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Heterogenously catalyzed one-step alkylation and carboxylation of *N*-methylimidazole with dimethyl carbonate in continuous flow

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Abstract

The alkylation of *N*-methylimidazole with dimethyl carbonate yields the respective solid zwitterion *N,N′*-dimethylimidazolium-2-carboxylate, a versatile precursor for manufacturing non-halide-containing ionic liquids (ILs). This reaction requires high p,T-conditions, i.e., up to 200°C and 70 bar pressure, and even then requires reaction times up to several days under autoclave batch conditions. To perform these reactions continuously in stainless steel tubes with inner diameters in the millimeter range, precipitation of the salts must be suppressed to avoid any blockage. The achievable yield of the zwitterion is remarkably increased when a packed Al_2O_3 catalyst is used instead of an empty tube. For example, with a catalyst-packed column, a nearly 100% yield of *N,N′*-dimethylimidazolium-2-carboxylate can be achieved within 20 min at 200°C, whereas only a 67% yield in 50 min can be obtained without a catalyst at the same temperature. The transfer of the autoclave process into continuous flow is advantageous and allows a more economical scale-up.

Keywords: alkylation; carboxylation; ionic liquid; *N*-methylimidazole.

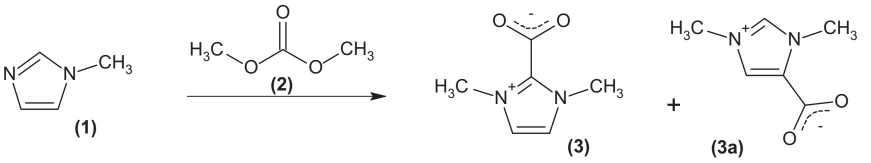
1. Introduction

The synthesis and applications of ionic liquids (ILs) are described in numerous books and publications in detail [1–3]. Although ILs are commonly considered to be designer solvents, their real and final advantages for chemical processing should be questioned [4, 5]. The synthesis of these compounds on a larger scale is often challenging, e.g., in some cases, the reaction proceeds spontaneously with high heat release [6]. Accordingly, to perform this type of reaction on a production scale, a sophisticated heat management system is required. Otherwise, long processing times, up to days, must be accepted to avoid thermal overshooting [7]. When the reactants are less soluble in the formed ILs, two phases appear [8]. The very low vapor pressure of ILs makes it impossible to use distillation for product purification. The only feasible separation path is to remove the remaining reactants with high effort, e.g., by vacuum short path distillation or perforation [9]. In addition, ILs with elevated melting points can be purified by sequential melt crystallization procedures [10].

To avoid these drawbacks, IL syntheses were performed with equimolar reactant ratios in micro-structured reactors under continuous flow conditions [11–13]. The idea here is that ideally, i.e., in case of 100% conversion (and selectivity), only the pure product is formed. But pumping exact molar ratios for a long time requires specially designed pumps. Also, the viscosity of the formed IL can be very low compared to the reactants, and therefore maldistribution in multichannel feed arrangements (of the commonly used interdigital micromixers) as well as distorted multilamellae formation (essential for the mixing) can be expected. In addition to these processing difficulties, the direct synthesis of ILs with unusual anions, e.g., acetate, lactate, carbamate, etc., is not possible, and a multi-step synthesis based on anion exchange from ILs with halide anions is necessary [14, 15]. Continuous flow electrodialysis methods were developed to enhance the anion exchange [16]. Anion exchange with soluble silver salts can also be used when the metathesis leads to insoluble silver halides, which can be filtered off subsequently [17]. ILs, which must fulfill the requirements of halide-free electrolytes used for batteries and super-capacitors, must be purified further or cannot be obtained.

The alkylation reaction of *N*-methylimidazole (**1**) (MIM) with dimethyl carbonate (**2**) (DMC) has been under investigation (Scheme 1) for a couple of years [18–20]. Dimethyl carbonate (**2**) is an environmentally friendly alkylating agent compared to others, especially in contrast to the widely used, highly carcinogenic and toxic dimethyl sulfate [21]. In particular, synthetic routes for N- and O-alkylation are well explored (for example [22, 23]).

The carboxylation of (**1**) leads to two products, namely *N,N′*-dimethylimidazolium-2-carboxylate (**3**) and *N,N′*-dimethylimidazolium-4-carboxylate (**3a**) depending on the reaction conditions. Reaction temperatures above 140°C should shift to the thermodynamically controlled substitution in the 4-position of the imidazole ring (**3a**) [19]. As reported in literature, the non-catalyzed alkylation reaction is performed in low-volume autoclaves that require a high temperature and pressure as well as economically unacceptable long reaction times. For example, the synthesis of (**3**) requires 24 h at 120°C (2.5ml) [24] and 50 h at 120°C (75 ml) [25].



Scheme 1 Reaction equation for the alkylation/carboxylation or *N*-methylimidazole (**1**) with dimethyl carbonate (**2**).

Alternative protocols to obtain (**3**) describe the direct alkylation of *N,N′*-dialkylimidazolium chlorides with CO_2 (36 h at 110°C, 50 bar) [26] and monosubstituted imidazolium-chlorides with DMC (**2**) (8 h 170°C, autoclave) [27]. Other authors propose a carboxylation/decarboxylation equilibrium between the alkylimidazole or alkylimidazolium salts with CO_2 in the presence of catalysts with a high basicity like KOtBu or potassium hexamethyldisilylazide (KHMDS) [28–30].

The alkaline catalyst forms a stable N-heterocyclic carbene (NHC) (**4**) which can be isolated and purified for further use (compare Scheme 2) [28, 29].

DMC (**2**) undergoes a reversible cleavage depending on the temperature and the catalyst used (see Scheme 3) [31, 32]. When DMC is decomposed, preferably at temperatures above 150°C, gaseous methanol and CO2 are released, which leads to a pressure increase under autoclave conditions.

The abovementioned catalysts are disadvantageous for the synthesis of pure (**3**) with DMC because additional separation steps are necessary. Due to the very low reaction rate, a suitable catalyst should be used to enhance the speed remarkably. The basicity of Al_2O_3 is high enough to attack the proton in the 2-position of (**1**) for the carboxylation reaction but not strong enough to form stable NHCs. Also, the given batch protocols are not suitable for scale-up procedures. Therefore, the carboxylation reaction was investigated using a continuous flow system with Al_2O_3 as a catalyst.

2. Experimental

N-Methylimidazole (**1**) (99%) and alkaline Al_2O_3 catalyst powder (impurities >100 ppm; particle size 70% <0.2 mm) with pH values in the range of 8.5–10.5 (10%) were purchased from Carl Roth GmbH, Germany. *N*-Methylimidazole (**1**) was purified by short-path vacuum distillation before use. Dimethyl carbonate (**2**) (>99%) and methanol (anhydrous, >99.8%) were delivered from Sigma-Aldrich, Germany.

HPLC pumps (Varian PrepStar™, SD-1, 50 mL-Ti pump heads) were used to apply a continuous and nearly pulsation-free flow of reactants (volume flow deviation approx. 0.3% [33]).

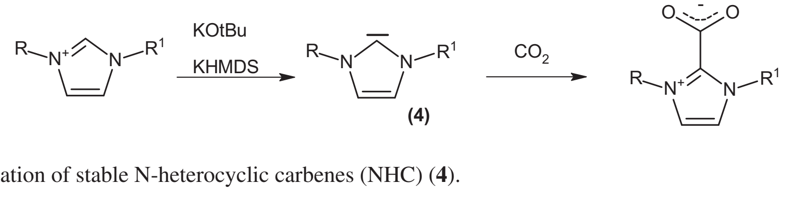
Temperature measurements were performed with NiCrNi thermocouples (TC Mess- und Regeltechnik, Mönchengladbach, Germany) in combination with a Voltkraft™ K204 (Conrad Electronic, Hirschau, Germany) data logger.

The obtained products were dissolved in deuterated methanol and characterized by H-NMR spectroscopy (Bruker™ AC 300).

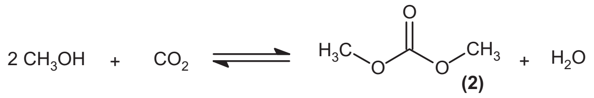
Product yields were monitored by ATR-IR (DiProbe ATR infrared fiber sensor, DiProbe GmbH, Germany) on-line measurements with a Thermo Nicolet 380 FT-IR spectrometer (USA). The corresponding calibration curve is given in Figure 1. In addition, the yields of (**3**) were validated by gravimetric methods.

A general flow-scheme is given in Figure 2. As the reaction rate of (**1**) with (**2**) at room temperature is negligible, the reactants can be premixed prior to investigation (vessel A, Figure 2). To ensure continuous and nearly pulsation-free pumping, vessel (A) is charged with 1 bar nitrogen. An HPLC pump delivers the reaction mixture to a pre-heater (optional) and subsequently to a tube reactor. The pre-heater is a ¼" tube with a 5 ml volume. Two types of ½" Swagelok™ tube reactors were used. Type 1 is an empty tube with an inner volume of 13.5 ml and a length of 165 mm, whereas type 2 represents a 230-mm long tube filled with Al_2O_3 catalyst. The solid Al_2O_3 particles reduce the free tube volume to approximately 14.9 ml. In addition, flow rates were adapted to ensure comparable residence times for both tube reactors.

Two Swagelok™ stainless steel inline filters (pore size 5 μm) fix the catalyst packing inside the tube. The pre-heater and the tube reactor are in close proximity but separately electrically heated. A thermal coupling between them cannot be fully excluded but is minimized by insulation. A pressure relief valve controls the pressure inside the reactor. Because CO_2 is released in remarkable amounts, the flow pattern changes from a single liquid phase flow at the reactor entrance to a gas/liquid plug-flow at the outlet. The pressure relief valve is too tardy to control the release of alternated liquid and gas plugs. To avoid uncontrolled pressure fluctuations, an additional needle valve is used to reduce the flow velocity of the CO_2 gas. The liquid raw product is collected in



Scheme 2 Catalytic formation of stable N-heterocyclic carbenes (NHC) (**4**).



Scheme 3 Equilibrium between dimethyl carbonate and methanol/CO_2.

vessel (B) to degas it from CO_2 and subsequently monitored by IR measurement.

Performing the carboxylation process described above in tube-reactors under flow conditions is challenging due to the formation of a non-soluble solid product (**3**). Therefore, the reaction mixture must be diluted with methanol to avoid precipitation inside the tube reactor. For all alkylation/carboxylation experiments, a methanol solution containing 2.5 mol L^{-1} MIM (**1**) and 3.25 mol L^{-1} DMC (**2**) was used.

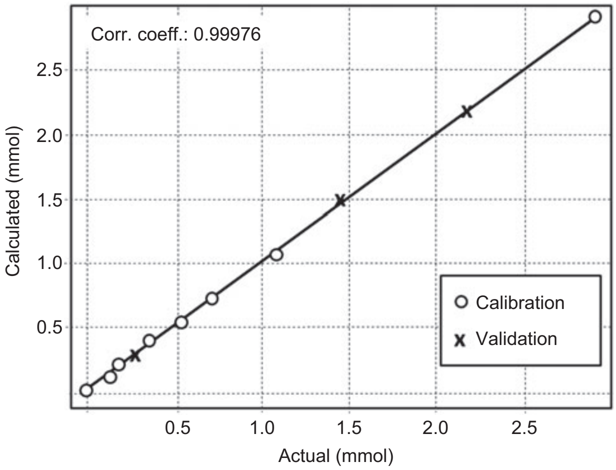


Figure 1 Calibration of IR-ATR measurements for *N,N′*-dimethylimidazolium-2-carboxylate (**3**).
The IR peak between the wavenumbers 1150 to 1200 cm^{-1} is used. Calibration and validation data points fit with a correlation coefficient of 0.99976.

The moderate excess of DMC (**2**) compensates for the thermally induced decomposition of this compound to CO_2 and methanol. The operational pressure and temperatures varied, ranging from 6.0 to 8.0 MPa and from 180°C to 250°C, respectively. The reaction times vary between 10 min and 100 min.

3. Results and discussion

It can be assumed that the alkylation/carboxylation reaction is in competition with the thermal decomposition of DMC to methanol and CO_2 at higher temperatures [31, 34]. Below 130°C, a decomposition of DMC could not be detected. Increasing the temperature up to 175°C precipitates decomposition at a slow rate, whereas at 200°C, 75% of DMC is decomposed within 10 min. At 220°C, the decomposition is completed at the same time. No significant differences in decomposition rates could be detected independent from the use of an Al_2O_3 catalyst packed column or a blank one. Also, no differences could be observed by simulating the applied reaction conditions with the replacement of the MIM (**1**) amount by toluene (see Figure 3).

The alkylation/carboxylation reaction was performed in continuous flow without catalyst with comparable parameters as given in the literature mentioned above. Surprisingly, a maximum of the yield of (**3**) was achievable within times below one h, which is remarkably faster than times given in the literature. At temperatures of 175°C and 200°C, yields of about 55% to 67% could be obtained within 25 to 50 min (Figure 4). Temperatures above 225°C shorten the reaction time to approximately 15 min. For a reaction temperature of 225°C, a maximum yield of (**3**) of approximately 75% could be detected. However, at higher temperatures up to 250°C, undisclosed side products were formed due to the decomposition of DMC (**2**), which resulted in brown tar formation and, finally, blockage of the tube reactor. The same problem occurs at longer reaction times; for example, (**3**) could not be detected by IR-measurements after 50 min residence time at 225°C.

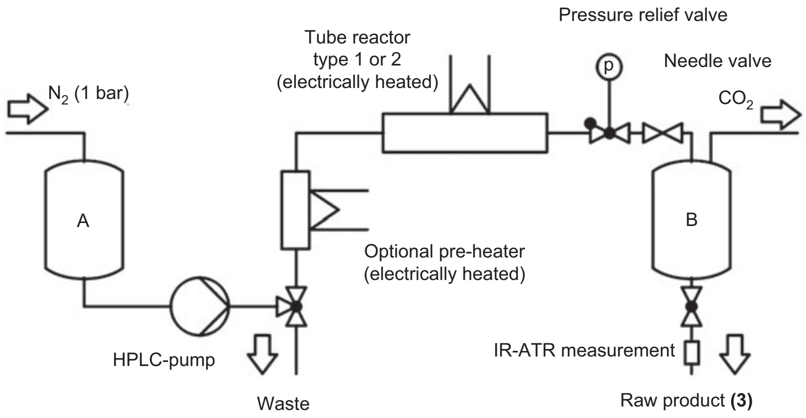


Figure 2 Scheme of the experimental setup.
The pre-heater is optional and is only mounted just before use. The IR measurement was performed with degassed samples flowing out from vessel B.

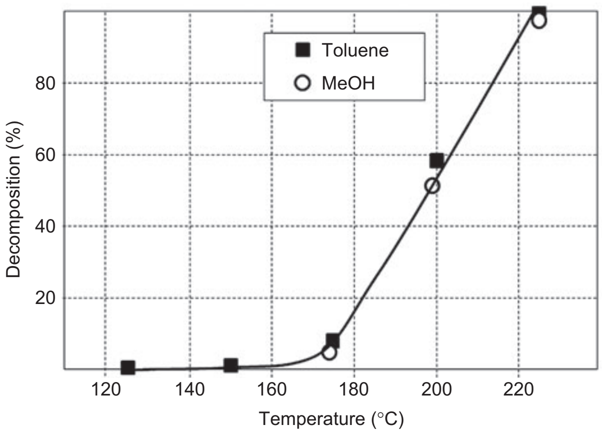


Figure 3 Decomposition of DMC (**3**) under continuous flow conditions.
Al_2O_3 packed column; (■) methanol only, (○) methanol partly replaced with toulene.

After the removal of methanol by vacuum distillation, a black-brownish-colored crude product was obtained. Further purification by repeated precipitation from ethyl acetate was necessary to obtain a white crystalline product.

The use of a tube reactor filled with a heterogeneous catalyst, e.g., alkaline Al_2O_3 particles (50–200 μm diameter), enhances the reaction speed and yield significantly. A nearly 100% conversion of MIM (**1**) to (**3**) was achieved at 200°C and 80 bar pressure within 20 min residence time (Figure 5). The yield of (**3**) does not decrease by an increase of the reaction temperature from 200°C up to 220°C, albeit the trend is similar to the experimental results achieved from the empty tube. It appears that the Al_2O_3 catalyst not only accelerates the reaction but also stabilizes the formed product (**3**). Discoloration was not observed, and the product could be precipitated as white fine particles by dropping the reaction mixture directly into ethyl acetate.

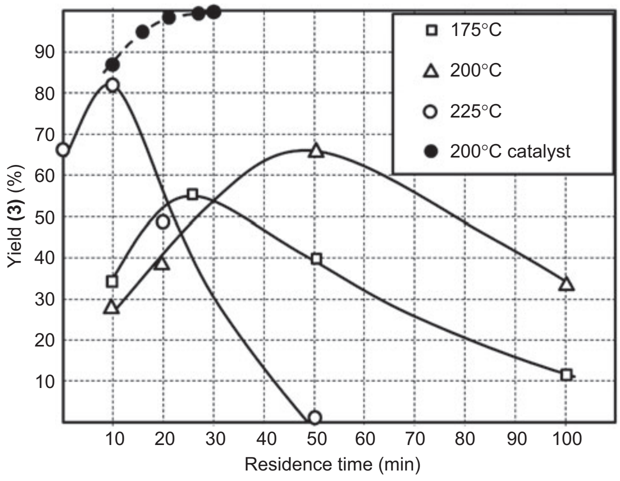


Figure 4 Synthesis of (**3**) under continuous flow conditions without catalyst.
For comparison, the yield with Al_2O_3 catalyst for 200°C is given (● dotted line).

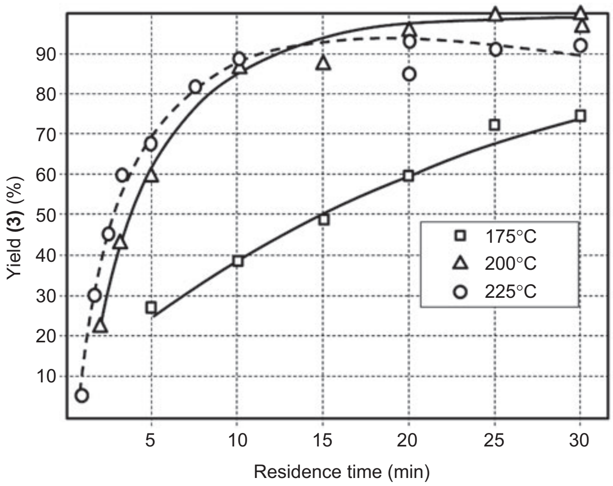


Figure 5 Catalyzed alkylation/carboxylation reaction in continuous flow.
Yield of (**3**) is given depending on reaction temperature and residence time [(□) 175°C; (Δ) 200°C; (○) 220°C]. At long residence times and temperatures above 220°C, the decomposition of (**3**) can be observed.

All previously described experiments were performed without preheated reactant solutions, i.e., the time for heating up is included in the given residence times. Due to remarkable decomposition of DMC (**2**) at temperatures above 130°C, the preheating temperature of the reactant mixture has to be restricted to 125°C. Similar to the non-preheated catalytic reaction, maximum yields were achieved within 20 min at 200°C and 225°C, respectively. At a temperature of 250°C, the best yield was reached after 2.5 min, but dropped to 52%. Also, the product became discolored, and the yield broke further down dramatically with an increase of residence time (Figure 6).

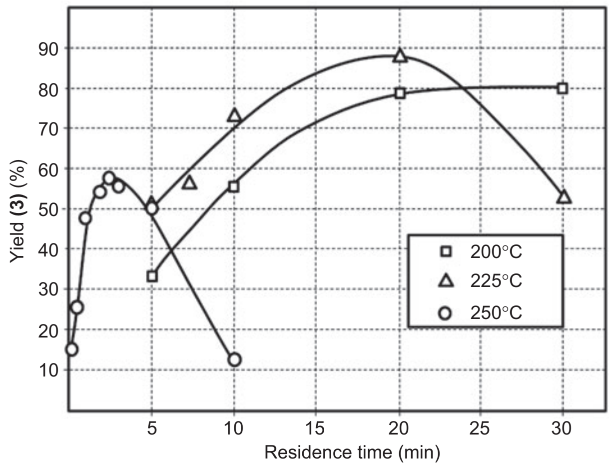


Figure 6 Catalyzed alkylation/carboxylation reaction in continuous flow [(□) 200°C; (Δ) 225°C; (○) 250°C].
The reaction mixture is heated up to 125°C prior to the entrance of the packed reactor.

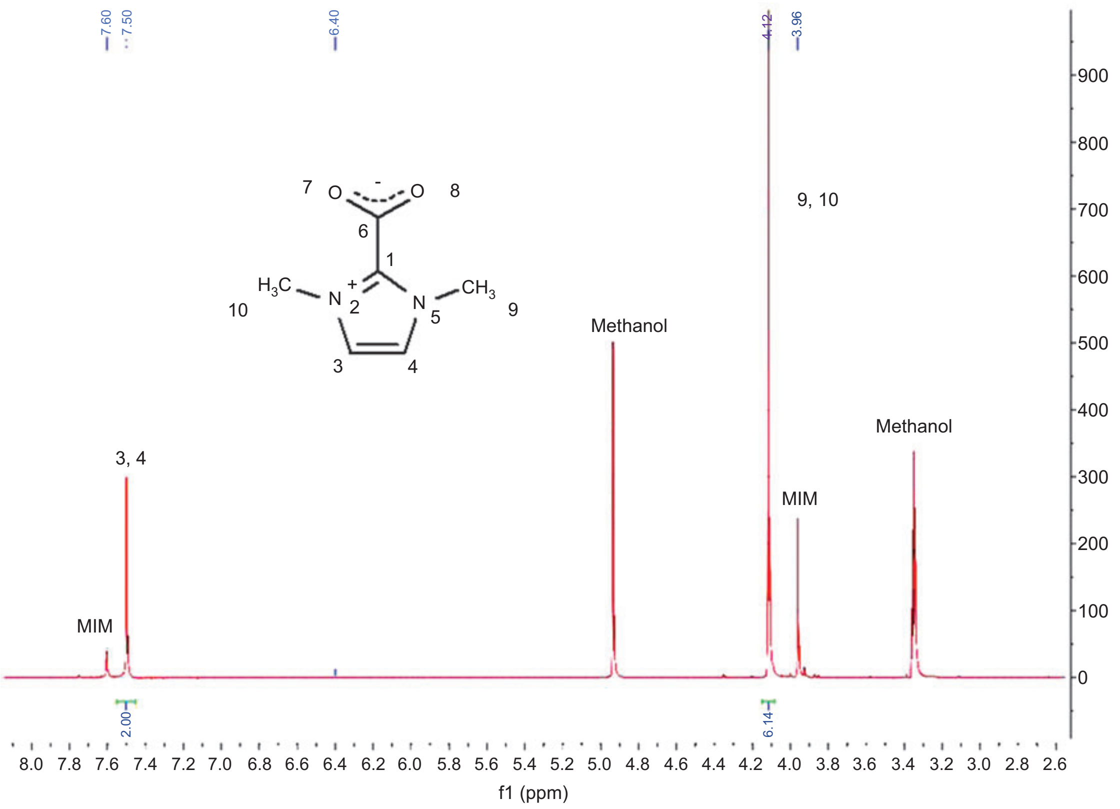


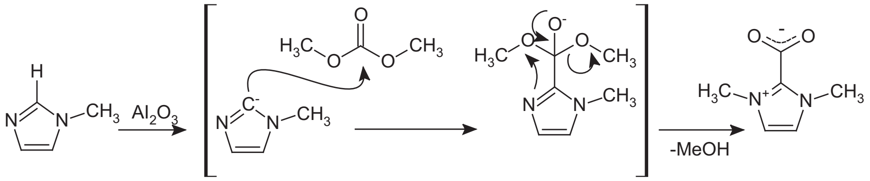
Figure 7 ^{1}H-NMR spectrum (300 Hz) of the raw product achieved under continuous flow conditions in a Al_2O_3 packed tube at 200°C. There is no evidence for *N,N′*-dimethylimidazolium-4-carboxylate (**3a**) formation.

In accordance with [24], *N,N′*-dimethylimidazolium-2-carboxylate (**3**) is the only achieved product, even at higher temperatures. No H-NMR investigations gave evidence for a loss of the hydrogen atom in the 4-position of the imidazole core (**3a**). Exemplarily, an H-NMR spectrum of a raw product is given in Figure 7. The residence time at a high temperature under continuous flow conditions is too short for a subsequent conversion of (**3**) into the thermodynamic stable *N,N′*-dimethylimidazolium-4-carboxylate (**3a**) molecule.

The mechanism of the alkylation/carboxylation is not fully understood [24, 35]. DMC (**2**) can react either by an alkylation path, the so called B_{AL}2-mechanism, or as a carboxymethylating agent by a B_{AC}2-mechanism. Taking the B_{AL}2-mechanism into account, the *N*-methylimidazole (**1**) is alkylated in a first step by DMC, and the remaining methyl carbonate anion abstracts the acidic H at the 2-position of the *N,N′*-dialkylated imidazole to form the respective heterocarbene (NHC). The thermally instable methyl carbonate decomposes, and the formed CO_2 reacts subsequently with the carbene to give the carboxylate (**3**) [24, 36]. This mechanism can explain the observed reaction without additional catalyst.

For the catalytic reaction, a different reaction pathway can be assumed similar to the proposed mechanism in literature for the formation of isolable NHC [22, 29, 30]. For a catalyst with much lower basicity, e.g., as for the Al_2O_3 used here, carbene formation was not observed. It can be speculated that carbene forms as an intermediate that attacks the DMC (**2**) first, followed by a subsequent concurrent alkylation step combined with the release of methanol (Scheme 4).

Several competitive reactions occur at the same time: i) the decoposition of DMC, ii) the non-catalyzed alkylation/carboxylation and iii) the catalyzed carbene formation and subsequent concurrent alkylation and carboxylation. A phenomenological approach shows that, for the non-catalyzed reaction at temperatures below 200°C, the alkylation/carboxylation is slower than the decomposition of DMC (**2**), which results in low yields of (**3**). At high temperatures above 200°C, the decarboxylation of (**3**) takes places remarkably,



Scheme 4 Proposed alkylation/carboxylation mechanism.

and side-products are formed. The catalyzed reaction is much faster compared to the non-catalyzed one and the decomposition of the DMC (**2**) and might be counterbalanced by the proposed intermediate carbene formation (see Scheme 4), which results in higher yields of (**3**).

4. Summary

The carboxylate (**3**) is a precursor for the synthesis of numerous ILs by decarboxylation and anion exchange, even for the respective halides. It can be simply synthesized, purified and stored. However, the batch processing in autoclaves lacks industrial application due to some economic drawbacks. A catalyst-supported synthesis in continuous flow shortens the reaction time by a factor of 100. Depending on the flow rate, a space-time yield of approximately 700 $g \cdot h^{-1} \cdot l^{-1}$ could be achieved with lab-scale equipment. The obtained zwitterions can be easily purified by washing and recrystallization from solvents with low boiling points. Unreacted MIM (**1**) remains in the solvent and can be reused after purification. The above-described process is applicable to the synthesis other N-based ILs, e.g., with piperidine or pyrrolidine cores. The anion metathesis could then be performed simply by titration with protic acids under mild conditions [19]. Carbon dioxide and methanol would constitute the only side products.

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Professor Holger Löwe obtained his PhD 1984 from the former Technical University Merseburg after some years of working in industry. Later, he moved to the faculty of electrochemistry at the Technical University in Ilmenau, Germany to work as a research assistant and lecturer. In 1991, he began his work at the IMM Institut fuer Mikrotechnik Mainz, GmbH. In 1999, as a director of R&D for this institute, he established the Chemistry/Micro-Reaction Technology Department and a bio-microfluidic group at IMM. Since 2005, he has been a professor for micro process technology at Mainz University. In 2007, he was appointed as visiting professor at the Dalian University of Technology. Since 2008, he has been a guest professor at the East China University, Shanghai, China, and he was appointed professor at Zhejiang University, Hangzhou, China, in 2011. His current research activities comprise chemical synthesis and engineering and processing in combination with aspects of microfluidics. The application of magnetic ionic liquids for C-C coupling reactions and the combination of micro-nanoparticles for catalytic purposes are presently of major research interest to Prof. Löwe.