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Connected nucleophilic substitution-Claisen rearrangement in flow – Analysis for kilo-lab process solutions with orthogonality

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HIGHLIGHTS

- Orthogonality analysis for connected flow chemistries of large synthetic value.
- Proposal to overcome hurdles through in-flow separations and a kinetic approach.
- Scale-out process schemes for kilolab operation, further in-flow intensification.

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ABSTRACT

The two-step synthesis of phenol to 2-allylphenol in micro flow is investigated. This synthesis involves a nucleophilic substitution (S_N2) reaction of phenol with allyl bromide towards allyl phenyl ether and the thermal Claisen rearrangement of allyl phenyl ether to 2-allylphenol. This carbon–carbon bond forming reaction route would provide a valuable path towards complex molecules. Flow cascades have turned into a powerful approach to provide chemical diversity (process-design intensification). This is enabled by chemical intensification of the Claisen rearrangement in micro flow, by reducing the reaction time to minutes without the need of a catalyst. While both individual reaction steps have been optimized separately in earlier research, an initial directly connected two-step synthesis gave low selectivity.

Accordingly, the main topic investigated is how to achieve orthogonality in case of reagent mismatch between the two reactions. First, four flow process protocols using three different kinds of in-flow separation and one kinetic approach, are developed at laboratory scale. From there, process design sheets for kilolab processing set-ups of the suited approaches are developed which shed first light on their industrial practicality. In particular, it has been found that the main causes for the drop in selectivity are the presence of the base DBU and the reactant allyl bromide during the Claisen rearrangement. Three of the four investigated separation approaches demonstrated the ability to improve the overall yield – acid–base extraction, acid absorption by using ion exchange resin, using heterogeneous base, and dilution as kinetic approach. Finally, for every option, the proposed respective production set-up, anticipated advantages and drawbacks are given to facilitate a decision.

1. Introduction

The rearrangement of allyl vinyl ethers into γ,δ-unsaturated carbonyl compounds was developed by Claisen in 1912 [1,2]. In general it presents the simplest example of so called [3,3]-sigmatropic shifts. After its development the rearrangement has been widely studied [3]. Commonly, a concerted pathway is assumed [3]. Kinetic experiments by Schuler [4] demonstrated the unimolecularity of the Claisen rearrangement. The Claisen rearrangement is feasible for a large variety of aliphatic and aromatic ethers and has become one of the most synthetically useful reactions of organic chemistry [5,6]. Substituted allyl vinyl ethers undergo Claisen rearrangement to give the unsaturated aldehydes with quantitative yields and high degree of stereoselectivity [7,8].

In the last two decades, microreactor technology has emerged. It has become mature for applications and even been applied on industrial scale [9], including investigations of the Claisen rearrangement in flow [10–13]. It has become almost routine for

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chemical reactor engineers and, recently, an even larger number of chemists have been attracted by the new synthesis tool. A major point for the chemists is that the new tool opens doors to new chemistries, in particular under so far non-accessible operation regimes such as harsh conditions. Novel process windows have widened the synthetic possibilities and have become typical for whole flow chemistry [14–17]. They add chemical intensification to the prior developed transfer intensification of microreactors. This is most evident from the order-of-magnitude shrinkage in reaction time; most conveniently done by short-time, high-temperature processing at high pressure to prevent evaporation or boiling.

This was also applied to the Claisen rearrangement which is already conventionally, a typical high-temperature reaction. Here, novel process windows have been identified as follows. Higher yields were obtained for the product 2-allyl-4-chlorophenol and other para-substituted phenyl allyl ethers in flow as compared to batch at the same temperature of 200 °C [10,18]. Flow residence times amount to only 24 min as opposed to reaction times of 3 h in batch.

While concentration effects are not strong due to the unimolecular nature of the reaction, solvent-free processing can still make a considerable difference [10]. An important benefit of the new high temperature-high pressure window is that solvent selection is not restricted anymore by the solvent's boiling point. Low-boiling solvents can be used in flow at the desired high temperature when superheated operation is chosen, and replace former costly high-temperature solvents [10]. Following these lines, the Claisen rearrangement of allyl phenyl ether to ortho-allyl phenol was performed in subcritical water [11,19]. In a conventional water-free method, o-AP was produced with 85% yield at 220 °C, ambient pressure, and at a reaction time of 6 h. While in a similar batch process, but using subcritical water, the reaction time shortened significantly to 10 min at 240 °C and 3.4 MPa, giving a yield of 84%. With flow, the reaction time was further reduced to 2.5 min. A comprehensive investigation of solvent effects on the Claisen rearrangement to give ortho-allyl phenol showed that among alcoholic solvents 1-butanol was optimal and even smart differences between isomers (1- and 2-propanol) were visible [10] (see also [12]). In this superheated way and without need for advanced supercritical operation, the reaction time was further shrunk to 4 min (quantitative yield, 280 °C and 100 bar).

As a net result, space–time yields obtained with micro-flow reactors typically are significantly higher (up to a factor of 80) than batch reactors [20]. The impact of pressure is ambiguously documented [18]. A detailed discussion is given whether pressure can have kinetic effect or relates to physical phenomena such as volume expansion under temperature and compressibility under pressure [10] (see also [17,21–23].

A detailed comparison of the Claisen rearrangement in batch and flow was given; see Table 10 in [24].

Besides such chemical intensification, a second major flow chemistry motivation is the connection of flow processes into a chain. This is part of process integration and we have termed the effects thereof as process-design intensification. Such flow cascade is a biomimetic analogue of nature's metabolic and signaling pathways [25]. Cascades in batch have attracted attention also in chemistry [26]. Also in flow, cascades have turned into a powerful and speedy approach for providing complex products. Subsecond organometallic flash chemistries [27,28], deliver – without any separation – a 3- or 4-step product in about one second [29,30]. Flow syntheses have been described with many more, longer-timed steps to yield complex molecules, e.g. natural products [31–33]. However here, interim flow separations are needed, mostly by scavenger cartridges [34]. A full orthogonality of all reactions cannot be achieved anymore.

The latter is our motivation in this paper over here. Rather aiming at an orthogonality for a multi(>5)-step flow synthesis providing analytical amounts of a complex molecule, we investigate a comparatively simple two-step flow synthesis, yet under considerations of engineering it finally to a scale which can provide substantial amounts of product – e.g. sufficient for an industrial kilo-lab (in pharmacy).

Concerning our chemistry, we took phenol as frequently used building block, a cheap and widely available chemical which is converted into allyl phenyl ether by a Williamson ether synthesis (a nucleophilic substitution). The formed ether is then reacted to 2-allyl phenol using the Claisen rearrangement (see Fig. 1). The same reaction path is also available for use with a number of functional groups positioned on the phenol substrate [35], increasing the number of possible applications of this synthesis.

Earlier in this group, in addition to the thermal Claisen rearrangement, the Williamson ether synthesis of phenol to allyl phenyl ether has been optimized in micro flow. A conversion of 80% was obtained after 4 min residence time using n-butanol as a solvent and the organic homogeneous base DBU as a base at 100 °C [36]. However, attempts to directly connect the Williamson ether synthesis to the Claisen rearrangement have been initially unsuccessful. A subsequent Claisen rearrangement resulted in an undesirably low yield, with formation of a dark colored product and numerous different side products; see the 'Section 3' chapter below.

Thus the objective of this paper is to find process conditions which allow performing a two-step flow synthesis at an overall yield threshold of 80%. This is based on experimental evidence from the single Williamson ether synthesis having almost quantitative yield and from the Claisen rearrangement having about 80% yield. During this study, the application in continuous production is to be considered. Important factors here are the price of required chemicals and equipment, the complexity of operation, the overall productivity of the set-up and the energy requirements.

2. Experimental procedures

2.1. Microchannel experiments

Microchannel experiments that have been performed in the reactor set-up, are depicted in Fig. 2. The input mixtures are pumped using HPLC pumps (Knauer Azura P4.1S). The two pumps are connected to a T-piece (Valco). The stream is then led through a Hastelloy-C® capillary tube reactor (ID 0.03″, OD 1/16″, 3.3 m). 2.3 m of this reactor length is immersed in a heating bath (Lauda C6 CS) containing thermal oil (Lauda Ultra 300) with a set temperature; the remaining 1 m is immersed in a cooling bath (Lauda Ecoline StarEdition RE104) filled with demineralized water at 15 °C. The mixture then flows through a 6-port sample valve (VICI) with a sample loop of 100 μl, in order to take samples before the back pressure regulator, where circulation might occur due to internal volume. After the sample valve, a back pressure regulator is attached, either of the type Bronkhorst EL-PRESS or the type IDEX cartridge, both set at 69 bar.

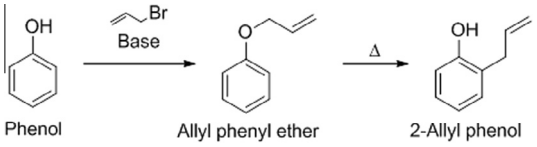

Fig. 1. Two-step synthesis of 2-allyl phenol from phenol.