ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Communication

Scale-up study of benzoic acid alkylation in flow: from microflow capillary reactor to a milliflow reactor

Christophe Penverne, Benjamin Hazard, Christian Rolando, and Mael Penhoat

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00246 • Publication Date (Web): 01 Nov 2017

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Scale-up study of benzoic acid alkylation in flow: from microflow capillary reactor to a milliflow reactor.

Christophe Penverne,[†] Benjamin Hazard,[†] Christian Rolando,[†] Maël Penhoat[†]*

[†]USR 3290, MSAP, Miniaturisation pour la Synthèse l'Analyse et la Protéomique, and FR 2638, Institut Eugène-Michel Chevreul, Université de Lille, F-59000 Lille, France

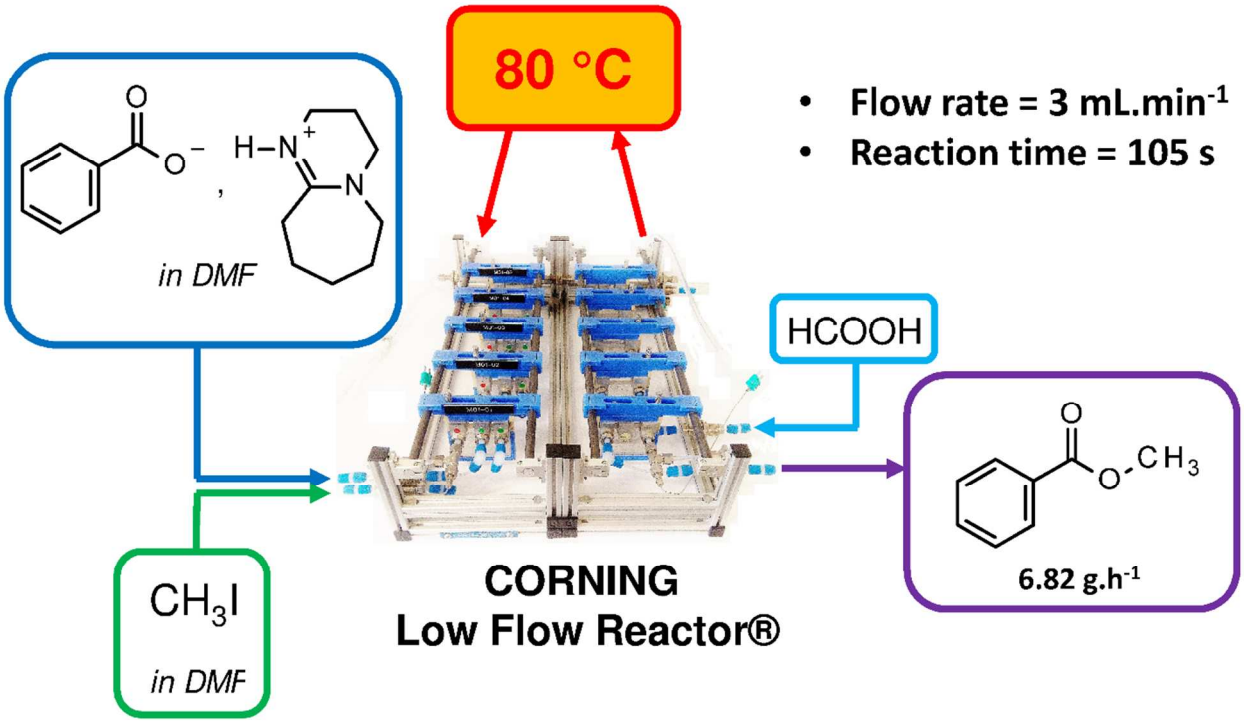


Table of Contents graphic. Esterification of benzoic acid (benchmark reagent) by alkylation in the presence of superbase/CH_3I in continuous flow is described. The reaction is scaled-up from 282 $mg.h^{-1}$ at 75 °C in a microflow capillary reactor (13.2 µL) to 6.82 $g.h^{-1}$ at 80 °C in a CORNING Low Flow Reactor® (5.25 mL).

ABSTRACT

Esterification reaction is one of the most important reaction in organic chemistry and the development of scalable continuous flow conditions is of high interest. Here we describe a scaling-up study of benzoic acid alkylation by MeI in the presence of superbases from a capillary reactor (282 $mg.h^{-1}$ at 75 °C) to Low Flow Reactor® (LFR, 6.82 $g.h^{-1}$ at 80 °C). First, the optimization of the base demonstrated that DBU was a good compromise in term of basicity and price. Comparison between batch and LFR reaction showed similar kinetic rates. We also observed a maximum reactivity for a flow rate of 3 $mL.min^{-1}$ which corresponds to an optimum mixing of the entering fluids. A colorimetric study permits to show a visual change in the flow regime (dispersed to stratified) by varying the flow rate with a maximum conversion obtained at 3 $mL.min^{-1}$ corresponding to 105 s residence time, demonstrating that the studied reaction is sensitive to mixing conditions and that LFR presents some mixing limitations for low flow rates. After thermal optimization (80 °C) the reaction has been improved to a productivity of 6.82 g/hour at the lab scale using DBU as the base and Eyring/Arrhenius plots permitted to extract activation energies.

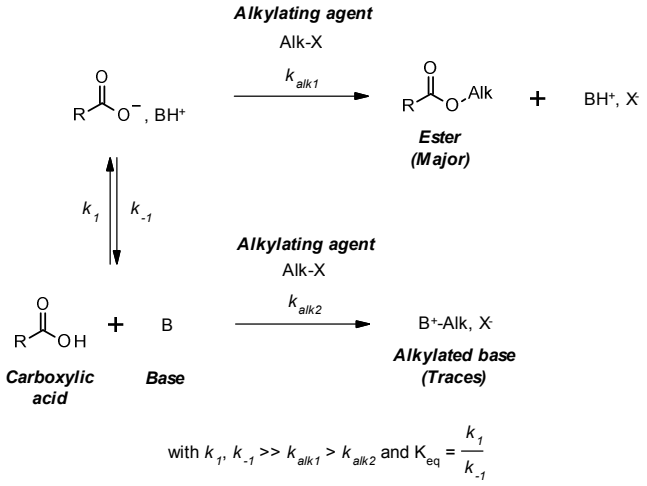
KEYWORDS: Scale-up, microflow reactor, milliflow reactor, esterification, alkylation, organic superbases.

INTRODUCTION

To pass from laboratory scale to industrial scale is a recurrent crucial step for every synthetic chemists. Along last decades continuous chemistry or flow chemistry appeared as a solution to overcome scaling-up difficulties.[1] Continuous technologies allow realizing studies or production by using miniaturized continuous reactors (microreactor or microstructured technologies) presenting higher surface area to volume ratio, higher mass and heat transfer compared to batch technology.[2,3] These reactors differ by their channel sizes which can vary from the micrometer to the millimeter scale. Optimization reaction is usually performed in a single continuous pilot reactor (200 $g.h^{-1}$) and scale up is realized by numbering-up (up to $ton.d^{-1}$).[4] Recently, new commercially reactors have been introduced to pass from lab scale (10 $g.h^{-1}$) [Corning Low Flow Reactor® (LFR)] to pilot scale (200 $g.h^{-1}$) [Advanced Flow Reactor® (AFR)] by increasing the flow reactor dimensions with a very limited optimization effort.[5] In term of green process engineering a particularly interesting approach concerns the optimization of the continuous reaction conditions at a very low scale (few $mg.min^{-1}$) followed by scaling from microfluidic to mesoscale systems (few $g.min^{-1}$) such as the one described recently by Jensen.[6] Using this approach, the production rate was increased up to 700 times in the scaling process from a spiral microreactor (6.4 $mg.min^{-1}$) to a LFR mesosystem (0.37 $g.min^{-1}$) and then to an AFR production system (4.08 $g.min^{-1}$) that can be later numbered up to access industrial scale.

Our team has recently described innovative esterification reaction conditions by alkylation of carboxylic acids in the presence of an organic superbase and an alkylating agent (ex: CH_3I) in a capillary microflow setup presenting a very low reaction volume (13.2 µL).[7] This device is particularly interesting to study very specific and expensive conditions at the lab scale since the system is highly reproducible and only few mmol of reagents are necessary to perform precise

physical organic chemistry studies. In this example *N,N*′-1,8- naphthalenediylbis[*N,N,N′,N*′-tetramethyl]-guanidine (TMGN) superbase was found to fit various criteria of high basicity ($pK_{BH+\text{ in DMF}}$ = 16.4–17.5), low Mayr nucleophilicity parameter ($N_{\text{ in DMF}}$ = 7.8) and high steric hindrance in order to optimize the present alkylation reaction and to avoid any self-alkylation side reactivity.[8] Indeed, in such reaction mechanism (Scheme 1), the acid-base equilibrium being fast compared to both alkylation rates (k_1,k_{-1} > k_{alk1}, k_{alk2}), the overall mechanism should be kinetically treated as an extension of Curtin-Hammett type mechanism[9] similar to Kurz study on acid-base catalysis.[10]



Scheme 1. Alkylation of carboxylic acids in the presence of a superbase and an alkylating agent - Curtin-Hammett type mechanism.

As a consequence, if the acid-base equilibrium is fully displaced toward the carboxylate form (k_1 >> k_{-1}, high pK_{BH+}), and if k_{alk1} and k_{alk2} are in the same order of magnitude, then the major product should be the ester with a high degree of selectivity according to Curtin-Hammett/Winstein-Holness kinetics:

$$\frac{[Ester]}{[Alkylated\ base]} = \frac{k_{alk1}}{k_{alk2}} Keq = \frac{k_{alk1} \times k_1}{k_{alk2} \times k_{-1}} = e^{\left(\frac{-\Delta\Delta G^{\ddagger}}{RT}\right)} \quad (1)$$

Were $\Delta\Delta G^{\ddagger}$ relates to the difference in activation free energy for these two alkylation reactions. When alkylation of the base can be neglected ($k_{alk1} \times K_{eq} >> k_{alk2}$) the overall rate of the reaction can be approximated to $k_{obs} \approx k_{alk1} \times K_{eq}$ and consequently any change of base pK_{BH+} value will affect the rate of the reaction. In such mechanism, the protonated base which is the counter ion of the carboxylate should affect the k_{alk1} value depending on its steric hindrance, hydrophobicity and electronic properties. In order to avoid any preliminary side alkylation of the base, fast acid-base reaction has to be performed before alkylation step. Since acid-base reaction is realized instantly, a convenient method when performing the reaction in a continuous reactor is to prepare a solution of carboxylate (carboxylic acid + base) prior to inject it for mixing with the alkylating agent introduced in a second entry.

The productivity of the previously studied capillary microflow system (i.d. = 75 µm, l = 300 cm), in the presence of TMGN base, was low after optimization (282 $mg.h^{-1}$ at 70°C) due to the low volume of the capillary reactor but was found particularly interesting in order to perform expensive reaction conditions and physical organic studies at the mg scale. The kinetic study established a clean second order reaction rate law ($k_{obs(75°C)}$ = 8.9 $L.mol^{-1}.s^{-1}$) and by varying the temperature the enthalpy and the entropy of activation have been estimated to be $\Delta H^{\neq}$ = 40.3 $kJ.mol^{-1}$ and $\Delta S^{\neq} = -112.2\ J.K^{-1}.mol^{-1}$ leading to a standard free energy of activation $\Delta G^{\neq}$ = 73.3 $kJ.mol^{-1}$ at 293 K. In the present study we were interested in scaling up this esterification reaction into a CORNING Low-Flow Reactor® composed of 8 reaction plates and one quenching plate, designed for lab-scale studies (Figure 1).

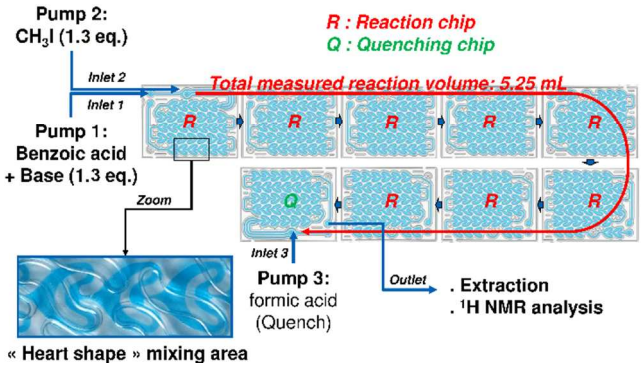


Figure 1. Description of the fluidic set-up.

EXPERIMENTAL SECTION

Materials. All chemicals were in the highest purity available and were used as received without further purification. DMF was HPLC grade.

Methods. The set-up is composed of three pumps connected (Dual Pump KP-22D-13DC, Flom, Tokyo, Japan) to the Low Flow Reactor® (Corning, Avon, France) in order to introduce a solution of CH_3I (0.473 M) and a solution of benzoic acid (0.364 M) mixed with the base (1.3 equiv.) in the two separate entries of the first plate, followed by 7 residence time units for the reaction to take place (total residence time volume = 5.25 mL). Another selected acidic quenching solution (formic acid in excess, 2.66 M) is introduced in the last plate to stop the reaction by protonation of every basic species (free base/carboxylate), and to avoid any ester hydrolysis. At the outlet, the reaction mixture is collected, worked up and then analyzed by ^{1}H NMR analysis in deuteriated chloroform (BRUKER AC 300, Billerica, USA). In this system the temperature can be controlled by circulating a calorimetric fluid throw a layer covering the reaction channel at every plates. The temperature being applied (5-85 °C) by a chiller (Huber® Petite Fleur, Offenburg, Germany). Two thermometers (Selectronic, SEL 96-10, Fretin, France)

are connected to the entry and the outlet of this calorimetric layer to control the evolution of temperature along time.

For kinetic monitoring, the flow rate was modified at each pumps and 10 mL sample of reaction medium are collected at the outlet after quenching by formic acid solution. The solution is then extracted by 3 × 37.5 mL of dichloromethane, organic phases are combined and washed with a solution of hydrochloric acid (3 × 37.5 mL, 1 M). Organic phases are then dried over magnesium sulfate, evaporated under vacuum and finally analyzed by NMR spectroscopy.

For kinetic monitoring in batch a similar work up and initial concentrations than for the flow version are used on a total volume of DMF of 140 mL. For the monitoring 20 mL of reaction medium are taken at various reaction times. For mixing conditions, a 250 mL round bottom flask equipped with magnetic stirrer (IKA®, RCT standard model) and an olive shaped stirring bar was used at 900 RPM.

Typical preparative procedure for optimum conditions in LFR:

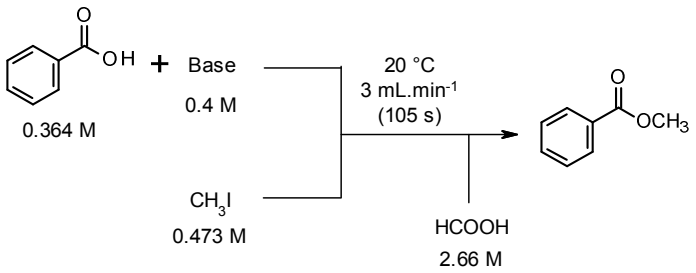
Temperature is fixed at 80 °C on the chiller and the reaction is initiated after complete stabilization of the temperature at 80°C. At the first entry, DBU (0.473 M) and benzoic acid (0.364 M) in DMF are introduced at 1.5 $mL.min^{-1}$. At the second entry, CH_3I (0.473 M) in DMF is delivered at 1.5 $mL.min^{-1}$. At the third entry, formic acid (2.66 M) in water is delivered at 1 $mL.min^{-1}$). After 5 minutes of reaction, the collection of the crude mixture is realized at the outlet of the LFR for 10 minutes corresponding to a total volume of 40 mL. The solution is then extracted by 3 × 100 mL of dichloromethane, organic phases are combined and washed with a solution of hydrochloric acid (3 × 100 mL, 1 M) to remove DBU excess and DMF. Organic phases are then extracted by 40 mL of Na_2CO_3 solution (0.6 M) to remove unreacted benzoic

acid and then washed with NaCl solution. After drying over $MgSO_4$ and filtration, the organic phases are evaporated under vacuum to deliver a pale yellow oil (628 mg, 84%).

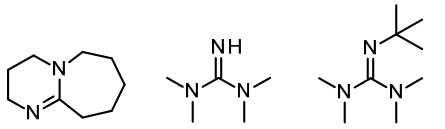
RESULTS AND DISCUSSION

Due to the larger quantities used in this study we re-orientated our process toward the use of cheaper bases (1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), 1,1,3,3-tetramethylguanidine (TMG), 2-tertbutyl-1,1,3,3-tetramethylguanidine = Barton's base) for which basicities ($pK_{BH+(DMF)}$ 14.7–16.8)[11,12] are in the same range than the one of TMGN and sufficiently basic to fully deprotonate benzoic acid ($pKa_{(DMF)}$ = 12.27).[13] We first studied conditions previously described by Mal in the presence of DBU in acetonitrile (Table 1, entry 1) and DMF (entry 2) demonstrated to be a much better solvent.[14,15] This can be explained by higher polarity of DMF compared to CH_3CN that avoids the formation of aggregates or strong ion pairs.[16] The study of various organic superbases (entries 2-4) showed similar conversions after 105 s and we finally decided to continue our study with DBU as the base which was a good comprise in term of pKa and price. Since it is extracted during the aqueous work-up, no trace of the methylated base side product has been detected.

Table 1. Base and solvent study at 20 °C and 3 mL.min^{-1} in a Corning Low Flow Reactor.



Bases



DBU TMG Barton's base

Entry[a]	Base	Solvent	pK_{BH+} (CH_3CN)	pK_{BH+} (DMF)[d]	T (°C)	Time[e] (s)	Conv. (%)
1	DBU	CH_3CN	24.33[b]	15.7-16.8	20	105	8
2	DBU	DMF	24.33[b]	15.7-16.8	20	105	47
3	TMG	DMF	23.3[b]	14.7-15.8	20	105	43
4	Barton's base	DMF	23.56[c]	14.9-16.0	20	105	52

[a]Conditions: benzoic acid 0.364 M and molar ratios of base and iodomethane to benzoic acid of 1.3, in HPLC grade solvents used as received. $pK_{BH+(CH3CN)}$ values: [b]from ref. 10; [c]from ref. 11. [d]from ref. 8. [e]Time calculated as following $t_R = V_R/Q = 60 \times 5.25/3 = 105$ s with t_R = residence time in s; V_R = residence volume in mL; Q = flow rate in mL.min^{-1}.

We next monitored the kinetics of the reaction with DBU in DMF at 20 °C in order to optimize the reaction time (Figure 2). At short residence time (t_R < 105 s, flow rates > 3 mL.min^{-1}), the kinetic curve follow a second order rate law (k_{20LF} = 0.021 L.mol^{-1}.s^{-1}) nevertheless for longer

residence times (t_R > 105s, flow rates < 3 mL.min^{-1}) the kinetic curve decrease linearly with a slope of -2.23 × 10^{-4} mol.L^{-1}.s^{-1}. This result strongly suggest that the reaction, when performed in the low flow reactor, is sensitive to mixing conditions.[17]

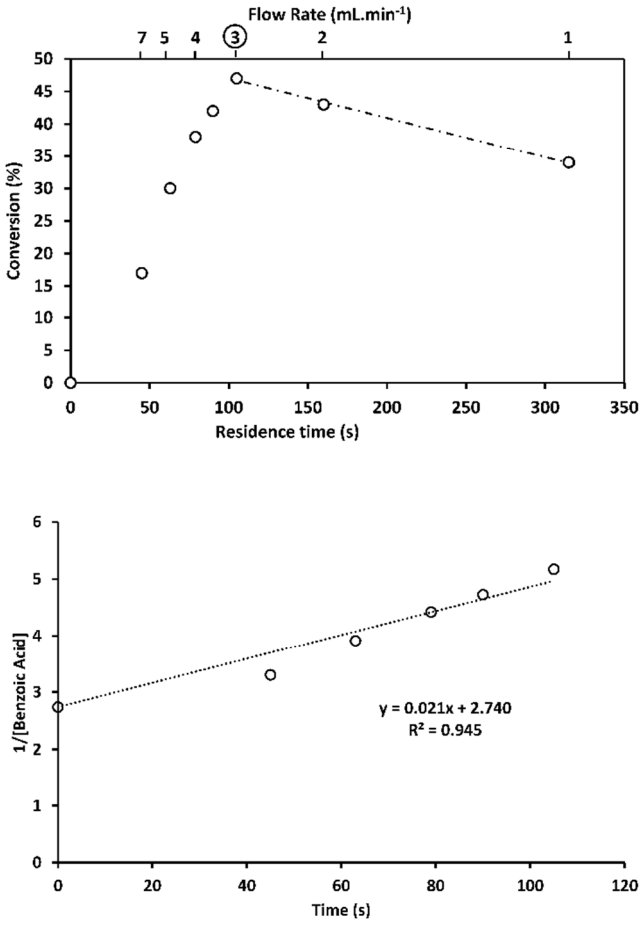


Figure 2. Kinetics of benzoic acid alkylation by CH_3I in the presence of DBU in the Low Flow reactor. Observation of the change in regime (upper panel). Second order kinetic treatment (bottom panel).

In order to verify this hypothesis, we performed the same reaction in a batch reactor at 20 °C at longer times (> 105 s) under strictly identical conditions (temperature, concentrations, work-up).

The kinetics measurements show that at longer times in batch the reaction follow a second order rate law (k_{20B} = 0.020 L.mol^{-1}.s^{-1}) that finely superimpose with the kinetics measurements performed in the Low Flow reactor, demonstrating that the change in reactivity is due to a change in the flow regime (Figure 3).

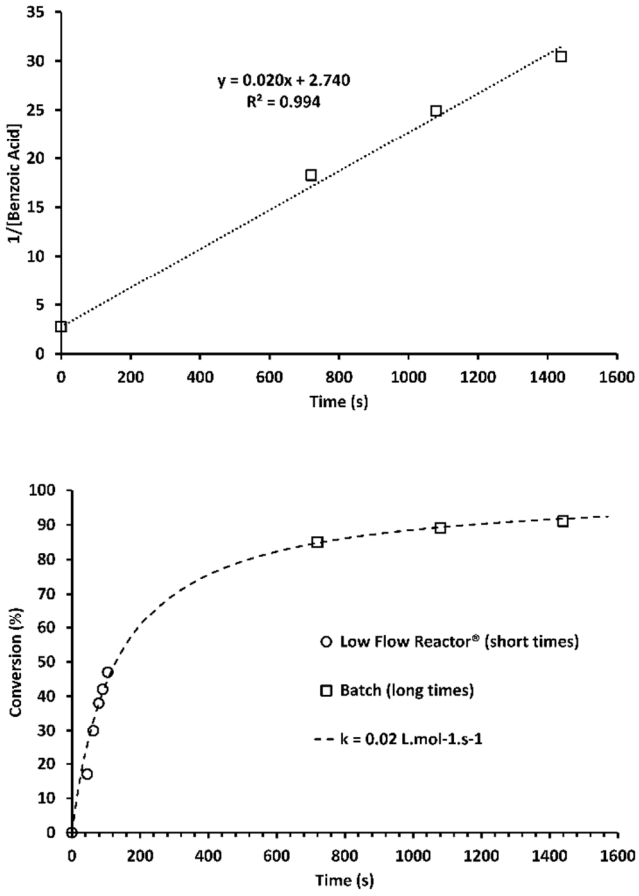


Figure 3. Kinetics of benzoic acid alkylation by CH_3I in the presence of DBU in a batch reactor. Second order kinetic treatment (upper panel). Batch (long times) and Low Flow (short times) superimposition (bottom panel).

Such phenomena is usually attributed to a change from engulfment (dispersed) flow at high flow rates (high Reynolds number *Re*) to a stratified flow at low flow rates (Low *Re*),[18] and it has been recently discussed by Jensen and Kuhn in the particular case of Corning Low Flow (LF) and

Advanced Flow (AF) reactors.[19,20] In order to demonstrate visually this effect we introduced a blue dye (Coomassie Blue) diluted in DMF at an entry of the Low flow reactor and pure DMF at the second entry. By varying the flow rates we were able to observe visually the change in the flow regime from stratified flow (Flow rate < 3 mL.min^{-1}) to dispersed flow (Flow rate > 3 mL.min^{-1}) (Figure 4).

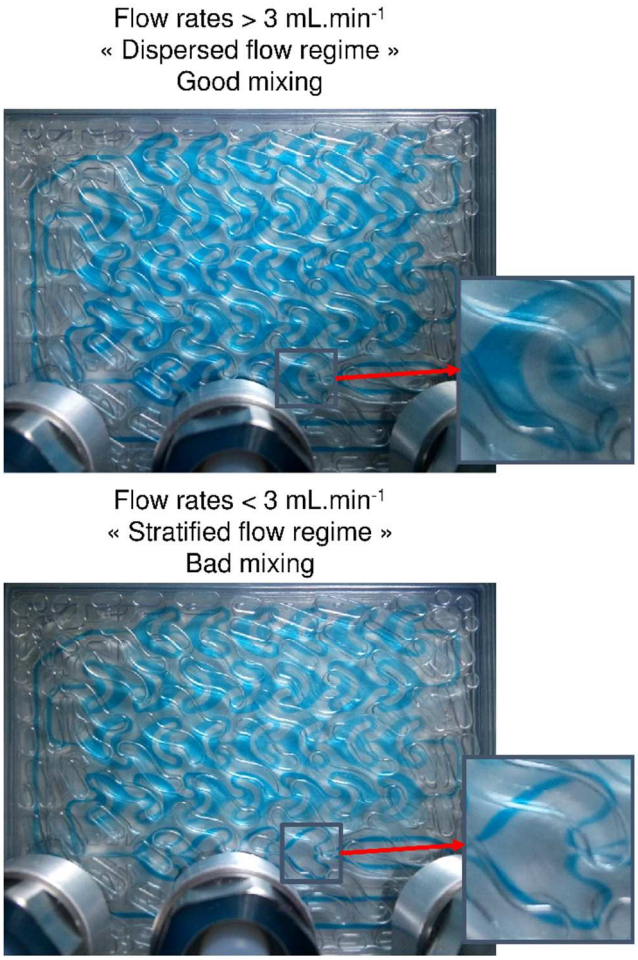


Figure 4. Observation of the change between dispersed flow regime (upper panel) to stratified flow regime (bottom panel) by decreasing the flow rate (for a better view of the phenomena the first heart mixing area has been zoomed).

Consequently, due to mixing limitations, the time can't be extended to optimize the conversion and we started a temperature study from 5 °C to 80 °C. The results are summarized in table 2. Higher is the temperature higher is the rate of the reaction, and the conversion at 3 $mL.min^{-1}$ (105 s). Under optimized conditions, the conversion rise to 85% corresponding to a productivity of 6.82 $g.h^{-1}$. The rate constants were used to construct an Arrhenius plot (Figure 5) which is linear (R^2 = 0.95) in the studied temperature range (5−80 °C) and gives a value of 30.8 $kJ.mol^{-1}$ for the activation energy. From these data the enthalpy and the entropy of activation are estimated to be $\Delta H^{\neq}$ = 28.2 $kJ.mol^{-1}$ *and* $\Delta S^{\neq}$ = −182.76 $J.K^{-1}{\cdot}mol^{-1}$ leading to a standard free energy of activation $\Delta G^{\neq}$ = 81.8 $kJ.mol^{-1}$ at 293 K. This value is higher than the previous value obtained for TMGN ($\Delta G^{\neq}_{TMGN}$ = 73.3 $kJ.mol^{-1}$). This difference can be partially explained by the calculated pK_{BH+} value of DBU in DMF (15.7-16.8) which is 0.7 units lower than the one of TMGN and which representing a difference of 4 $kJ.mol^{-1}$. We also suppose that the higher steric hindrance of TMGN compared to DBU greatly contribute to its higher reactivity by dissociating the carboxylate anion from the protonated base (weaker ion pair). A similar hypothesis can be proposed to explain the higher reactivity of Barton's base, which is also highly hindered, compared to DBU (Table 1 entries 2,4).

Table 2. Temperature study in a Corning Low Flow Reactor®.

Entry[a]	T (K)	1/T ($\times 10^{-3}$)	k_{obs} ($L.mol^{-1}.s^{-1}$)	$\ln(\frac{k_{obs} \times h}{k_B \times T})$	Conv. (%)[b]	Productivity ($g.h^{-1}$)[b]
1	278	3.59	6.5×10^{-3}	-34.42	20	1.60
2	293	3.41	2.3×10^{-2}	-33.21	47	3.77
3	328	3.05	4.4×10^{-2}	-32.67	63	5.05
4	338	2.96	9.2×10^{-2}	-31.96	78	6.26
5	353	2.83	1.47×10^{-1}	-31.54	85	6.82

[a]Conditions: benzoic acid 0.365 M and molar ratios of DBU and iodomethane to benzoic acid of 1.3, in HPLC grade solvents used as received at various temperatures. [b]Determined at 3 $mL.min^{-1}$ (t_R = 105 s).

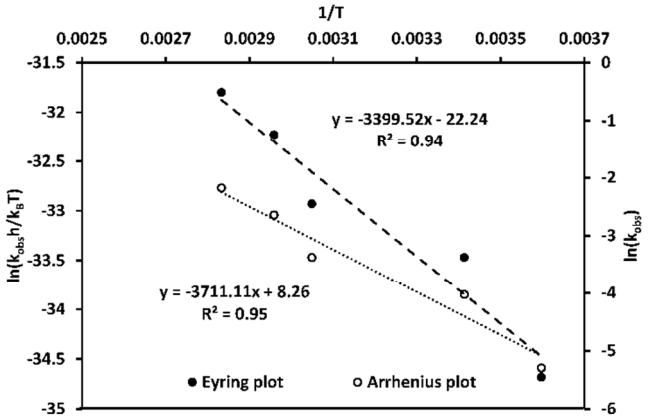


Figure 5. Eyring and Arrhenius plots.

CONCLUSION

To summary, Low Flow Reactor® permits to scale up benzoic acid alkylation from micro-flow to milli-flow conditions by a factor of 24 in term of productivity. Replacing the base (TMGN) with a cheaper one (DBU) presenting a similar basicity and by increasing the temperature to 80 °C permitted to keep a high level of reactivity. Along this study, we also demonstrate that Low Flow reactor presents some mixing limitations for flow rates lower than 3 $mL.min^{-1}$ (stratified flow regime) and that higher temperature or adding more residence time units should be considered for slow reactions. The result obtained with Barton's base along optimization is of particular interest since it presents characteristics close to TMGN in term of basicity and steric hindrance. Nevertheless such base is particularly expensive and can't be easily scaled-up. However, considering the small difference in term of conversion observed for TMG at 20 °C, it could be an economic solution.

ASSOCIATED CONTENT

Supporting Information. Description of the flow set-up, NMR spectra and kinetic measurements data.

The following files are available free of charge.

Supporting information.pdf

AUTHOR INFORMATION

Corresponding Author

* Maël Penhoat – e-mail: mael.penhoat@univ-lille1.fr – phone: +33 (0) 3.20.33.70.75

Funding Sources

This work was supported by the Conseil Régional Haut de France, France. The NMR and Mass Spectrometry facilities used in this study were funded by the European Community (FEDER), the Région Haut de France (France), the CNRS, and the Université de Lille. MP thanks the Region Haut de France for a Young Investigator Grant funded by the Contrat de Projet État-Région (CPER) to the Institut Michel E. Chevreul (FR CNRS 2638).

ACKNOWLEDGMENT

MP thanks the Region Haut de France for a Young Investigator Grant funded by the Contrat de Projet État-Région (CPER) to the Institut Michel E. Chevreul (FR CNRS 2638).

ABBREVIATIONS

LFR, Low Flow Reactor®; AFR, Advanced Flow Reactor®; *Re*, Reynolds number; TMGN, *N,N*′-1,8- naphthalenediylbis[*N,N,N′,N*′-tetramethyl]-guanidine; DBU, 1,8-diazabicyclo[5.4.0]-undec-7-ene; TMG, 1,1,3,3-tetramethylguanidine.

REFERENCES

(1) Hessel, V. *Chem. Eng. Technol.* **2009**, *32*, 1655-1681.
(2) Roberge, D. M.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, B. *Chem. Eng. Technol.* **2005**, *28*, 318-323.
(3) Roberge, D. M.; Zimmermann, B.; Rainone, F.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. *Org. Process Res. Dev.* **2008**, *12*, 905-910.
(4) Calabrese, G. S.; Pissavini, S. *AIChE J.* **2011**, *57*, 828-834.
(5) Rossi, E.; Woehl, P.; Maggini, M. *Org. Process Res. Dev.* **2012**, *16*, 1146-1149.
(6) Zhang, Y.; Born, S. C.; Jensen, K. F. *Org. Process Res. Dev.* **2014**, *18*, 1476-1481.
(7) Gholamipour-Shirazi, A.; Rolando, C. *Org. Process Res. Dev.* **2012**, *16*, 811-818.
(8) Gholamipour-Shirazi, A.; Rolando, C. *Org. Biomol. Chem.* **2012**, *10*, 8059-8063.
(9) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83-134.
(10) Kurz, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 987-991.
(11) Ishikawa, T. *Superbases for organic synthesis: guanidines, amidines, phosphazenes and related organocatalysts*; John Wiley & Sons, 2009.
(12) Stańczyk-Dunaj, M.; Jarczewski, A. *Pol. J. Chem.* **2005**, *79*, 1025-1032.
(13) Kolthoff, I. M.; Chantooni, M. K.; Smagowski, H. *Anal. Chem.* **1970**, *42*, 1622-1628.
(14) Mal, D. *Synth. Commun.* **1986**, *16*, 331-335.

(15) Mal, D.; Jana, A.; Ray, S.; Bhattacharya, S.; Patra, A.; De, S. R. *Synth. Commun.* **2008**, *38*, 3937-3946.
(16) Alexander, R.; Ko, E. C. F.; Parker, A. J.; Broxton, T. J. *J. Am. Chem. Soc.* **1968**, *90*, 5049-5069.
(17) Bourne, J. R. *Org. Process Res. Dev.* **2003**, *7*, 471-508.
(18) Engler, M.; Kockmann, N.; Kiefer, T.; Woias, P. *Chem. Eng. J.* **2004**, *101*, 315-322.
(19) Woitalka, A.; Kuhn, S.; Jensen, K. F. *Chem. Eng. Sci.* **2014**, *116*, 1-8.
(20) Wu, K.-J.; Nappo, V.; Kuhn, S. *Ind. Eng. Chem. Res.* **2015**, *54*, 7554-7564.