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## COMMUNICATION

## Umpolung reactions in an ionic liquid catalyzed by electrogenerated N-heterocyclic carbenes. Synthesis of saturated esters from activated $\alpha$ , $\beta$ -unsaturated aldehydes<sup>†</sup>

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The umpolung reaction of  $\alpha$ , $\beta$ -unsaturated aldehydes to saturated esters has been carried out in an ionic liquid by organocatalysis of electrogenerated NHC. The roles of solvent, precatalyst and proton donor of the ionic liquid have been verified and good to high yields of esters have been obtained using a "green" and mild methodology.

The remarkable versatility of esters as building blocks and as protecting groups in organic synthesis and their significant importance for industrial applications have spurred an extensive investigation aimed to improve the methods for their preparation as well as to develop new strategies for synthesis.<sup>1</sup>

The classical procedures for the synthesis of esters involve the reaction of activated carboxylates with suitable nucleophiles (esterification) or the exchange of an alkoxy moiety between an ester and an alcohol (transesterification).<sup>2</sup> Recently, the oxidative esterification of aldehydes, catalyzed by N-heterocyclic carbenes (NHCs),<sup>3</sup> has been proposed as an alternative strategy.<sup>4</sup> In this reaction, the inversion of the normal polarity of the aldehyde moiety (umpolung) is achieved by addition of an NHC to the carbonyl group, followed by the H<sup>+</sup> shift to yield the "Breslow intermediate".5 After reaction with the nucleophile (an alcohol), the corresponding ester is obtained. The organocatalyst (an NHC) is usually produced by chemical deprotonation of a suitable imidazolium or thiazolium salt (using DIPEA, DBU, KOtBu, etc. as bases) in an organic solvent (THF, toluene, etc.). The oxidation of the aldehyde to ester is accomplished by the reduction of an external oxidant (O<sub>2</sub>, MnO<sub>2</sub>, quinone, azobenzene)<sup>4</sup> or by the reduction of a functional group present in the aldehyde itself (double or triple bond, carbon-halogen bond).<sup>6</sup> So, when an  $\alpha$ ,  $\beta$ -unsaturated aldehyde is used, after an internal redox reaction a saturated ester is obtained.

As part of efforts focused on the development of ecofriendly electrochemical methodologies in ionic liquids, based on the

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use of imidazolium salts in the double role of solvent and precatalyst,<sup>7</sup> we have investigated the possibility to obtain esters from  $\alpha,\beta$ -unsaturated aldehydes and alcohols, by internal redox reaction catalyzed by electrogenerated NHC. The advantages of this methodology reside in the use of a "green" deprotonating reagent, the electron (cheap, easy to dose, and without byproducts), in a very polar solvent, the ionic liquid, which should stabilize the charged intermediates and lead to good yields in products. Moreover, the use of a solvent with virtually null vapour pressure allows us to reuse the solvent, limiting the costs for waste disposal and avoiding air pollution.<sup>8</sup>

The monoelectronic galvanostatic reduction of an imidazolium salt (at a Pt cathode, in a divided cell) leads to the formation of the corresponding NHC and H<sub>2</sub> (Scheme 1, eqn (1)).<sup>7,9</sup> The addition of cinnamaldehyde **1a** to the catholyte, followed by benzyl alcohol **2a**, gives the corresponding saturated ester **3aa** (Scheme 1, eqn (2)). In addition, if the NHC–aldehyde adduct reacts with a molecule of aldehyde,  $\gamma$ -butyrolactone **4aa** is obtained as a byproduct. In the absence of current, no ester was isolated from the reaction between 1-butyl-3-methylimidazolium tetrafluoroborate (Bmim-BF<sub>4</sub>), aldehyde **1a** and alcohol **2a**, and the starting material was recovered (Table 1, entry 1).

The yield of ester **3aa** is affected by many factors (IL, Faradays per mole of aldehyde, mole ratio alcohol/aldehyde), as reported in Table 1. When cinnamaldehyde **1a** and benzyl alcohol **2a** (in equimolar amounts) were added to previously electrolyzed (0.5 F mol<sup>-1</sup> **1a**) Bmim-BF<sub>4</sub>, saturated ester **3aa** was isolated in 54% yield (Table 1, entry 2), along with a significant amount of  $\gamma$ -butyrolactone **4aa**, a byproduct obtained due to the reaction of the NHC–aldehyde adduct with another molecule of aldehyde.<sup>7d</sup> In order to suppress this side reaction, an excess of alcohol must be used (Table 1, entries 3 and 4). A crucial role in this reaction is played by the

$$\begin{array}{c} M_{e}^{e} \\ & &$$



Scheme 1 Scheme for the electrogenerated NHC-catalysed reaction between cinnamaldehyde and benzyl alcohol.

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Table 1Umpolung reaction in electrolyzed ILs. $^{a}$  Reactivity ofcinnamaldehyde 1a vs.benzyl alcohol 2a (Scheme 1)

					Products <sup>d</sup> (yields %)		
Entry	IL, R	$Q^b$ / F mol <sup>-1</sup>	<b>2</b> a/1a <sup>c</sup>	t/h	<b>3</b> aa	4aa	Rec. 1a
1	Butyl	_	3	2	_	_	96
2	Butyl	0.5	1	2	54	38	
3	Butyl	0.5	2	2	64	28	_
4	Butyl	0.5	3	2	67	21	_
5	Butyl	0.2	3	4	6		71
6	Butyl	0.4	3	4	62	6	28
7	Butyl	0.5	3	2	69	4	_
8	Butyl	0.7	3	1	91	Tr.	_
9	Butyl	1.0	3	1	85		_
10	Ethyl	0.7	3	1	72		_
11	Ethyl	1.0	3	1	63	20	
12	Methyl	0.7	3	1	85		_
13	Hexyl	0.7	3	1	82		_
$14^e$	Butyl	0.7	3	1	84		_

<sup>*a*</sup> Electrolyses of ILs were carried out in a divided cell (Pt electrodes) under galvanostatic conditions ( $I = 20 \text{ mA cm}^{-2}$ ; T = 60 °C). <sup>*b*</sup> Number of Faradays per mole of **1a** supplied to the electrodes. <sup>*c*</sup> Mole ratio **2a/1a**, **1a** and **2a** were added to the catholyte at the end of the electrolysis; then the catholyte was stirred for a time *t* at 60 °C. <sup>*d*</sup> Isolated yields with respect to starting **1a**. <sup>*e*</sup> PF<sub>6</sub><sup>-</sup> was used as a counterion of IL.

amount of catalyst (Table 1, entries 5–9), 0.7 F mol<sup>-1</sup> being the optimum (91% yield). The nature of the imidazolium salt is less influential, and good yields in ester were obtained using ILs with aliphatic chains on the nitrogen atom (Table 1, entries 10–14). The best experimental conditions seem to be Bmim-BF<sub>4</sub> as IL, 0.7 F mol<sup>-1</sup> of catalyst and a mole ratio **2a**/1**a** of 3/1, in order to suppress the side reaction (Table 1, entry 8).

The proposed mechanism<sup>6a</sup> for this reaction is reported in Scheme 2. The competition between the formation of expected ester and  $\gamma$ -butyrolactone lies in the extent of the protonation of homoenolate **II**, the more the protonation, the less the byproduct. Scheidt and Chan<sup>6a</sup> reported the necessity to add to the reaction mixture an external proton donor in order to efficiently protonate intermediate **II**; the addition of a phenol of suitable acidity and steric hinderance gives high yields of expected ester, suppressing the formation of any byproduct. In contrast, Bode and Sohn<sup>6b</sup> reported the necessity of the presence of weak amine bases (NEt<sub>3</sub>, DIPEA) as proton shuttles to have excellent conversions.

It should be noted that this electrochemical reaction does not need the use of an external proton donor or of a proton shuttle; therefore it can be inferred that the ionic liquid acts as a proton donor towards homoenolate **II** (Scheme 2),<sup>10</sup> its acidity being suitable for this reaction (its  $pK_a$  has been evaluated in the range of 21–24 in DMSO and water).<sup>11</sup> This possibility was also suggested by Bode in reference to a triazolium salt.<sup>6b</sup>

To raise the efficiency of the overall procedure, the possible reuse of the ionic liquid has been studied. After ethereal extraction of the catholyte and isolation of the products, the catholyte itself was kept under vacuum (to eliminate Et<sub>2</sub>O traces) and reused in subsequent electrolyses (up to five times). Using Bmim-BF<sub>4</sub>, after supplying 1.0 F mol<sup>-1</sup> each time, ester **3aa** was isolated as the only product (85, 76, 70, 72, 73%) with no significant decrease in the yield.<sup>12</sup>

In order to test the generality of this electrochemical methodology in ionic liquids, we have subjected to reaction



Scheme 2 Proposed mechanism for  $\alpha,\beta$ -unsaturated aldehydes umpolung to esters.<sup>6 $\alpha$ </sup>

activated α,β-unsaturated aldehydes 1a-c and alcohols 2a-h (Table 2), under the optimized experimental conditions (Table 1, entry 7). Starting from cinnamaldehyde, hydrocinnamic esters have been obtained in very good yields using benzyl alcohols with donor groups, while the use of benzyl alcohols with EWG leads to lower yields. Aliphatic alcohols work well, but the secondary one (cyclohexanol) is less reactive, while  $\alpha$ ,  $\beta$ -unsaturated aldehydes with donor groups work as cinnamaldehyde with benzyl alcohol, yielding good amounts of esters. When a non-activated  $\alpha,\beta$ -unsaturated aldehyde is used, *i.e. trans* 2-hexenal 1d, the corresponding saturated ester 3da was isolated in very poor yield (10%). This result seems to be consistent with the inferences of our previous investigations.<sup>7a</sup> In fact, in the case of saturated aliphatic aldehydes the formation of the Breslow intermediate in cathodically reduced Bmim-BF4 is not efficient enough: either aldol condensation products or NHC-aldehyde stable adducts have been isolated in high yields.

Nevertheless, spurred by the suggestions of a referee, we have tried to carry out this redox esterification of 2-hexenal in the presence of a different NHC precursor, i.e. 1,3-dimesityl imidazolium chloride (IMes-Cl)<sup>6b</sup> or 1,3-dimethyl benzimidazolium iodide (BI-I),<sup>6a</sup> probably more efficiently. These salts are solid (m.p. > 300 °C), but more acidic than the Bmim cation, so we have added to reduced Bmim-BF<sub>4</sub> 1 mmol of IMes-Cl or BI-I, in view to obtain a more reactive NHC. After the addition of 2-hexenal 1d and benzyl alcohol 2a to this solution, the corresponding saturated ester 3da was isolated in 28% yield with IMes-Cl (Table 2, last entry) and 13% with BI-I. Therefore, in Bmim-BF<sub>4</sub> as solvent the formation of the Breslow intermediate from not activated aldehydes is not efficient enough also using more suitable NHCs. Any attempt to isolate an adduct between NHC and 2-hexenal from the cathodic solution failed.

Last, we have tested the reactivity of a nucleophile different from an alcohol, in order to broaden these reaction applications; the use of benzylamine instead of benzyl alcohol led to the

Aldehyde	Alcohol	Ester <sup><math>b</math></sup> (yield)
СССНО	ССОН	
<b>1</b> a	2a	<b>3aa</b> (91%)
ССНО	<sub>Н₃С</sub> ССОН	
1a	2b	<b>3ab</b> (83%)
ССНО	н₃соЮ	
1a	2c	<b>3ac</b> (91%)
ССНО	сі Сі	
1a	2d	<b>3ad</b> (56%)
ССНО	O₂N () OH	
<b>1</b> a	2e	<b>3ae</b> (55%)
СССНО	EtOH	O-Et
1a	2f	<b>3af</b> (84%)
ССНО	$\mathcal{M}_7^{OH}$	
1a	$\bigcirc^{\mathrm{2g}}$	<b>3ag</b> (71%) ○
1а	2h €	3ah (59%)
н₃со≁∕∕	~	
1b €∕сно	2а	<b>3ba</b> (86%)
1с	2а	3ca (82%)
1d <sup>c</sup>	2a	<b>3da</b> (28%)

**Table 2** Umpolung reaction in electrolyzed Bmim-BF<sub>4</sub>. Reactivity of aldehydes **1a–c** *vs.* alcohols **2a–h**<sup>*a*</sup>

<sup>*a*</sup> The syntheses were carried out following the experimental condition reported in Table 1, entry 7. <sup>*b*</sup> Isolated yields with respect to starting aldehyde. <sup>*c*</sup> 1 mmol of 1,3-dimesitylimidazolium chloride was added to the catholyte at the end of the electrolysis and 10 min before the addition of 2-hexenal and benzyl alcohol.

formation of 47% yield of hydrocinnamic benzylamide after supplying 1.0 F mol<sup>-1</sup>, with 20% of imine (deriving from the reaction between cinnamaldehyde and benzylamine, not involving NHC). Work on this reaction is at present in progress in order to suppress imine formation and to increase the yield of amide.

In conclusion, we have reported the first example (to the best of our knowledge) of synthesis of saturated esters from  $\alpha$ , $\beta$ -unsaturated aldehydes and alcohols in ionic liquids, *via* umpolung reaction catalyzed by electrogenerated N-heterocyclic carbene.

The manifold role of the cheap ionic liquid  $Bmim-BF_4$ (solvent, precatalyst and proton donor) has been established and no additive was needed to obtain good to high yields in esters. Moreover, the use of the electron as base and of an ionic liquid (not air-pollutant and recyclable) renders this synthesis in agreement with the principles of "green chemistry".

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