Electrochimica Acta 89 (2013) 692–699

Contents lists available at SciVerse ScienceDirect

Electrochimica Acta

journal homepage: www.elsevier.com/locate/electacta

Internal redox amidation of α,β-unsaturated aldehydes in ionic liquids. The electrochemical route

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ARTICLE INFO

Article history:
Received 14 September 2012
Received in revised form
14 November 2012
Accepted 15 November 2012
Available online 27 November 2012

Keywords:
Amides
N-Heterocyclic carbenes
α,β-Unsaturated aldehydes
Room temperature ionic liquids
Organic electrosynthesis

ABSTRACT

A simple, N-heterocyclic carbene (NHC) activated synthesis of amides has been performed via electrolysis, carried out under galvanostatic control, of an ionic liquid (Bmim-BF_4) followed by addition to the catholyte of an α,β-unsaturated aldehyde and amine. Amides have been isolated, in good to elevated yields, in the absence of any base, co-catalyst and organic solvent. The selectivity of amidation, versus the formation of imine as by-product, has been related to the molar ratio electrogenerated NHC/aldehyde. The results, obtained using ionic liquids and electrochemical procedures, have been compared with those obtained using organic solvents and classical procedures.

1. Introduction

The noticeable presence, as a *peculiar mark*, of amide functionality in biological systems (e.g. the chemical bonds that link aminoacids together to give proteins) and the significant role played in many pharmaceutically active molecules and in versatile polymers, have spurred a continuous investigation targeted to set up efficient procedures of synthesis. Hence, a plethora of strategies for the amide bond formation have been reported [1–6].

To overcome the ammonium salt formation, the direct amidation of carboxylic acids must be carried out at high temperature ($T > 180\,^{\circ}C$, Scheme 1) [7].

However, these procedures are incompatible with the presence in the substrates of other sensitive functional groups. Therefore, at present, the most used strategies of synthesis of amides rely on the activation, with coupling reagents, of a carboxylic acid (which is electron deficient) towards the nucleophilic attack of an amine (which is electron rich). The activation consists of the replacement of the hydroxyl group of the carboxylic acid with a leaving group, as the acid would otherwise simply form a salt with the amine (Scheme 2).

Carbodiimide, HOBt- or HOAt-based uronium, phosphonium and immonium salts, chloroformate, pyridinium compounds, are frequently utilized as coupling agents [2]. Despite the general efficiency of these procedures, different authors have emphasized some serious limits: stoichiometric use of the reagents, low product/waste ratio, poor atom economy, hard product isolation [8].

To overcome some of these drawbacks, enzymatic methods [9], as well as the use of non metal catalysts (organocatalysts and boron reagents) [10] have been reported. However, high isolation costs and limited substrate range must be taken into account.

At present, increasing attention is devoted to developing procedures of amide bond synthesis employing metal catalysts [8]. Generally, metal-catalyzed protocols allow the amide bond formation starting from substrates other than carboxylic acids (oximes, aldehydes, nitriles, alcohols, esters, etc.).

Protocols for the direct amide formation from carboxylic acids and amines have been lately set up using zirconium (IV) as catalyst (toluene as solvent, $T = 110\,^{\circ}C$ [11], THF as solvent, $T = 70\,^{\circ}C$ [12]) or $AlMe_3$ as coupling reagent (toluene as solvent, rt) [13].

Despite the numerous procedures, the state of the art of amide bond formation is not quite satisfactory, as emphasized by the American Chemical Society Green Chemistry; the motion "amide formation avoiding poor atom economy reagents" has been voted as the top challenge for organic chemistry in 2007 [14].

Therefore, the amide bond synthesis requires a careful rethinking. The new generation of emerging procedures has been extensively discussed in recent reviews [15,16].

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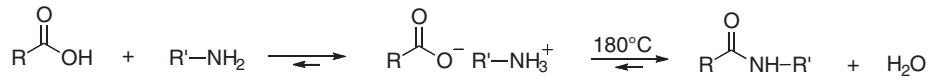
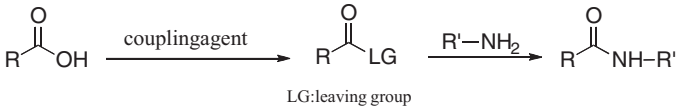
http://dx.doi.org/10.1016/j.electacta.2012.11.061



Scheme 1. Synthesis of amides fom carboxylic acids.



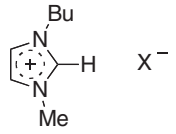
Scheme 2. Synthesis of amides starting from carboxylic acids and coupling agents.

In the last decade, N-heterocyclic carbenes (NHCs, generally obtained in situ from azolium salts and suitable bases) have been frequently utilized as legants in organometallic catalysts [17,18] and as versatile organocatalysts [19,20] in a very broad range of organic reactions. The possible NHC-catalyzed oxidative amidation of aldehydes has been investigated by different authors [21–23]. These syntheses have been carried out in CH_2Cl_2 solutions containing, in addition to aldehyde and amine, the precatalyst (an azolium salt), the base (NEt_3), the oxidant (NCS), and the additive (BtOH) [21].

In addition to the concept of atom economy, the redox economy (the internal exchange of oxidation states between adjacent functional groups, targeted at avoiding the utilization of stoichiometric redox reactants) has been recently stormed into organic synthesis. According to the redox economy requirement, a further intriguing NHC-catalyzed synthesis (from αfunctionalized aldehydes, in the absence of any external redox agent) of esters [24–28] and amides [29–31] has been investigated. A hard drawback in this procedure of synthesis of amides is the presence of a very competitive reaction, i.e. the reaction between the aldehyde and the amine yielding an imine. The authors have overcome this trouble utilizing the so-called promoter or co-catalyst (1-hydroxy-7-azobenzotriazole, 1-hydroxybenzotriazole, imidazole, 4-(dimethylamino) pyridine, etc.). According, the procedures have been carried out in complex systems: solutions of THF or CH_2Cl_2 as solvents containing αfunctionalized aldehyde (α,β-unsaturated aldehydes, α-chloroaldehydes), amine, precatalyst (triazolium salt), base and promoter (Scheme 3).

In the course of our ongoing interest in the set up of green electrochemical methodologies, we have extensively investigated the possible utilization of the intermediate NHCs, electrogenerated via cathodic reduction of room temperature ionic liquids (RTILs), as mediators (bases, organocatalysts, etc.), in alternative procedures of organic syntheses [32–39]. At present, we are engaged in studying the reactivity of α,β-unsaturated aldehydes and amides, in previously electrolyzed RTILs **1a-d** (as solvents, containing NHCs, Scheme 4).

Aims of this investigation, carried out by classical voltammetric measurements and electrolyses in galvanostatic conditions, are: a) the set up of a simple and efficient green synthesis of amides from α,β-unsaturated aldehydes and amines carried out in electrolyzed RTILs in the absence of organic solvents, bases and co-catalysts; b) to inquire into the effective role played by the ionic liquid and by the derived NHC.



RTIL 1a-d

X = a: BF_4 ; b: PF_6 ; c: $MeSO_4$; d: I

Scheme 4. Room temperature ionic liquids used in this work.

2. Experimental

2.1. Starting material

Ionic liquids **1a-d** (IoLiTec) were commercially available and used as pure compounds (impurities reported: water < 0.02%, chloride <100 mg/Kg), after being kept at reduced pressure at 70 °C for 24 h. DBU, aldehydes **4a-c** and amines **5a-l** were commercially available and used as received.

2.2. Instrumentation

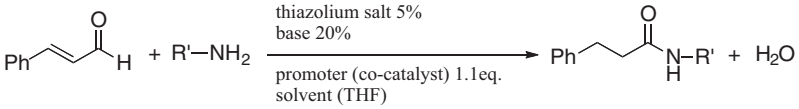
^1H and ^{13}C NMR spectra were recorded using a Bruker AC 200 spectrometer using $CDCl_3$ as internal standard.

Voltammetric measurements were performed with an Amel 552 potentiostat equipped with an Amel 566 function generator and an Amel 563 multipurpose unit in a three-electrode cell; the curves were displayed on an Amel 863 recorder. A 492/Pt/1 Amel microelectrode was employed, using a Pt counter electrode and an Ag quasi reference electrode (q.r.e.).

Constant current electrolyses were carried out (using an Amel 552 potentiostat equipped with an Amel 771 integrator) in a glass two-compartment home-made cell. Anolyte (ca. 0.5 ml) and catholyte (ca. 1.5 ml) were separated through a glass disk (porosity 4). The electrode apparent surface areas were 1.0 cm^2 for the cathodic Pt flat spiral (99.9%) and 0.8 cm^2 for the anodic Pt flat spiral (99.9%). The current density was 20 mA/cm^2.

2.3. Typical electrochemical procedure and workup

Electrolyses were carried out at 60 °C, under nitrogen atmosphere, using BMIM-BF_4 as anolyte and catholyte. After the consumption of 1.4 Faradays per mol of aldehyde (or a different amount, as reported in Table 1), the current was switched off and aldehyde (0.5 mmol) was added to the catholyte under stirring; when the dissolution was complete, amine (1.0 mmol, or the amount reported in Table 1) was added. The mixture was kept at 60 °C for 2 h. The catholyte was extracted with diethyl ether, the solvent was removed under vacuum and the residue was analyzed by ^1H-NMR and purified by flash-chromatography (using



Scheme 3. Synthesis of amides from aldehydes by internal redox reaction.

Table 1
Reactivity of cinnamaldehyde **4a** versus benzylamine **5a** in pre-electrolyzed ionic liquid **1**. Effect of the number of Faradays per mol of **4a** (Q) and of the **5a**/**4a** molar ratio (ρ) on the yields of amide **6aa** and imine **7aa** (Scheme 5).[a]

Entry	RTIL	Q[b]	ρ[c]	**6aa** (yield, %)[d]	**7aa** (yield, %)[d]
1	1a	-	2.0	-	95
2	1a	0.3	2.0	15	84
3	1a	0.7	2.0	42	35
4	1a	1.0	2.0	57	21
5	1a	1.4	2.0	88	tr
6	1a	1.4	3.0	63	12
7	1a	1.4	1.0	49	31
8[e]	1a	0.7	1.0	tr	95
9[f]	1a	0.7	1.0	tr	95
10	1b	1.4	2.0	58	23
11	1c	1.4	2.0	tr	95
12	1d	1.4	2.0	61	18

[a] 10.0 mmol of RTIL were subjected to electrolysis (see experimental) and, after the consumption of a prefixed number of Faradays per mol (Q), cinnamaldehyde **4a** (0.5 mmol) and, 5 minutes later, benzylamine **5a** in a prefixed molar ratio (ρ) were added to the catholyte.
[b] Number of Faradays per mol of 4a supplied to the electrodes.
[c] Molar ratio **5a**/**4a** added to the catholyte.
[d] Isolated yields with respect to starting **4a**.
[e] **4a** and **5a** were added simultaneously to the catholyte.
[f] Amine **5a** was added before **4a** to the catholyte.

n-hexane/ethyl acetate from 7/3 to 1/1 as eluent), affording the corresponding pure amide. All amides are known compounds and gave spectral data in accordance with the ones reported in the literature.

2.4. Recycle of catholyte

After ethereal extraction of the cathodic Bmim-BF_4 and isolation of amide **6aa**, the catholyte was kept under vacuum under stirring at 60 °C for 1 h, then the catholyte was used in a new electrolysis for the synthesis of **6aa**. The same ionic liquid was used three times, obtaining (after 1.4 F/mol of **4a** each time) **6aa** in 88, 66, 49% yields, respectively.

2.5. Isolated products

2.5.1. *N-Benzyl-3-phenylpropanamide* ***6aa***. [31]

R_f (30% ethyl acetate in n-hexane) 0.23; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.53 (t, J = 7.6 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 4.41 (d, J = 5.6 Hz, 2H), 5.6 (bs, 1H), 7.14-7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.7, 38.5, 43.6, 126.3, 127.4, 127.7, 128.4, 128.5, 128.5, 128.6, 138.2, 140.8, 171.9.

2.5.2. *N-benzylcinnamaldehyde imine* ***7aa***. [40]

R_f (20% ethyl acetate in n-hexane) 0.40; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.73 (d, J = 1.2 Hz, 1.8H), 4.84 (d, J = 1.4 Hz, 0.2H), 6.98-7.01 (m, 2H), 7.29-7.41 (m, 8H), 7.47-7.52 (m, 2H), 8.14-8.18 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 65.3, 127.2, 127.3, 128.0, 128.1, 128.5, 128.9, 129.2, 135.8, 139.2, 141.9, 163.4.

2.5.3. *N-Phenethyl-3-phenylpropanamide* ***6ab***. [41]

R_f (30% ethyl acetate in n-hexane) 0.27; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.43 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 6.9 Hz, 2H), 2.96 (t, J = 7.4 Hz, 2H), 3.48 (q, J = 6.9 Hz, 2H), 5.4 (bs, 1H), 7.09-7.13 (m, 2H), 7.18-7.35 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.7, 35.7, 38.5, 40.6, 126.2, 126.5, 128.4, 128.5, 128.6, 128.7, 138.9, 140.9, 172.0.

2.5.4. *3-Phenyl-N-(3-phenylpropyl)propanamide* ***6ac***. [42]

R_f (30% ethyl acetate in n-hexane) 0.28; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.77 (quint, J = 7.4 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 3.26 (q, J = 7.6 Hz, 2H), 5.4 (bs, 1H), 7.13-7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 31.8, 33.2, 38.6, 39.2, 126.0, 126.3, 128.4, 128.5, 141.0, 141.4, 172.1.

2.5.5. *N-Butyl-3-phenylpropanamide* ***6ad***. [43]

R_f (30% ethyl acetate in n-hexane) 0.31; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.17-1.48 (m, 4H), 2.46 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 7.6 Hz, 2H), 3.21 (q, J = 6.8 Hz, 2H), 5.4 (bs, 1H), 7.18-7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 20.0, 31.6, 31.8, 38.6, 39.2, 126.2, 128.3, 128.5, 140.9, 172.0.

2.5.6. *N-(Cyclohexylmethyl)-3-phenylpropanamide* ***6ae***. [44]

R_f (30% ethyl acetate in n-hexane) 0.26; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.74-0.91 (m, 2H), 1.13-1.43 (m, 4H), 1.55-1.72 (m, 5H), 2.45 (t, J = 7.6 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H), 3.05 (t, J = 6.4 Hz, 2H), 5.3 (bs, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8, 26.4, 30.7, 31.8, 37.8, 38.6, 45.7, 126.2, 128.4, 128.5, 140.9, 172.0.

2.5.7. *N-Cyclohexyl-3-phenylpropanamide* ***6af***. [31]

R_f (30% ethyl acetate in n-hexane) 0.23; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93-1.45 (m, 6H), 1.56-1.88 (m, 4H), 2.44 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 7.6 Hz, 2H), 3,67-3.84 (m, 1H), 5.1 (bs, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.8, 25.5, 31.9, 33.1, 38.7, 48.1, 126.2, 128.4, 128.5, 140.9, 171.1.

2.5.8. *N-Cyclopentyl-3-phenylpropanamide* ***6ag***. [45]

R_f (30% ethyl acetate in n-hexane) 0.27; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23-1.31 (m, 2H), 1.56-1.64 (m, 4H), 1.86-1.98 (m, 2H), 2.44 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 7.6 Hz, 2H), 4.11-4.23 (m, 1H), 5.2 (bs, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6, 31.9, 33.0, 38.7, 51.1, 126.2, 128.4, 128.5, 140.9, 171.6.

2.5.9. *N-Cycloheptyl-3-phenylpropanamide* ***6ah***. [45]

R_f (30% ethyl acetate in n-hexane) 0.33; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21-1.89 (m, 12H), 2.43 (t, J = 7.6 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 3.86-4.01 (m, 1H), 5.3 (bs, 1H), 7.18-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0, 28.0, 31.9, 35.1, 38.8, 50.3, 126.2, 128.4, 128.5, 140.9, 170.8.

2.5.10. *3-Phenyl-1-(piperidin-1-yl)propan-1-one* ***6ai***. [31]

R_f (30% ethyl acetate in n-hexane) 0.43; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44-1.65 (m, 6H), 2.58-2.67 (m, 2H), 2.94-3.02 (m, 2H), 3.34 (app. t, J = 5.3 Hz, 2H), 3.57 (app. t, J = 5.3 Hz, 2H), 7.17-7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.5, 25.6, 26.4, 31.6, 35.2, 42.7, 46.6, 126.1, 128.4, 128.5, 141.5, 170.4.

2.5.11. *1-Morpholino-3-phenylpropan-1-one* ***6aj***. [Commercial]

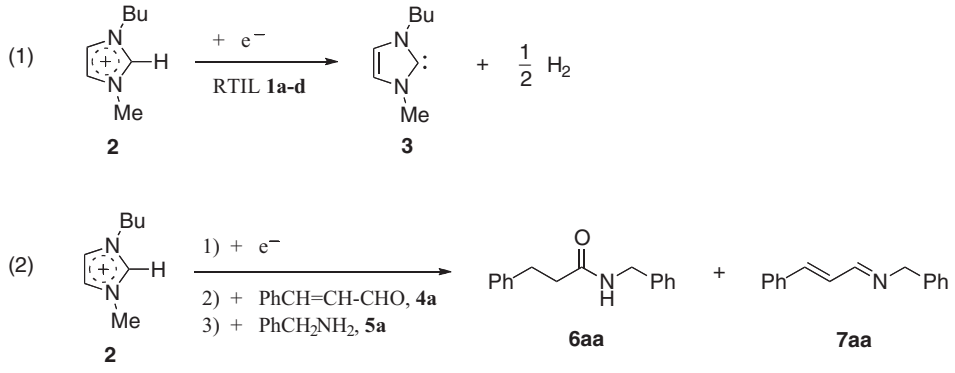
R_f (30% ethyl acetate in n-hexane) 0.43; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.62 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 3.36 (app. t, J = 4.6 Hz, 2H), 3.52 (app. t, J = 4.6 Hz, 2H), 3.63 (s, 4H), 7.20-7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.5, 34.8, 41.9, 46.0, 66.5, 66.9, 126.3, 128.5, 128.5, 141.1, 170.8.

2.5.12. *N-(2-Hydroxy-2-phenylethyl)-3-phenylpropanamide* ***6ak***. [46]

R_f (30% ethyl acetate in n-hexane) 0.18; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.49 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 3.26 (ddd, AB, $\Delta\nu$ = 78 Hz, J_{AB} = 14.0 Hz, J = 7.0, 5.0 Hz, 1H), 3.4 (bs, 1H), 3.65 (ddd, AB, $\Delta\nu$ = 78 Hz, J_{AB} = 14.0 Hz, J = 7.9, 3.3 Hz, 1H), 4.75 (dd, J = 7.9, 3.3 Hz, 1H), 5.9 (bs, 1H), 7.17-7.38 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.7, 38.3, 47.5, 73.6, 125.8, 126.3, 127.8, 128.4, 128.5, 128.6, 138.9, 140.7, 141.7, 173.5.

2.5.13. *N-(4-Hydroxybutyl)-3-phenylpropanamide* ***6al***. [45]

R_f (1% EtOH in ethyl acetate) 0.26; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50-1.53 (m, 4H), 1.8 (bs, 1H), 2.46 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 7.6 Hz, 2H), 3.20-3.30 (m, 2H), 3.60-3.65 (m, 2H), 5.6 (bs, 1H),



Scheme 5. Generation and reactivity of NHC.

7.20-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.2, 29.6, 31.8, 38.5, 39.2, 62.3, 126.2, 128.4, 128.5, 140.9, 172.2.

*2.5.14. Benzyl 3-(4-methoxyphenyl)propanamide **6ba**. [47]*

R_f (30% ethyl acetate in n-hexane) 0.21; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.49 (t, J = 7.5 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 3.79 (s, 3H), 4.40 (d, J = 5.6 Hz, 2H), 5.6 (bs, 1H), 6.80-6.84 (m, 2H), 7.10-7.17 (m, 4H), 7.27-7.31 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.9, 38.8, 43.5, 55.2, 113.9, 114.0, 127.4, 127.7, 128.6, 129.3, 129.3, 132.8, 138.2, 158.1, 171.9.

*2.5.15. N-Benzyl-3-(furan-2-yl)propanamide **6ca**. [30]*

R_f (40% ethyl acetate in n-hexane) 0.47; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.55 (t, J = 7.4 Hz, 2H), 3.02 (t, J = 7.4 Hz, 2H), 4.42 (d, J = 5.6 Hz, 2H), 5.8 (bs, 1H), 6.02-6.04 (m, 1H), 6.27-6.29 (m, 1H), 7.20-7.33 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.1, 35.0, 43.6, 105.6, 110.2, 127.5, 127.7, 128.7, 138.2, 141.2, 154.3, 171.5.

3. Results and discussion

In a preliminary investigation, carried out via voltammetric analysis, we have tested the different behaviour of cinnamaldehyde **4a** (in the absence and in the presence of benzylamine **5a**) in Bmim-BF_4 **1a** with respect to the one in electrolyzed Bmim-BF_4 **1a** (Scheme 5) [48].

The voltammetric curves, recorded at a Pt cathode for RTIL **1a** (ν = 0.2 Vs^{-1}, 25 °C) do not show meaningful values of the reduction current as regard the potential window from–0.40 V to -1.65 V (vs Ag pseudo reference electrode; Fig. 1, curve a). Voltammetric measurements, reported by us in previous papers [32,49,50] prove that the cathodic reduction of cation $Bmim^+$, in pure $BmimBF_4$, is effective at a cathodic potential more negative than -2.0 V (*vs* Ag r.e.).

On the contrary, voltammetric curve of a solution of **1a**, containing aldehyde **4a**, displays the presence of an irreversible peak (Ep = -1.15 V, *vs* Ag r.e.), marked by a broad pre-peak (Ep = –0.9 V, *vs* Ag r.e.) (Fig. 1, curve b). Therefore, the cathodic current recorded in curve b must be related to the reduction of the carbonyl group of aldehyde **4a**. The value of the peak current of curve b, monitored versus time, is stable. According, any reaction of aldehyde **4a** with ionic liquid **1a** can be ruled out.

The addition of amine **5a** (an electroinactive substrate in the experimental conditions considered by us) to the solution of 1a containing aldehyde **4a**, causes the disappearance of the irreversible peak at -1.15 V, and of the related broad pre-peak at–0.9 V, and the appearance of a new peak at -1.48 V *vs* Ag r.e. (Fig. 1, curve c).

This change in the voltammetric curves (curve c vs curve b) could be related to the fast reaction between aldehyde **4a** and amine **5a** yielding imine **7aa**. To test this hypothesis, immine **7aa** was synthesized from **4a** and **5a** in **1a** as solvent (in quantitative yield) and the cyclic voltammetry of this solution showed a reduction peak at -1.48 V.

On the contrary, voltammetric curves recorded for solutions of pre-electrolyzed RTILs (containing NHC **3**) do not show the presence of the specific reduction peak at -1.15 V vs Ag r. e. after the addition of aldehyde **4a**, as well as no reduction peak (at E = - 1.48) has been observed after the following addition of amine **5a**. According, the presence of **4a** and of **7aa** can be excluded, and the reaction between **4a** and **5a** must related to a different route.

Spurred by these initial results, we have evaluated the reactivity of **4a** vs **5a** in RTIL **1a** (in the absence and in the presence of the derived NHC **3**) according the following procedure: Bmim-BF_4 **1a** was electrolyzed under galvanostatic conditions (divided cell, N_2 atmosphere, at 60 °C in order to enhance the medium conductivity). After the consumption of a prefixed number of Faradays, the current was switched off and cinnamaldehyde **4a** and, 5 minutes later, benzylamine **5a** (in a prefixed molar ratio) were added to the catholyte. The mixture was stirred at 60 °C for 2.0 h. Conventional workup of this final solution allows to isolate the products and to assess the yields (Table 1).

We were pleased to find that, in the experimental conditions selected by us (i.e. electrolyzed RTIL **1a**), the amidation of **4a** to

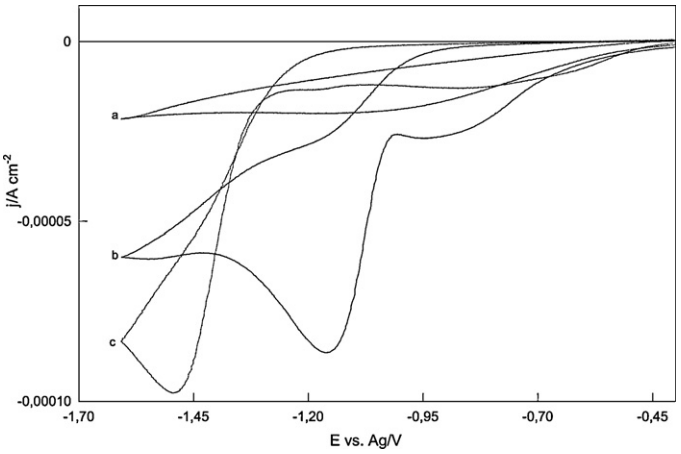
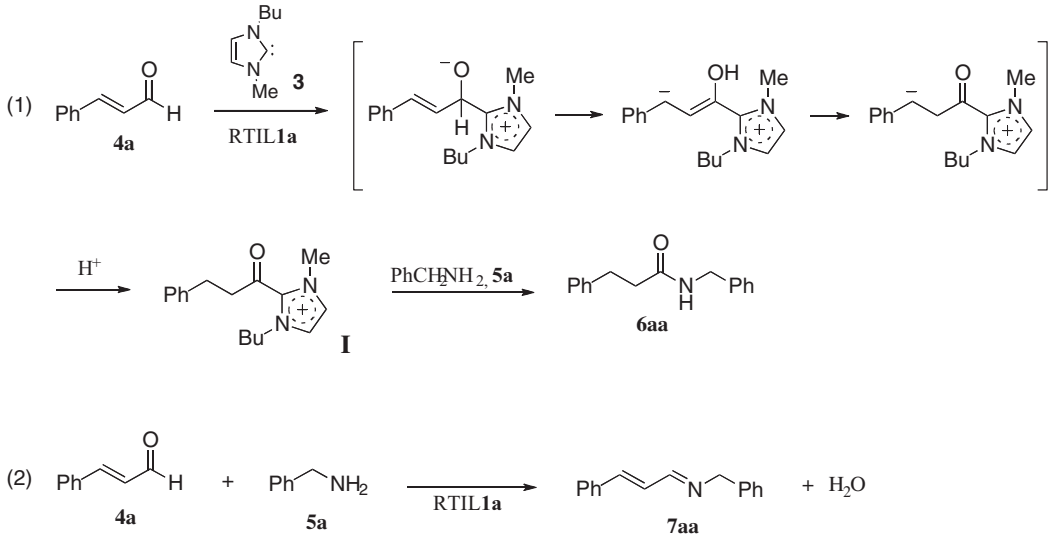


Fig. 1. Voltammetric curves, at a Pt cathode (vs Ag, ν = 0.2 V s^{-1}, T = 25 °C) of Bmim-BF_4 (2 ml, curve a), Bmim-BF_4 and **4a** (0.5 mmol, curve b), Bmim-BF_4 and **4a** and **5a** (1.0 mmol, curve c).



Scheme 6. Reaction between cinnamaldehyde and NHC or benzylamine.

6aa could be achieved in the absence of any co-catalyst, base and organic solvent.

The number of Faradays per mole of **4a** supplied to the electrode (Q, Table 1, entries 2-5) and the molar ratio **5a**/**4a** (ρ, Table entries 5-7) both significantly affect the yields of isolated **6aa** and **7aa**. An increase of Q (i.e. of the concentration of **3** in the solution) causes an increase of the yields of amide **6aa** and a consistent decrease of imine **7aa**. In the optimized condition (Q = 1.4 Faraday mol^{-1} and **3** present in stoichiometric quantity), amide **6aa** has been isolated in elevated yield (88%) and the presence of imine **7aa** in the mixture of the reaction has been ruled out (Table 1, entry 5). On the contrary, imine **7aa** was the only product (in quantitative yields) when the reaction between **4a** and **5a** was carried out in Bmim-BF_4 in the absence of electricity (Table 1, entry 1), as reported also by Andrade and coworkers [51].

When the synthesis was carried out adding **4a** and **5a** at the same time to the catholyte (or **5a** before **4a**), imine **7aa** was isolated in quantitative yields (95%) and the presence of amide **6aa** was excluded (Table 1, entries 8 and 9). This result suggests that the reaction between **4a** and **5a** yielding imine **7aa** (Scheme 6, reaction 2) is faster than the reaction between **4a**, **5a** and NHC **3** yielding amine **6aa** (Scheme 6, reaction 1).

Last, the nature of the anion in the starting ionic liquid could significantly modify the yields of the isolated products (Table 1, entries 10-12).

In previous communications about the NHC-catalyzed synthesis of amides via internal redox oxidation of α-functionalized aldehydes (carried out in organic solvent, using a triazolium salt in the presence of a base as precatalyst), the fast formation of imines, leading to an extensive inhibition of the desired catalytic amidation process, has been avoided by adding suitable promoters (the so-called co-catalysts) [29–31]. In the absence of co-catalysts the amide was isolated in 5% yield [29]. In the opinion of the authors, the first step of the overall process involves the reaction between the aldehyde and the promoter yielding the relative acyl-promoter species (NHC-catalyzed internal oxidation of the aldehyde). The second step regards the nucleophilic attack of the amine to the acyl-promoter species yielding the desired amide.

Our experimental data, compared with the previous investigations, suggest that the peculiar system RTIL **1a** (as solvent)/**3** (as NHC) is able to promote the formation of **6aa** in elevated yield in the absence of any co-catalyst (provided **3** is present in stoichiometric amount).

This unexpected efficiency could be related to the reaction of aldehyde **4a** and carbene **3**, in Bmim-BF_4, yielding the stable cationic adduct **I** (as reported in previous communications [32–39]), and to the following nucleophilic attack of the amine **5a** to adduct **I**. On the contrary, the formation of imine **7aa** derives from the direct reaction between the amine **5a** and residual aldehyde **4a** (i.e. "free" aldehyde **4a**, not consumed by the formation of adduct **I**, Scheme 6).

An increase of the number of Faradays per mole of aldehyde **4a** supplied to the electrodes (i.e. an increase of the number of moles of carbene **3** per mole of aldehyde **4a**) provokes an increase of the "activated" aldehyde (via formation of the structure **I** by reaction of **4a** with **3**) and a decrease of the "free" aldehyde. Consequently, an increase of the consumed number of Faradays causes an increase of the yield of amide **6aa** and a decrease of imine **7aa**. According to a stoichiometric consumption of Faradays, **4a** has been efficiently activated as adduct **I** and amide **6aa** has been isolated in elevated yield (88%), while imine **7aa** was absent in the reaction mixture. The catholyte was then reused for two more electrolyses (under the same conditions) and **6aa** was isolated in 66 and 49% yields respectively.

In order to acquire further data to clear the limits of this methodology, we have studied the reactivity of **4a** versus **5a** in different solvents (organic solvents, VOCs) in the presence of NHC **3** generated according to the classical chemical procedure (deprotonation of the parent Bmim-BF_4 with a suitable base, DBU; Table 2).

Table 2
Reactivity of cinnamaldehyde **4a** versus benzylamine **5a** in the presence of Bmim-BF_4 and DBU. Effect of the solvent on the yields of amide **6aa** and imine **7aa** (Bmim-BF_4: 1.0 mmol; DBU: 1.0 mmol; **4a**: 0.5 mmol; **5a**: 1.0 mmol).[a]

Entry	Solvent	**6aa** (yield, %)[b]	**7aa** (yield, %)[b]
1	THF	18	12
2	MeCN	24	4
3	DMF	78	22
4	Toluene	42	12
5	CH_2Cl_2	16	3
6	Bmim-BF_4	52	4

[a] 1.0 mmol Bmim-BF4 and 1.0 mmol DBU were added to 2 ml of solvent, under nitrogen atmosphere. Then 0.5 mmol of cinnamaldehyde **4a** and, 5 minutes later, 1.0 mmol of benzylamine **5a** were added to the mixture, which was kept at 60 °C (50 °C for THF and 30 °C for CH_2Cl_2) for 2 hours. Usual workup gave **6aa** and **7aa** in the yields reported.

[b] Isolated yields respect to starting **4a**.

Table 3
Electrochemical synthesis of amides **7** via reaction of aldehydes **4a-c** and amines **5a-l** in pre-electrolyzed Bmim-BF_4.[a]

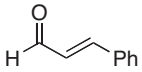
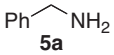
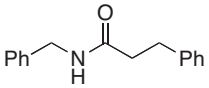
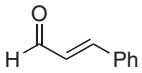
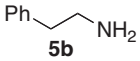
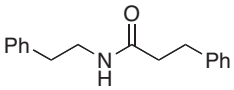
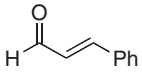
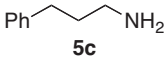
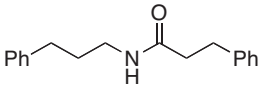
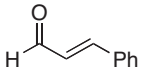
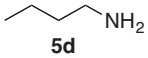
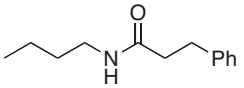
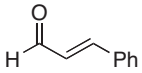
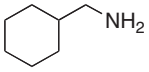
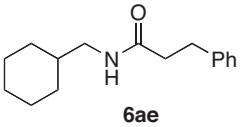
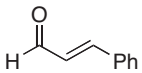
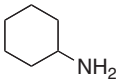
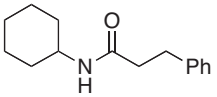
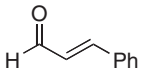
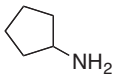
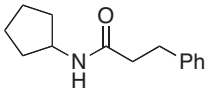
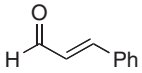
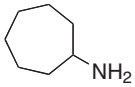
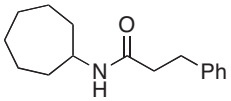
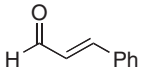
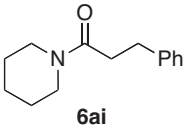
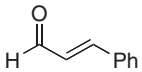
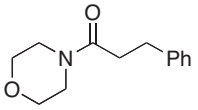
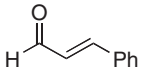
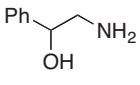
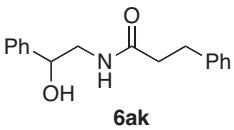
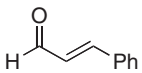
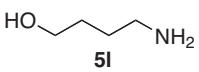
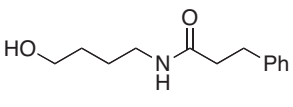
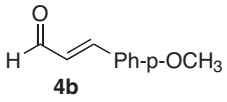
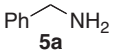
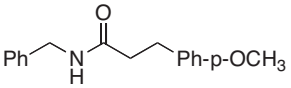
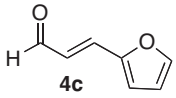
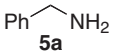
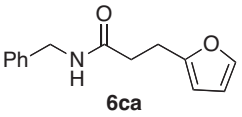
Entry	Aldehyde	Amine	Amide **6** (yield, %)
1[c]	 **4a**	 **5a**	 **6aa** 88
2	 **4a**	 **5b**	 **6ab**
3	 **4a**	 **5c**	 **6ac**
4	 **4a**	 **5d**	 **6ad**
5	 **4a**	 **5e**	 **6ae**
6	 **4a**	 **5f**	 **6af**
7	 **4a**	 **5g**	 **6ag**
8	 **4a**	 **5h**	 **6ah**
9	 **4a**	 **5i**	 **6ai**
10	 **4a**	 **5j**	 **6aj**
11[d]	 **4a**	 **5k**	 **6ak**
12[d]	 **4a**	 **5l**	 **6al**

Table 3 (*Continued*)

Entry	Aldehyde	Amine	Amide **6** (yield, %)
13	 **4b**	 **5a**	 **6ba**
14	 **4c**	 **5a**	 **6ca**

[a] Synthesis carried out following the experimental conditions reported in Table 1, entry 5.
[b] Isolated yields respect to starting aldehyde.
[c] Entry 5 of Table 1, reported here for comparison.
[d] No amino ester was isolated, only unreacted amino alcohol.

The results show that the efficiency of the procedure of amidation is strongly affected by the nature of the solvent (Table 2) as well by the procedure adopted (classical or electrochemical, Table 1, entry 5 versus Table 2, entry 6); it should be kept in mind that the amount of NHC **3** in the two different methodologies could be different.

In order to verify the effectiveness and generality of this procedure, we have extended the investigation to amines **5b-l** and aldehydes **4b-c**, carrying out the synthesis under the optimized condition reported in Table 1 (entry 5). In all cases, the amidation was obtained in good to elevated yields, irrespective of the nature of the amine (primary, secondary, linear or cyclic; Table 3, entries 1-10) and of the aldehyde (Table 3, entries 13 and 14), while when using amino alcohols **5k** and **5l** the reaction led to a complete selectivity versus the amine moiety (giving the corresponding hydroxy amide) and no amino ester was obtained (Table 3, entries 11 and 12).

4. Conclusions

A simple electrochemical methodology (the electrolysis in galvanostatic conditions of the common and inexpensive ionic liquid Bmim-BF_4) provides a medium (RTIL/NHC) able to activate the amidation of α,β-unsaturated aldehydes via NHC-catalized internal oxidation.

Imines could be obtained as by-products, via the direct reaction of "free" aldehyde with amines. The procedure, carried out in the absence of any base, promoter and organic solvent, allows to isolate amides **6** in good to elevated yields.

The amidation of cinnamaldehydes has been related to the nucleophilic attack of the amine to the intermediate cationic structure **I** (derived by the reaction of aldehyde and carbene **3** in the presence of ionic liquid **1a**). According, the formation of **I** actives the amidation and therefore decreases the concentration of "free" aldehydes in the solution and the yield of isolated imine as by-product.

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