Operational Aspects of Continuous Pharmaceutical Production

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Introduction

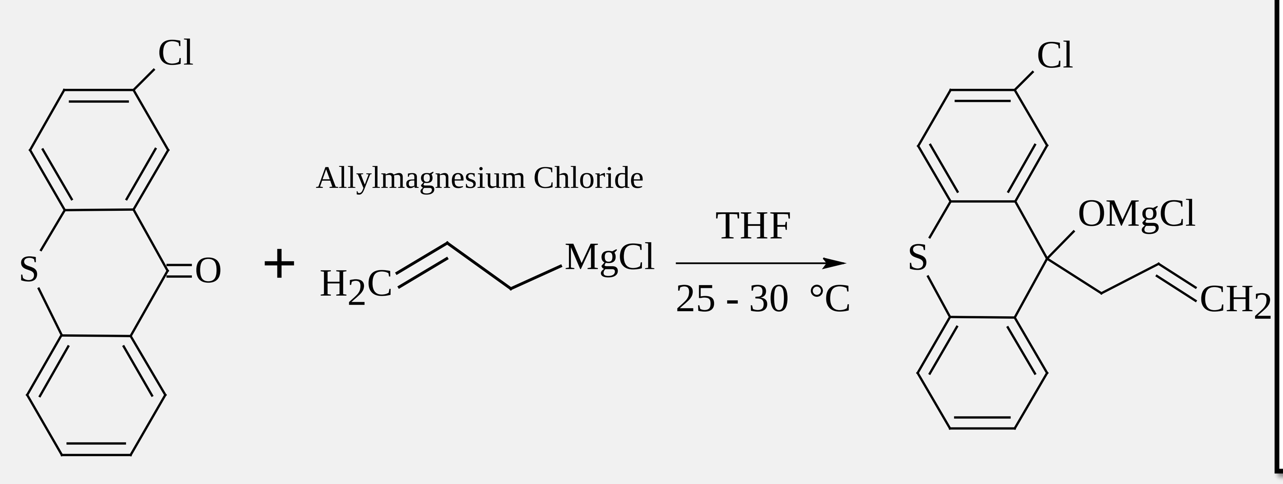
- Continuous production of zuclopenthioxol, an API manufactured by H. Lundbeck A/S, should be completed with the main focus on acceleration of slow chemical reactions and establishment of in-line process monitoring and control
- The beginning phase with Grignard alkylation, hydrolysis and separation of two immiscible liquids has been completed successfully
- The fourth process step, the dehydration reaction, is carried out in a mini-scaled tubular reactor giving high conversions of reactants but very low selectivity of the desired product
- Hydroamination, as the last step, should be accelerated from current 24 hours to very low reaction times

Process Description

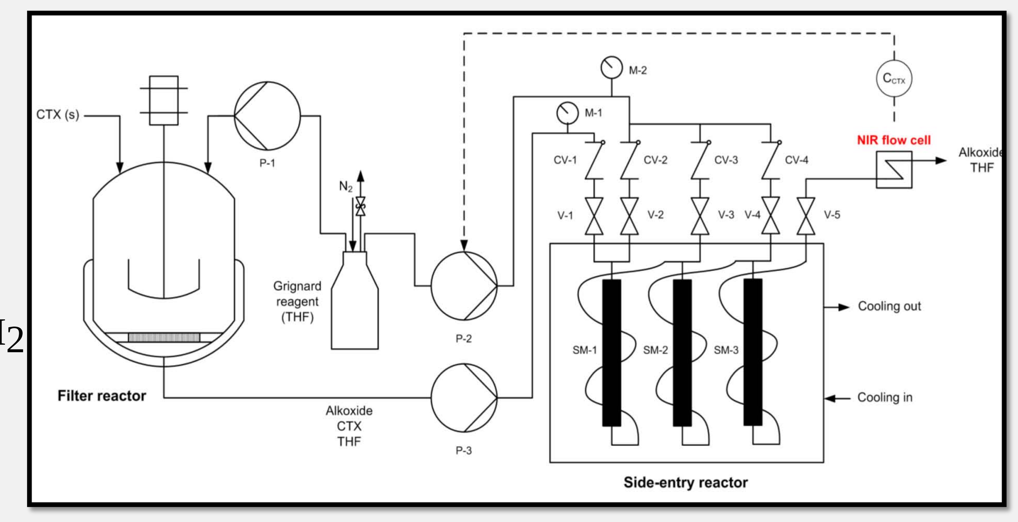
Grignard alkylation

2-Chlorothioxanthene-9-one

Intermediate compound

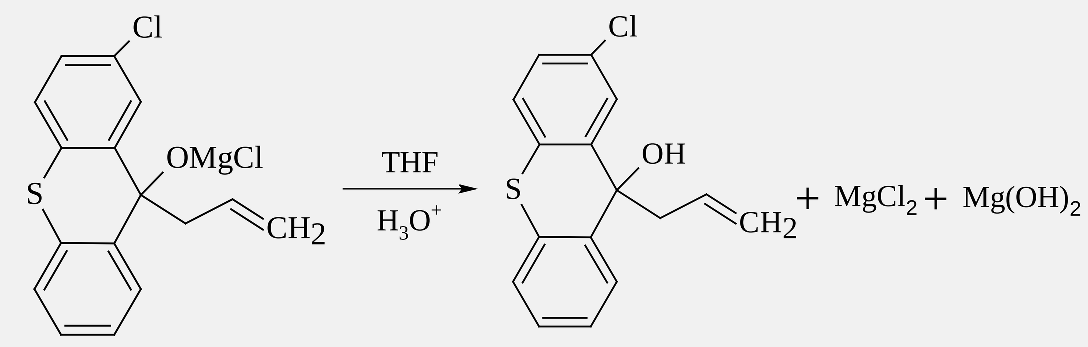


CTX Grignard reagent Alkoxide



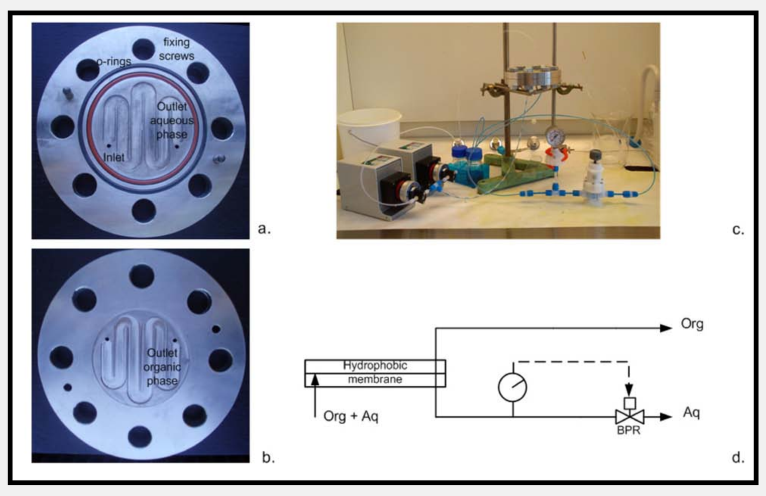
- Fast exothermic reaction suitable for mini-scaled tubular reactors
- Side-entries in the reactor were designed
- Avoidance of hot spots and increase of heat and mass transfer are achieved
- Improved yield and selectivity
- In-line process monitoring and control is established by using NIR spectroscopy methods [1]

Hydrolysis



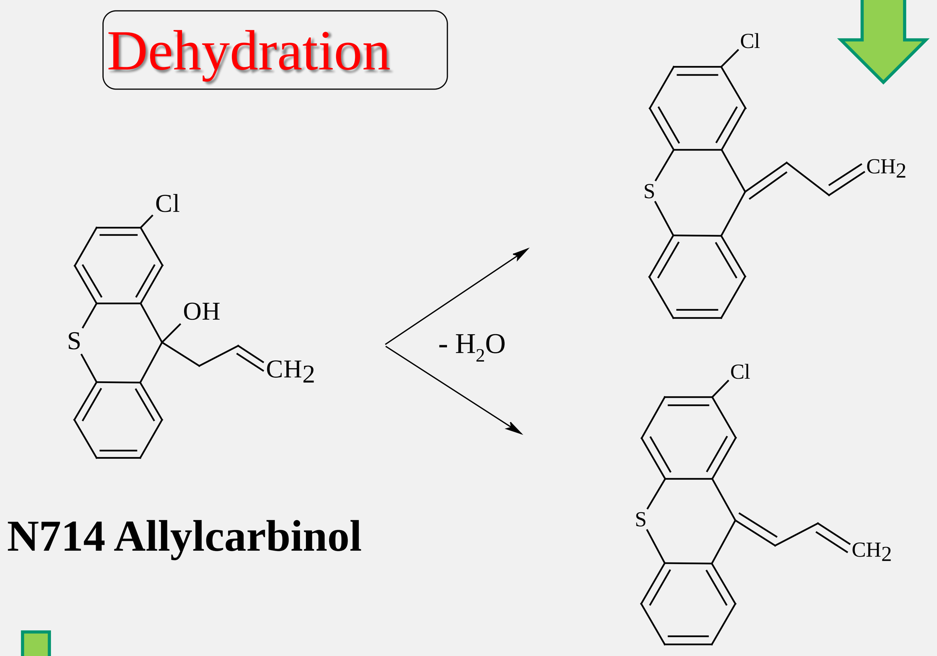
Alkoxide N714 Allylcarbinol

Separation L-L



- Surface forces have been proven as a good choice for separation of two immiscible liquids in micro-scale devices [2]
- A micro-separator with PTFE membrane has shown a great efficiency in separating toluene/aqueous and THF/aqueous mixtures [3]

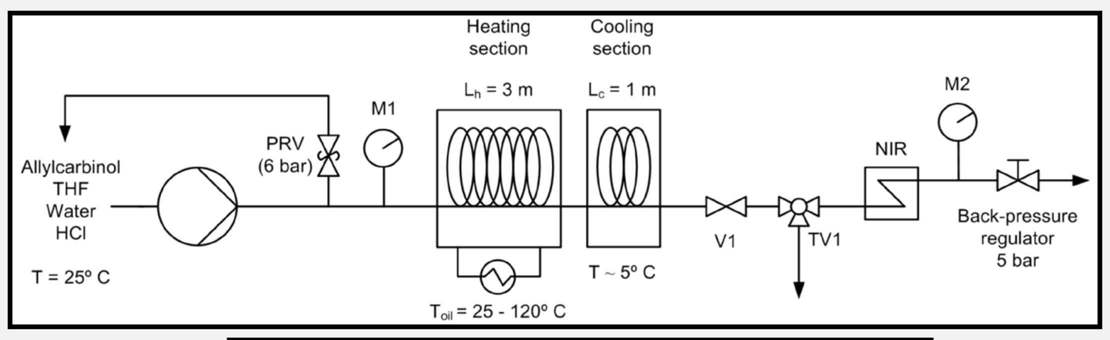
Dehydration

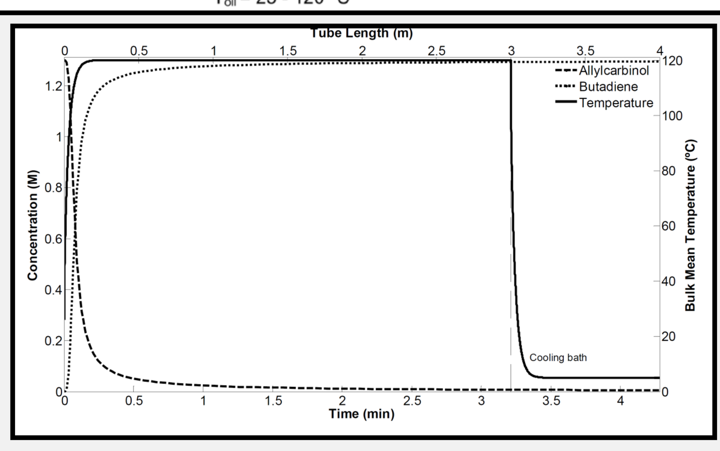


N714 Allylcarbinol

cis/trans-N746 Butadiene

cis/trans-9H-thioxanthene, 2-chloro-9-(2-propenyldiene)-(Cl)

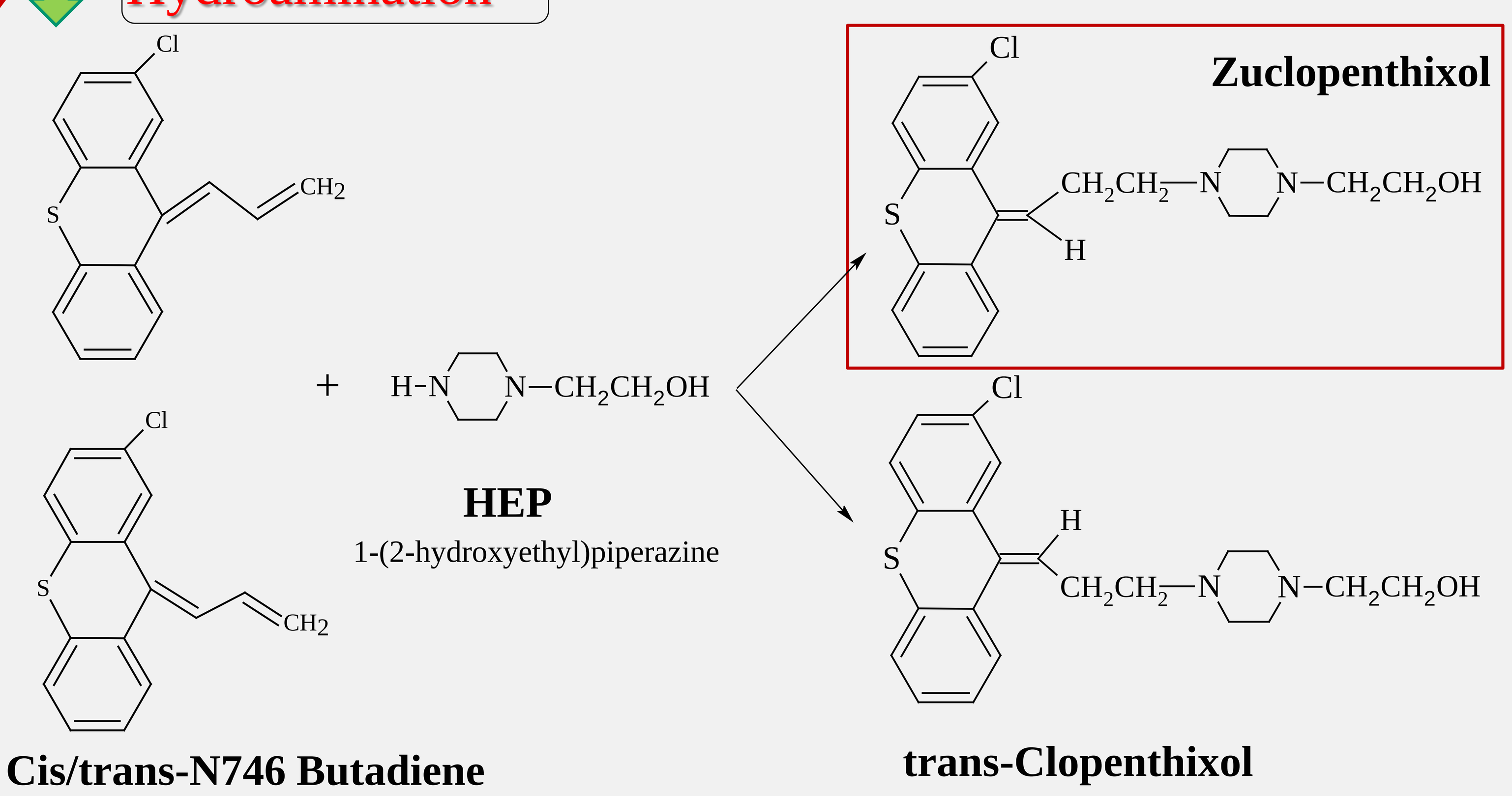




- Strong acid (HCl) is used as a catalyst
- Pressurized tubular reactor (up to 6 bars) enables higher reaction rates by increasing reaction temperatures above normal boiling point of the used solvent (THF)
- Very high conversion is achieved, but selectivity of desired cis-isomer is low (around 50%)

Hydroamination

cis-Clopenthixol



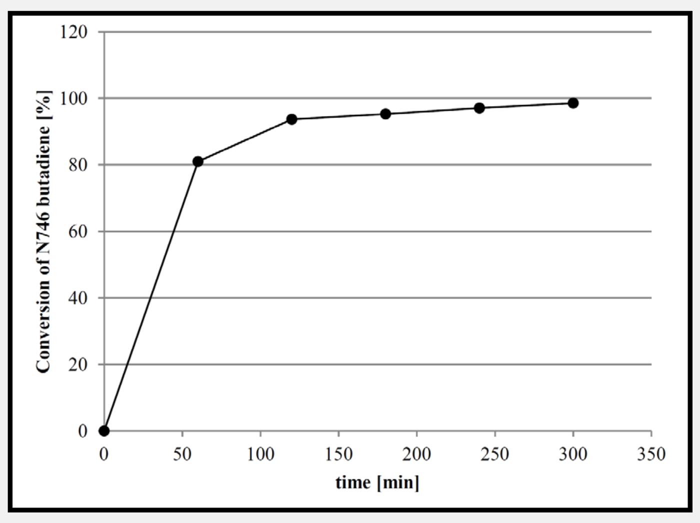
Cis/trans-N746 Butadiene

HEP

1-(2-hydroxyethyl)piperazine

trans-Clopenthixol

Cis/trans-4-[3-(2-Chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol



- Intermolecular hydroamination based on anti-Markovnikov principle is desired
- MAOS (Microwave assisted organic synthesis) has been tested successfully obtaining almost total conversion of butadienes into chlopenthioxol

Conclusions and Future Work

- Continuous Grignard alkylation improves yields compared to batch processing
- Micro-separator with PTFE membrane has shown a great performance
- Dehydration reaction performed under higher pressure allows higher reaction rates. Further work is focused on stereo-selectivity of this process step
- MAOS applications allow very high conversion of N746 Butadienes in clopenthixol. Longer exposures above 120°C cause by-product formations.
- Establishment of in-line process analysis, as well as control of the overall continuous process is the future work

References:

[1] A. E. Cervera-Padrell, J. P. Nielsen, M. J. Pedersen, K. M. Christensen, A. R. Mortensen, T. Skovby, K. D. Johansen, S. Kiil, K. V. Gernaey, Org. Process Res. Dev. 16 (2012) 901-914

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[3] A. E. Cervera-Padrell, S. T. Morthensen, D. J. Lewandowski, T. Skovby, S. Kiil, K. V. Gernaey, Org. Process Res. Dev. 16 (2012) 888-900

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