Intensification of phase transfer catalyzed N-alkylation of a lysergic acid derivative by sonication

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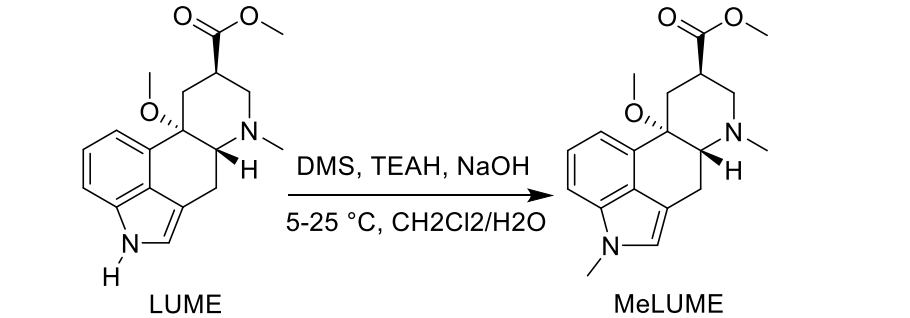
Highlights

- Use of sonication for intensification of phase transfer catalyzed reaction.
- Positive effect of sonication on reaction efficiency.
- Comparison of three different reactors.

1. Introduction

Reactions taking place between two reactants present in two immiscible phases proceed very slowly. Phase transfer catalysis (PTC) can be used to increase the efficiency and rate of such reactions. The PTC uses phase transfer reagents whose chemical structure allows them to be present in both phases[1]. There are several mechanisms of PTC reactions. This paper discusses a mechanism where the main step is a deprotonation of starting material by a base. Subsequently, the negatively charged ion of the starting material is transferred to the organic phase by a bulk organic cation of a phase transfer agent. The alkylation itself occur only in the organic phase. The hypothesis of the research was that sonication would allow the surface area of the dispersed phase to increase by breaking it into smaller droplets and facilitating the mass transfer through the phase interface[2, 3]. The positive effect of sonication on the PTC reaction duration and yield has been published several times, but most of publications have performed experiments only in a batch setup[4, 5]. The reaction studied was the alkylation of 10α-methoxydihydrolysergic acid methyl ester (LUME) to form 1-methyl-10α-methoxydihydrolysergic acid methyl ester (MeLUME). The chosen methylation reaction is part of the production of nicergoline, a drug used to promote cognitive function in patients suffering from senile and presenile syndrome of vascular or degenerative origin.



LUME
10-methoxydihydrolysergic acid methyl ester

MeLUME
1-methyl-10-methoxydihydrolysergic acid methyl ester

2. Methods

Three different flow apparatuses were used for experimental verification of PCT N-alkylation in continuous regime. The first apparatus consisted of a FlowPlate® MicroReactor (LONZA) and a modular microreactor system. In this setup, sonication was applied specifically to the outlet capillary (the capillary draining the mixture after the reaction in the microreactor into the collection vessel). The second apparatus composed of static mixers of the modular microreactor system. This apparatus was sonicated throughout its entire volume. The last apparatus was constructed simply from capillaries and

microfluidic fittings. This apparatus was also sonicated throughout the volume. HPLC-MS analysis was used to evaluate the experiments.

3. Results and discussion

For the first apparatus studied, a positive effect on the course of the reaction was experimentally verified. Experiments were performed under constant reaction conditions only effect of ultrasound was studied. Experiments with the ultrasound on showed an increase in both the conversion of the starting material and the selectivity of the reaction product. Product selectivity increased at the expense of by-products. These experiments confirmed the increase of the rate of deprotonation at the phase interface, thereby accelerating the desired reaction. Based on these results, experiments were performed at to study residence time variation with ultrasound turned on. By reducing the residence time, the formation of by-products was significantly suppressed, while full conversion of the starting material was achieved.

Based on these positive results, a second reactor consisting of static mixers was designed and built. For this reactor, about three series of experiments were performed with ultrasound on and off. All series of experiments showed zero effect of ultrasound on the reaction carried out in this apparatus. These results led to the conclusion that the ultrasound bath used was too weak to penetrate the reactor walls and enhance mixing in the reaction channels.

The third reactor studied consisted of a fluoropolymer (FEP) capillary. This capillary was used mainly because it was possible to visually observe reaction mixture inside the reactor. This capillary was also used in the first apparatus where the positive effect of ultrasound was demonstrated. For this apparatus, the experiments to investigate the effect of ultrasound turned on and off were performed. The positive effect of ultrasound was even more pronounced here than for the apparatus with the LONZA reactor. This could be due to the absence of static mixers in the capillary reactor and hence very low mixing intensity without ultrasound. A flow-through phase separator was also tested for this apparatus, which allowed easier processing of the reaction mixture. On this reactor it was possible to measure the kinetics of the studied reaction. Because the reaction time is very short, and to keep identical flow conditions, it was necessary to measure the kinetics by changing the volume of the reactor i.e. capillary length. The great advantage of this reactor is the ease of modification and manipulation. The results were comparable to those obtained with the first apparatus FlowPlate® MicroReactor (LONZA).

4. Conclusions

Three different continuous reactors were studied for phase transfer catalyzed N-alkylation reaction. A positive effect of ultrasound on the reaction progress was observed for the LONZA reactor and the capillary reactor. It was experimentally proven that ultrasound increases the mass transfer between phases, in particular the rate of deprotonation at the phase interface. The best results were obtained with the capillary reactor that was proven to be the best, both for its low cost and its simplicity and ease of manipulation. The positive effect of ultrasound was also confirmed in the flow apparatus.

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Keywords

Sonication; N-alkylation; PTC reaction; microreactor