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Multistep Flow Synthesis of 4-(4-Methoxyphenyl)butan-2-one and Benzylacetone using Micropacked Bed Reactors

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Highlights

- A yield of 56% was achieved in the continuous multistep synthesis of benzylacetone.
- The multistep system included oxidation, coupling, reduction and oxygen gas removal.
- Continuous flow enabled process intensification as compared to a batch system.
- Water inhibition was observed and avoided by using feeds with less than 3 M alcohol.

1. Introduction

The aim of this work is to highlight some of the challenges, solutions and benefits experienced when converting a batch catalytic cascade system to multistep flow. This is achieved through the case study of the synthesis of two substituted benzylacetone molecules; benzylacetone and 4-(4methoxyphenyl)butan-2-one, starting from different substituted forms of benzyl alcohol. This system was chosen as these products have high commercial value in the fine chemical industries and because the recently developed batch cascade, using AuPd catalysts supported on TiO_2 and MgO, was successful, being more selective and producing less waste than current commercial production methods [1]. The individual reactions (oxidation, coupling and reduction) are all common catalytic reactions in industry enabling this work to be used as a guide for other systems. The flow multistep system can facilitate process intensification, as it allows the separation of the three reaction steps, enabling the operating conditions and catalyst for each reaction to be chosen separately. Furthermore the flow microreactors offer intensified heat and mass transport, benefitting the fast oxidation and reduction reactions which can be limited by gas mass transfer [2].

2. Methods

The multistep flow system feed was either benzyl alcohol or 4-methoxybenzyl alcohol in acetone solvent. The reaction steps were alcohol oxidation to aldehyde, coupling of the aldehyde with acetone, and a reduction step. The three reaction steps were studied in isolation before connecting the reactors in series. Inhibition studies were carried out to investigate if side products from previous reactions would inhibit downstream reactions. The catalysts used were $AuPd/TiO_2$ for oxidation, TiO_2 for coupling and Pd or Pt/TiO_2 for reduction. The reactions were conducted in silicon–glass micropacked bed reactors of channel cross section 600 μm x 300 μm [3] and in packed tube reactors of internal diameter 1 mm. A Teflon AF2400 tubular membrane was used for continuous oxygen separation and the liquid product was collected and analyzed by GC. Typical liquid flowrates varied from 10-40 μL/min and gas flowrates varied from 0.6-5 NmL/min. The multistep reactor system is shown in Figure 1.

3. Results and discussion

The multistep flow synthesis of both 4-(4-methoxyphenyl)butan-2-one and benzylacetone were successful with maximum yields of 53% and 56% respectively. The flow system produced a slightly lower yield of 4-(4-methoxyphenyl)butan-2-one than the corresponding batch synthesis (63%), but achieved higher yields of benzylacetone than the batch (8%), as shown in Figure 2. A major advantage of the multistep flow system was its increased productivity and reduced catalyst mass requirements, as it needed a catalyst contact time (per gram of alcohol) approximately an order of magnitude lower than in a batch cascade. Furthermore, the

amount of nanoparticle supported catalyst was reduced from 500 mg in batch to just 20 mg in flow, by identifying that the catalyst for the coupling reaction, could be replaced with just the TiO_2 support instead of using AuPd/MgO. Various challenges were encountered and overcome, including water inhibition, deactivation, oxygen separation and flow stability. The generation of water as a by-product of the oxidation reaction led to water inhibition of the coupling reaction. However, it was found that if the alcohol feed concentration to the oxidation reaction was kept below 3 M, the amount of water produced was sufficiently low so as not to cause downstream inhibition. This is shown in Figure 2, where high yields of the desired benzylacetone product (shown in black) were obtained at low feed concentrations, but not at 3 M. The flow system was also able to operate continuously for 13 hr with only a minor drop in performance by using a small excess of catalyst to account for deactivation.

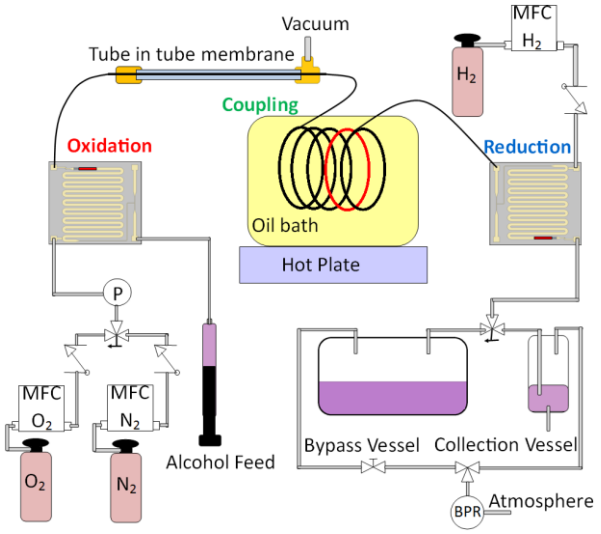

Figure 1. Experimental set-up for the multistep synthesis of benzylacetone and 4-(4- methoxyphenyl)butan-2-one. The red sections in the reactors represent the catalyst packed bed, MFC stands for mass flow controller, BPR for back pressure regulator and P for pressure sensor.

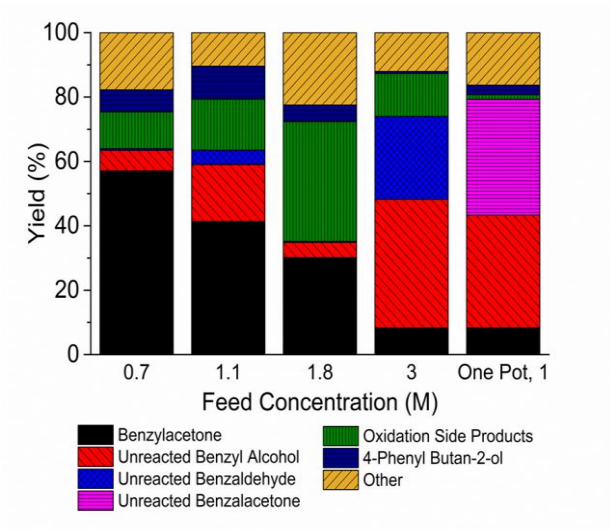

Figure 2. Yield of the various reaction products from the multistep flow synthesis of benzylacetone in flow at four different inlet concentrations of benzyl alcohol (0.7, 1.1, 1.8 and 3 M) and also in the one pot synthesis using 1 M feed. The desired final product, benzylacetone is shown in black.

4. Conclusions

The successful synthesis of benzylacetone and 4-(4-methoxyphenyl)butan-2-one with high yields in a flow multistep system demonstrated the advantages of flow systems for cascade reactions. The most critical advantage of the multistep flow system compared to a one-pot batch system was the ability to separate the three reactions, allowing more freedom to choose different catalysts and operating conditions for each reaction. This facilitated a decrease in catalyst contact time and the use of cheaper catalysts than the one-pot system. Finally, the flow system is flexible enough to work with different substituted forms of benzyl alcohol.

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"Cascade Reactions", "Catalytic Reactor", "Oxidation", "Hydrogenation"