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An organocatalytic ionic liquid†

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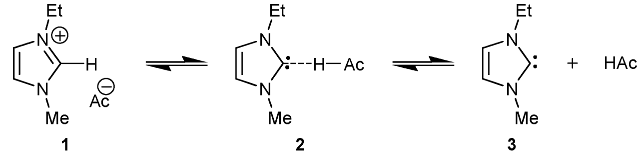
The carbene concentration in 1-ethyl-3-methylimidazolium-acetate ionic liquid is sufficiently high to act as a catalyst in benzoin condensation, hydroacylation and also in oxidation of an alcohol by using CO_2 and air. This observation reveals the potential of ionic liquid organocatalysts, uniting the beneficial properties of these two families of compounds.

Ionic liquids[1] (ILs) exhibit an outstanding variety of advantageous properties, such as high stability, non-flammability, low volatility and unique solution features.[1o–r] They have successfully been used as solvents for many catalytic reactions,[1j,k,o,p] either organometallic or purely organic (organocatalytic). Some of these syntheses could not be performed in any of the classic molecular solvents.[1j–k]

Although in most of these reactions the IL is merely the solvent, there are a few reports[2] showing that imidazolium based ionic liquids can be used as precatalysts for N-heterocyclic carbene (NHC) catalyzed[3] reactions, whereby the catalyst can be obtained by deprotonation. However, while triazolium and thiazolium salts can be deprotonated relatively easily[4] (note also the biological activity[5] of vitamin B1), the most robust IL cations, imidazolium derivatives, need strong deprotonating agents (*e.g.* DBU[2b] or NaOMe with ultrasonic activation[2e]). In recent studies[6] electrolytic reduction of the imidazolium salt to the carbene has been reported,[6a] and the carbene produced this way has been shown to act as a catalyst in various reactions,[6] including the benzoin condensation.[3a–d,5,7]



1 2 3

Fig. 1 Formation of carbenes from EMIM-acetate.

In our previous study[8] we have shown that with basic anions (*e.g.* acetate) imidazolium salts can be deprotonated in the gaseous phase resulting in carbenes (Fig. 1). In the bulk of the liquid phase, however, the interaction with the surrounding charged particles stabilizes the ionic form.[8] Nevertheless, the carbene could be trapped by palladium(II) acetate from imidazolium-based ILs[2c–d] including the acetate,[9a] or by elemental chalcogens[9a] from 1-ethyl-3-methylimidazolium acetate (EMIM-Ac) forming imidazole-2-chalcogenones.[9a] Surprisingly, EMIM-Ac in a 1 : 1 mixture with benzaldehyde was shown[9a] to form a carbene–benzaldehyde adduct,[9] in contrast with the previous experiments with added base, or electrochemically generated carbenes, where the organocatalyzed benzoin-condensation was observed. Our present investigations reveal that EMIM-Ac is an organocatalyst in the benzoin condensation and also in other processes.

After the dissolved gases and volatile impurities were removed from EMIM-Ac (80 °C, 0.4 mbar, 1 h), benzaldehyde was added to the IL in excess (2.4 equiv.) and the reaction mixture was stirred under argon at 60 °C for six hours.[10] Although no attempts were made to optimize the reaction, benzoin **4** (Fig. 2) could be isolated in good yields (67%) after workup. 4-Bromobenzaldehyde and 4-isopropylbenzaldehyde gave the corresponding benzoin derivatives in similar yields in identical processes. While the same procedure resulted in similar yields with 1-butyl-3-methylimidazolium acetate (isolated yield 66%), no product formation was observed with ILs containing non-basic anions, such as 1-ethyl-3-methylimidazolium methanesulfonate.

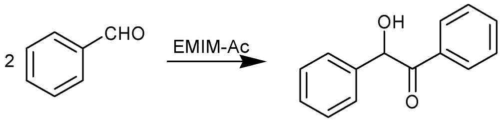


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Fig. 2 Benzoin condensation in degassed EMIM-Ac.

To investigate the possible solvent effects, we used toluene and dichloromethane. Toluene formed a biphasic system with EMIM-Ac resulting in a similar yield as obtained for the neat IL (63% at 60 °C, six hours). In contrast, in dichloromethane, which mixes well with EMIM-Ac, no product formation could be observed by NMR, even after refluxing (at 40 °C) for 24 h.

The reaction was also performed in the presence of air. For these experiments the IL was used as it was obtained from BASF, without the removal of the dissolved air and water. After addition of benzaldehyde at room temperature the solution instantly showed the characteristic yellow colour of benzil **5**. After stirring the reaction mixture for six hours at 60 °C and separating

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the products, benzil **5** (traces), 2-oxo-1,2-diphenylethyl benzoate **6** (21%: observed also in the benzoin condensation catalysed by NHCs generated *via* electrochemical reduction[6c]) and benzoic acid **7** (22%) could be isolated, together with the residual benzaldehyde (Fig. 3).

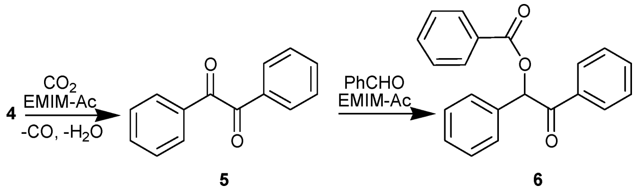

Fig. 3 Oxidation of benzoin by air (CO_2), and the subsequent hydroacylation, catalyzed by EMIM-Ac.

Considering that all products obtained in this reaction (**5**,**6** and **7**) are oxidized, and no reduced organic product could be observed,[11] it is reasonable to assume that (one component of) air has served as an oxidizing agent. **4** is known to be stable under air, and it shows no sign of oxidation even by melting at 137 °C, or by heating in conventional organic solvents. Carbon dioxide[12] was, however, reported recently to oxidize aromatic aldehydes[13a,b] to the corresponding acids by *NHC catalysis*,[13] although it is debated, whether it is the oxidant in the reaction.[13c–e] Repeating the reaction of the degassed EMIM-Ac sample under a CO_2 atmosphere, the same products were obtained as in the presence of air, showing the crucial role of CO_2 in the oxidation process, resulting in benzoic acid[13] and apparently also in **5**. To our best knowledge, this is the first NHC-catalyzed oxidation of an alcohol (benzoin) to an aldehyde. Since the facile NHC catalyzed formation of **6** by hydroacylation from **5** and benzaldehyde is also known,[14] the formation of all the products (including the small concentration of intermediate **5**) is understandable. The instantaneous formation of **6** could indeed be observed from a mixture of benzaldehyde, benzil (**5**), and EMIM-Ac at room temperature and under an inert atmosphere in an apparently highly exothermic reaction, with good yields (87%).

To further investigate the formation of **6**, benzoin (**4**) was dissolved at room temperature in EMIM-Ac (in the presence of air). Interestingly, not only the fast oxidation to **5** (shown also by the yellow discolouration) could be observed, but also the formation of **6** (40%), and **7** (27%). This finding indicates that benzoin was not only oxidized, but also decomposed to benzaldehyde—apparently in a reverse benzoin condensation. To understand the reversibility of this reaction, DFT calculations (see the ESI†) were performed. The mechanism was considered analogous to that proposed by Breslow for thiazole-2-ylidenes,[5] and investigated computationally for triazole-3-ylidenes.[15] The energies of the starting materials, intermediates and product are indeed similar, while the corresponding barriers are quite low. This is in agreement with the description of the condensation process as an equilibrium, and can also explain the lack of catalytic activity with somewhat different ratio[9a] of the reactants.

Since the basicity of the IL controls the carbene concentration, the catalytic activity is very susceptible to acidic contamination. Nevertheless, after the careful removal of the benzoic acid from the substrate, benzoin could be isolated in good yield (76%) even at an EMIM-Ac : benzaldehyde molar ratio of 1 : 10. However, due to the aforementioned facile formation of benzoic acid in the presence of CO_2 and air, the IL shows very low catalytic activity after recycling, which necessitates air contact. Addition of triethylamine has, however, reactivated the catalytic process showing that the non-desirable effect is indeed attributable to the presence of the acid formed.

As a summary of the results described above, imidazolium acetates are effective catalysts for benzoin condensation, and also show catalytic activity in NHC catalyzed hydroacylation. Moreover, oxidation reactions were also activated by the EMIM-Ac used, and further investigation of this observation together with other EMIM-Ac catalyzed processes is in progress in our laboratory. Accordingly, imidazolium acetates uniting the beneficial properties of ILs and organocatalysts are of high potential in such processes, provided that no acid formation takes place.

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We want to thank BASF SE and New Hungary Development Plan (Project ID: TAMOP-4.2.1/B-09/1/KMR-2010-0002) for the financial support. Thanks are due to Dr József Balla and Dr Áron Szőllősi for measuring the GC-MS and NMR spectra, respectively.

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10 The same products were also observed at room temperature although they formed at a much lower rate. Since the formation of the carbene catalyst involves the dissociation of the H-bonded **2** (Fig. 1), at elevated temperatures not only the rate constant, but also the concentration of the free carbene catalyst is increasing.

11 It should be noted that Orsini *et al.* (ref. 6c) have observed 2,2-dihydroimidazole, but they did not report benzyl formation in the benzoin condensation catalyzed by electrochemically reduced NHC. Since they did not investigate the role of the possibly contaminating CO_2 oxidizing agent, the exploration of this aspect under the electrochemical conditions is of importance.

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