An Efficient Tandem Oxidation of Cyclohexanol to ε-Caprolactone with Peroxyacids and TEMPO Catalyst in Ionic Liquids as Solvents

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Abstract: The new one-pot tandem oxidation of cyclohexanol to ε-caprolactone with potassium peroxomonosulfate or *m*-chloroperoxybenzoic acid as oxidation agents and ionic liquids as solvents is described. A 2,2,6,6-tetramethylpiperidine-1-oxyl radical with tetrabutylammonium bromide as the co-catalyst was used. A solution of $KHSO_5$ in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 facilitates the tandem oxidation of alcohol to lactone. In classic solvents, this reaction can only be carried out to the ketone formation step. This is most probably due to the ability of [bmim]BF_4 to dissolve both alcohol and $KHSO_5$. In the case of using *m*-chloroperoxybenzoic acid, ionic liquids provide an efficient medium for this reaction. This new method enables ε-caprolactone formation with high yields (75–80%).

Key words: ionic liquids, oxidation, alcohols, tandem reaction, lactones

The oxidation reactions of alcohols to ketones and ketones to lactones are some of the most important transformations in organic synthesis and are used in many different applications, including the synthesis of antibiotics, steroids, pheromones, and monomers for polymerisation.[1] Among these reactions is the crucial synthesis of ε-caprolactone. The major use of ε-caprolactone is in the production of polycaprolactone. This is a biodegradable polyester that is used as an additive in resins or as an implantable biomaterial. For this reason, the synthesis of ε-caprolactone has become a model reaction for this study.

The oxidation of ketones to lactones or esters in the Baeyer–Villiger (BV) reaction uses organic peroxyacids or hydrogen peroxide as the most commonly used oxidants. However, Baeyer and Villiger used Caro's acid (potassium peroxomonosulfate, $KHSO_5$) in their pioneering work; this oxidising agent was used for BV reactions only occasionally.[2] For the oxidations with $KHSO_5$, an aqueous reaction medium must be employed, which can lead to the hydrolysis of lactones or esters. In previous work, an alternative method with ionic liquids (IL) as solvents was presented.[3]

Although the BV reaction is relatively easy to carry out, the oxidation of alcohols, especially these secondary to ketones, is much more problematic. During the broad range of research, nitroxyl radicals, e.g., TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), have become the catalysts of choice for this reaction, in which oxygen, sodium hypochlorite, potassium peroxomonosulfate, or bis(acetoxy)iodobenzene can serve as oxidants.[4]

The tandem reaction concerning the one-pot oxidation of secondary alcohols to lactones or esters would be beneficial for organic chemists. Only limited information concerning this problem can be found in the literature. Sepulveda et al.[5] described the oxidation of cyclohexanol with 70% H_2O_2 in acetonitrile in the presence of the catalysts: $H_3PW_{12}O_{40}$ and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ at 90 °C. Although the conversion is influenced by the pressure of oxygen, the decomposition of H_2O_2 was observed. The selectivity of ε-caprolactone was achieved from 16–27%. Other effective methods for the one-pot conversion of alcohol to lactone were based on the use of *m*-chloroperoxybenzoic acid (MCPBA) as an oxidant. Lipton et al.[6] presented a method using catalytic amounts of cyclic chromate ester, which facilitated the oxidation of cyclohexanol to lactone in dichloromethane as a solvent at room temperature with 93% yield. Cella et al.[7] discussed another method involving the utilisation of MCPBA and 2,2,6,6-tetramethylpiperidine hydrochloride as catalysts for the effective oxidation of cyclohexanol to ε-caprolactone in dichloromethane at room temperature with high yields. An interesting method describing a strategy for oxidation of cyclohexanol to ε-caprolactone involves molecular oxygen and *N*-hydroxyphthalimide as a catalyst.[8] During the oxidation at 75 °C, one molecule of H_2O_2 is created in situ and, combined with a Lewis acid, serves as the reaction conditions for lactone formation.

Herein, a new method for the one-pot tandem oxidation of alcohol to lactone is presented. The method is based on the use of MCPBA or Oxone® (commercial source of potassium peroxomonosulfate) as oxidants with a TEMPO radical and tetrabutylammonium bromide (TBAB) as the oxidant system in IL solvents. To the best of the author's knowledge, this is the first method describing the one-pot oxidation of alcohol to lactone in IL with MCPBA as an oxidant. Additionally, there are no reports concerning the use of $KHSO_5$ for a tandem oxidation.

In Table 1, the results of the oxidation of cyclohexanol to ε-caprolactone are presented. Among the IL, 1-butyl-3-methylimidazolium tetrafluoroborate {[bmim]BF_4} was chosen as the solvent.

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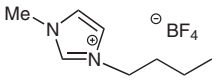
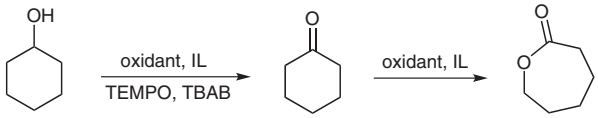
Table 1 Oxidation of Cyclohexanol to ε-Caprolactone[a]

Entry	Solvent	Oxidant	TEMPO/TBAB (mol%)	Time (h)	Yield (%)[b]
1	 [bmim]BF_4	MCPBA	3/1	2	82 (78)
2	[bmim]BF_4	MCPBA	3/–	2	52
3	[bmim]BF_4	MCPBA	–/1	2	–
4	CH_2Cl_2	MCPBA	3/1	5	75
5	[bmim]BF_4	Oxone®	5/3	10	78 (75)
6	[bmim]BF_4	Oxone®	5/–	10	38
7	[bmim]BF_4	Oxone®	–/3	10	–
8	CH_2Cl_2	Oxone®	5/3	10	3[c]

[a] Reaction conditions: cyclohexanol (1 mmol), 40 °C, solvent (3 mL), MCPBA/Oxone® (4 mmol).
[b] Yield of ε-caprolactone was determined by GC with 100% conversion of alcohol and ketone, in parentheses are the isolated yields.
[c] Yield: 0.75 mmol of cyclohexanone were detected.

1-Butyl-3-methylimidazolium tetrafluoroborate was found in previous work[3] to be an efficient solvent for $KHSO_5$, resulting in a homogeneous reaction system. In the literature, [bmim]BF_4 is described as an efficient solvent for ketone oxidation with MCPBA.[9] Additionally, the reactions were carried out in dichloromethane as a typical solvent for BV oxidation for comparison (Table 1, entry 4 and 8). The radical TEMPO with the addition of tetrabutylammonium bromide (TBAB) served as catalysts for the first step of the oxidation to cyclohexanone. The second step of the oxidation of ketone to ε-caprolactone did not require any additional catalyst (Scheme 1).



Scheme 1

The standard experimental procedure was as follows: cyclohexanol (1 mmol), MCPBA (4 mmol) or $KHSO_5$, TEMPO (0.03–0.05 mmol), TBAB (0.01–0.03 mmol), and [bmim]BF_4 (3 mL) were introduced into the round-bottom flask. The molar ratio of alcohol/Oxone® was 1:2. This triple salt consisted of $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The reaction mixture was stirred at 40 °C for 2–10 h, depending on the reaction rate. The progress of the reaction was monitored by GC.

In the case of using an IL as a solvent, utilising MCPBA as an oxidant resulted in a very efficient reaction. The yield of ε-caprolactone was high: 82% with 100% conversion of alcohol and ketone created in situ, which was controlled by GC (Table 1, entry 1).

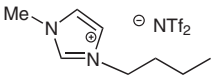
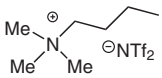
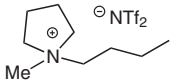
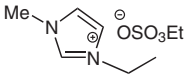
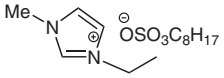
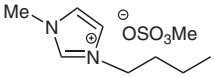
As was demonstrated in Table 1 (entry 3 and 7) none of the tandem reactions preceded without radical TEMPO, and the yields decreased when TBAB was eliminated (entry 2 and 6). Similar results with a slightly lower yield of ε-caprolactone were obtained for the oxidation in dichloromethane (Table 1, entry 4). The use of IL instead of classic solvents has many advantages and may result in significant steps toward greener processes for the synthesis of ε-caprolactone. Ionic liquids possessing negligible vapour pressures with the ability to dissolve many organic and inorganic substances and being readily recyclable, have been described as some of the most promising new reaction media and alternatives to volatile organic solvents.[10] It should be noted that typical organic solvents, used in conventional BV reactions are often environmentally undesirable because of their toxicity, flammability, and volatility.

When Oxone® is used as the oxidant, the situation is different. Oxone® is a stable oxidising agent, which is easy to handle, nontoxic, generates nonpollutant byproducts, and is relatively inexpensive. One report discusses the oxidation of primary and secondary alcohols to ketones with $KHSO_5$ and radical TEMPO in dichloromethane.[11] However, in classic solvents (Table 1, entry 8) this reaction can only be carried out to the ketone-formation step. The method described in this study uses [bmim]BF_4 as the reaction solvent and allows this reaction to proceed without any additional catalysts up to the lactone formation (Table 1, entry 5). This result is most likely due to the ability of [bmim]BF_4 to dissolve both cyclohexanol and $KHSO_5$, providing homogeneous conditions. Dichloromethane and other typical organic solvents used for BV reactions do not dissolve $KHSO_5$, this property eliminates this solvent for the tandem oxidation reaction.

The influence of the structure of the IL on the oxidation of cyclohexanol is illustrated in Table 2. For the reaction with MCPBA as an oxidant, a variety of IL can be used with high conversions of alcohol and yields of ε-caprolactone. Both hydrophobic (based on NTf_2 anions) and hy-

drophilic IL (based on BF_4 and alkylsulfates anions) were used. An interesting observation was noted. In the case of using IL based on NTf_2 anions, the reaction system is homogeneous only in the beginning of the reaction, but after some time, the precipitation of *m*-chlorobenzoic acid was observed. In IL based on alkylsulfate anions, the reaction mixtures stay homogeneous throughout the entire process. This factor can influence the reaction rate and the isolation step. The best results were obtained using [bmim]BF_4 and [bmim]OSO_3Me, in which the reaction was complete after two to three hours. The yields of lactone were in the range of 70–84%. A longer reaction time was necessary for the reaction carried out in [emim]OSO_3Oc, due to the higher viscosity of this system.

Table 2 Oxidation of Cyclohexanol with Peroxyacids in Ionic Liquids as Solvents[a]

Solvent	Oxidant	TEMPO/TBAB (mol%)	Time (h)	Yield (%)[b]
 [bmim]NTf_2	MCPBA	3/1	3	82
 [bma]NTf_2	MCPBA	3/1	3	81
 [bmp]NTf_2	MCPBA	3/1	3	79
 [emim]OSO_3Et	MCPBA	3/1	3	75
 [emim]OSO_3Oc	MCPBA	3/1	5	70
 [bmim]OSO_3Me	MCPBA	3/1	3	84 (80)
[bmim]NTf_2	Oxone®	5/3	10	9[c]
[bmim]OSO_3Me	Oxone®	5/3	10	5[d]

[a] Reaction conditions: cyclohexanol (1 mmol), 40 °C, solvent (3 mL), MCPBA/Oxone® (4 mmol).
[b] Yield of ε-caprolactone was determined by GC with 100% conversion of alcohol and ketone, in parentheses are the isolated yields.
[c] Yield: 0.65 mmol of cyclohexanone were detected.
[d] Yield: 0.85 mmol of cyclohexanone were detected.

The tandem reaction in IL with Oxone® occurs only in [bmim]BF_4 as the reaction medium. The use of [bmim]NTf_2 and [bmim]OSO_3Me allows the reaction to be carried out only to the step of the ketone formation. The results show that it is possible to carry out the oxidation of cyclohexanol with a TEMPO/TBAB catalytic system in IL with Oxone® as an oxidant. However, the Baeyer–Villiger oxidation requires homogeneous conditions.

It is known that peroxy compounds are relatively unstable and easily decompose in the presence of various reagents. For this reason, it was important to test the stability of potassium peroxomonosulfate and MCPBA by stirring them with the IL to be studied at 40 °C for five hours. After this time, the amount of peroxy compound in these test samples, as checked by iodometric titration, was not changed. These results can confirm that the oxidants are stable in the presence of IL. Additionally, after the completion of the tandem oxidations the unreacted oxidants were detected by iodometric titration. The study showed that the nonproductive oxidant decomposition was not observed.

The performance of TEMPO was largely influenced by the presence of quaternary ammonium salts (Table 1). The influence of the nitroxyl radical and Br^- source on the oxidation of cyclohexanol with MCPBA in [bmim]BF_4 and [bmim]NTf_2 is presented in Table 3. The use of 4-hydroxy-2,2,6,6-tetramethyl-piperidinooxy (4-hydroxy-TEMPO) with TBAB gives the same results as applying the TEMPO/TBAB system (Table 3, entry 1 and 3). TEMPO is generally an expensive chemical. The nitroxyl radical derivatives functionalised in the 4-position, such as 4-hydroxy-TEMPO, are much cheaper because they can be obtained from the cheap precursor triacetoneamine.[12] TBAB serves as a source for the bromide ion cocatalyst. The bromide ion reacts with peroxyacid to generate hypobromous acid in situ, which is a stronger oxidant. The subsequent oxidation of the nitroxyl radical to an *N*-oxoammonium bromide performs the usual TEMPO-catalysed oxidation of the alcohol substrate.[11] It is possible to eliminate TBAB by using 2,2,6,6-tetramethylpiperidine hydrobromide (TMP·HBr; Table 3, entry 2 and 4). However, the oxidation reactions must be conducted for a longer period of time.

Table 3 The Influence of the Nitroxyl Radical and Br^- Source on the Oxidation of Cyclohexanol with MCPBA and in Ionic Liquids as Solvents[a]

Entry	Solvent	Nitroxyl radical source	Br^- source	Time (h)	Yield (%)[b]
1	[bmim]BF_4	4-hydroxy-TEMPO	TBAB	2	82
2	[bmim]BF_4	TMP·HBr	–	6	70
3	[bmim]NTf_2	4-hydroxy-TEMPO	TBAB	3	83
4	[bmim]NTf_2	TMP·HBr	–	6	66

[a] Reaction conditions: cyclohexanol (1 mmol), 40 °C, solvent (3 mL), MCPBA (4 mmol), nitroxyl radical (3 mol%), TBAB (1 mol%).
[b] Yield of e-caprolactone was determined by GC.

The possibility of recycling the IL in tandem oxidation of cyclohexanol with MCPBA was studied (Table 4). After each cycle, the post-reaction mixture was extracted with diethyl ether (6 × 10 mL). The residue was dissolved in CH_2Cl_2, washed with a saturated aqueous $NaHCO_3$, dried

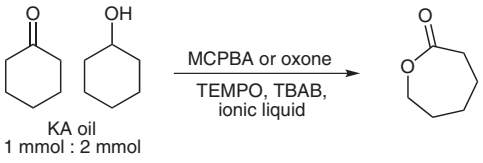
over anhydrous $MgSO_4$, and concentrated. Recovered IL was dried in a vacuum (60 °C, 8 h) before every cycle. [bmim]NTf_2 was used in four cycles without significant loss of activity. High recovery of the IL was observed (92–95%).

Table 4 Recycling of [bmim]NTf_2 in the Oxidation of Cyclohexanol to ε-Caprolactone with MCPBA[a]

Recycle of IL	Yield of ε-caprolactone (%)[b]	[bmim]NTf_2 recovered (%)
Fresh, nonrecycled IL	82	95
1st	80	93
2nd	82	94
3rd	81	92

[a] Reaction conditions: cyclohexanol (2 mmol), [bmim]NTf_2 (6 mL), MCPBA (8 mmol), TEMPO (0.06 mmol), TBAB (0.02 mmol), 40 °C, reaction time 3 h.
[b] Yield of ε-caprolactone was determined by GC with 100% conversion of alcohol and ketone.

Currently, most ε-caprolactone is prepared by the oxidation of cyclohexanone using either O_2/acetaldehyde or peroxyacetic acid as the oxidation agent. Cyclohexanone is obtained from a cyclohexanone/cyclohexanol mixture (KA oil) which is a crude product from the aerobic oxidation of cyclohexane.



Scheme 2

Table 5 Oxidation of the Ketone/Alcohol Mixture with MCPBA/Oxone® in Ionic Liquids as Solvents[a]

Solvent	Oxidant	TEMPO/TBAB (mol%)	Time (h)	Yield (%)[b]
[bmim]BF_4	MCPBA	3/1	5	85 (80)
[bmim]NTf_2	MCPBA	3/1	5	81 (75)
[bmim]OSO_3Me	MCPBA	3/1	5	86 (80)
[bmim]BF_4	Oxone®	5/3	10	81 (77)

[a] Reaction conditions: ketone/alcohol 0.5:1 (mmol/mmol), 40 °C, IL (5 mL), MCPBA/Oxone® (5 mmol).
[b] Yield was determined by GC with 100% conversion of alcohol and ketone and recalculated with the assumption that the maximum yield of lactone is 1.5 mmol, in parentheses are the isolated yields.

The use of KA oil as a raw material for ε-caprolactone synthesis would avoid both the separation of the KA oil, and the consequential dehydrogenation of cyclohexanol to cyclohexanone particularly because the cyclohexanol content of KA oil is higher than cyclohexanone. This problem is important from a synthetic and an industrial point of view.

In Table 5 the oxidation of the ketone/alcohol mixture is demonstrated.[13] In both cases using MCPBA or Oxone® as oxidising agents, the system is very active. The presence of additional amounts of ketone does not influence the yield of ε-caprolactone (Scheme 2).

In summary, a new and efficient reaction system for the tandem oxidation of cyclohexanol with MCPBA or Oxone® and a TEMPO/TBAB catalytic system in IL as novel media is presented. It is possible to obtain ε-caprolactone in high yields using MCPBA and a broad spectrum of IL as reaction media. Since the oxidation of cyclohexanol with Oxone® is strongly solvent dependent, only [bmim]BF_4 was found to be an efficient solvent for this system. In looking for green solutions in organic oxidations to minimise the environmental impact resulting from the use of oxidising agents and solvents, the implementation of Oxone® and IL is an effective combination. The simplicity of the methodology, high yields, mild conditions, lack of byproducts, and the possibility of recycling the IL can make this reaction attractive as a synthetic method for lactone formation.

More work is in progress to show whether the novel solvents may find broader applications in tandem one-pot oxidation reactions.

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(12) Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245.
(13) **Standard Experimental Procedure for KA Oil Oxidation**
Into the round-bottom flask cyclohexanol (1 mmol), cyclohexanone (0.5 mmol), TEMPO (0.03–0.05 mmol), TBAB (0.01–0.03 mmol), MCPBA or $KHSO_5$ (5 mmol) and IL (5 mL) were introduced at r.t. The reaction mixture turned orange upon addition of the peroxy acid. The reaction mixture was stirred at 40 °C for 5–10 h. The progress of the reaction was monitored by GC. After this time, the orange colour had faded away, and the post reaction mixture was dissolved in CH_2Cl_2 and filtered from Oxone® inorganic salts. Next, the filtrate was concentrated. The IL was then extracted with Et_2O (6 × 5 mL); the extract was washed with a sat. aq $NaHCO_3$ to remove all residual peroxy compounds and was concentrated. The yields of ε-caprolactone after the purification by column chromatography with hexane–EtOAc (4:1) as the eluent were 75–80%.