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Electrogenerated *N*-Heterocyclic Carbenes in the Room Temperature Parent Ionic Liquid as an Efficient Medium for Transesterification/Acylation Reactions

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N-Heterocyclic carbenes (NHCs), generated by electrochemical reduction under galvanostatic control of 1,3-dialkylimidazolium-based ionic liquids, were employed as catalysts in transesterification reactions in the parent, room temperature ionic liquids (RTILs) as solvents, without the utilisation of any volatile organic solvent or base. The reaction between isopropenyl or ethyl acetate and an alcohol (not efficient in the absence of catalyst) was induced by the presence of an electrogenerated NHC, which seems to assist the proton transfer from the alcohol to the ester, yielding the corresponding acetate. The reaction also proceeds with methyl nicotinate as starting ester and 2-(diethylamino)ethanol or benzyl alcohol as alcohols and leads to the corresponding biologically active compounds, nicametate and benzyl nicotinate, in good yields. All products were isolated in good to excellent yields and complete recyclability of the ionic liquid as solvent has been demonstrated.

Introduction

The remarkable ubiquity of the ester function in chemistry, its utilization as a protecting group and the significant role of esters as intermediates in organic chemistry have been frequently emphasised.[1] Usually, esters are synthesised from carboxylic acids and alcohols, either in the presence of a condensing agent or directly under harsh reaction conditions. The transesterification reaction (i.e., alkoxy moiety exchange between an ester and an alcohol) is regarded as a more advantageous procedure than ester synthesis from carboxylic acids and alcohols and it could represent an efficient alternative route. In fact, it should be borne in mind that some carboxylic acids are not very soluble in organic solvents and/or are labile or difficult to isolate. In addition, some esters (particularly methyl or ethyl esters) are often more readily and commercially available starting materials than the carboxylic acids.[2]

Transesterification reactions catalyzed by acid or base, organometallic catalysts, as well as by enzymes, have been the subject of extensive investigations. Nevertheless, some authors have reported possible limits and complications related to these catalysts such as low substrate selectivity, formation of byproducts, acid- or base-sensitivity of the substrate, toxicity and cost of the catalysts, and high catalyst loadings. Therefore, remarkable efforts have been made to discover new catalysts.

N-Heterocyclic carbenes (NHCs)[3] have attracted considerable interest as non-toxic and non-pirophoric ligands (phosphane mimics) in organometallic chemistry[4] as well as organocatalysts.[5] The NHC-catalyzed transesterification reaction has been reported by Nolan and co-workers[6] and, independently, by Hedrick and co-workers.[7,8] In the classical procedures of NHC-catalyzed transesterification, substituted alkyl- and/or aryl-imidazolium-2-ylidenes have been synthesised in an independent route, following the Arduengo procedure {NaH in THF and catalytic amounts of dimsyl anion [$^-CH_2S(O)CH_3$]}.[3d]

Alternatively, *N*-heterocyclic carbenes have been generated in situ by deprotonation of their salts in organic solvents containing a suitable strong base, generally KO*t*Bu, NaH, or an organic base such as 4-(dimethylamino)pyridine (DMAP),[9] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[10] or 1,4-diazabicyclo[2.2.2]octane (DABCO).[11] However, the use of these bases might be problematic for more sensitive substrates.[2a,12]

Therefore, the imidazolium salts can be regarded as precatalysts in the transesterification reactions. Following this idea, an extensive investigation on the reaction conditions has been performed, focusing on the influence of the nature of the ester and of the alcohol, on the structure of the precatalyst, and on the effect of base, solvent, and temperature on the product yields and on the reaction times.[13] Accordingly, other authors have recently reported a new strategy

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aimed at the separation, recovery and reuse of NHC-catalysts in transesterification reactions (benzene as solvent; ImesHCl, KO*t*Bu as precatalyst; 80 °C).[14]

In this context, many authors have remarked on the need for an extensive study to establish environmentally friendly and more sustainable synthetic procedures. Particular targets in these investigations are the development and use of benign "green" solvents (instead of the volatile, toxic, or hazardous chemicals) and catalysts.[15]

Room temperature ionic liquids (RTILs), for example substituted imidazolium, pyrrolidinium, and thiazolium salts, owing to their specific properties (chemical and thermal stability, solvating ability, etc.) have been frequently used as "green" reaction media in clean organic synthetic procedures as substitutes for conventional, toxic and volatile organic solvents (VOCs).[16] Therefore, the use of an imidazolium salt as both solvent and as a precursor of an NHC reagent is possible and could be a valid alternative in the synthetic procedure.

During the last years, we have generated *N*-heterocyclic carbenes by cathodic reduction of suitable ionic liquids in the absence of bases and organic solvents. The electrolyzed RTILs have been utilized as solvent/catalyst systems in some *N*-heterocyclic carbene catalyzed reactions, including the benzoin condensation, the Staudinger reaction, γ-butyrolactone synthesis, and the Stetter reaction.[17]

Herein, we wish to report the results of a subsequent investigation concerning the possible utilization of an electrogenerated NHC/RTIL system as reaction medium in the transesterification/acylation reaction.

Results and Discussion

As part of our efforts towards the development of environmentally friendly electrochemical methodologies in ionic liquids, based on the use of imidazolium salts as both solvent and precatalyst,[17] we have investigated the possibility of obtaining esters by transesterification reaction catalyzed by electrogenerated NHC. The advantages of this methodology lie in the use of a deprotonating reagent, the electron, which is inexpensive, easy to dose, and does not typically result in byproducts, in a very polar solvent (the ionic liquid), which could stabilize dipolar intermediates and favour the outcome of the reaction. Moreover, the use of a solvent with virtually null vapour pressure allows its easy reuse, which can be regarded as an important synthetic goal.[18]

The intrinsic chemistry of imidazolium-based room temperature ionic liquids, related to the acidity of the C-2 position in the imidazolium cation **I**, can be modified by cathodic cleavage of this C–H bond. In fact, the monoelectronic galvanostatic reduction of an imidazolium salt **1a**–**c** (Figure 1) at a Pt cathode, in a divided cell, leads to the formation of the corresponding NHC **II** and molecular hydrogen [Scheme 1, Equation (1)].[7,9] The addition of alcohol **3** to the catholyte, followed by ester **2**, gives the corresponding product **4** [Scheme 1, Equation (2)].

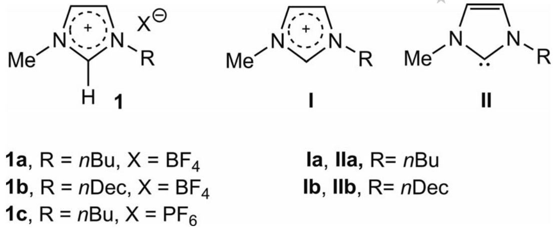
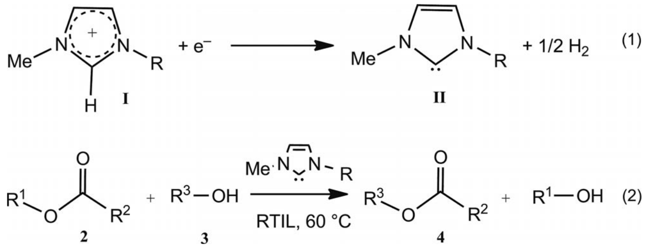


Figure 1. Ionic liquids and NHC used as solvents, precatalysts and catalysts.



Scheme 1. General scheme for the reaction.

In preliminary studies, we have used isopropenyl acetate **2a** and benzyl alcohol **3a** as model substrates. 1-Butyl-3-methylimidazolium tetrafluoroborate (BMIM-BF_4; **1a**) was electrolyzed under galvanostatic control (I = 15 mA cm^{-2}) in a divided cell (Pt as cathode and anode; T = 60 °C) with continuous bubbling of N_2 (Figure 2); after the consumption of 0.35 Faradays mol^{-1} of alcohol, the current was switched off and a mixture of ester **2a** and alcohol **3a** (mol ratio **2a**/**3a** ρ = 3:1, see below) was added to the catholyte (Scheme 2). The resulting solution was stirred at 60 °C for 2.0 h to afford, after subsequent workup, benzyl acetate **4a** (isolated yield 52%). When a solution of nonelectrolyzed BMIM-BF_4 containing a mixture **2a**/**3a** (mol ratio 3:1) was stirred at 60 °C for 2.0 h, no ester **4a** was isolated and **2a** and **3a** were completely recovered from the solution.

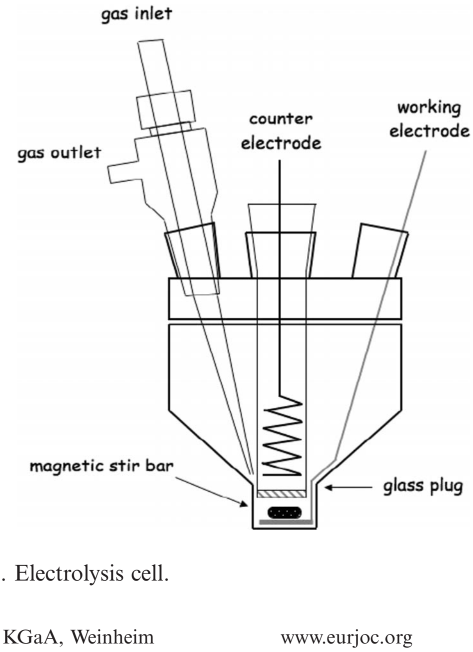
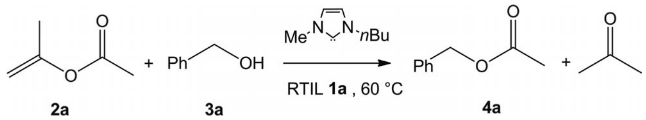


Figure 2. Electrolysis cell.



Scheme 2. Electrogenerated NHC in the acetylation reaction.

These results showed the requirement for a catalyst in the reaction and the ability of electrogenerated NHC, in the parent BMIM-BF_4, to assist the proton transfer from alcohol to ester.

The yield of ester **4a** is affected by many factors such as RTIL, Faradays per mol of alcohol, and mol ratio ester/alcohol. Moreover, we should consider that the transesterification process is an equilibrium so it is advisable to vary the reaction parameters to shift the equilibrium towards the desired direction. The initial choice of isopropenyl acetate **2a** as acylating agent was targeted to remove the alkoxide byproduct from the equilibrium; in fact, it is rapidly converted into the low-boiling acetone, shifting the equilibrium towards the product.[6]

First, we investigated the effect of the mol ratio ester/alcohol on the equilibrium of transesterification. We verified that when the concentration of **3a** was kept constant, a increase in the mol ratio from 1 to 3, promoted an increase in the yield of isolated **4a**, according to the shift of the transesterification equilibrium in the direction of **4a**, respectively from 45 to 92% yield. Further increases caused a significant decrease in the atom economy of the overall process, but did not noticeably affect the yield of **4a**.

We then analyzed the effect of the number of Faradays per mol of **3a** consumed at the electrodes (*Q*), i.e., of the amount of NHC. The chemical yield of isolated **4a** was found to increase with increasing *Q* (Figure 3). As regards this last matter, we think that the efficiency of the reaction yielding NHC [Scheme 1, Equation (1)] could be significantly affected by several factors: (i) the non-Faradaic component of the whole measured number of Faradays (*Q*); (ii) the presence, in the RTIL, of cathodically reducible impurities; (iii) the stability of electrogenerated NHC, which could be removed from the catalytic cycle through formation of dimers.[19] Considering that the *N*-heterocyclic carbene has been obtained by monoelectronic cathodic reduction of **1a**, the value of *Q* (number of Faradays per mol of alcohol **3a** supplied to the electrode) is, in any case, greater than the number of mol of electrogenerated NHC per mol of alcohol **3a** (really present and operating as catalysts). Nevertheless, the mol ratio carbene **IIa**/substrate **3a** in any case increases on increasing *Q*.

The optimum for the electrochemical efficiency was estimated to be $Q = 0.5\,\mathrm{F\,mol^{-1}}$. Therefore, applying the most suitable experimental conditions (mol ratio **2a**/**3a** of 3:1, $BMIMBF_4$ as RTIL and $0.5\,\mathrm{F\,mol^{-1}}$ of charge), the yield of isolated **4a** was 92% [with $0.7\,\mathrm{F\,mol^{-1}}$ the yield of **4a** was only slightly higher (95%); Figure 3]. Following the described protocol, comparable results were achieved by utilizing ionic liquids **1b** and **1c** (yield of isolated **4a**: 73 and 93%, respectively).[20]

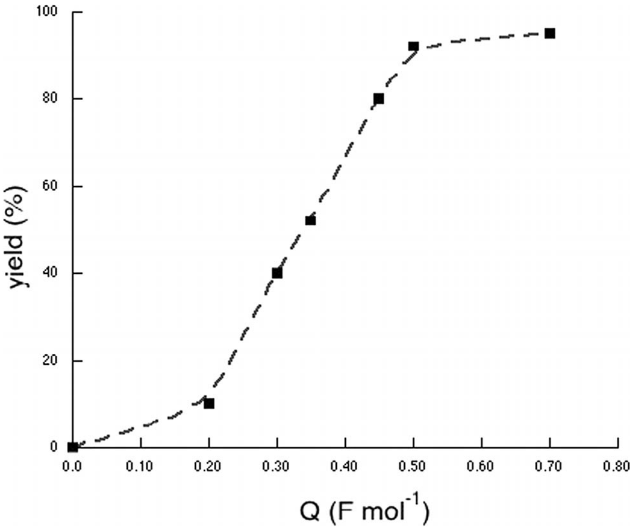


Figure 3. Yield of the isolated product **4a** vs. *Q* (number of Faradays per mol of alcohol **3a** supplied to the electrodes), in BMIM-BF_4 **1a** and electrogenerated carbene **IIa**.

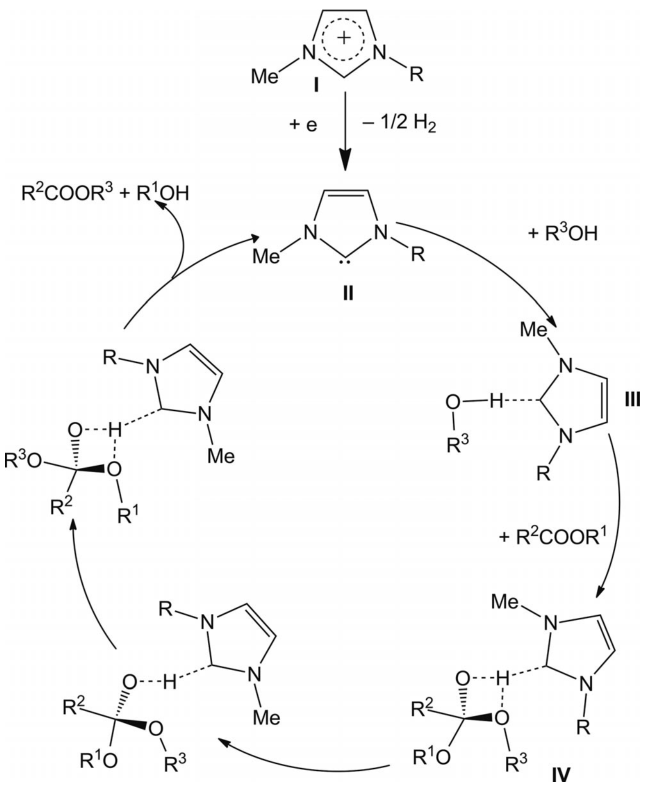
These results emphasise the fact that the NHC-catalyzed transesterification reaction can be carried out in electrolyzed ionic liquids in the absence of classical organic solvents and bases. Therefore, the electrogenerated-NHC/RTIL system as reaction medium is very efficient in this transesterification reaction.

In agreement with the mechanism proposed by a number of authors,[14,21] the NHC-catalysed transesterification can be considered to be a catalytic cycle based on the interaction of the *N*-heterocyclic carbene **II** and an alcohol forming a hydrogen-bonded complex **III**. The role of the NHC is to assist the proton transfer from alcohol to the carbonyl oxygen of the ester (via the hydrogen-bonded carbene-alcohol complex) forming the tetrahedral intermediate **IV**, which then evolves into the product (Scheme 3).[21a]

The strength and the nature of the hydrogen bond interaction and, consequently, the efficiency of a specific NHC to facilitate proton transfer are related to the nature of both alcohol and solvent.[22] Our results suggest a significant ability of *N*-heterocyclic carbene **IIa** to assist the proton transfer, from alcohol to ester, particularly when **1a** and **1c** are used as solvents.

A major advantage of the use of an ionic liquid as reaction medium is that the solvent can be recovered and recycled in subsequent runs. The ease of recovery of the ionic liquid is strongly affected by its nature as well as by the synthetic methodology used. In fact, recovery protocols should be established for each synthetic procedure. Therefore, the possible reuse of the ionic liquid in this system has been investigated. After ethereal extraction of the catholyte (using $BMIMBF_4$, after 0.5 F/mol each time) the catholyte itself was held under vacuum to eliminate diethyl ether traces and reused in subsequent electrolyses.

Ester **4a** was isolated as the only product up to ten times, in very high yields, confirming the usefulness of this "green" electrochemical methodology (Figure 4).



Scheme 3. Proposed mechanism for the transesterification.[21a]

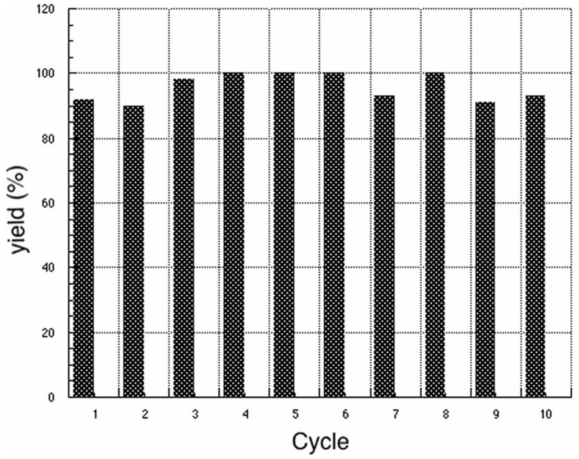


Figure 4. Recycling RTIL **1a** and the yield of isolated **4a** in ten subsequent runs.

To test the generality of this transformation, the reactivity of alcohols **3b**–**l** vs. **2a** has been investigated; the reaction was carried out by using the simple protocol described above. We have verified the considerable efficiency of the procedure with both benzyl (irrespective of the nature of the substituent on the aromatic ring; Table 1, entries 1–9) and aliphatic alcohols (Table 1, entries 10–12). To extend the applicability of the reaction, we also investigated the reactivity of ethyl acetate **2b**, commonly used as solvent and readily and commercially available, vs. alcohols **3a**–**d**. Under these conditions the corresponding esters were isolated in elevated yields (Table 1, entries 13–16).

This methodology can also be applied to acylation reactions other than acetylation. In this case, when the acyl part of the molecule is more valuable, it is advisable to use the starting ester and alcohol in a 1:1 mol ratio (sacrificing the yield) or to use an excess of alcohol (instead of ester). So the reaction between methyl benzoate **2c** and benzyl alcohol **3a** in a 1:1 mol ratio leads to the formation of benzyl benzoate **4m** in 63% yield (Table 1, entry 17), whereas the reaction between methyl nicotinate **2d** and benzyl alcohol **3a** leads to the formation of benzyl nicotinate **4n** in 62% yield (mol ratio **2d/3a** 1:2, Table 1, entry 18). Using a less reactive alcohol, for example, 2-(diethylamino)ethanol (**3m**), the corresponding nicametate **4o** was obtained in 45% yield by

Table 1. NHC-catalyzed transesterification reaction of esters and alcohols in $BMIMBF_4$.[a]

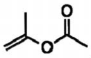
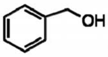
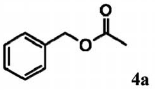
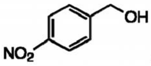
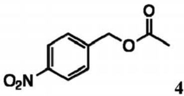
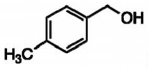
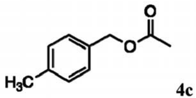
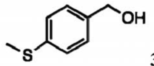
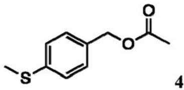
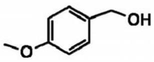
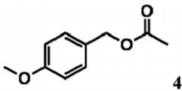
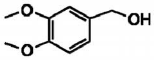
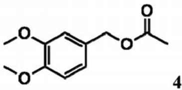
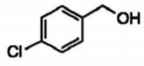
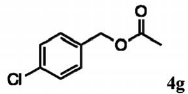
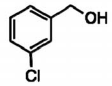
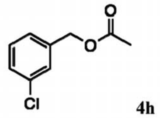
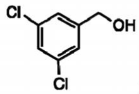
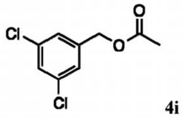
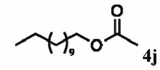
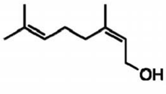
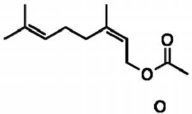
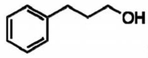
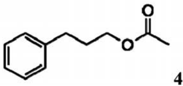
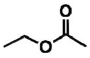
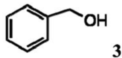
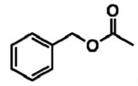
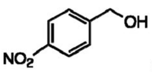
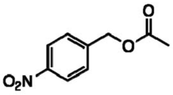
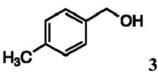
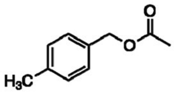
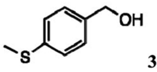
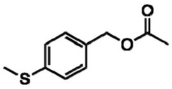
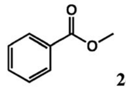
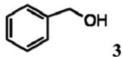
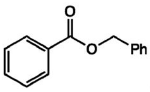
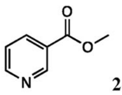
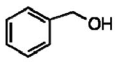
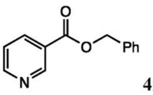
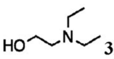
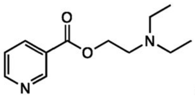
Entry	Ester	Alcohol	Product	Yield [%][b]
1	 **2a**	 **3a**	 **4a**	92
2	**2a**	 **3b**	 **4b**	98
3	**2a**	 **3c**	 **4c**	98
4	**2a**	 **3d**	 **4d**	98
5	**2a**	 **3e**	 **4e**	95
6	**2a**	 **3f**	 **4f**	90
7	**2a**	 **3g**	 **4g**	82
8	**2a**	 **3h**	 **4h**	98
9	**2a**	 **3i**	 **4i**	98
10	**2a**	1-dodecanol **3j**	 **4j**	75
11	**2a**	 **3k**	 **4k**	52
12	**2a**	 **3l**	 **4l**	70

Table 1. *(continued)*

Entry	Ester	Alcohol	Product	Yield [%][b]
13	 **2b**	 **3a**	 **4a**	75
14	**2b**	 **3b**	 **4b**	80
15	**2b**	 **3c**	 **4c**	89
16	**2b**	 **3d**	 **4d**	98
17	 **2c**	 **3a**	 **4m**	63[c]
18	 **2d**	 **3a**	 **4n**	62[d]
19	**2d**	 **3m**	 **4o**	62

[a] Electrolyses of RTIL **1a** were carried out in a divided cell (Pt cathode and anode) under galvanostatic conditions (I = 15 mA cm^{-2}, T = 60 °C). Number of Faradays per mol of alcohol supplied to the electrode: Q = 0.5 F mol^{-1}; alcohol (1 mmol) and ester (3 mmol) were added to the catholyte at the end of the electrolysis, then the catholyte was stirred for 2.0 h at a controlled temperature of 60 °C. [b] Isolated yield with respect to the starting alcohol. [c] Alcohol (1 mmol) and ester (1 mmol) were added to the catholyte at the end of the electrolysis. [d] Alcohol (1 mmol) and ester (2 mmol) were added to the catholyte at the end of the electrolysis.

using a 1:1 mol ratio of **2d/3m**, however, upon enhancing this ratio to 1:3, nicametate **4o** was obtained in 62% yield (Table 1, entry 19). Nicotinate esters have important applications in cosmetic and pharmaceutical industries. Many publications have reported the pharmacological properties of various nicotinate esters as A3 adenosine receptor antagonists, cholesteryl ester transfer protein inhibitors, blood circulation promoters and anti-inflammatory agents.[23]

These results suggest that the procedure is widely applicable and that the system comprising electrogenerated-NHC/RTIL as reaction medium is compatible with a range of functional groups.

Conclusions

We have reported the successful application of electrogenerated *N*-heterocyclic carbene/room temperature ionic liquid as a catalyst/solvent system for the transesterification of alcohol to acetate, using isopropenyl or ethyl acetate as acetyl donor. This protocol allows the use of strong bases and volatile organic solvents to be avoided, and enables this transformation to be carried out under mild conditions, due to the use of an ionic liquid as solvent and the electron as reagent.

The system of electrogenerated-NHC/RTIL is able to assist in the proton transfer from alcohol to ester with significant efficiency. A recycling protocol has been demonstrated by reusing the system in ten subsequent runs with no reduction in the yield. The simplicity of the system (basic electrochemical equipment, RTILs as solvent/supporting electrolyte/precatalysts) make these results of high interest for electrochemical and organic synthesis. This methodology can also be applied to other acylation reactions, leading to compounds of noticeable pharmaceutical interest.

Experimental Section

General: All reagents are commercially available (Aldrich) and used as received. Ionic liquids (Iolitec) were used after heating under vacuum at 45 °C for 2 h. Electrolyses under galvanostatic control were carried out with an Amel 552 potentiostat equipped with an Amel 721 integrator. A two-compartment cell was used; the cathode was a Pt spiral (apparent area 1.0 cm^2) and the counter electrode a cylindrical platinum gauze (apparent area 0.8 cm^2). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 200 spectrometer using $CDCl_3$ as internal standard.

General Procedure for the Transesterification of Esters with Alcohols: Anolyte (1.0 cm^3 of ionic liquid) and catholyte (ca. 2.0 cm^3 of ionic liquid) were separated through a G-4 glass septum. The electrolysis was carried out at 60 °C under a nitrogen atmosphere and at constant current (15 mA cm^{-2}). The electrolysis was stopped after 49 Coulombs. At the end of the electrolysis, alcohol (1 mmol) and ester (3 mmol) were added sequentially to the catholyte, the temperature was maintained at 60 °C, and the mixture was stirred for 2 h. The reaction mixture was then extracted with diethyl ether (3 × 10 cm^3; stirring with diethyl ether for 15 min each time). After removal of the solvent from the combined ethereal layers under reduced pressure, the crude reaction mixture was analysed by ^{1}H NMR and TLC. All products were purified by using flash chromatography [*n*-hexane/ethyl acetate (95:5); CH_2Cl_2/ethyl acetate (98:2), respectively, for products **4m** and **4n**] and identified on the basis of NMR spectroscopic analysis by comparison with reported data.

Supporting Information (see footnote on the first page of this article): Complete experimental details and spectroscopic data of all products.

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