Master's Thesis Engineering Technology

2021-2022

Optimization of the green synthesis of potential anti-ageing compounds

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Introduction

The traditional linear economy has shown that earth's valuable resources are starting to diminish. The **current linear economy must be redesigned into a circular economy** where waste and pollution are eliminated, products and materials are recirculated and nature is restoring some balances which are now unbalanced [1].

In this work, the synthesis of potential anti-ageing compounds is optimized by opting for the use of **eco-friendly solvents, catalysts and reagents**. These compounds can be made in 2 reaction steps as illustrated in figure 1. The first reaction is the N-carboxy benzylation illustrated in figure 2 and the second reaction is the ester amidation shown by figure 3.

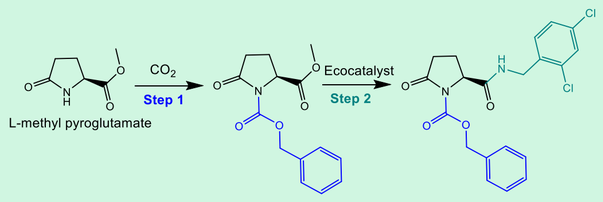


Figure 1: reaction steps for the synthesis of the anti-ageing compounds

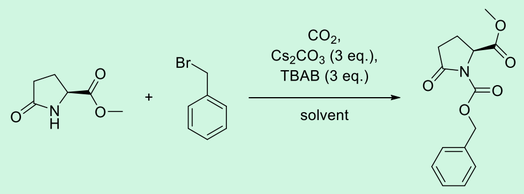


Figure 2: N-carboxybenzylation of PGM with CO2 and benzyl bromide [2].

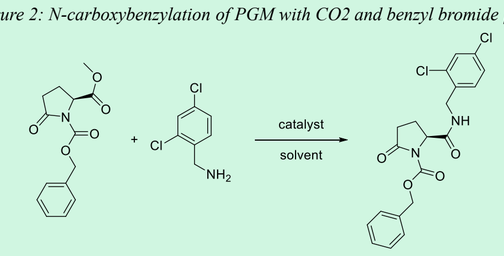


Figure 3: Ester amidation of methyl N-carboxybenzyl pyroglutamate with 2,4-dichlorobenzylamine

Conditions tested for **step 1**:
- Solvent effect
- Temperature effect

Conditions tested for **step 2**:
- Solvent effect
- Amine electronic effect
- Temperature effect
- Catalyst effect

Materials & Methods

Experimental setup for respectively step 1 and 2

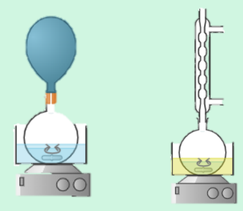


Figure 4: Experimental setup for the N-carboxy benzylation and ester amidation

Purification steps
- Filtration
- Flash chromatography

Analysis
- TLC
- ^{1}H-NMR
- Polarimetry
- Melting point

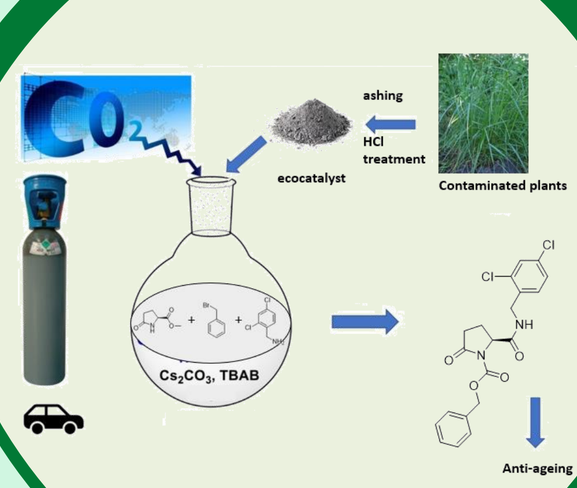
N-carboxy benzylation and ester amidation reaction

For the **N-carboxy benzylation** shown by figure 2, 3 equivalents of phase transfer agent tertiary butylammonium bromide (**TBAB)** and base **cesium carbonate** are added into a round bottom flask. Then 1 equivalent of L-pyroglutamate (**PGM)** is added together with 15 mL of **solvent**. The round bottom flask is then purged with CO_2 gas. Eventually the **benzyl bromide** is added, and the reaction mixture is stirred with a magnetic stirrer under a **CO_2 atmosphere** provided by the balloon as shown in figure 4.

For the **ester amidation**, 100 mg of **ecocatalyst** or 0.05 equivalent of **$ZrCl_4$** is added to a round bottom flask. Then the **carbamate** is added together with the **amine** and 5 mL of **solvent**. The flask is then placed in a hot oil bath on the hotplate together with a magnetic stirrer. The condenser is then secured on top of the flask as illustrated in figure 4.

Experimental plan

For each experiment, the reaction conditions are changed **factor by factor**. The effect on the reaction rate of the different levels of each factor were compared with each other to draw conclusions. The conversion of all the experiments were followed by **^{1}H-NMR** with the different reaction conditions. Samples are taken at fixed time intervals during the reaction. This analysis method provides a good comparison between the different conditions.



Results & Discussion

Catalyst effect

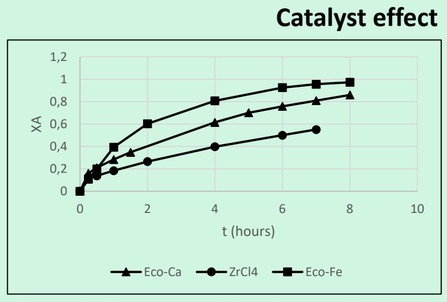


Figure 8: Conversion of A vs time graph of catalyst experiments

Catalyst orderd from best activation to worst:
1) Ecocatalyst rich in iron
2) Ecocatalyst rich in calcium
3) $ZrCl_4$

Temperature effect

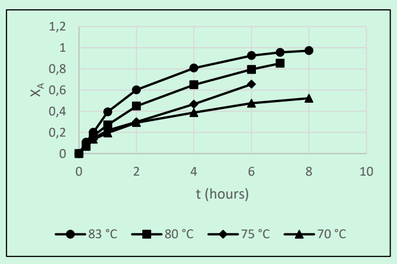


Figure 9: CA vs t graph for the temperature effect experiments

T↑ → reaction rate↑

Optimum temperature is **83°C** →reflux temperature of ACN

Amine electronic effect

Electro donating effect↑ → reaction rate↑

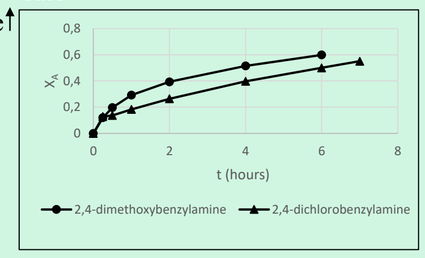


Figure 10: conversion vs time for the amine electronic effect

Results & Discussion

Step 1: *N*-carboxy benzylation

Temperature effect

A temperature of **30° C** has the best effect on the reaction rate.

40°C → lower reaction rate

Optimal temperature lays around 30°C

Possible Reason: reaction itself gets faster but less CO_2 diffuses in the reaction mixture at 40° C.

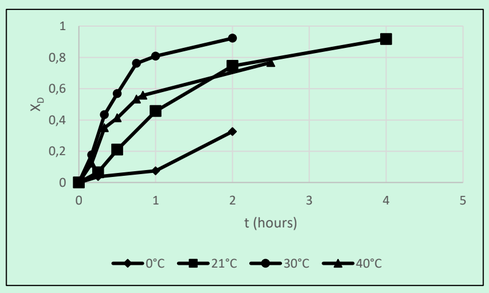


Figure 5: temperature effect on the N-carboxy benzylation reaction

Step 2: ester amidation

Obtained molecule

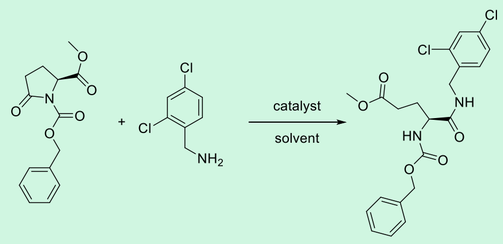


Figure 6: obtained molecule from the ester amidation

The possible reason why an **open ring molecule** is obtained, is because the **methanolate** from methanol attacked on the carbonyl carbon of the 5-ring.

Synthetic alternative to access closed ring target compound

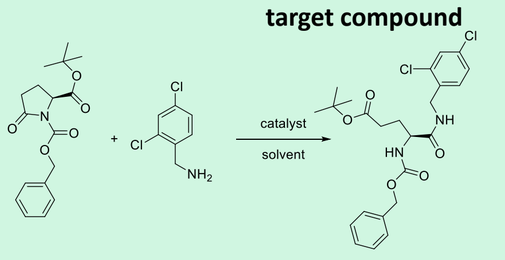


Figure 7: ester amidation with tert-butyl ester

the obtained molecule was also the **opened ring compound** with a ***tert*-butyl ester group** instead of methyl. Thus, the **ring opening** reaction **still occurred** even with the bulky *tert*-butyl ester group.

Conclusions

The **ecocatalysts** showed promising results on the reaction rate. The other metal chlorides had better effect on the activation of the ester amidation reaction compared to $ZrCl_4$. The solvent **ACN** had the best result for both reactions. An **electro donating effect** on the amine for the ester amidation reaction had a **positive effect** on the reaction rate. The best results were obtained with **2,4-dimethoxybenzylamine** as a reagent. The yield for the ***N*-carboxy benzylation** and the **ester amidation** with the best reaction conditions, identified upon optimization study, gave a yield of respectively **73.4 %** and **64.3 %**. This study could be of interest for the industrializing of these type of reactions by the pharmaceutic or cosmetic industry.

Supervisors / Co-supervisors / Advisors

Prof. Dr. ir. Thomassen Leen
Prof. dr. Ghinet Alina

References:

[1] E. MacArthur, "Ellenmacarthurfoundation.org." https://ellenmacarthurfoundation.org/circulate-products-and- materials (accessed Apr. 08, 2022).

[2] G. Homerin, A. S. Nica, A. Aitouche, B. Rigo, E. Lipka, and A. Ghinet, "Carbon dioxide transformation as a green alternative to phosgene and chloroformates: *N*-carboxyalkylation of lactams and analogues," *J. CO_2 Util.*, vol. 54, no. September, p. 101782, 2021, doi: 10.1016/j.jcou.2021.101782.