Master's Thesis Engineering Technology 2017-2018

Design and characterisation of a cascade of continuous stirred-tank reactors for a Grignard reaction

Cornelissen Dries, Debrie Robin

Masters of Chemical Engineering Technology

Introduction

Currently, the pharmaceutical and fine chemical industry performs Grignard reactions in large semi-batch reactors. Due to the exothermic nature of this reaction, heat dissipation problems occur. This requires dosing of reagents and therefore a long reaction time. Also, each batch needs an initiation, causing varying product quality. A continuous-flow process improves heat dissipation, has only one transient startup initiation and decreases production area, which increases production capacity and stability. This Master's thesis describes the design and characterization of a continuous-flow Grignard process of which the research was executed in Lab$_4$U.

First, a screening of different reaction initiation methods was performed to obtain a instantaneous and reliable initiation [1] [2]. Based on literature research [3] a reactor setup was designed, consisting of two Continuously Stirred Tank Reactors (CSTRs) in series with a solids settler in between to keep magnesium in the first reactor. Next, the reactor setup and the reactions (Figure 1 and 2) were characterized. The residence time distribution was measured for the CSTR cascade and separate CSTRs.

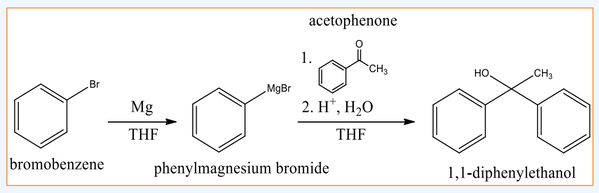


Figure 1: Reaction scheme for 1,1-diphenylethanol synthesis

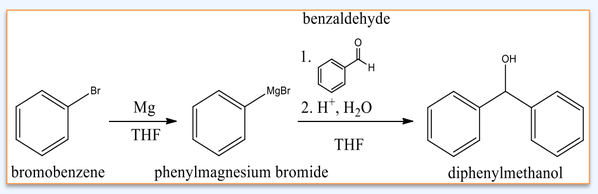


Figure 2: Reaction scheme for diphenylmethanol synthesis

Materials & Methods

Reaction characterisation was performed in an Easymax 102 (Figure 3) to maintain a constant temperature.
The cascade tests were performed in the setup shown in Figure 4. The solids settling system consisted of the double angled settling pipe and a magnesium trap. The first CSTRs had a reaction volume of 50 ml, the second 55 ml. All tests were done with a ratio of 2:1 Magnesium:Bromobenzene and 1:1 Bromobenzene:Acetophenone or Benzaldehyde.

The reaction initiation is a crucial part, to research which technique described in the literature was the most effective. The experiments shown in Table 1 were performed.

Figure 3: Easymax 102 [4]

Table 1: Reaction initiation tests

	Reaction initiation technique			
Experiment	Iodine in THF	Iodine in THF (heated)	Iodine vapour	Phenylmagnesium bromide addition
1	x			
2		x		
3			x	
4	x			x
5				x
6	x		x	x

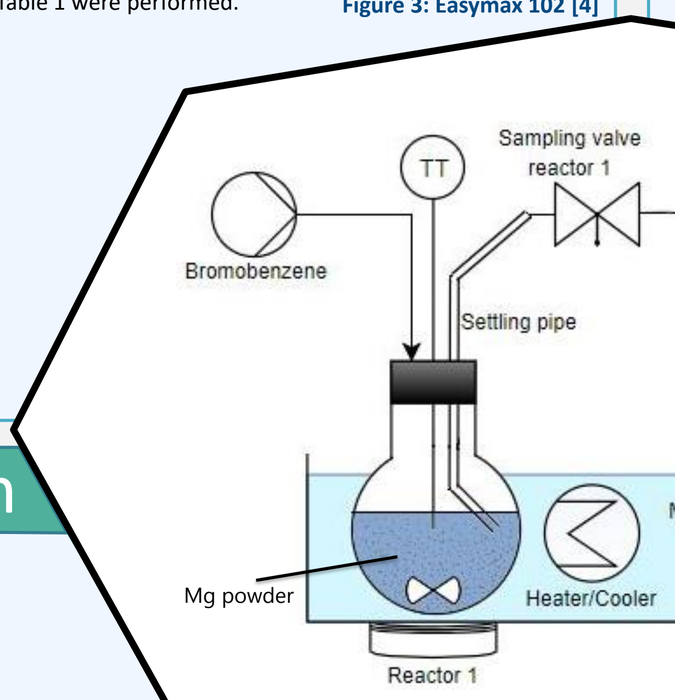


Figure 4: Reaction setup for the cascade tests

Materials & Methods

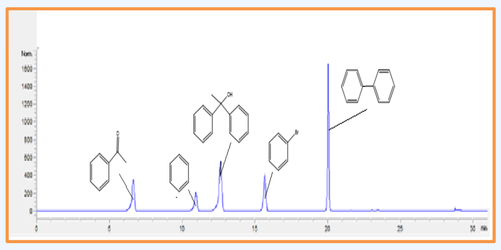


Figure 5: HPLC Chromatogram for reaction 1

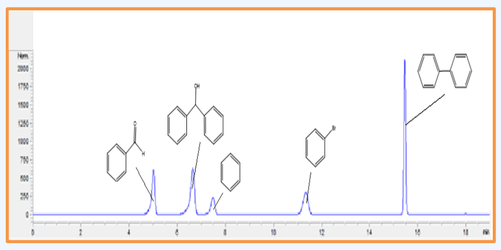


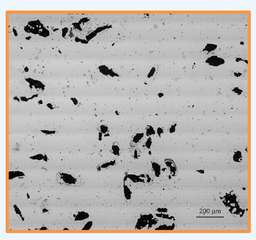
Figure 6: HPLC Chromatogram for reaction 2

Samples were 1000x diluted with acetonitrile and analyzed with a HPLC with a Alltima HP C18 5 µm column (250 mm x 4.6 mm ID) and an UV-detector measuring at wavelength 210 nm. The chromatograms of both reaction products are shown in Figure 5 and 6.
The yield of the reaction was calculated by using validated calibration curves in ppm.
The residence time distributions of both separate reactors and the cascade CSTR setup were determined by measuring the conductivity using the negative step method with a 0.1 M KCl solution. It resulted in a mean residence time of 11 min 40 sec for the cascade with a D/µL of 0.19

Results & Discussion

Table 2: Reaction initiation results

Activation technique	Activation of magnesium	Initiation when adding bromobenzene	Reaction intensity
1	/	initiation Mg/activation 3.5 min afterwards	Moderate (< 50°C)
2	By addition of bromobenzene	Instantly	Very mildly (< 30 °C)
3	By addition of bromobenzene	Instantly	Heavy reaction (50 °C < T < 66 °C)
4	Instantly	Instantly	Boiling (T = 66 °C)
5	Instantly	Instantly	Boiling (T = 66 °C)
6	Instantly	Instantly	Heaviest reaction (T = 66 °C)



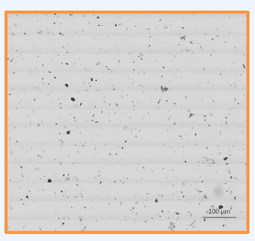


Figure 9: Magnesium particles in the magnesium trap (left) and in final cascade flow (right) with double angled settling pipe

The combination of iodine vapour, iodine in THF and phenylmagnesium bromide addition (experiment 6) results in the most intense activation and initiation, as shown in Table 2. All experiments were carried out with this initiation technique.
In Figure 9, it can be observed that magnesium up to 200 µm is withhold by the double angled settling pipe. The additional magnesium trap retains particles up to 25 µm. The retention of magnesium is important as he magnesium could damage pumps and forms H_2 when the reaction mixture is quenched in later process parts.

Results & Discussion

The variation of the concentration of bromobenzene (blue relative to red) and concentration of magnesium (blue relative to black) in Figure 7 appears to be a second-order relation.
The reaction characterisation results in the equation:
$-r_A = 2.04 * 10^7 * e^{\frac{-44\,828.3}{R*T}} * C_{Bromobenzene} * S_{Magnesium}$
The yield of diphenylmethanol is not displayed in Figure 8 because this result is ambiguous.

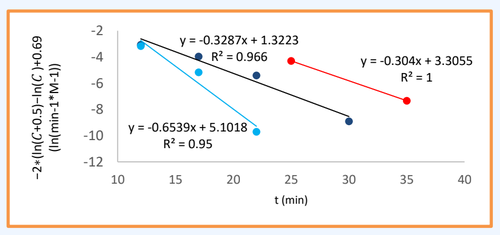


Figure 7: concentration variation of bromobenzene and magnesium

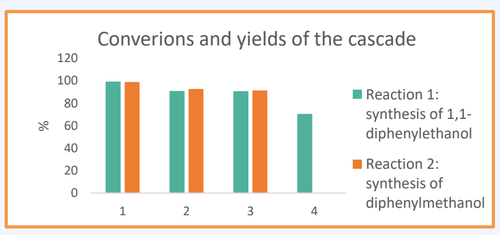


Figure 8: with 1: conversion of bromobenzene, 2: yield of phenylmagnesium bromide, 3: conversion of acetophenone (green)/benzaldehyde (orange), 4: yield of 1,1-diphenylethanol

Conclusion

In this Master's thesis, the design and characterisation of a cascade of continuous stirred tank reactors for a Grignard reaction is examined. The initiation tests show that the combination of iodine vapour, iodine in THF and phenylmagnesium bromide addition ensures the most instantaneous and reliable initiation. A total yield of 70% 1,1-diphenylethanol is achieved when the Grignard reaction is carried out with acetophenone in the CSTR cascade at a total flow rate of 1.2 l/h. No particles above 25 µm are found in the final product flow, and the double angled settling pipe has proven effective up to particles of 200 µm. Both the cascade test with reaction 1 (acetophenone) and 2 (benzaldehyde) obtain a 91% yield of phenylmagnesium bromide and 99% conversion of bromobenzene in the first reactor. In the second reactor a 91% conversion of acetophenone/benzaldehyde is reached.
The residence time distribution shows a CSTR character with a dispersion of 0.19. The cascade of CSTRs has a time lag of 2 min 30 sec, included in the mean residence time of 11 min 40 sec.
Lastly, the reaction characterisation of the reaction with bromobenzene and magnesium powder results in a second-order reaction, with an activation energy of of 44828.3 J/mol.

Supervisors / Cosupervisors: Prof. Dr. Ir. Thomassen C.J. Leen, Ing. Claes Joris

[1]: U. Tilstam and H. Weinmann, "Activation of Mg metal for safe formation of Grignard reagents on plant scale," Org. Process Res. Dev., vol. 6, no. 6, pp. 906–910, 2002
[2]: T. S. Eckert, "An improved preparation of a Grignard reagent," J. Chem. Educ., vol. 64, no. 2, p. 179, 1987
[3]: S.-W. Wong, S. M. Changi, R. Shields, W. Bell, B. McGarvey, M. D. Johnson, W.-M. Sun, T. M. Braden, M. E. Kopach, R. D. Spencer, G. Flanagan, and M. Murray, "Operation Strategy Development for Grignard Reaction in a Continuous Stirred Tank Reactor," Org. Process Res. Dev., vol. 20, no. 2, pp. 540–550, Feb. 2016
[4]:Mettler Toledo, *'EasyMax 102 Advanced Synthesis Workstation'* [Online]. Available: https://www.mt.com/be/nl/home/products/L1_AutochemProducts/Chemical-Synthesis-and-Process-Development-Lab-Reactors/Synthesis-Reactor-Systems/EasyMax-Synthesis-Reactor.html