Electrogenerated NHC as an organocatalyst in the Staudinger reaction†

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Electrogenerated *N*-heterocyclic carbene can behave as an organocatalyst in the Staudinger reaction (from imine and acyl chloride) in a very polar solvent, such as an ionic liquid.

N-Heterocyclic carbenes (NHCs) have recently received much attention as organocatalysts[1] in a large variety of reactions, such as the annulation of enals and sulfonylimines,[2] the aza-Morita–Baylis–Hillman reaction of cyclic enones and *N*-tosylimines,[3] the benzoin condensation,[1,4] the Stetter reaction,[1,5] the Mannich reaction,[6] the Staudinger reaction,[7] *etc.*

These stabilized singlet carbenes behave, in fact, as nucleophilic organic catalysts, due to the presence of π-donor heteroatoms adjacent to the divalent carbon atom.[8]

The most common strategy to generate NHCs is the deprotonation of imidazolium, triazolium or thiazolium salts (Scheme 1, chemical route). This deprotonation is carried out by a chemical base (NEt_3, *t*-BuOK, Cs_2CO_3, potassium hexamethyldisilazane (KHMDS), *etc.*, depending on the acidity of the substrate) in a classical molecular solvent (THF, toluene, Et_2O, *etc.*).[1–7]

NHCs can also be generated by electrochemical reduction of suitable imidazolium or thiazolium salts, in a one-electron process (Scheme 1, electrochemical route).[9]

These electrogenerated NHCs have been successfully used as basic catalysts in the synthesis of β-lactams *via* cyclization of linear amides,[9d] in the Henry reaction,[10] *N*-functionalization of benzoxazolones or oxazolidinones,[11] and as nucleophilic catalysts in the benzoin condensation[12] and in the Stetter reaction.[13]

The Staudinger reaction is a well-known [2 + 2] ketene–imine cycloaddition that leads to the formation of the β-lactam skeleton (Scheme 2).[14]

The Staudinger reaction usually starts with the generation of the ketene, generally by dehydrohalogenation of an acyl halide or by the Wolff rearrangement of an α-diazocarbonyl compound, and the reaction between the "*in situ*" generated ketene and an imine in a molecular solvent.[15]

Although Staudinger reported this reaction for the first time in 1907, its mechanism is still controversial, especially with regards to the stereochemical outcome.[16] In fact, the reactivity and the stereochemistry of the products (typically *cis* or *trans* β-lactams) depend on the substituents on the ketene and imine structures. It seems that, after the attack of the imine on the ketene and the formation of a zwitterionic intermediate, the product *cis*/*trans* ratio depends only on the rate constants of the direct ring closure and of the isomerization (rate constants that, therefore, rely on the imine and ketene structures).[16a]

This reaction can also be catalyzed by an organocatalyst, an NHC. In this case again, the mechanism seems to rely on the substituents on the ketene and imine, but in order to obtain good yields, a strongly electrophilic imine seems necessary (N-Ts, N-Boc).[7] The carbene is obtained by deprotonation of the suitable precursor in THF or Et_2O, in the presence of the imine, and the ketene (previously prepared) is added at the end.[7]

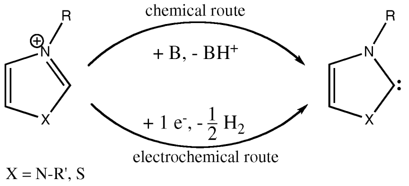
Ionic liquids (ILs) have been described as "green solvents" mainly due to their virtually null vapour pressure, which allows them to be easily recycled, many times.[17] Organic reactions carried out in ILs may follow different pathways with respect to the reactions in classical molecular solvents, due to the ionic structures of ILs which create a very polar environment for reagents, intermediates and products. Only two papers (to the best of our knowledge) report the Staudinger cycloaddition in ionic liquids.[18,19]

In previous papers about the Staudinger reaction, ILs have been employed as precatalysts in the presence of bases in molecular solvents,[7] or as solvents in which a catalyst is used (ytterbium(III) triflate[18] or a task-specific IL[19]).

In this communication we report an easy electrochemical methodology for the synthesis of β-lactams *via* the Staudinger reaction, directly from imine and acyl chloride, in which ILs play the dual role of solvents and precatalysts. Our preliminary results are reported here.

After the galvanostatic cathodic reduction of 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIM\text{-}BF_4$, 0.15 to 0.50 eq. of theoretical electrogenerated carbene), the imine was dissolved in the catholyte at 60 °C, then phenylacetyl chloride was added. After 2 h and usual workup, the corresponding β-lactam was isolated as reported in Table 1.‡

As the reaction between NHCs and strongly electrophilic imines seems to be rarely reversible,[3,7a] especially in a very polar solvent which should stabilize the zwitterionic adduct, we decided to employ less reactive imines.



X = N-R', S
B = NEt_3, *t*-BuOK, Cs_2CO_3, KHMDS, etc.

Scheme 1 Generation of NHCs.

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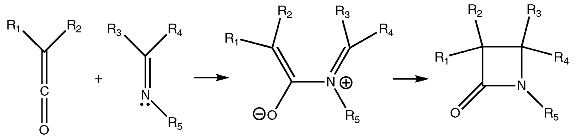
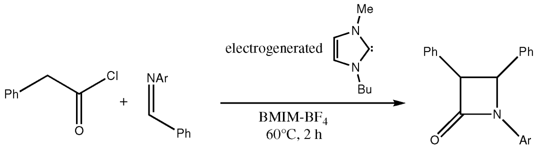


Scheme 2 The Staudinger reaction.

Table 1 NHC-catalyzed Staudinger reaction in BMIM-BF$_4$[a]



Entry	Ar	F/mol	NEt$_3$ (eq)[b]	Yield (%)[c]	*cis*/*trans*
1	*p*-MeO-Ph	—	—	—	—
2	*p*-MeO-Ph	0.30	—	36	10/90
3	*p*-MeO-Ph	0.50	—	66	9/91
4	*p*-MeO-Ph	1.00	—	38	16/84
5	*p*-MeO-Ph	1.70	—	35	11/89
6[d]	*p*-MeO-Ph	0.50	—	4	*trans*
7[e]	*p*-MeO-Ph	0.50	—	33	13/87
8	Ph	0.15	—	—	—
9	Ph	0.50	—	16	*trans*
10	Ph	—	1.0	3	*trans*
11	Ph	0.50	0.3	42	14/86
12	Ph	0.50	1.0	22	*trans*
13	Ph	0.15	1.0	64	11/89
14	Ph	0.15	0.5	55	11/89

[a] Divided cell, Pt electrodes, BMIM-BF$_4$ as anolyte and catholyte, N_2 atmosphere, 60 °C, galvanostatic conditions (15 mA cm^{-2}); at the end of the electrolysis, imine and acyl chloride were added to catholyte. [b] Triethylamine (when necessary) added with imine. [c] Isolated yield of the mixture of diastereomers. The *cis*/*trans* ratio was determined by ^{1}H-NMR spectroscopy of the crude mixture. [d] In BMIM-PF$_6$. [e] In BMIM-CH$_3$SO$_4$.

When the imine was *N*-benzylidene-4-methoxyaniline, a good yield (66%) of β-lactam was obtained with 0.5 equivalents (theoretical) of carbene (entry 3), with a 9/91 *cis*/*trans* ratio.[20] This result suggests that the NHC can behave both as an organocatalyst and as a base (as we did not previously prepare the ketene). Higher or lower amounts of NHC did not improve the reaction (entries 2–5); if the reaction was carried out at rt, the yield decreased to 3%, while if ultrasound irradiation was used (instead of 60 °C), the yield was 35%. As reported in the literature, the addition order of the reagents is very important in this reaction; in fact, if the acyl chloride was added first, as well as if imine and acyl chloride were mixed before the addition, the β-lactam was isolated in lower yields (21% and 24% respectively). Also the anion of the IL plays a crucial role: when $CH_3SO_4^-$ or PF_6^- were used instead of BF_4^-, the yields decreased drastically (entries 6 and 7) ($CH_3SO_4^-$ seems to act as methylating agent). The addition of a base (as reported in the literature) does not improve the yields (32% with 1 eq. NEt$_3$).

If *N*-benzylideneaniline (a less nucleophilic imine) is used, a low yield of β-lactam is obtained (entries 8 and 9) and the presence of a base, NEt$_3$, seems necessary (entries 10–14); on the other hand, the presence of NHC is essential, as NEt$_3$ alone is not efficient (entry 10), and in this case the NHC seems to act exclusively as an organocatalyst (entry 13). The nucleophilicity of the imine nitrogen atom therefore plays a crucial role and we think that, in this case, the mechanism of NHC catalysis is different from the one reported in the literature using strongly electrophilic imines. In fact, when *N*-benzylidene-4-methoxyaniline is used, *N*-(4-methoxyphenyl)-2-phenylacetamide (11% in entry 3) is obtained as a by-product, suggesting a direct attack of the imine on the carbonyl group of the ketene as in the catalyzed version of the Staudinger reaction.

In conclusion, we have reported the first example of the Staudinger reaction in an IL (in the dual role of solvent and precatalyst), catalyzed by NHC, starting from non-electrophilic imines. We are now studying the role of this electrogenerated carbene in the reaction mechanism and the extension of this reaction to other substrates.

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Notes and references

‡ Experimental 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 a nitrogen atmosphere, using BMIM-BF$_4$ as anolyte and catholyte. After the consumption of the number of Faradays per mol of imine reported in Table 1, 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 Table 1), 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 spectroscopy and purified by flash-chromatography, affording the corresponding pure β-lactam. All β-lactams are known compounds and gave spectral data in accordance with those reported in the literature.

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20 The authors of ref. 18 report the action of IL *N*-butylpyridinium tetrafluoroborate as a base in the Staudinger reaction (34% of β-lactam in the absence of $Yb(OTf)_3$). We are not able to exclude such an eventuality also using $BMIM\text{-}BF_4$ as an IL, which could account for the non-stoichiometric amount of β-lactam (66%) with respect to the amount of carbene (0.5 eq.). In our procedure the use of NHC is, however, necessary (see Table 1, entry 3 *vs.* entry 1) to obtain the product.