

UNDERSTANDING THE SOLVENT EFFECTS TO ACHIEVE UNPRECEDENTED YIELD OF METHYL-ESTERIFICATION WITH DIAZOMETHANE IN A MICROREACTOR

CF Yang¹, G Qian¹, L Mleczko², XZ Duan^{1,*} and XG Zhou¹

¹ State Key Laboratory of Chemical Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

² Bayer Technology Services GmbH, Technology Development, Building E-41, Kaiser-Wilhelm-Allee Street, Leverkusen 51368, Germany

Abstract

Microreaction technology (MRT) offers a safe way to deliver useful, highly active but hazardous diazomethane on demand within a closed system and then realize in-situ conversion to the desired product. In this work, the two-stage MRT is employed for the integrated synthesis of diazomethane and its consecutive conversion with isobutyric acid. An underlying mechanism of the solvent effects on the low ester yields, mainly arising from the hydrolysis of the methyl ester products, is unraveled. When methanol is used as solvent, unprecedented high ester yield of above 99.5% is obtained. This overcomes the obstacle to practical application of methylesterification with in-situ generated diazomethane.

Keywords

Microreaction technology, Diazomethane, Methyl-esterification, Solvent effects, Hydrolysis

Introduction

Diazomethane (CH_2N_2) is a versatile and useful C_1 building block to perform as methylation reagent as well as carbene and cyclo-addition sources in organic synthesis. However, its broad applicability has been impeded by the inherent explosive and toxic characteristics, despite that it is readily available on lab- and industrial-scale by using expensive and special equipment. Micro-reaction technology (MRT), featuring continuous consumption capacity and small internal volume to minimize the inventory of hazardous intermediates, is ideally suited for facile and safe preparation and utilization of CH_2N_2 (Struempel, et al.,2008). Compared to some novel dual-channel/tube-in-tube/tube-in-flask microreactor (Maurya, et al.,2011; Mastronardi, et al.,2013), two-stage MRT shows much higher productivity and full utilization of CH_2N_2 without compromising with hazardous wastes, which is promising for practical applications. However, the product yield obtained by the two-stage MRT is lower than the one (i.e., 96%) obtained by using N_2 stream to transport the generated diazomethane into the quench vessel in the

traditional technology. In order to discriminate the key factors resulting in the low product yield of methyl-esterification with in-situ generated diazomethane in a two-stage MRT, we have investigated the effects of the reaction conditions (e.g., the total flow rate, residence time, temperature and reactant ratio), heat transfer and solvents in our previous work (Yang, et al., 2018). The results suggest that the low product yield mainly arises from the detrimental effect of water solvent. The objective of this study is to unravel the underlying nature of the solvent effects and thus guide the selection of appropriate solvents to eliminate their detrimental effects.

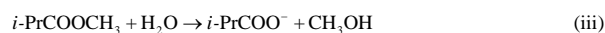
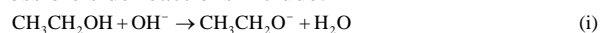
Results and Discussion

In-situ generation and consecutive conversion of diazomethane was carried out in a two-stage continuous MRT. The solution of Diazald/DMSO was delivered to contact with that of KOH/ethanol followed by direct conversion of the generated diazomethane with isobutyric

*Corresponding author: xzduan@ecust.edu.cn

acid (*i*-PrCOOH) to methyl isobutyrate, where the ethanol–water mixture for the *i*-PrCOOH. Based on our previous work (Yang, et al., 2018), it is possible to improve the ester yield by significantly decreasing water amount in the *i*-PrCOOH solution. Surprisingly, in spite of using non-aqueous KOH and *i*-PrCOOH feeds, the yield of methyl isobutyrate of 67.6% was still very low, calling for revealing the underlying nature of the solvent effects.

Considering the methyl-esterification in the second step reaction was quantitative and instantaneous together with less exothermic, it was reasonable to assume that the target product (methyl ester) has undergone further reactions that result in the low yields. It was noted that direct transferring of the effluents of the first step reaction brings base (from use of use of over-stoichiometric base for complete Diazald conversion), water (from raw Diazald and the reaction of KOH with *i*-PrCOOH) and ethanol (as solvent) to the second reaction stage, and leaves the target product vulnerable to transesterification and hydrolysis. Possible side reactions include:



In order to elucidate if the dominant side reaction was the transesterification or hydrolysis of methyl isobutyrate, two other alcohols (i.e., isopropanol and *n*-butanol), which have different nucleophile strengths of their charged forms, were used as the solvents of base and *i*-PrCOOH feeds. The nucleophile strengths of the solvents follow the order of $\text{CH}_3\text{CH}_2\text{O}^- > \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}^- > (\text{CH}_3)_2\text{CHO}^-$. As expected, the order of the yield was isopropanol > *n*-butanol > ethanol. However, the maximum yield was only up to 80.1% (Figure 1). This indicates that the nucleophile substitution was still not the dominating side reaction resulting in the low yields.

Finally, hydrolysis of methyl isobutyrate becomes the most probably reason for the yield loss. Taking into account the reversible nature of the hydrolysis, methanol was employed as the solvents of base and *i*-PrCOOH feeds to inhibit the occurrence of the hydrolysis. The yield of methyl isobutyrate reaches above 99.5% (Figure 1). This confirms that the dominating side reaction resulting in the low yields was the hydrolysis of methyl isobutyrate rather than its transesterification.

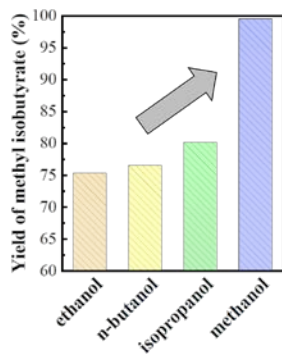


Figure 1. Effects of solvents on yield of methyl isobutyrate.

Conclusions

In summary, we have reported an underlying mechanism of the solvent effects on the low ester yields, mainly arising from the hydrolysis of the methyl ester products. When the solvents were replaced with methanol, the side reactions can be almost inhibited, and thus unprecedented high ester yield of above 99.5% is achieved. This study confirms once more that recipes developed in batch have to be adapted to the limitations given by the continuous operation in micro-channels.

Acknowledgments

This work is financially supported by the Bayer Technology Services GmbH and the 111 Project of Ministry of Education of China (B08021)

References

- Mastronardi, F., Gutmann, B., Kappe, C. O. (2013). Continuous flow generation and reactions of anhydrous diazomethane using a teflon AF-2400 tube-in-tube reactor. *Org. Lett.*, 15, 5590.
- Maurya, R. A., Park, C. P., Lee, J. H., et al. (2011). Continuous in situ generation, separation, and reaction of diazomethane in a dual-channel microreactor. *Angew. Chem. Int. Ed.*, 50, 5952.
- Struempel, M., Ondruschka, B., Daute, R., et al. (2008). Making diazomethane accessible for R&D and industry: generation and direct conversion in a continuous microreactor set-up. *Green Chem.*, 10, 41.
- Yang, C., Shi, Y., He, K., et al. (2018). Understanding of two-stage continuous microreaction technology for in-situ generation and consecutive conversion of diazomethane. *J Taiwan Inst. Chem. E.*, doi:10.1016/j.jtice.2018.06.022.