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Investigation of the Role of Electrogenerated N-Heterocyclic Carbene in the Staudinger Synthesis in Ionic Liquid

Marta Feroci
Department of Foundamental and Applied Sciences for Engineering (*SBAI*), *Sapienza University of Rome*, *Rome*, *Italy*
E-mail: *marta.feroci@uniroma1.it*
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Abstract

Electrogenerated N-heterocyclic carbene (NHC), obtained by cathodic reduction of Bmim-BF_4, behaves as organocatalyst and base in the Staudinger synthesis from an acyl chloride and a deactivated imine in ionic liquid to yield β-lactams. The effect of many parameters (temperature, amount of electricity, substituents, presence of an external base) has been evaluated and a tentative mechanism for the Staudinger synthesis in a very polar medium like the ionic liquid reported. The yields of isolated β-lactams are good, starting from non-electrophilic imines, and predominantly *trans* lactams are obtained with a good diastereomeric ratio.

Keywords: Electrosynthesis, NHC, Staudinger Synthesis, β-Lactams, Organocatalyst, Ionic Liquid

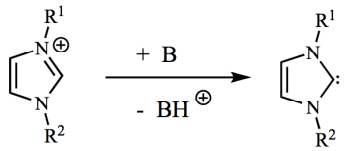
1. Introduction

The use of ionic liquids (ILs) [1-3] as solvents in organic reactions has, during the last two decades, undergone a rapid acceleration as these salts can, in many cases, substitute the classical organic solvents (VOCs), which can be considered air-pollutant due to their volatility. In fact, ionic liquids have a virtually null vapour pressure and this characteristic leads to their easy recycling.

One of the most studied and used class of ILs in organic chemistry is the imidazolium based one, due to its air and water-stability, low cost and wide temperature window of the liquid phase [4,5]. Nevertheless, these ILs are not mere solvents. In fact, recently the "non innocent" nature of imidazolium ILs has been described by many authors, [6,7] as, in particular experimental conditions, these cations can give rise to the formation of N-heterocyclic carbenes (NHC). NHC can be easily prepared by deprotonation of imidazolium cations [8] not substituted in the 2-position (**Scheme 1**) [9-17].

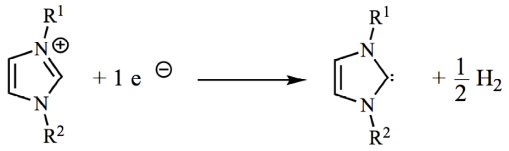
N-Heterocyclic carbenes have been frequently used in organic chemistry as ligands and, more recently, as organocatalysts [18-21] in many reactions, such as the annulation of enals and sulfonylimines, [10,11] the Aza-Morita-Baylis-Hillman reaction of cyclic enones and N-tosylimines, [12] the benzoin condensation, [9,13] the Stetter reaction, [9,13] the Mannich Reaction [15] and the Staudinger reaction [16,17]. These stabilized singlet carbenes behave as nucleophilic organic catalysts, due to the presence of p-donor heteroatoms adjacent to the divalent carbon atom [22].

ILs can be conveniently used in electrochemistry as valid substituents of common solvent-supporting electrolyte systems, as they are molten salts (and so, electrolytes) [23]. Electrochemistry can also be useful in the generation of NHCs from the corresponding IL. In fact, the monoelectronic cathodic reduction of an imidazolium cation leads to the formation of the corresponding carbene and molecular hydrogen (**Scheme 2**) [19,24-26].



B: Et_3N, *t*-BuOK, Cs_2CO_3, KHMDS, etc.

Scheme 1. Chemical generation of NHCs.



Scheme 2. Electrochemical generation of NHCs.

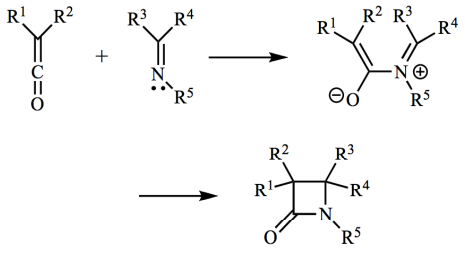
Many reactions have been successfully catalyzed by electrogenerated NHC, such as the Henry reaction, the N-functionalization of benzoxazolones or oxazolidinones, the benzoin condensation, the Stetter reaction and the cyclization of linear amides to *β*-lactams [26,27].

β-Lactams are well known molecules whose importance spreads over many fields, from industrial and chemical to pharmaceutical and biological [28,29]. There are many reactions to form the azetidin-2-one ring, but probably the most important is the Staudinger synthesis. It is described as a [2 + 2] ketene-imine cycloaddition (**Scheme 3**) [30].

Although reported for the first time in 1907, its mechanism is still now uncertain and object of many studies. [31-34]. Both ketene and imine are species that can act as either nucleophiles or electrophiles, depending on their substituents, so the mechanism and outcome (*cis* or *trans* *β*-lactams) depend on the structure of the reagents. However, usually this is a reaction that needs catalysis. [35-37] Among the catalysts, NHCs have been recently used in the Staudinger synthesis [10,16,17,38-40] starting from highly electrophilic imines (e.g., N-Boc, N-Ts and N-*p*Ns imines). These reactions are successfully carried out in classical VOCs, using a disubstituted ketene (pre-prepared) and an electrophilic imine, in the presence of an NHC as organocatalyst.

As reported by Smith and coworkers, [17] the order of addition of reactants is critical to the successful genearation of *β*-lactams, the right order being ketene+NHC and then the imine. In fact, it seems that in these conditions (disubstituted ketene and electrophilic imine in aprotic solvent) a NHC activation of ketene is probable, as confirmed by Ye and coworkers, [16] while the reaction NHC-electrophilic imine leads to a stable adduct (in some cases isolated). On the other hand, Wilhelm and coworkers [38] add all reagents (N-*p*Ns imine, ketene and NHC) in toluene and obtain the desired *β*-lactam, proposing that both activation of ketene and of imine are, in principle, possible and their studies could not rule out one of them.

To the best of my knowledge, only two papers have been published in which the Staudinger synthesis has been carried out in ionic liquids, the first using ytterbium(III) triflate [41] as catalyst in *N*-butylpyridinium tetrafluoroborate, while the second reports the use of an IL-supported imine, [42] an acyl chloride and triethylamine in 1-butyl-3-methylimidazolium hexafluorophosphate; in no case an NHC was used as an organocatalyst in IL.



Scheme 3. The Staudinger synthesis.

In a previous short communication, [43] our first results on a Staudinger synthesis in ionic liquids, from imine and acyl chloride, catalyzed by an electrogenerated NHC were described. Here extension of the method and a hypothesis of mechanism is reported. In this case, 1-butyl-3-methylimidazolium tetrafluoroborate (Bmim-BF_4) acts both as a solvent and as a precatalyst.

2. Experimental

General Procedure

Constant current electrolyses were carried out using 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 spiral (99.9%) and 0.8 cm^2 for the anodic Pt spiral (99.9%). The current density was 15 mA/cm^2. Electrolyses were carried out at 60˚C, under nitrogen atmosphere, using BMIM-BF_4 as anolyte and catholyte. After the consumption of the number of Faradays per mol of imine reported in **Tables 1** and **2**, the current was switched off and imine (1 mmol) was added to the catholyte under stirring; when the dissolution was complete, phenylacetyl chloride (1 mmol) was added. The mixture was kept at 60˚C for 2 h. In the cases in which triethylamine was necessary (see **Tables 1** and **2**), NEt_3 was added to the catholyte with the imine. The catholyte was extracted with diethyl ether, the solvent was removed under vacuum and the residue was analyzed by ^{1}H-NMR and purified by flash-chromatography, affording the corresponding pure *β*-lactam. All *β*-lactams are known compounds and gave spectral data in accordance with the ones reported in the literature. Recycling of the catholyte: after the ethereal extraction, the catholyte was kept under reduced pressure at 60˚C for 1 hr to eliminate completely diethyl ether traces, then it was reused for a new electrolysis.

Trans **1,3,4-Triphenylazetidin-2-one 2a.** [44] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38 - 7.21 (m, 14H), 7.09 - 7.02 (m, 1H), 4.95 (d, J = 2.5 Hz, 1H), 4.27 (d, J = 2.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.6, 137.5, 137.4, 134.7, 129.3, 129.1, 129.0, 128.6, 127.9, 127.4, 125.9, 124.0, 117.2, 65.1, 63.7. $C_{21}H_{17}NO$: calcd. C 84.25, H 5.72, N 4.68; found C 83.84, H 6.03, N 4.52.

Trans **1-(4-Methoxyphenyl)-3,4-diphenylazetidin-2-one 2b.** [44] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 - 7.24 (m, 12H), 6.78 (d, J = 9.2 Hz, 2H), 4.89 (d, J = 2.2 Hz,

1H), 4.24 (d, J = 2.2 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.9, 156.1, 137.6, 134.8, 131.0, 129.2, 129.0, 128.6, 127.8, 127.4, 125.9, 118.5, 114.3, 65.1, 63.8, 55.4. $C_{22}H_{19}NO_2$: calcd. C 80.22, H 5.81, N 4.25; found C 80.04, H 6.12, N 4.21.

Trans **1,4-bis(4-methoxyphenyl)-3-phenylazetidin-2-one 2c.** [44] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 - 7.27 (m, 9H), 6.93 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.88 (d, J = 2.4 Hz, 1H), 4.25 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.2, 159.9, 156.1, 135.0, 131.1, 129.4, 129.0, 127.8, 127.5, 127.3, 118.6, 114.7, 114.3, 65.2, 63.6, 55.4, 55.3. $C_{23}H_{21}NO_3$: calcd. C 76.86, H 5.89, N 3.90; found C 76.67, H 6.11, N 3.77.

Trans **1-(4-methoxyphenyl)-4-(4-nitrophenyl)-3-phenyl azetidin-2-one 2d.** [45] ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.41 - 7.24 (m, 7H), 6.84 (d, J = 9.0 Hz, 2H), 5.03 (d, J = 2.6 Hz, 1H), 4.26 (d, J = 2.6 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.3, 156.6, 148.1, 144.9, 134.0, 133.3, 129.4, 128.6, 127.5, 126.9, 124.6, 118.5, 116.3, 65.3, 62.9, 55.5. $C_{22}H_{18}N_2O_4$: calcd. C 70.58, H 4.85, N 7.48; found C 70.41, H 4.93, N 7.32.

3,3-dichloro-1-(4-methoxyphenyl)-4-phenylazetidin-2-one 2e. [46] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46 - 7.43 (m, 3H), 7.35 - 7.26 (m, 4H), 6.86 - 6.82 (m, 2H), 5.48 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.9, 157.3, 131.8, 129.9, 129.3, 129.2, 127.8, 119.5, 114.6, 84.2, 74.1, 55.5. $C_{16}H_{13}Cl_2NO_2$: calcd. C 59.65, H 4.07, N 4.35; found C 59.48, H 4.13, N 4.22.

Trans **1-benzyl-3,4-diphenylazetidin-2-one 2f.** [47] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43 - 7.20 (m, 15H), 4.99 (d, J = 14.8 Hz, 1H), 4.37 (d, J = 2.2 Hz, 1H), 4.22 (d, J = 2.2 Hz, 1H), 3.85 (d, J = 14.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.3, 137.2, 135.6, 135.0, 129.1, 128.9, 128.8, 128.7, 128.6, 127.8, 127.6, 127.4, 126.5, 65.2, 63.1, 44.6. $C_{22}H_{19}NO$: calcd. C 84.31, H 6.11, N 4.47; found C 84.17, H 6.23, N 4.32.

1-benzyl-3,3-dichloro-4-phenylazetidin-2-one 2g. [46] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47 - 7.44 (m, 3H), 7.36 - 7.33 (m, 3H), 7.28 - 7.23 (m, 2H), 7.18 - 7.13 (m, 2H), 4.98 (d, J = 14.8 Hz, 1H), 4.85 (s, 1H), 3.96 (d, J = 14.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.9, 133.5, 131.7, 129.9, 129.1, 128.8, 128.4, 128.1, 128.0, 84.9, 73.3, 45.0. $C_{16}H_{13}Cl_2NO$: calcd. C 62.76, H 4.28, N 4.57; found C 62.68, H 4.32, N 4.51.

Trans **3,4-diphenyl-1-*p*-tolylazetidin-2-one 2h.** [48] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41 - 7.36 (m, 10H), 7.28 - 7.24 (m, 2H), 7.10 - 7.06 (m, 2H), 4.94 (d, J = 2.6 Hz, 1H), 4.27 (d, J = 2.6 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3, 137.7, 134.9, 134.8, 133.7, 129.6, 129.3, 129.0, 128.6, 127.9, 127.5, 125.9, 117.2, 65.1, 63.7, 20.9. $C_{22}H_{19}NO$: calcd. C 84.31, H 6.11, N 4.47; found C 84.02, H 6.13, N 4.32.

Reaction of electrogenerated 1-butyl-3-methylimidazol-2-ylidene with imine 1b.

Preparative electrolysis was carried out as previously described and the current was switched off after 97 C (1 mF). Then, 1 mmol of 4-benzylidene-4-methoxyaniline **1b** was added and the catholyte was kept under stirring at 60°C for two hours. Then the usual workup gave a crude that was purified by crystallization from hexane. The mother liquor gave a mixture of imine **1b** and dimer 1-butyl-2-(1-butyl-2,3-dihydro-3-methyl-1*H*-imidazol-2-yl) -2,3-dihydro-3-methyl-1*H*-imidazole **5** (every attempt to purify **5** led to its decomposition) and column chromatography of the precipitate giave *N*-(4-methoxy phenyl) benzamide **3** and *N*-((1-butyl-1*H*-imidazol-2-yl) (phenyl) methylene)-4-methoxybenzenamine **4**.

***N*-(4-methoxyphenyl)benzamide 3.** [49] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 - 7.85 (m, 2H), 7.8 (bs, 1H), 7.59 - 7.49 (m, 5H), 6.92 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.6, 156.6, 135.0, 131.0, 129.1, 127.4, 126.6, 122.5, 114.5, 55.7. $C_{14}H_{13}NO_2$: calcd. C 73.99, H 5.77, N 6.16; found C 73.78, H 5.85, N 6.02.

***N*-((1-butyl-1*H*-imidazol-2-yl)(phenyl)methylene)-4-methoxybenzenamine 4.** [50] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 - 7.87 (m, 2H), 7.69 - 7.36 (m, 7H), 7.21 - 7.17 (m, 2H), 3.67 (t, J = 7.0 Hz, 2H), 3.19 (s, 3H), 1.70 - 1.62 (m, 2H), 1.41 - 1.34 (m, 2H), .96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.6, 158.9, 143.4, 139.0, 131.9, 129.1, 128.8, 127.0, 124.9, 124.6, 120.1, 60.3, 39.2, 30.0, 19.8, 13.4. $C_{21}H_{23}N_3O$: calcd. C 75.65, H 6.95, N 12.60; found C 75.33, H 7.18, N 12.32.

1-butyl-2-(1-butyl-2,3-dihydro-3-methyl-1*H*-imidazol-2-yl)-2,3-dihydro-3-methyl-1*H*-imidazole 5 in mixture with starting imine **1b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.10 - 6.08 (m, 4H), 3.75 (d, J = 5.9 Hz, 2H), 3.51 (app. t, J = 7.2 Hz, 4H), 3.16 (s, 3H), 1.59 - 1.52 (m, 4H), 1.32 - 1.20 (m, 4H), 0.85 (t, J = 7.2 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 114.3, 113.9, 111.1, 109.9, 43.2, 31.5, 30.3, 19.7, 13.6.

Reaction of electrogenerated 1-butyl-3-methy-limidazol-2-ylidene with phenylacetyl chloride.

Preparative electrolysis was carried out as previously described and the current was switched off after 97 C (1 mF). Then, 1 mmol of phenylacetyl chloride was added and the catholyte was kept under stirring at 60°C for two hours. Then column chromatography of the catholyte gave 1-(1-methyl-1*H*-imidazol-2-yl)-2-phenylethenol **6**.

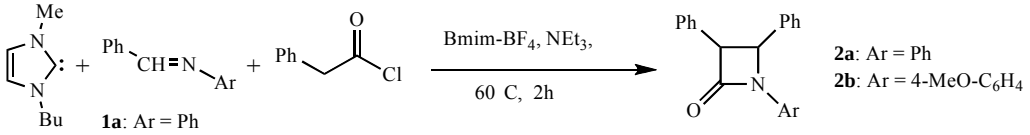
1-(1-methyl-1*H*-imidazol-2-yl)-2-phenylethenol 6. [51] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41 - 7.34 (m, 5H), 7.22 - 7.21 (m, 3H), 6.73 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.1, 132.6, 130.9, 130.1, 129.5, 129.1, 127.9, 119.7, 114.6, 41.0. GC-MS (EI) *m/z*: $M^{+\cdot}$ absent, 144 (1%), 118 (26%), 91 (100%), 77 (2%), 65 (18%), 51 (6%).

3. Results and Discussion

In this work, non-electrophilic imines were used as it is reported that strongly electrophilic imines form an adduct with NHC that seems to be rarely reversible [10,16] (especially in a very polar solvent which should stabilize the zwitterionic adduct). Moreover, having previously proved the behaviour of this NHC as a base, [52,53] an acyl chloride was used instead of pre-generating the corresponding ketene. NHC (1-butyl-3-methylimidazol-2-ylidene) was obtaind by galvanostatic electrochemical reduction of Bmim-BF_4 (**Scheme 2**, R^1 and R^2: Me and Bu). In **Table 1**, entries 1-11, the results are reported using phenylacetyl chloride and *N*-benzylidene-4-methoxy aniline as reagents. The best result (66% of β-lactam, entry 3) was obtained using 0.5 equivalents (theoretical, admitting a 100% current yield) of carbene, with a good diastereomeric ratio (9/91 *cis/trans*); higher or lower amounts of carbene lead to worse results (entries 2-5; the effect of high amounts of carbene seems not readily explainable in a ketene-imine model of reaction, in which the base necessary to yield the ketene should be stoichiometric). The nature of the counter ion of the $Bmim^+$ cation seems to be crucial, with a noticeable decrease in the yields of β-lactam using Bmim-PF_6 or Bmim-CH_3SO_4 (entries 6 and 7).

As reported in the literature [17] (and also in these experiments), the order of addition of the reagents seems very important, but we found an inverted order; the best results were obtained adding the imine to the NHC-IL solution and, after dissolution, adding the acyl chloride. If phenylacetyl chloride is added to NHC-IL and subsequently the imine (entry 8), the yield lowers to 21%, while adding a mixture of acyl chloride-imine-IL to NHC-IL (entry 9) only 24% yield of β-lactam is obtained. Also, the best method to furnish energy to this reaction seems to be heating at 60˚C (3% at room temperature, entry 11), while using ultrasound irradiation just 35% of β-lactam was obtained (entry 10). When the best reaction conditions (entry 3) were used with a less nucleophilic imine (*N*-benzylideneaniline, entries 12 - 18), only 16% of the corresponding β-lactam was reached (entry 13). In this case, the presence of an external base seems necessary and the addition of triethylamine (1 equivalent) gave a

Table 1. NHC-catalyzed Staudinger synthesis in Bmim-BF_4[a].



1a: Ar = Ph
1b: Ar = 4-MeO-C_6H_4

2a: Ar = Ph
2b: Ar = 4-MeO-C_6H_4

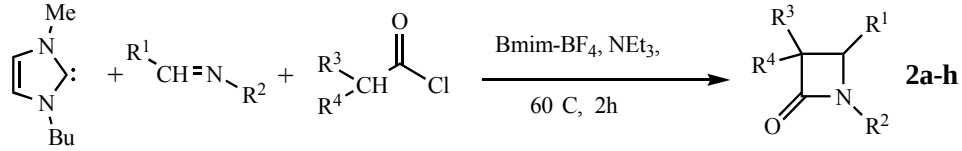
Entry	Ar	F/mol[b]	NEt_3[c]	β-lactam[d]	*cis/trans*[e]	PhCHO[f]	amide[g]
1	*p*-MeO-C_6H_4	-	-	-	-	32%	16%
2	*p*-MeO-C_6H_4	0.30	-	36%	10/90	35%	10%
3	*p*-MeO-C_6H_4	0.50	-	66%	9/91	10%	11%
4	*p*-MeO-C_6H_4	1.00	-	38%	16/84	18%	14%
5	*p*-MeO-C_6H_4	1.70	-	35%	11/89	43%	39%
6[h]	*p*-MeO-C_6H_4	0.50	-	4%	*trans*	21%	12%
7[i]	*p*-MeO-C_6H_4	0.50	-	33%	13/87	8%	6%
8[j]	*p*-MeO-C_6H_4	0.50	-	21%	7/93	63%	37%
9[k]	*p*-MeO-C_6H_4	0.50	-	24%	6/94	12%	12%
10[l]	*p*-MeO-C_6H_4	0.50	-	35%	11/89	21%	13%
11[m]	*p*-MeO-C_6H_4	0.50	-	3%	*trans*	39%	38%
12	Ph	0.15	-	-	-	28%	28%
13	Ph	0.50	-	16%	*trans*	26%	18%
14	Ph	-	1.0	3%	*trans*	20%	16%
15	Ph	0.50	0.3	42%	14/86	47%	31%
16	Ph	0.50	1.0	22%	*trans*	36%	28%
17	Ph	0.15	1.0	64%	11/89	18%	9%
18	Ph	0.15	0.5	55%	11/89	30%	11%

[a]A part of this table has already been reported in ref. 18. Divided cell, Pt anode and cathode, Bmim-BF_4 as solvent/reagent (2 ml as catholyte and 1 ml as anolyte), N_2 atmosphere, 60˚C, galvanostatic conditions (15 mA·cm^{-2}); at the end of the electrolysis, imine (1 mmol) and then phenylacetyl chloride (1 mmol) were added to the catholyte. [b]With respect to starting imine. [c]Triethylamine (1 equivalent) was added to the catholyte with imine. [d]Isolated yields of the mixture of diastereoisomes. [e]The cis/trans ratio was determined by ^{1}H-NMR spectroscopy of the crude mixture. [f]Benzaldehyde was obtained by decomposition of imine. [g]Amide was obtained by reaction of phenylacetyl chloride with amine obtained by decomposition of imine. [h]In Bmim-PF_6. [i]In Bmim-CH_3SO_4. [j]Phenylacetyl chloride was added before the addition of imine. [k]Phenylacetyl chloride and imine were mixed together in a small amount of ionic liquid before their addition to the catholyte. [l]Ultrasound irradiation was used, instead of keeping the reaction mixture at 60˚C. [m]Reaction carried out at room temperature.

good yield (entry 17, 64% with a *cis/trans* ratio of 11/89) only lowering the amount of carbene to 0.15 theoretical equivalents. Again, it is diffucult to understand the different behaviour of NHC varying the imine in a ketene-imine model of reaction (NHC should deprotonate the same acyl chloride in both cases).

The presence of NHC as an organocatalyst seems necessary also using triethylamine; in fact, using solely NEt_3 in Bmim-BF_4 only 3% of β-lactam was isolated (entry 14). It has to be underlined that Bmim-BF_4 behaves with imines not only as a solvent. In fact, when this reaction is carried out in the absence of both NHC and triethylamine (**Table 1**, entry 1), part of the starting imine decomposes into its constituents (aldehyde and amine) and the same behaviour is obtained in the presence of NHC and base (**Table 1**, all other entries), although in these cases it is difficult to rule out a participation of these two reagents. To better understand this reaction, which seems to be hardly explained with reported models, this methodology was extended to imines of different nucleophilicity and to dichloroacetyl chloride using two different sets of experimental conditions (depending on the starting imine). These results are reported in **Table 2**. The yields of β-lactams obtained in the absence of triethylamine are sometimes higher than the stoichiometric 50% value (**Table 2**, entries 3, 5, 9, 11 and 13), assuming that electrogenerated NHC acts as a base with acyl chloride to yield the corresponding ketene; in fact, hypothesizing a current yield of 100% in the electroreduction of the $Bmim^+$ cation, with the generation of 0.5 equivalents of carbene in a monoelectronic process (0.5 F/mol of imine, odd entries of **Table 2**), the theoretical maximum amount of ketene (obtained by NHC-deprotonation of the acyl chloride) is 0.5 equivalents, corresponding to a maximum yield of 50% of β-lactams. These results are therefore not in line with a ketene-imine model of reaction. It should be considered, however, that Bmim-BF_4 is not a neutral solvent for imines; in fact (**Table 1**, entry 1), as previously stated, this IL is able to decompose this molecule into its constituents, aldehyde and amine (and the amine is isolated as amide, after reaction with the acyl chloride). It is therefore possible that the amine, which derives from the decomposition of the imine, takes part in the Staudinger synthesis, enhancing the yields.

Table 2. NHC-catalyzed Staudinger reaction in Bmim-BF_4[a].



Entry	R^1	R^2	R^3	R^4	F/mol[b]	NEt_3[c]	β-lactam[d]	*cis/trans*[e]
1	Ph	Ph	Ph	H	0.50	-	**2a**, 16%	trans
2	Ph	Ph	Ph	H	0.15	1 eq.	**2a**, 64%	11/89
3	Ph	4-MeO-C_6H_4	Ph	H	0.50	-	**2b**, 66%	9/91
4	Ph	4-MeO-C_6H_4	Ph	H	0.15	1 eq.	**2b**, 32%	trans
5	4-MeO-C_6H_4	4-MeO-C_6H_4	Ph	H	0.50	-	**2c**, 65%	6/94
6	4-MeO-C_6H_4	4-MeO-C_6H_4	Ph	H	0.15	1 eq.	**2c**, 22%	trans
7	4-NO_2-C_6H_4	4-MeO-C_6H_4	Ph	H	0.50	-	**2d**, 23%	22/78
8	4-NO_2-C_6H_4	4-MeO-C_6H_4	Ph	H	0.15	1 eq.	**2d**, 33%	trans
9	Ph	4-MeO-C_6H_4	Cl	Cl	0.50	-	**2e**, 63%	
10	Ph	4-MeO-C_6H_4	Cl	Cl	0.15	1 eq.	**2e**, 14%	
11	Ph	Ph-CH_2	Ph	H	0.50	-	**2f**, 56%	21/79
12	Ph	Ph-CH_2	Ph	H	0.15	1 eq.	**2f**, 22%	35/65
13	Ph	Ph-CH_2	Cl	Cl	0.50	-	**2g**, 61%	
14	Ph	Ph-CH_2	Cl	Cl	0.15	1 eq.	**2g**, 30%	
15	Ph	4-Me-C_6H_4	Ph	H	0.50	-	**2h**, 9%	trans
16	Ph	4-Me-C_6H_4	Ph	H	0.15	1 eq.	**2h**, 68%	9/91

[a]Divided cell, Pt anode and cathode, Bmim-BF_4 as solvent/reagent (2 ml as catholyte and 1 ml as anolyte), N_2 atmosphere, 60°C, galvanostatic conditions (15 mA·cm^{-2}); at the end of the electrolysis, imine (1 mmol) and then acyl chloride (1 mmol) were added to the catholyte. [b]With respect to starting imine. [c]Triethylamine (1 equivalent) was added to the catholyte with imine. [d]Isolated yields of the mixture of diastereoisomes. [e]The cis/trans ratio was determined by ^{1}H-NMR spectroscopy of the crude mixture.

Following this hypothesis, it is possible to correlate the yields of *β*-lactams with the basicity of the amine released in the cathodic solution from the decomposition of starting imine. Concerning this matter, Johnson [1] reports that "Bases in ionic liquids appear to act in accordance with their gas phase proton affinities" instead of behaving in line with their pK_bs in water. In **Table 3** the values of pK_a of the conjugate ammonium ions (BH^+) are reported, in water and DMSO, along with the values of the gas phase proton affinities of the amines (B) used in this paper.

The three basicity scales are quite concordant. From **Table 2**, it can be seen that in the cases of aniline and 4-Me-aniline (entries 1 and 15) the yields of *β*-lactams are low (16% and 9%, respectively), while adding NEt_3 (entries 2 and 16) these products are obtained in good yields (64% and 68%, respectively). These last experiments confirm that the yields of *β*-lactams (in all cases of this paper) are not dependent on the imine structure, but on the strength of the base. In the cases of 4-MeO-aniline and benzylamine (**Table 2**, entries 3 and 5) the yields of *β*-lactams (in the absence of NEt_3) are higher than stoichiometric (66% and 65%, respectively), explicable only admitting that the amine (which derives from the decomposition of starting imine) plays a role in this reaction and that in these two cases the amines have a sufficient basicity to carry on the synthesis. An excess of base leads to the decomposition of the starting material (**Table 2**, entries 4 and 6, synthesis carried on in the presence of triethylamine) and to a lowering in the yields of product (32% and 22%, respectively).

In this way, it can be therefore located a border in the basicity value (between 215 and 217 kcal mol^{-1}, if expressed by means of gas phase proton affinity), below which the amine present in the reaction mixture is not able to catalyze this Staudinger synthesis.

In order to have an insight into the mechanism of this NHC-catalyzed Staudinger synthesis in IL, we have carried out two different reactions, the first between electrogenerated NHC and imine **1b** and the second between NHC and phenylacetyl chloride. These experiments were carried out to understand if electrogenerated NHC reacts preferentially with one of the two reagents.

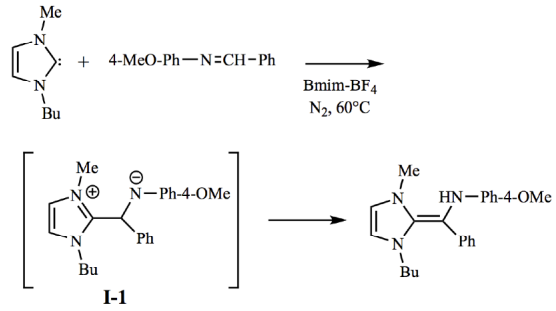
Table 3. pK_a Values of ammonium ions and gas phase proton affinities of amines [54-60].

Entry	Amine (B)	pK_a (BH^+) in H_2O	pK_a (BH^+) in DMSO	PA (kcal mol^{-1})[a]
1	aniline	4.58	3.82	213.39
2	4-Me-aniline	5.08	4.5	215.13
3	4-MeO-aniline	5.34	5.08	216.96
4	benzylamine	9.38	10.16	218.07
5	triethylamine	10.72	9.07	229.1

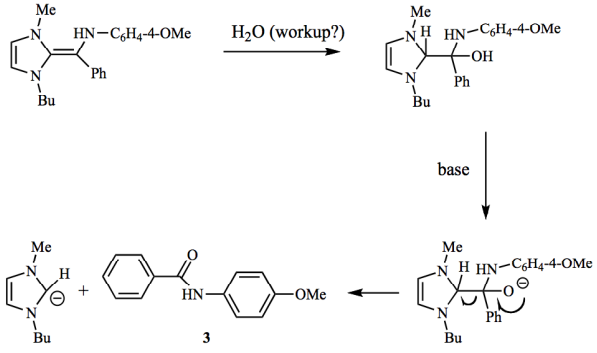
[a]Gas phase proton affinities; the values are reported in kcal·mol^{-1} and not in kJ·mol^{-1} to be faithful with the original literature.

When NHC reacts with *N*-benzylidene-4-methoxyaniline **1b**, the expected product of coupling between the two reagents (a sort of Breslow's intermediate [61] between NHC and imine, see **Scheme 4**) has not been isolated nor evidenced. This kind of intermediate has been previously reported by Ye and coworkers [12,16] using N-Ts imines and it is quite stable, while using a non electrophilic imine this addition has been obtained exclusively by intramolecular way [62] (a molecule containing both carbene and imine moieties).

On the other hand, we decided to use non-electrophilic imines just to avoid the formation of a non-reversible adduct NHC-imine. From this reaction (electrogenerated NHC and imine) three products (along with unreacted imine), after workup and column chromatography, have been obtained (see **Figure 1**). It is speculated that both products **3** and **4** have reference with the adduct of **Scheme 4**; in fact (**Scheme 5**) this adduct can add a molecule of water and, in a base-catalyzed decomposition, give rise to the formation of amide **3**. Product **4** is less easy to be explained and it seems closely correlated to the adduct of **Scheme 4**, but it has to be kept in mind that the electrochemical reduction of imidazolium salts leads often to dealkylation products. [24]



Scheme 4. Addition reaction between NHC and imine 1b.



Scheme 5. Hypothesis of mechanism of formation of product 3.

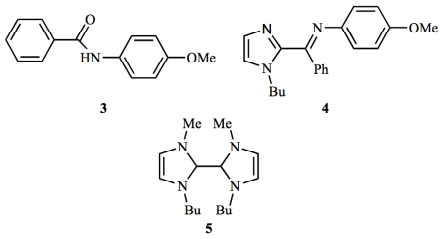


Figure 1. Products of the reaction between NHC and imine 1b.

Product **5**, finally, seems to derive from a dimerization reaction during the electrochemical process. [63] It has to be stressed that this dimerization reaction is not active (only traces are detected) when both reagents (imine and acyl chloride) are added to the catholyte and the Staudinger product is obtained.

The reaction between electrogenerated NHC and phenylacetyl chloride gave, among many decomposition products, compound **6** (**Figure 2**).

The formation of this molecule can be explained hypothesizing the reaction between NHC and the acyl chloride (**Scheme 6**), with a successive Hofmann elimination. Intermediates similar to **I-2** have been hypothesized by many authors, [11,15,64,65] but never isolated. It cannot be excluded that product **6** is an artefact of the column chromatography used trying to isolate possible addition products. However, Townsend and coworkers [66] report that the hydrolysis of a 2-acylated NHC leads to the formation of the corresponding carboxylic acid; indeed we evidenced the formation of phenylacetic acid in this experiment, but we cannot exclude a simple hydrolysis of acyl chloride during the workup.

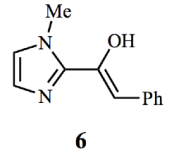
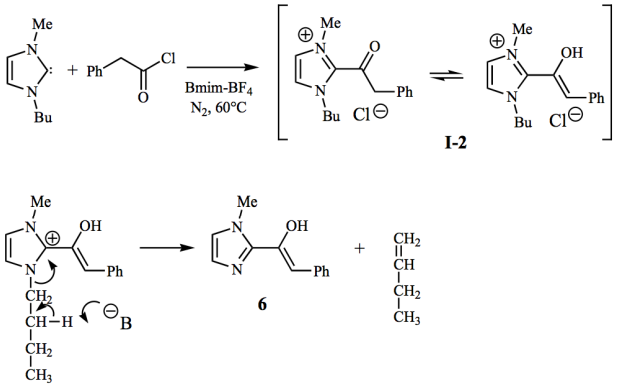


Figure 2. Product of the reaction between NHC and phenylacetyl chloride.

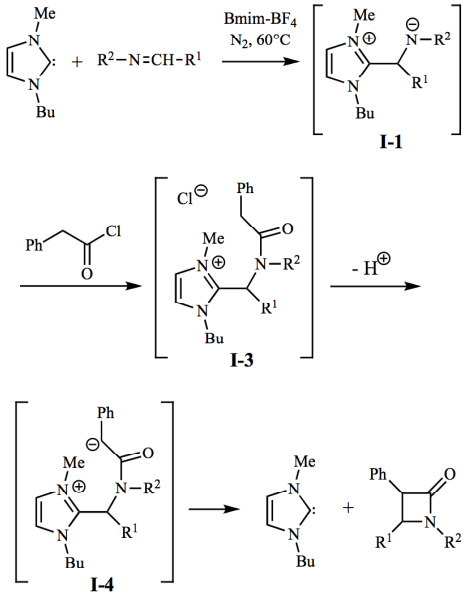


Scheme 6. Hypothesis of mechanism of formation of product 6.

From these results, it seems difficult to understand the mechanism of this Staudinger synthesis. It is speculated that that the first reaction of electrogenerated NHC is not with acyl chloride to yield the corresponding ketene, both because if the acyl chloride is added to the catholyte before the imine, β-lactam can be isolated in very low yields and because the formation and yields of β-lactams depend exclusively on the nature of amine and not on the nature of the imine present in the reaction mixture (see **Table 2**, entries 1 vs 2 and 15 vs 16), for the same acyl chloride. It is thus probable that NHC reacts at first with imine (giving the non stable intermediate **I-1**, reported also in **Scheme 4**) and successively this intermediate reacts with the acyl chloride to give intermediate **I-3** (**Scheme 7**).

Intermediate **I-3** has to be deprotonated in the 2-position (with respect to the carbonyl group) to yield the corresponding β-lactam; the "acidic" methylene should suffer from the distal effect of the substituents on the nitrogen atom, [67] *i.e.* the lone pair of electrons of the nitrogen atom of intermediate **I-4** can partecipate in resonance with the carbonyl group: the more the lone pair is available, the more the stabilization of the enolate anion is effective, [68] following the trend for the gas phase proton affinity reported in **Table 3**.

Many papers about the stereochemical outcome of the Staudinger synthesis are reported, trying to indentify the factors that influence the *cis/trans* selectivity. Xu and coworkers [69] report that, being the Staudinger synthesis a multi step one, involving the addition of imine and ketene to give a linear zwitterionic intermediate (**I-4**, in



Scheme 7. Possible mechanism of electrogenerated NHC-catalyzed Staudinger synthesis in ionic liquid.

our hypothesis) and the subsequent ring closure of this intermediate (**Scheme 3**), "the product ratio (*cis/trans*) only depends on the rate constants of the direct ring closure (k_1) and the isomerization (k_2)". In fact, the zwitterionic intermediate can isomerize by rotation along the N-C bond of the imine portion of the intermediate itself.

It seems that when the ring closure of the zwitterion is fast, a *cis* β-lactam is obtained, when it is slow (in comparison with the isomerization) a *trans* product is gained. The competition between these two reactions relies on electronic effects of the substituents on imine and ketene, and on the steric hindrance of the same.

The solvent can play a role in this reaction; in particular, apolar solvents favour *cis* β-lactams, while polar solvents favour *trans* ones, probably because polar solvents stabilize the zwitterionic intermediate, permitting its isomerization. The solvent of this reaction is an ionic liquid, highly polar, and the main product is a *trans* β-lactam, on line with this theory.

As regards the possibility of recycling the cathodic ionic liquid after the isolation of the products, the IL used in **Table 2**, entry 3, was kept under vacuum (to eliminate residual diethyl ether) and used for a new electrolysis. In this case, however, the yield in β-lactam fell to 29%, and only traces of product were obtained during the third cycle. This is probaly due to a gradual degradation of the ionic liquid during the cathodic reduction, with the formation of by-products which could interfere with this synthesis.

4. Conclusions

The first example of synthesis of β-lactams via Staudinger synthesis in ionic liquid catalyzed by an N-heterocyclic carbene is described. This NHC is easily obtained by cathodic reduction of Bmim-BF_4, under galvanostatic conditions, and it behaves as base and/or nucleophilic organocatalyst (so, under these experimental conditions, IL plays the double role of solvent and precatalyst). Good yields of β-lactams, in predominantly *trans* configuration have been obtained starting from non electrophilic imines and acyl chloride and a hypothesis of mechanism is given, not involving the formation of a ketene.

5. Acknowledgements

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