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Cyanuric chloride catalyzed Beckmann rearrangement of ketoximes in biodegradable ionic liquids

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ABSTRACT

Imidazolium-based ionic liquids (ILs) containing ester moieties in the side chain were successfully used as an alternative to traditional ILs in the Beckmann rearrangement of ketoximes catalyzed by 2,4,6-trichloro[1,3,5]triazine. The procedure is mild and suitable for both aromatic and cycloaliphatic substrates affording the rearrangement products in good to quantitative yields. The process is eco-sustainable since these ILs are biodegradable and in addition they can be recovered and reused.

1. Introduction

The Beckmann rearrangement is an important reaction for the transformation of ketoximes into amides, which has been successfully utilized to produce ε-caprolactam and lauryl lactam in industry.[1] It generally requires high reaction temperatures and an excess or stoichiometric quantities of strongly acidic and dehydrating media.[1] As a consequence, this reaction leads to large amounts of by-products and is not applicable to sensitive substrates. Among the various attempts of realizing a clean Beckmann rearrangement under milder conditions,[2] the use of room temperature ionic liquids (ILs) has recently been reported.[3–6]

Ionic liquids (ILs) are attracting increasing interest as a potential eco-sustainable alternative to harmful volatile organic solvents (VOCs) that should be utilized only in limited quantities due to their significant environmental impact.[7] They possess many appealing properties that include extremely low volatility, low flammability, ease of recovery and recycling, and applicability to catalytic processes.[7] However, their excellent thermal and chemical stability, often combined with water solubility, could raise concerns about the potential for IL accumulation in the environment. As a consequence, additional factors, such as biodegradability and toxicity, need to be carefully investigated before processes are scaled-up in ionic liquids.[7g,8]

Biodegradable ILs were prepared by Boethling et al. starting from the same principles used to improve biodegradation of the structurally closed surfactants.[9] Gathergood and Scammells were the first to introduce functional groups, which would be susceptible to enzymatic hydrolysis (esters/amides) into the IL imidazolium cation side chain. They found that incorporation of an ester group into the IL side chain significantly improved the biodegradation, whereas amide analogues proved resistant to biodegradation. The presence of the ester in the side chain, in fact, reasonably provides a site for possible enzymatic cleavage to give the parent imidazolium fragment and the corresponding primary alcohol that can readily be metabolized via fatty acid β-oxidation.[10–12]

It is worth noting, however, that favourable biodegradability must be balanced by the required stability of the solvent and practical applicability. In catalytic hydrogenation reactions, for example, imidazolium ILs are preferred to the more biodegradable pyridinium salts due to their higher stability. In a recent paper, Gathergood et al. reported that *trans*-cinnamaldehyde is selectively hydrogenated to hydrocinnamaldehyde with little or no overreduction of the aldehydic group in biodegradable imidazolium-based ILs containing ester and ether moieties in the side chain.[13] The selectivities are in all cases higher than those found in common organic solvents and in conventional ILs. Analogous pyridinium-based ILs were synthesised by Scammells et al. and utilized as the solvent in Diels–Alder reactions of cyclopentadiene with a range of dienophiles.[14] The results showed that both yield and *endo*-selectivity were clearly enhanced in these biodegradable

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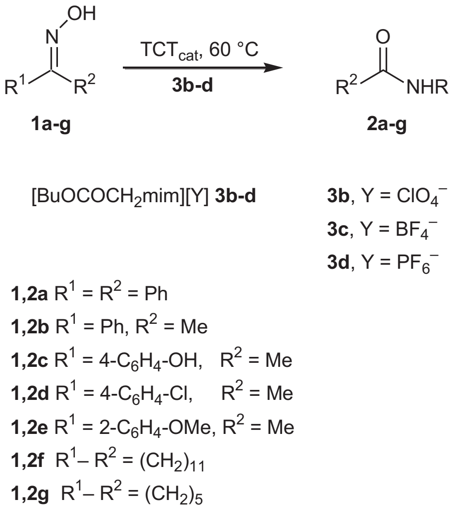
ILs when compared with those performed in molecular organic solvents.[14]

Recently, our group successfully utilized 1-hexyl-3-methylimidazolium-based ILs as an alternative to common VOCs in the Beckmann rearrangement of a representative series of ketoximes promoted by catalytic amounts of 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT).[15] The reactions were found to be fully regioselective, affording the *N*-substituted amides in very good to quantitative yields.[15] In view of the scale-up of this fundamental reaction we envisaged the possibility of using more eco-sustainable solvents, such as biodegradable and/or low toxicity ILs. However, since the reaction medium must be strongly acidic, it was very important to verify the applicability of biodegradable ILs containing ester moieties in the side chain under these conditions.

Here we wish to report on the TCT-catalyzed Beckmann rearrangement of a range of representative aromatic and cycloaliphatic ketoximes **1a**–**g** to the corresponding amides **2a**–**g** in biodegradable 3-methyl-1-(*n*-butoxycarbonylmethyl) imidazolium-based ionic liquids [$BuOCOCH_2mim$][Y] **3b**–**d** (Scheme 1). The results have been compared with those obtained in the common 1-hexyl-3-methylimidazolium-based ILs (**3′b**–**d**) under the same reaction conditions.

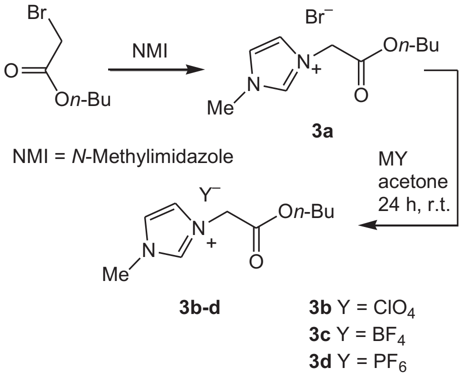


Scheme 1. Beckmann rearrangement of ketoximes **1a**–**g**.

2. Results and discussion

The synthesis of the ILs **3b**–**d** was carried out in two steps to give 3-methyl-1-(*n*-butoxycarbonylmethyl)imidazolium bromide (**3a**) followed by halide anion exchange, to ClO_4, BF_4, PF_6, according to a previously reported method (Scheme 2).[11,16]

In the TCT-catalyzed rearrangement process, the oximes **1a**–**g** (0.6 mmol) were dissolved in the ILs (**3b**–**d**) (2 mL) and combined with the appropriate quantity of catalyst (TCT ~ 6–20 mol %). Catalyst amounts of ~6 mol % for **1a**–**e** and 20 mol % for **1f** and **1g** were found to be a good compromise for obtaining satisfactory reaction times and yield. With a lower TCT quantity (2 mol %) the time remarkably increased reducing the conversion to the amide. On the other hand, the higher quantity of catalyst (20%), required for **1f** and **1g** (Table 1, entries 6 and 7), is due to the well known lower tendency to rearrange of these aliphatic oximes.[1,17] The mixture was left under stirring at 60 °C and monitored by TLC until completion. The amide was isolated by continuous extraction with MTBE or by direct chromatography (silica gel) of the reaction mixture (eluant ethyl acetate/petroleum ether) and identified (^1H NMR spectroscopy) by comparison with the authentic sample.[15]



Scheme 2. Synthesis of ionic liquids **3b**–**d**.

As reported in Table 1, the ketoximes **1a**–**g** selectively rearranged affording the *N*-substituted amides **2a**–**g** generally in excellent yields (85–97%). In the case of non-symmetrical ketoximes **1b**–**e**, only one of the two possible amides was isolated. In line with the Beckmann mechanism, the reaction times change with the nature of the ketoxime: with electron-withdrawing substituents on the aromatic ring (Cl, Table 1, entry 4) the rearrangement is slower than that of the unsubstituted oxime **1b** (2.7 h for **1d** instead of 0.75 for **1b**). By contrast, the reactions are faster with electron-donating substituents like OH and OCH_3 (0.42 and 0.33 for **1c** and **1e**, respectively).

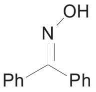
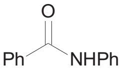
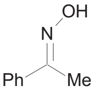
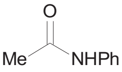
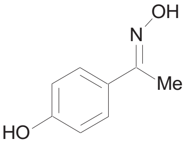
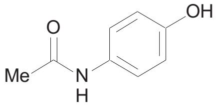
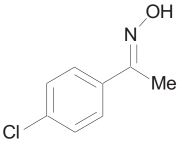
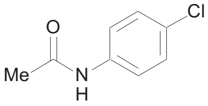
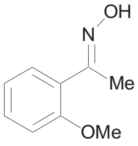
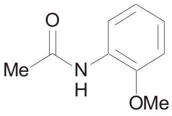
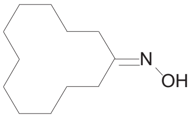
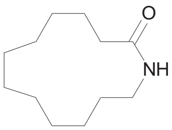
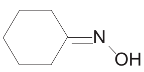
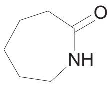
Interestingly, a high yield (85%) of lauryl lactam (**2f**), the nylon 12 monomer, was obtained from the cyclododecanone oxime (**1f**) in the presence of 20 mol % of catalyst (TCT) after 2 h (Table 1, entry 6). However, unlike **1f**, the reaction of the six-membered cyclohexanone oxime (**1g**) gave the product ε-caprolactam (**2g**) in poor yield (30%) under the same conditions (Table 1, entry 7). Analogous behaviour was obtained by Ishihara and Yamamoto in CH_3CN with cyanuric chloride[17] and more recently by Deng et al. with an organophosphorus catalyst.[18]

Comparison with the corresponding 1-hexyl-3-methylimidazolium-based ILs [hmim][Y] [Y=ClO_4 (**3′b**), BF_4 (**3′c**), PF_6 (**3′d**)] shows that both yields and reaction times are similar in all cases (Table 2). The higher reactivity in ILs if compared with that found in acetonitrile (Table 1, entry 1) is likely due to the involvement of the hydrogens of the imidazolium cation (in particular the most acidic H-2) in the rearrangement reaction.[15,17] In this case no Lewis acids or Brønsted acids were necessary as cocatalysts.[15,17] In addition, in ILs, due to their ionic nature, both the cation and the anion are engaged in the reaction so producing a different reactivity of the charged species depending on the IL-solute interactions.[7] This can explain the different reaction times found for the ILs **3b**–**d** (Table 2).

Finally, almost quantitative recycling of the IL **3b**–**d** was achieved without significant loss of activity. Thus, the residue obtained by continuous extraction of the reaction product can be reused after removal of trace amounts of MTBE and dehydration under high vacuum.[19]

For example, the benzophenone oxime (**1a**) rearranged to the corresponding amide **2a** in similar reaction times and yield of the first run for almost two cycles in [$BuOCOCH_2mim$][ClO_4] **3b** (Table 2, entries 2,3) and in [$BuOCOCH_2mim$][PF_6] **3d** (Table 2, entries 10,11).

Table 1
TCT-catalyzed Beckmann rearrangement of oximes **1a**–**g** in [BuOCOCH$_2$mim][BF$_4$], at 60 °C[a]

Entry	Ketoxime	Amide	Cat (mol %)	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	5.6	0.68 (1.02)[c]	94
2	 **1b**	 **2b**	5.6	0.75	95
3	 **1c**	 **2c**	5.6	0.42	90
4	 **1d**	 **2d**	5.6	2.7	97
5	 **1e**	 **2e**	5.6	0.33	86
6	 **1f**	 **2f**	20	2.0	85
7	 **1g**	 **2g**	20	2.0	30

[a] A solution of oxime (0.6 mmol) and TCT (5.6–20 mol %) in the IL (2 mL).
[b] Isolated yield by chromatography of the IL solution.
[c] Time for the same reaction performed in CH$_3$CN is reported under brackets.

3. Conclusion

The results as a whole show that ILs **3b**–**d**, that contain ester moieties in the side chain, can be successfully utilized even in catalytic Beckmann-type reactions that are known to require strongly acidic media. Under these conditions this novel class of ILs represent a valid alternative to traditional imidazolium-based ILs **3′b**–**d**. The procedure is mild and suitable not only for aromatic but also for cycloaliphatic ketoximes, such as cyclododecanone oxime (**1f**), affording the rearrangement products in good to quantitative yield.

The process is eco-sustainable since these ILs can be easily recovered and reused several times and in addition they are biodegradable.

4. Experimental section

4.1. General remarks

Melting points were determined on a BÜCHI 535 and are corrected. NMR spectra were recorded on Bruker AC 300 or AC 200 spectrometers, operating at 300.13 or 200.13 MHz for ^{1}H

Table 2
Effect of the IL nature and catalyst amount on the Beckmann rearrangement of benzophenone oxime **1a**, at 60 °C[a]

Entry	Ionic liquid	Cat (mol %)	Time (h)	Yield (%)
1	[BuOCOCH$_2$mim][ClO$_4$] **3b**	5.8	0.42	93
2	**3b**[b]	5.8	0.58	95
3	**3b**[c]	5.8	0.58	92
4	**3b**	10	0.33	92
5	[hmim][ClO$_4$] **3′b**	10	0.50	95
6	[BuOCOCH$_2$mim][BF$_4$] **3c**	5.8	0.68	94
7	**3c**	10	0.50	85
8	[hmim][BF$_4$] **3′c**	10	0.50	92
9	[BuOCOCH$_2$mim][PF$_6$] **3d**	5.8	0.58	85
10	**3d**[b]	5.8	0.58	90
11	**3d**[c]	5.8	0.58	96
12	**3d**	10	0.50	95
13	[hmim][PF$_6$] **3′d**	10	0.40	90

[a] A solution of oxime **1a** (0.6 mmol) and TCT (5.8–10 mol %) in the IL (2 mL).
[b] First recycle of ionic liquid.
[c] Second recycle of ionic liquid.

NMR and 75.3 or 50 MHz for ^{13}C NMR. Coupling constants *J* are in hertz. Chemical shifts were reported by using CHCl$_3$ as external standard (7.24 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR). Column chromatography on silica gel (230–400 mesh) was performed by the flash technique. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C. ESI Mass spectra were measured on a LCQ Advantage Thermo-Finnigan spectrometer. The water content of each IL was measured using a coulometric Karl-Fischer titrator (Metrohm 684 KF Coulometer). Samples were prepared by dissolving 0.250–0.350 g of IL in anhydrous acetonitrile in a 2 mL calibrated flask and duplicate determinations were performed on each sample with results agreeing to within 5%. Potentiometric titrations were carried out with a Metrohm 751 GPD Titrino using a combined silver electrode isolated with a potassium nitrate bridge.

4.2. Synthesis of ionic liquids

4.2.1. Synthesis of [BuOCOCH$_2$mim][ClO$_4$] ***3b****.* A dry flask was charged with 3-methyl-1-(butoxy carbonylmethyl) imidazolium bromide (**3a**) (16.81 g, 60 mmol) and acetone (50 mL) under a nitrogen atmosphere. After dissolution, NaClO$_4$ (9.80 g, 80 mmol) was added and the suspension was stirred vigorously for 24 h at room temperature. The complete exchange Br$^-$/ClO$_4^-$ was verified by argentometric titration. The white precipitate was filtered off and washed with acetone (2×5 mL). The solvent was removed by rotary evaporation and CH$_2$Cl$_2$ (50 mL) was added. The organic solution was washed with saturated Na$_2$SO$_4$ aqueous solution (2×5 mL), dried with anhydrous Na$_2$SO$_4$ and filtered. After removal of CH$_2$Cl$_2$ by rotary evaporation, the viscous oil was dehydrated by heating at 60 °C for 6 h under high vacuum to give the title compound **3b** (17.08 g, 95%). The water content of **3b** was determined to be 2321 ppm by Karl-Fischer analysis; δ_H (300 MHz, CDCl$_3$) 8.48 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.34 (s, 1H, ArH), 5.06 (s, 2H, N–C*H*$_2$), 4.21 (t, 2H, *J* 6.6 Hz, OC*H*$_2$), 3.96 (s, 3H, N–C*H*$_3$), 1.67 (m, 2H, OCH$_2$C*H*$_2$), 1.38 (m, 2H, –C*H*$_2$CH$_3$), 0.93 (t, 3H, *J* 7.4 Hz, C–C*H*$_3$); δ_C (75 MHz, CDCl$_3$) 166 (C), 137.9 (CH), 123.8 (CH$_2$), 123.0 (CH), 66.8 (CH$_2$), 50.0 (CH$_2$), 36.6 (CH$_3$), 30.3 (CH$_2$), 18.9 (CH$_2$), 13.5 (CH$_3$); *m*/*z* (ESI) 197.1 (100 BuOCOCH$_2$mim$^+$), 493.2 (38 [BuOCOCH$_2$mim]$_2$ClO$_4^+$).

4.2.2. Synthesis of [BuOCOCH$_2$mim][BF$_4$] ***3c*** *and [BuOCOCH$_2$mim][PF$_6$]* ***3d****.* Ionic liquids **3c** and **3d** are known compounds and have been prepared by using the same procedure described above for **3b**. Spectroscopic properties of **3c** and **3d** are identical to those previously reported.[16]

4.3. Typical procedure for the TCT-catalyzed Beckmann rearrangement

In a dry flask, ketoxime **1a** (118 mg, 0.6 mmol) was dissolved in the ionic liquid **3b** (2 mL, 2.34 g) and 2,4,6-trichlorotriazine was added (6.2 mg, 0.034 mmol). After stirring for 40 min at 60 °C the reaction mixture was directly extracted with MTBE by a liquid–liquid continuous extraction apparatus. The resulting MTBE solution of **2a** was filtered over a silica plug (eluant AcOEt/PE 1:4) to remove trace amounts of **3b**. Evaporation of the solvent under reduced pressure afforded 106 mg of *N*-phenyl-benzamide (**2a**) (106 mg, 90%), as a white solid, mp 164 °C (lit.[20] 164–165 °C). After removal of trace amounts of MTBE, followed by drying under vacuum, the IL residue **3b** (2.20 g, yield 95%) could be reused for further reactions.

Alternatively, the crude reaction mixture was directly subjected to column chromatography on silica gel (eluant AcOEt/PE 1–7) to give of *N*-phenyl-benzamide (**2a**) (111 mg, 94%). The ionic liquid **3c** was quantitatively recovered by eluting with AcOEt/MeOH (1:1).

The same procedure was used to generate amides **2b**–**g**, as pure compounds, whose physical and spectroscopic data match those previously reported.[21]

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