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Preparation of cyclic ketoximes using aqueous hydroxylamine in ionic liquids

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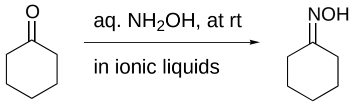
Abstract—Cyclohexanone oxime (the precursor for making ε-caprolactam) is readily prepared from cyclohexanone using aqueous hydroxylamine in ionic liquids. © 2001 Elsevier Science Ltd. All rights reserved.

With a wide temperature window and essentially no vapor pressure, the room temperature ionic liquids, particularly those based on the *1,3-dialkylimidazolium cations*, manifest physicochemical behaviors quite unlike water or organic solvents. These liquids possess adjustable Lewis and Brønsted acidities, adjustable hydrophobicity–hydrophilicity, and limited miscibility with certain organic solvents (solvophobicity).[1]

Beckmann rearrangement of ketoximes (mainly cyclohexanone oxime) to the corresponding amide has been used as a powerful method for manufacturing of ε-caprolactam in chemical industry.[2] We have disclosed a new catalytic route for Beckmann rearrangement of ketoxime using phosphorous pentoxide as catalyst in ionic liquids, particularly 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (bmiPF_6).[3]

However a survey of synthetic methods for cyclohexanone oxime used in this process shows that it has been manufactured at industrial scale at elevated temperature using hydroxylamine hydrochloride or other salts of inorganic acids, which poses as corrosive chemicals that should be avoided. A recent patent publication discloses that high purity oximes can be prepared from aqueous hydroxylamine and ketones reacted at room temperature overnight, without addition of acids.[4] We are therefore curious as to whether room temperature ionic liquids such as bmiPF_6 or bmiBF_4[5] can be applied as the recyclable reaction media for the formation of ketoximes (Scheme 1). We prefer the use of aqueous hydroxylamine as it is the most economical and environmentally friendly reagent, since the only by-product is water that can be evaporated under reduced pressure. Perhaps upon the removal of water, and addition of phosphorous pentoxide cyclohexanone oxime generated in situ can undergo Beckmann rearrangement to produce ε-caprolactam in one-pot fashion in ionic liquid media.[3]

Table 1 shows the formation of ketoximes from cyclohexanone or cycloheptanone using hydroxylamine or its salts in ionic liquids. A profound counter-anion effect regarding ionic liquids has been observed. We initially decided that water-immiscible bmiPF_6 may be a better choice for such reaction, since it presents a possibility of easy recycling by separating water or washing off acid catalyst if any. The earlier experiments involving cyclohexanone and hydroxylamine hydrogen chloride in bmiPF_6 ionic liquids completely failed even at elevated temperature for prolonged reaction time (entries 1 and 2). However, addition of 1 equiv. of sodium acetate brought about the desired reaction in high yield (entry 3). Similar result was achieved using the sulfate salt of hydroxylamine and sodium acetate (entry 4). When aqueous hydroxylamine alone was used in bmiPF_6, no reaction occurred until addition of methanesulfonic acid (entry 5).



Scheme 1.

Keywords: cyclohexanone; cyclohexanone oxime; hydroxylamine; ionic liquids.

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Table 1. Formation of ketoximes using hydroxylamine and it salts in ionic liquids via Scheme 1

Entry	Substrate	Ionic liquid	Hydroxylamine source	Additive	Temp. (°C)	Time (h)	Yield (%)
1	Cyclohexanone	$bmiPF_6$	$NH_2OH{\cdot}HCl$	–	rt	40	NR
2	Cyclohexanone	$bmiPF_6$	$NH_2OH{\cdot}HCl$	–	40	40	NR
3	Cyclohexanone	$bmiPF_6$	$NH_2OH{\cdot}HCl$	1 equiv. NaOAc	40	20	90
4	Cyclohexanone	$bmiPF_6$	$(NH_2OH)_2{\cdot}H_2SO_4$	1 equiv. NaOAc	40	20	90
5	Cyclohexanone	$bmiPF_6$	NH_2OH (aq.)	5% CH_3SO_3H	40	20	85
6	Cycloheptanone	$bmiPF_6$	$NH_2OH{\cdot}HCl$	1 equiv. NaOAc	40	20	85
7	Cycloheptanone	$bmiPF_6$	$(NH_2OH)_2{\cdot}H_2SO_4$	1 equiv. NaOAc	40	20	85
8	Cycloheptanone	$bmiPF_6$	NH_2OH (aq.)	5% CH_3SO_3H	40	20	80
9	Cyclohexanone	bmiCl	$NH_2OH{\cdot}HCl$	1 equiv. NaOAc	40	40	NR
10	Cyclohexanone	bmiCl	NH_2OH (aq.)	5% CH_3SO_3H	rt	40	NR
11	Cyclohexanone	bmiCl	NH_2OH (aq.)	5% CH_3SO_3H	40	40	NR
12	Cyclohexanone	$bmiBF_4$	$NH_2OH{\cdot}HCl$	–	rt	0.5	95
13	Cyclohexanone	$bmiBF_4$	$(NH_2OH)_2{\cdot}H_2SO_4$	–	rt	0.5	95
14	Cyclohexanone	$bmiBF_4$	NH_2OH (aq.)	–	rt	0.5	99

All reactions were all carried out in sealed vials at 2 M concentration in 1 ml of ionic liquid, monitored via GC/MS; NR: no reaction.

The same trend was observed for cycloheptanone substrate (entries 6–8). It is possible that the initially formed oxime may undergo fast hydrolysis in the presence of strong acid (HCl) and water, particularly in the ionic liquid media. Neutralization of hydrogen chloride by sodium acetate provided acetic acid, which could have much lowered acidity. It is also possible that $bmiPF_6$ may decompose[6] under the strongly acidic condition (such as HCl) in the presence of hydroxylamine, thus hampering the formation of cyclic ketoximes.

However, the formation of oxime failed completely in bmiCl[7] using $NH_2OH{\cdot}HCl$, even when sodium acetate was added (entry 9). When aqueous hydroxylamine was used, no reaction occurred. Addition of acid catalyst such as methanesulfonic acid did not help, even at elevated temperature (entries 10 and 11).

Surprisingly, $bmiBF_4$ gave very different results. For all the reactions carried out in $bmiBF_4$ ionic liquids, formation of oxime turned out to be very efficient, regardless of hydroxylamine sources (entries 12–14). The best reaction condition was by using aqueous hydroxylamine and $bmiBF_4$ (entry 14). Upon addition of aqueous hydroxylamine to a mixture of cyclohexanone in $bmiBF_4$, the oxime precipitated out of aqueous solution and the product was collected by simple filtration. The $bmiBF_4$ can be recycled via evaporation of water.

In conclusion, the preliminary results show that formation of cyclohexanone oxime from cyclohexanone can be conducted using aqueous hydroxylamine in ionic liquid $bmiBF_4$ without any other additive. The ionic liquid acts as the recyclable reaction media which facilitated such reaction under essentially neutral condition at room temperature. The effects of counter-anions on the ketoxime formation reaction are currently under investigation.

Acknowledgements

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References

1. For recent reviews on ionic liquids in green chemistry, see: (a) Carlin, R. T.; Wilkes, J. S. In *Advances in Nonaqueous Chemistry*; Mamantov, G.; Popov, A., Eds.; VCH: New York, 1994; (b) Chauvin, Y.; Olivier, H. *ChemTech* **1995**, *25*, 26; (c) Seddon, K. R. *J. Chem. Tech. Biotechnol.* **1997**, *68*, 351; (d) Olivier, H. *J. Mol. Cat. A: Chem.* **1999**, *146*, 285; (e) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (f) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772.
2. Gawly, R. E. *Org. React.* **1988**, *35*, 1 and references cited therein.
3. Ren, R. X.; Zueva, L. D.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8441.
4. Sahabari, J. J.; Russel, J. W. *WO0032562*, June 8, 2000.
5. Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; DeSouza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217–1219.
6. For a discussion of decomposition pathway of $bmiPF_6$ in high concentration of HNO_3, see: Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Griffin, S. T.; Rogers, R. D. *Ind. Eng. Chem. Res.* **2000**, *39*, 3596.
7. bmiCl is prepared via alkylation of 1-methylimidazole using *n*-chlorobutane. This ionic liquid has melting point slightly above room temperature and hydrophilic. Addition of trace amount of water can render it liquid-like.