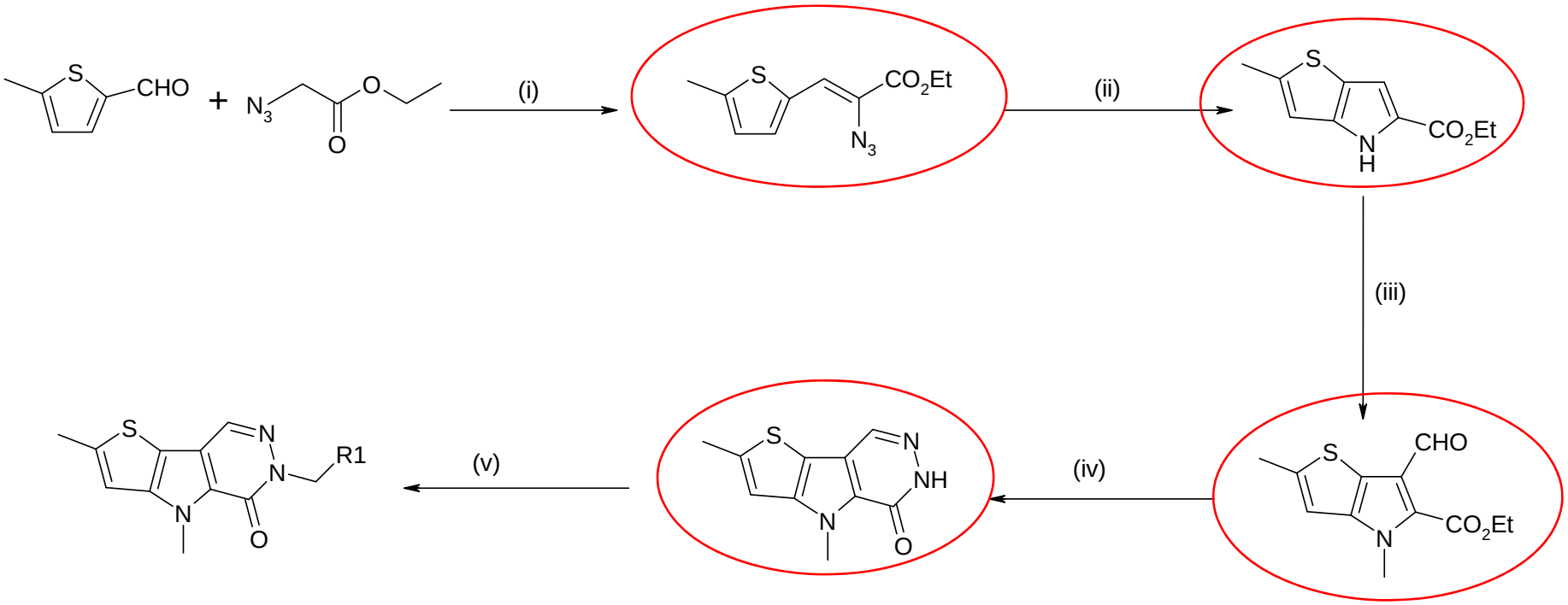
Synthesis of Thienopyrrole pyridazinones



Conditions and reagents: (i) Na, EtOH, 0°C; (ii) xylene, reflux; (iii) (a) $POCl_3$, DMF, 60°C, (b) MeI, K_2CO_3, DMF; (iv) 2-Ethoxyethanol, hydrazine, reflux; (v) alkyl bromide, KO^{t}Bu, DMF, r.t.

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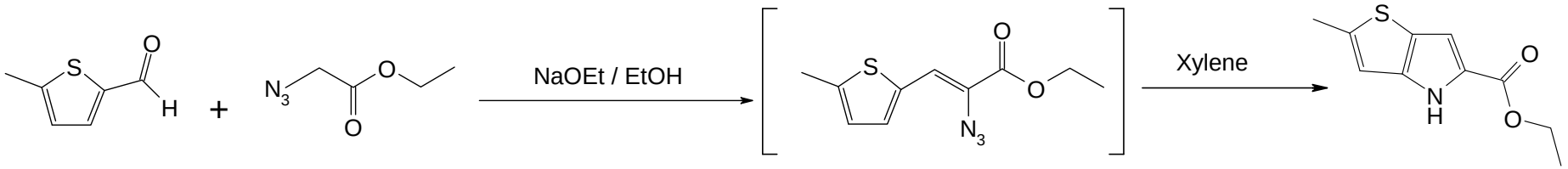
Synthesis of Thienopyrrole pyridazinones – Stage 1 + 2



Initial conditions: NaOEt (4eq) / EtOH 0^{o}C then xylene reflux, 30% over 2 steps

Charging less sodium ethoxide leads to incomplete reaction.

Telescoped reaction has a ‘dirty profile’. AQUEOUS WORK UP NECESSARY.

Modified conditions: NaOEt (4.0 eq), EtOH, NH_4Cl quench, Toluene extraction.

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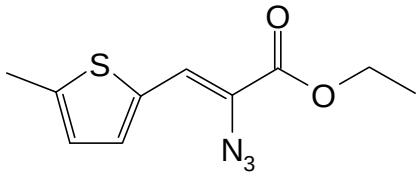
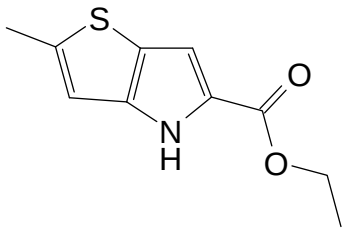
Synthesis of Thienopyrrole pyridazinones – Stage 1 + 2

Pump A / B



Toluene



Conditions

Concentration: 0.21 M

Coil: 5 mL HT PTFE

Temp: 130 °C

Residence Time: 1.5 min

Flow rate: 3.3 mL/min

Work Up:

Evaporate then chromatography.

Output: 5.6g, 57% yield.

Run Time: 60 minutes

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Synthesis of Thienopyrrole pyridazinones – Stage 3

Initial conditions: $POCl_3$ (2eq) / DMF 60°C for 2 hours 50% yield

Microwave Conditions: 4 reactions investigated stoichiometry (2 to 10 eq $POCl_3$).

Modified conditions: $POCl_3$ (10eq) / DMF 110°C for 10 minutes

Work Up: Basify (aq NaHCO3), filter and dry product

Yield: 67%

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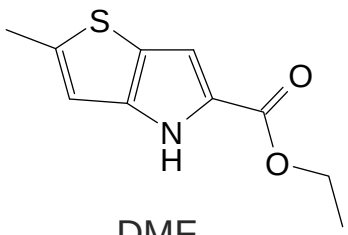
Synthesis of Thienopyrrole pyridazinones – Stage 3

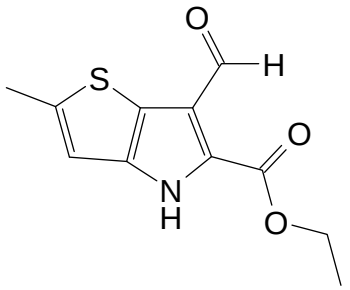
Pump A



DMF

Pump B

$POCl_3$ / DMF



Conditions

Concentration: 0.20 M

Coil: 20 mL PTFE

Temp: 110 ^{o}C

Residence Time: 10 min

Flow rate: 2 mL/min

Work Up:

Basify with NaOH, filter product then chromatography.

Output: 3.8g, 67% yield.

Run Time: 60 minutes

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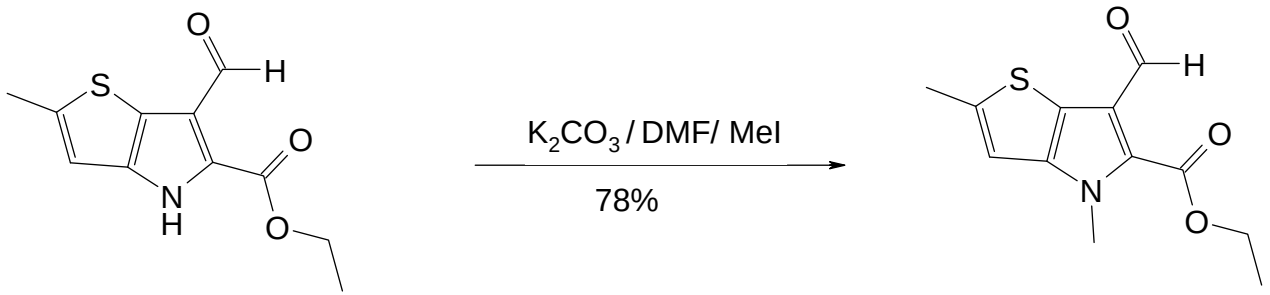
Synthesis of Thienopyrrole pyridazinones – Stage 4



Initial conditions: MeI / K_2CO_3 20°C for 3 hours 78% yield

Attempted in batch using organic bases

Bemp gave the best result (86% isolated yield)

$CaCO_3$ tried in a column reactor as base but unsuccessful

Bemp resin also works but very expensive.

Base	SM (%)	Product (%)
DIPEA	41	59
DBU	19	65
TMG	4	90
BEMP	0	97

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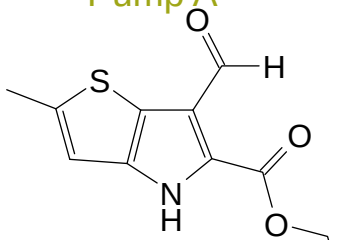
Synthesis of Thienopyrrole pyridazinones – Stage 4

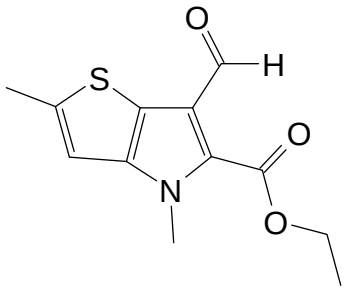
Pump A



MeI / DMF

Pump B

BEMP / DMF



Conditions

Concentration: 0.11 M

Coil: 2.5 mL PTFE

Temp: 80 ^{o}C

Residence Time: 10 min

Flow rate: 0.25 mL/min

Work Up:

Product not processed

Conclusion: Stick with batch conditions

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Synthesis of Thienopyrrole pyridazinones – Stage 5

Initial conditions: Hydrazine hydrate, 2-ethoxyethanol, reflux; 79% yield

Work Up: Product precipitates out, filter and dry.

Alternative solvents NMP, DMF give poor reaction profiles

Insolubility of the product makes flow non viable at the moment!!

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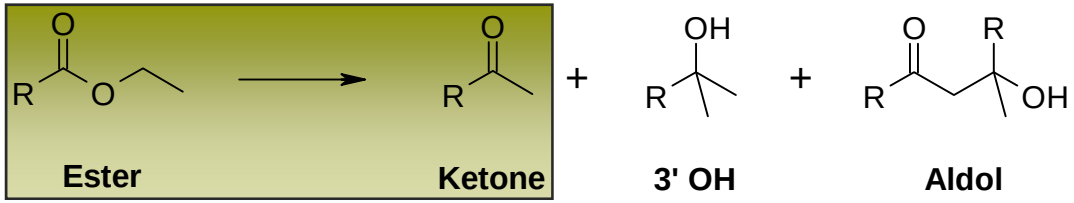
Case Grignard - background



- Desired reaction - Ester to Ketone
- Troublesome by-product formation, 3'OH and Aldol
  - Loss of yield
  - The reaction Ketone to 3'OH is faster than the desired reaction
  - Aldol is formed during quenching. A retro-Aldol reaction is not possible due to Ketone stability issues
- Un-reacted Ester is difficult to remove
  - A "high" conversion is desired

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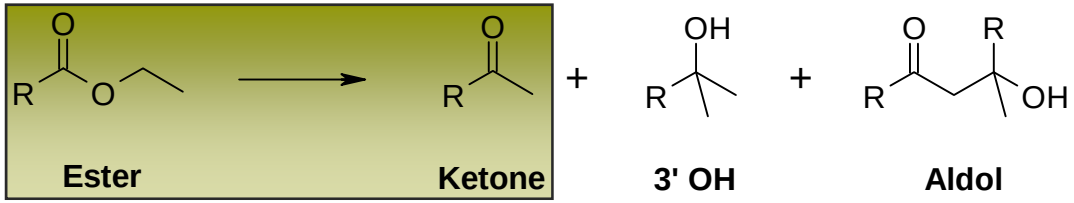
Grignard in batch



- MeMgBr (2 equiv.) and triethylamine in 2-MeTHF added drop wise to the Ester in 2-MeTHF
- 3 hrs at T ≤ -5°C
- Reaction mixture added to a quench solution of AcOH in 2-MeTHF (2 hrs)

Batch <2L
40-57% isolated yield
(1-2% 3'OH; 10% Aldol)

Batch1000L
30% isolated yield
(5% 3'OH; 40% Aldol)

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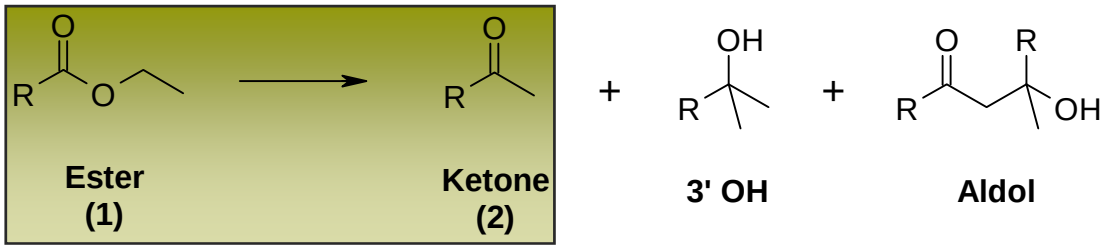
Next delivery

- Approximately 30-40 kg Ketone needed
- Isolated yield would have to be significantly increased

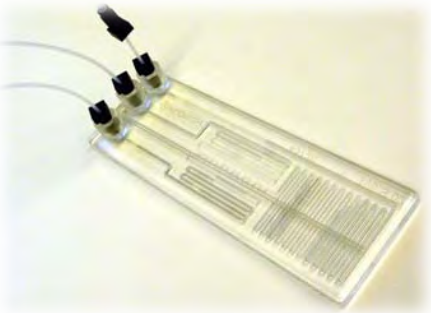
To meet that

- Batch manufacture would require a new route
- Continuous flow?

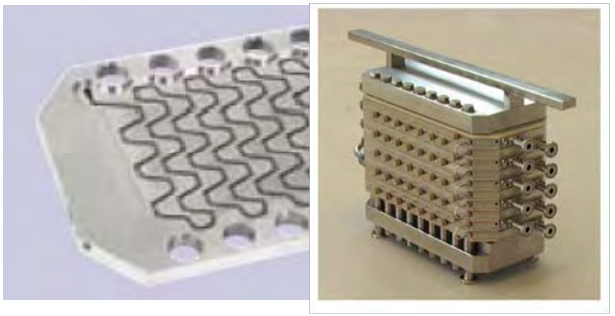
Leaving the Tap Open



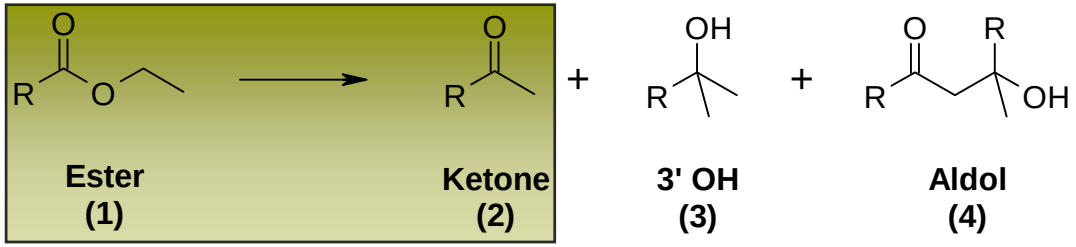
- Optimisation and manufacture in Sigma-Aldrich chip
  - Campaign 1, RSL Mölndal
  - 8 days of development
  - 300 g of (1) converted to 170 g ketone (2), isolated yield 63%.



- Process development and manufacture in Alfa Laval unit
  - Campaign 1c support, LSL Södertälje
  - Process adjustments over 5 days
  - 500 g of (1) converted to ketone (2), not isolated
  - 6L solution / 5 h (25 mL/min)



Grignard screening results



Reactor	Equiv Grignard	Residence Time (s)	Quench	HPLC (Area%)			
				1	2	3	4
Sigma- Aldrich	1.3	11	Batch	9	80	6	5
ART 1 mm	1.2	30	Batch	6	73	5	16
ART 1 mm	1.2	20	In situ	1.5	93	4	1.5
Sigma- Aldrich	2.2	9	In situ	1	91	9	<1
ART 2 mm	1.6	24	In situ	0	89	11	1

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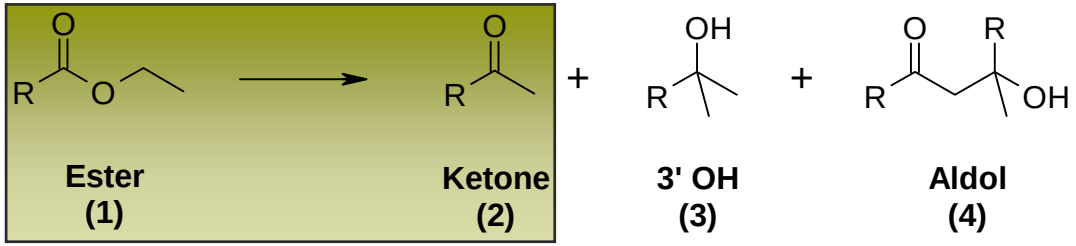
Conclusions from DoE



- Ester to Ketone conversion is *temperature sensitive*
- Quench reaction is *mixing sensitive*
- Window of operation to give desired quality of Ketone
  - 1.2-1.7 equivalents of MeMgBr
  - Temperature ≤0°C (cooling media)
  - The higher flow rate the better

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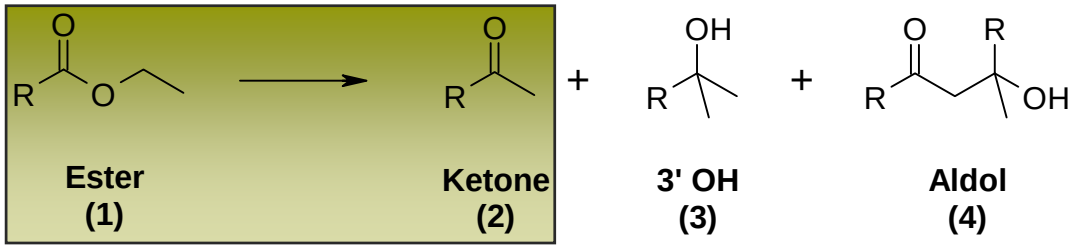
Large manufacture in summary

- Input of 34 kg Ester
- Flow rate 72 g/min
- Temperature 0ºC to -5ºC (cooling media)
- Effective pumping time 92 h

- Output of 27 kg Ketone
- Isolated yield 65%



Reactor	Equiv Grignard	Residence Time (s)	Quench	HPLC (Area%)			
				1	2	3	4
ART 2mm	1.2-1.7	12	In-situ	1-7	87-91	4-9	0-0.5

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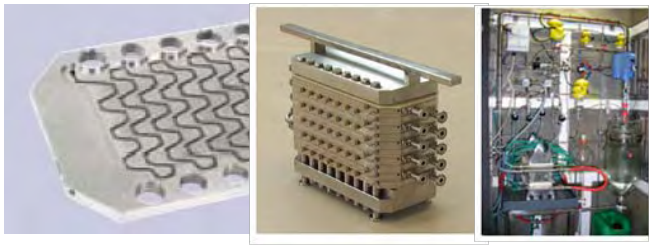
Summary

A Vision for the Future (in 2008)

2008
- Multi site, uncoordinated activity
- Flow chemistry band wagon
- A feeling this is worth doing

DRIVERS:
- **Less development:**
- **Cheaper processes**

Scope:
- **C2 delivery**



2011
A viable alternative to batch
- Global activity & Global skill
- Coordinated by a cross site/functional group:
- Lab equipment available on all sites
- Scale-up available

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Summary

- AZ has capability to deliver C1-C2 using Flow technologies
  - Next step: Embed as a core capability
  - Several options to expand scope beyond C2
- Flow Technologies compliment existing batch processes
  - Drivers based on reaction requirements
- Future developments in flow
  - Use of polymer supported reagents / scavengers
  - Collaborations for crystallisation and multi phase systems
  - Use of slurry pumps

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