LIGANDS FOR M-NHC SYNTHESIS: CONTINUOUS FLOW DI-*N*-ALKYLATION OF 1*H*-BENZIMIDAZOLE IN A FIXED BED REACTOR

T. Sauk[1,2], C. Heiduk[1,2], L. Henke[1,2], C. Xiao[1,2], S. Scholl[1,2*]

[1]Institute for Chemical and Thermal Process Engineering, TU Braunschweig
[2]Center for Pharmaceutical Engineering, TU Braunschweig
[*]Institute for Chemical and Thermal Process Engineering, TU Braunschweig,
Langer Kamp 7, DE-38106 Braunschweig, s.scholl@tu-bs.de (*Corresponding author)

ABSTRACT

The successful transfer from batch to a continuous flow process in a fixed bed reactor of a ligand in metalorganic API synthesis, the diazolium salt 1,3-methyl-benzoimidazol-3-ium iodide, is presented. Results show similar yields and conversion rates at corresponding process parameters in batch and continuous mode. By exceeding temperature limitation of a non-pressurized batch process, the pressurized continuous reactor system shows the potential for outperforming the batch synthesis regarding space time yield. Hence, process intensification by continuous flow presents itself as a viable approach for the heterogeneous di-*N*-alkylation of diazoles. Alternative basic reagents and solvents further enhance the viability of a continuous approach by addressing limitations such as side reactions and solubility of the reagent.

Keywords: Continuous flow synthesis, fixed bed reactor, heterogeneous synthesis, 1H-benzimidazole

INTRODUCTION

Over the last decades imidazole and benzimidazole derivatives gained interest due to their capability of forming stable *N*-heterocyclic carbenes (NHC) [Dröge 2010]. Since then NHC have been widely used as ligands in organometallic complex synthesis (M-NHC) [Jacobsen 2009]. The initial derivatives of e.g. benzimidazole can be prepared in various forms adjusting their properties and possible applications. Hence diazoles can be considered as scaffold chemicals for e.g. M-NHC synthesis with applications in catalysis and especially as active pharmaceutical ingredients (API) [Rubbiani 2011; Oehninger 2013; Aher 2014]. Carbenes are often synthesized by deprotonation of a corresponding diazolium salt. Diazolium salts can be synthesized e.g. by reductive cyclization which requires and metal catalysts (e.g. Pd) or by *N*-alkylation of diazoles [Boiani 2005; Jacobsen 2009; Guillena 2010; Grieco 2015]. Both routes are often also time-consuming. A transfer to continuous processing offers advantages due to process intensification and low holdup e.g. reducing overall time required for total conversion and precise as well as fast process controllability.

By establishing the *N*-alkylation in presence of a solid basic reagent and a halogenated alkylating agent for continuous operation another downside of both batch and continuous approaches can be addressed. Syntheses of diazolium salts can be performed with an abundant and non-expensive basic reagent such as K_2CO_3 instead of costly catalysts [Sauk 2019]. Catalysts which are often discarded or offer limited regeneration cycles.

In this work the successful transfer of the synthesis of 1,3-dimethyl-1H-benzoimidazol-3-ium iodide (DBI) from batch to continuous processing is presented. Synthesis is performed in a continuous flow fixed bed reactor via a di-*N*-alkylation of 1*H*-benzimidazole (see Fig. 1) in presence of methylene iodide and K_2CO_3.

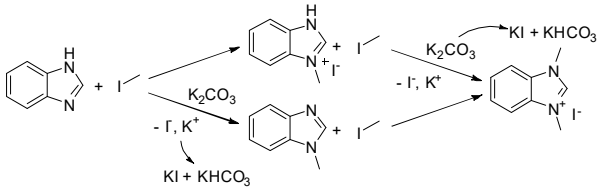

Figure 1: Assumed reaction scheme of the 2-step synthesis of 1,3-methyl-benzoimidazol-3-ium iodide (DBI) in the presence of a solid base (K_2CO_3) and methylene iodide (MI). Intermediate: 1-methyl-1H-benzoimidazol-3-ium iodide (MBI)

In addition, the viability but also limitations of this process are addressed such as negative effects of elevated reactor temperature on conversion rates and occurrence of side reactions. Chances to overcome these limitations and further enhance the process by screening for alternative solvents and basic reagents are addressed as well.

CONTINUOUS FLOW SYSTEM

Figure 2 presents the experimental set-up. The continuous flow synthesis is performed in an electrically heated HPLC column (L = 250 mm, ID = 8 mm). Peripheral components are two HPLC pumps as well as a mixer combining the reagents before entering the column. Subsequent to the column the back-pressure regulator (7 bar) protected by a filter secures constant system pressure. Valves (magnetic and manual) enable

https://doi.org/10.24355/dbbs.084-202001221415-0

sampling at certain stages of the process as well as switching between conditioning, cleaning and synthesis. In addition, a conductivity sensor is integrated enabling qualitative tracking of the synthesis progress.

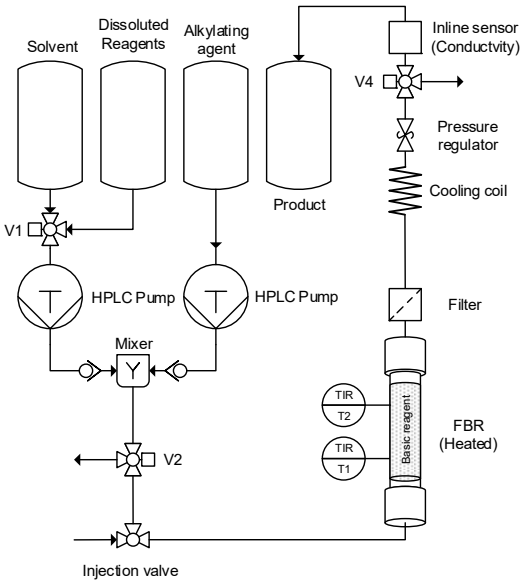

Figure 2: Process flow chart of the continuous flow synthesis of diazolium salts in a fixed bed reactor

CONTINUOUS FLOW PROCESSING

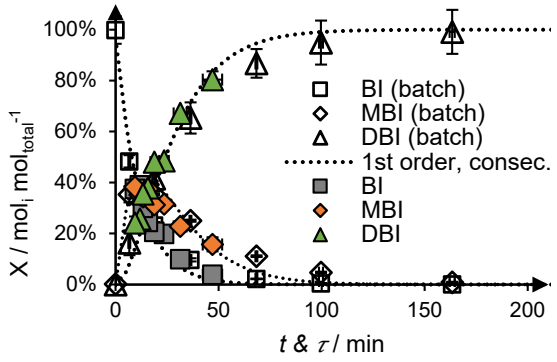

Figure 3: Comparison of conversion to DBI in batch and continuous processing with K_2CO_3 as basic reagent (r = 5 mol_{MI} mol_{BI}^{-1})

By performing the continuous synthesis at similar process parameters as the batch synthesis both show a good agreement (see Figure 3). In addition, the synthesis progress can be approximated by a kinetic model for consecutive reactions of first order as expected from the reaction scheme (see Figure 1). The pressurized continuous system enables higher reaction temperature (T > 82°C for acetonitrile) hence outperforming the batch system regarding accessibility (e.g. sampling), safety and potentially space time yield STY. Figure 4 shows the beneficial influence of the elevated fixed bed temperature on the synthesis. Nonetheless higher temperatures result in yet unknown side reactions reducing overall yield and purity of the product.

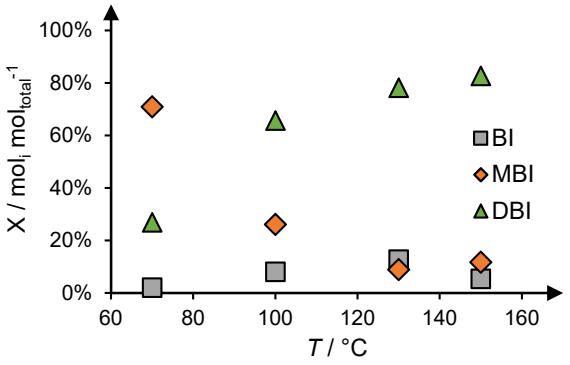

Figure 4: Influence of temperature on the reactor outlet composition in a continuous flow fixed bed reactor (K_2CO_3; n = 1 per temperature; $\dot{V}$ = 200 µL min^{-1}; r = 2.5 mol_{AX} mol_{BI}^{-1})

Thus, alternate synthesis approaches by changing the basic reagent and also solvent are addressed as well.

SCREENING OF BASE AND SOLVENT

Besides unfavorable side reactions, the formation of $KHCO_3$ (see Figure 1) and possible decomposition to CO_2, H_2O and K_2CO_3 thus degradation of the fixed bed is ubiquitous. Hence screening for alternative abundant and non-expensive basic reagents is performed.

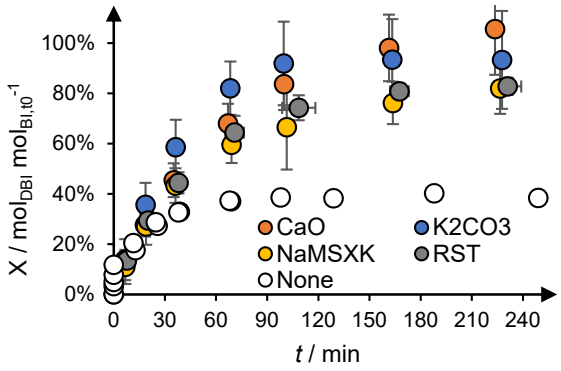

Figure 5: Conversion to DBI with none and a selection of basic reagents from the groups of metal oxides, activated carbon, zeolites and alkali (r = 2.5 mol_{MI} mol_{BI}^{-1}, batch, n = 3)

Figure 5 shows the conversion to the product when different basic reagents are applied in a batch synthesis. CaO offers the best similarity to K_2CO_3, whereas basic zeolites (NaMSXK) or basic activated carbon (RST) exhibit good conversion but also adsorption of the product, intermediate as well as initial reagent. Adsorption has been observed for several types of activated carbon as well as zeolites, hence both substances are not applicable for synthesis or as subsequent adsorbents for purification of the synthesis solution. Also, the necessity of a basic reagent is shown as the synthesis course without a basic reagent (None)

https://doi.org/10.24355/dbbs.084-202001221415-0

indicates the lowest and stagnating conversion to the product.

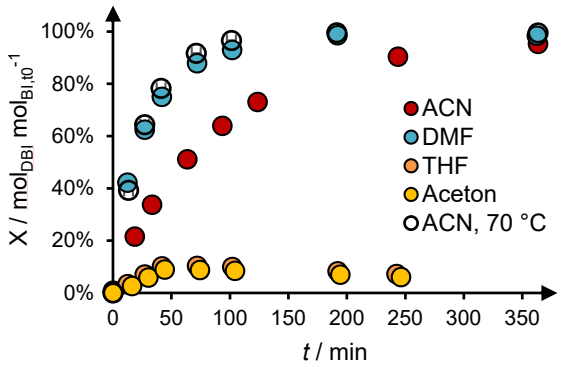

Figure 6: Conversion to DBI for different synthesis solvents (K_2CO_3, T = 50 °C, r = 5 mol_{MI} mol_{BI}^{-1}, batch, n = 3)

Batch syntheses for a selection of aprotic polar solvents have been conducted as shown in Figure 6. Regarding the low boiling point of acetone, batch syntheses have been performed at 50 °C. Both THF and acetone show low conversion rates as well as a decreasing ratio of product. This decrease is related to a low solubility of the product and precipitation rendering both solvents unsuitable for continuous operation. DMF exhibits conversion rates exceeding acetonitrile by a factor of 4 similar to a reaction in acetonitrile at 70 °C.

Results of both base and solvent screening indicate a high potential of e.g. calcium oxide (CaO) and DMF. Hence increase of space-time-yield (STY) by a factor of approximately up to 49 is possible due to high solubility and conversion rates of the reagents as well as low occurrence of side reactions.

CONCLUSIONS AND OUTLOOK

Continuous flow synthesis in a fixed bed of an exemplary diazolium salt has been successfully performed. In addition, first results of a selection of alternative basic reagents and solvents have been presented. Results show the potential and viability of a fixed bed reactor with basic reagents for di-*N*-alkylation of diazoles though further investigations on column degradation as well as side reaction must be conducted. Current investigation focuses on long term stability of the fixed bed as well as identification and reduction of side reactions.

ACKNOWLEDGMENT

This study was partially funded by the Lower Saxony Ministry for Science and Culture (MWK) in the joint research project *"Processing of poorly soluble drugs at small scale - µ-Props"* of the Center of Pharmaceutical Engineering (PVZ) of the Technische Universität Braunschweig.

NOMENCLATURE

BI		1*H*-benzimidazole
DBI		1,3-methyl-benzoimidazol-3-ium iodide
MBI		1-methyl-1*H*-benzoimidazol-3-ium iodide
MI		Methylene iodide
τ	[min]	Residence time
t	[***s***]	Time
T	[**°C**]	Temperature

REFERENCES

AHER, S.B., MUSKAWAR, P.N., THENMOZHI, K., AND BHAGAT, P.R. 2014. *European Journal of Medicinal Chemistry 81*, 408–419. http://www.sciencedirect.com/science/article/pii/S0223523414004504.

BOIANI, M., AND GONZALEZ, M. 2005. *MRMC 5*, 4, 409–424.

DRÖGE, T., AND GLORIUS, F. 2010. *Angew. Chem. 122*, 39, 7094–7107.

GRIECO, G., BLACQUE, O., AND BERKE, H. 2015. *Beilstein journal of organic chemistry 11*, 1656–1666.

GUILLENA, G., J RAMÓN, D., AND YUS, M. 2010. *Chemical reviews 110*, 3, 1611–1641.

JACOBSEN, H., CORREA, A., POATER, A., COSTABILE, C., AND CAVALLO, L. 2009. *Coordination Chemistry Reviews 253*, 5-6, 687–703.

OEHNINGER, L., RUBBIANI, R., AND OTT, I. 2013. *Dalton transactions (Cambridge, England : 2003) 42*, 10, 3269–3284.

RUBBIANI, R., CAN, S., KITANOVIC, I., ALBORZINIA, H., STEFANOPOULOU, M., KOKOSCHKA, M., MÖNCHGESANG, S., SHELDRICK, W.S., WÖLFL, S., AND OTT, I. 2011. *Journal of medicinal chemistry 54*, 24, 8646–8657.

SAUK, T., HENKE, L., XIAO, C., HARTIG, D., AND SCHOLL, S. 2019. *Chem. Eng. Technol., in revision*.

https://doi.org/10.24355/dbbs.084-202001221415-0