Tetrahedron Letters 51 (2010) 4125–4128

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A mild and efficient way to prepare ε-caprolactam by using a novel salt related with ionic liquids

Miguel Vilas, Emilia Tojo *

Department of Organic Chemistry, Faculty of Chemistry, University of Vigo, Campus Universitario, Vigo 36310, Pontevedra, Spain

ARTICLE INFO

Article history:
Received 23 April 2010
Revised 28 May 2010
Accepted 28 May 2010
Available online 2 June 2010

Keywords:
Ionic liquid
Beckmann rearrangement
Ketoximes
ε-Caprolactam

ABSTRACT

The Beckmann rearrangement of several ketoximes has been performed by treatment with tosyl chloride, using ionic liquids as both solvent and catalyst, without the need of any other promoter. High levels of conversion and selectivity were observed in the majority of experiments. Work-up is very simple and the product can be isolated in high yields. When the method was applied to cyclohexanone oxime, the novel salt [TMG][TsO] instead of the ionic liquid was used. This procedure afforded a conversion of 100% to obtain pure ε-caprolactam in a 98% yield. [TMG][TsO] is easy to prepare, cheap, and not corrosive. It can be recovered and reused.

1. Introduction

The conversion of ketoximes to the corresponding amides, known as the Beckmann rearrangement, is one of the classical and most popular reactions in organic chemistry.[1] It represents a powerful method in the chemical industry, particularly for manufacturing ε-caprolactam, the basic monomer for the production of the synthetic fibber Nylon 6.[2] The reaction generally requires high reaction temperatures and strongly acidic media, such as H_2SO_4 and $SOCl_2$,[3] which cause serious corrosion problems and large amount of by-products. Thus, milder routes are required and alternative methods both in organic liquids and in vapor-phase have been studied. Liquid-phase processes using catalysts such as $RuCl_3$,[4] sulfamic acid, antimony salts, silica-supported dichlorophosphate,[5] silica sulfate,[6] and chlorosulfonic acid[7] in organic solvents have been carried out. Beckmann rearrangements in vapor-phase using solid catalysts such as metal oxides and zeolites have also been reported, however, such conditions cause rapid catalyst deactivation.[8] A few examples of solvent-free organo-catalyzed Beckmann rearrangements have been reported,[9] as well as in supercritical water.[10] Beckmann rearrangements of ketoximes by treatment with *p*-toluenesulfonyl chloride (TsCl) and different ILs as solvent and catalytic media such as NaOH[11] and pyridine[12] were needed. Very recently,[13] during the development of the present work, TsCl-catalyzed Beckmann rearrangement of ketoximes without the need of any other promoter has been described, but the reactions must be carried out in an anhydrous system which highly reduces its application in an industrial scale.

Over the past decade, ionic liquids (ILs) have attracted great interest because of their unusual properties, including negligible vapor pressure, broad liquid temperature range, and high capacity as specific solvents.[14] Their use in place of hazardous volatile organic solvents makes organic synthesis environmentally benign.[15] In recent years they have been used in the Beckmann rearrangement with considerable success, but the use of some catalysts such as P_2O_5,[16] PCl_5,[17] other Lewis acid,[18] and metaboric acid[19] and high temperatures (75–120 °C), were always needed. New ILs have been designed for being used as both solvent and catalyst in the Beckmann rearrangement, such as caprolactam-based ILs,[20] or sulfonyl chloride-functionalized ILs,[21] however, the separation of the desired product from the reaction mixture was difficult to achieve.

Though numerous procedures to obtain ε-caprolactam from cyclohexanone oxime have been developed, further investigations to obtain milder reaction conditions profitable for industrial purposes, allowing a clean and simple extraction of ε-caprolactam, are still needed. The main purpose of this work was to find some IL that could be used as solvent and/or catalyst of the Beckmann rearrangement of cyclohexanone oxime by treatment with TsCl. Particularly we were interested in obtaining a simple and mild procedure applicable for industrial purpose, avoiding the use of expensive or corrosive catalysts, toxic solvents, and anhydrous conditions.

2. Results and discussion

Initially, acetophenone oxime **1** was used as the substrate to examine the feasibility of Beckmann rearrangement by treatment

* Corresponding author. Tel.: +34 986 812290; fax: +34 986 812262.
E-mail address: etojo@uvigo.es (E. Tojo).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.145

with TsCl using different ILs as the reaction medium (Scheme 1). The results are summarized in Table 1. After 3.5–4.5 h *N*-phenylacetamide **2** was obtained in excellent yields and mild conditions (50 °C) when some ILs such as [MMIm][MSO_4] were used. The formation of the second possible amide (*N*-methylbenzamide) was not observed. The highest reaction rate and yield were observed for [MMIm][MSO_4] (3.5 h, 95%).

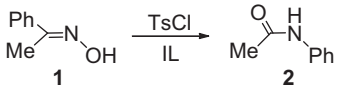
To explore the generality and scope of the method, it was applied to a series of alkyl and aryl oximes using [MMIm][MSO_4] (Scheme 2). This IL was also chosen for its easy preparation as well as its good balance of desirable physical and chemical properties. These include thermal stability, low viscosity, and a good capacity to dissolve organic substrates.

As expected, the best results were obtained when aryl ketoximes were used as substrates showing 100% of conversion and more than 75% of yield. Only one of the oximes (entry 1) was partially hydrolyzed to afford the corresponding acetone. The reactions are in general rapid and quantitative, one of the possible amides being the only product recovered from the reaction mixtures. All products were characterized by comparison of their melting points, IR, and ^1H and ^{13}C NMR spectra with those of the literature (see references Table 2). High levels of conversion and selectivity were observed in the Beckmann rearrangement of all ketoximes except for acetone oxime (entry 1) and cyclohexanone oxime (entry 7).

In order to increase the conversion of cyclohexanone oxime **3** to ε-caprolactam **4** (Scheme 3), the reaction using different ILs was investigated.

Very high levels of conversion and selectivity to afford ε-caprolactam were obtained with some ILs (Table 3) as shown by TLC. However, separation of the desired product from the reaction mixture through solvent extraction was very difficult to achieve. When [HMIm][TFA] or [HMIm][TsO] was used, a partial solubility of the product in the IL is observed, so ε-caprolactam is obtained impure as a mixture with the IL. In the case of [TMG][Ac] and [TMG][TFA], the reaction system became sluggish due to the formation of a solid salt that was identified by its spectral data as 1,1,3,3-tetramethylguanidine *p*-toluenesulfonate ([TMG][TsO], Scheme 4), which made difficult the product extraction. In order to avoid the anionic exchange that affords [TMG][TsO], this new salt was synthesized and employed instead of the IL to promote the rearrangement.

Taking into account the TsCl and [TMG][TsO] solubility, acetone as the reaction solvent was chosen (Scheme 5). Several experiments were carried out using different reagent concentrations (Ta-

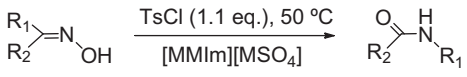


Scheme 1. Beckmann Rearrangement of acetophenone oxime **1** in ILs.

Table 1
Beckmann rearrangement of acetophenone oxime **1** in different ILs using 1.1 equiv of TsCl at 50 °C

Entry	Ionic liquid	Yield[a] (%)	Time (h)
1	[MMIm][MSO_4]	95	3.5
2	[HMIm][PF_6]	90	3.5
3	[HMIm][BF_4]	92	4.0
4	[TMG][TFA][b]	—	—
5	[HMIm][TFA][c]	—	—

[a] Yields referred to pure isolated product.
[b] Only traces of amide appeared in TLC after 24 h.
[c] No product was formed after 24 h.

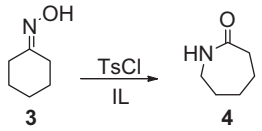


Scheme 2. Beckmann rearrangement of different oximes in [MMIm][MSO_4] using 1.1 equiv of TsCl at 50 °C.

Table 2
Beckmann rearrangement of different oximes in [MMIm][MSO_4] using 1.1 equiv of TsCl at 50 °C

Entry	R_1	R_2	Yield (%)	Time (h)	Ref.
1	Me	Me	15[b]	0.3	22
2	Ph	Me	98[a]	4	13
3	Ph	Ph	92[a]	5	13
4	*p*-(Me)-C_6H_4	Me	94[a]	4.5	13
5	*p*-(NO_2)-C_6H_4	Me	75[a]	7	23
6	$C_{10}H_7$	Me	95[a]	6	24
7	$(CH_2)_5$		50[c]	30	13

[a] Yields referred to pure isolated product.
[b] The oxime was partially hydrolyzed back to acetone.
[c] After 30 h of reaction only part of the starting material turns into ε-caprolactam.

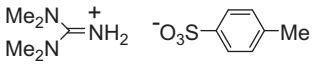


Scheme 3. Beckmann rearrangement of cyclohexanone oxime **3** to give ε-caprolactam **4** in different ILs.

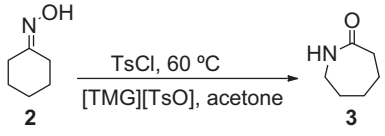
Table 3
Beckmann rearrangement of cyclohexanone oxime **3** in ILs using TsCl at 50 °C

Ionic liquid	Time (h)	Conv.%	Sel. (%)	Yield[a] (%)
[HMIm][PF_6]	>48	—	—	—[b]
[HMIm][TFA]	2.5	100	99	52[c]
[HMIm][TsO]	5.5	100	99	48[c]
[TMG][TFA]	5	100	99	24[d]
[TMG][Ac]	3.5	100	99	65[d]
[TMG][Lac]	>48	—	—	—[e]

[a] Yields referred to pure isolated product.
[b] The degradation of the IL is observed as the reaction progresses.
[c] After extraction with EtOAc the reaction product is obtained impure as a mixture with the IL.
[d] The reaction mixture becomes sluggish due to the formation of [TMG][TsO] which makes difficult the product extraction.
[e] Only traces of ε-caprolactam can be observed.



Scheme 4. 1,1,3,3-Tetramethylguanidine *p*-toluenesulfonate ([TMG][TsO]) structure.



Scheme 5. Beckmann rearrangement of cyclohexanone oxime **2** to give ε-caprolactam **3** by treatment with TsCl using [TMG][TsO] as the promoter.

Table 4
Beckmann rearrangement of cyclohexanone using TsCl in acetone/[TMG][TsO] at 60 °C

Entry	[TsCl] (equiv)	[[TMG][TsO]] (equiv)	Yield[a] (%)	Time (h)
1	1	1	95	18
2	1.5	1	98	12
3	2	1	97	9
4	1	2	95	13
5	2	2	98	6

[a] Yields referred to pure isolated product.

Table 5
Beckmann rearrangement of cyclohexanone using TsCl in acetone/[TMG][TsO] and under anhydrous conditions at 60 °C

Entry	[TsCl] (equiv)	[[TMG][TsO]] (equiv)	Yield[a] (%)	Time (h)
1	0.6	0.6	98[b]	11
2	0.6	—	28[c]	18

[a] Yields referred to pure isolated product.
[b] Product isolated by Section 4.2.
[c] Product isolated by column chromatography.

ble 4). The best result was obtained heating at 60 °C and using 2 equiv of both TsCl and [TMG][TsO]. Excellent levels of conversion (100%) and selectivity (99%) were obtained. The reaction finished in 6 h to obtain pure ε-caprolactam in a 98% yield. Pure [TMG][TsO] was recovered from the reaction medium and reused.

Knowing that the excess of TsCl needed was due to the presence of water that produces its hydrolysis, this effect was investigated by carrying out the reaction under anhydrous conditions. The solvent was dried over K_2CO_3 and distilled, TsCl was recrystallized and dried under vacuum, and the reaction was carried out under an inert atmosphere. As it is shown in Table 5, only catalytic amounts of TsCl are needed if the reaction is carried out under anhydrous conditions. If no [TMG][TsO] is added (entry 2), the reaction proceeds very slowly to give a mixture that after purification by column chromatography affords a low yield of pure ε-caprolactam (28%). These results indicate that [TMG][TsO] acts as a catalyst of both oxime tosylation and later rearrangement. In order to clarify the catalytic mechanism and the effect of [TMG][TsO], more experiments are now undergoing.

3. Conclusions

A new procedure to obtain ε-caprolactam has been developed. The Beckmann rearrangement of cyclohexanone oxime is carried out by treatment with TsCl using a new salt, [TMG][TsO], as the promoter. This procedure requires mild reaction conditions (60 °C) and affords high levels of conversion of 100% and selectivity (99%) to obtain pure ε-caprolactam in a 98% yield. The catalyst is cheap, easy to prepare, not corrosive and can be recovered and reused. The method does not require anhydrous conditions or toxic solvents. All these characteristics make the procedure applicable for an industrial purpose.

In addition, the Beckmann rearrangement of several ketoximes has been performed by treatment with tosyl chloride, using ionic liquids as both solvent and catalyst, without the need of any other promoter. High levels of conversion and selectivity were observed for aryl ketoximes, work-up is very simple and the product is isolated in high yields.

4. Experimental

The ILs [MMIm][MSO_4],[25] [HMIm][PF_6],[26] [HMIm] [BF_4],[27], [TMG][TFA],[28] [HMIm][TFA],[29] and [HMIm][TsO][30] were synthesized according to the previous papers. The oximes were either obtained from commercial sources or prepared by standard procedures.[31]

4.1. General procedure for Beckmann rearrangement of ketoximes in ILs (Tables 1–3)

The ketoxime (100 mg) and TsCl (1.1 equiv) were dissolved in IL (2 g). The mixture was stirred at 50 °C in a round-bottomed flask until completion of the reaction as indicated by TLC with hexane/AcOEt. The reaction mixture was then extracted with ethyl acetate (4 × 5 mL) or ^{t}BuOMe (4 × 5 mL) depending on the IL, and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed under vacuum affording a solid that was recrystallized from MeOH/H_2O (10:1).

4.2. General procedure for Beckmann rearrangement of cyclohexanone oxime promoted by TsCl/[TMG][TsO] (Table 4)

[TMG][TsO] (2 equiv) was dissolved in acetone (20 mL) heating at 60 °C. Cyclohexanone (100 mg) and TsCl (2 equiv) were added and the mixture was stirred at 60 °C for 6 h. Half of the acetone was eliminated under vacuum and the reaction mixture was cooled to 0 °C to precipitate [TMG][TsO], that was filtrated and recovered as a pure solid. The solvent was then completely removed under vacuum and water was added (10 mL) to precipitate the excess of TsCl (only for entries 3 and 5), that was filtered and recovered as a pure solid. Finally, ε-caprolactam was separated from the *p*-toluenesulfonic acid formed by extraction with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under vacuum affording ε-caprolactam as pure white crystals.

4.3. Synthesis of 1,1,3,3-tetramethylguanidine *p*-toluenesulfonate ([TMG][TsO])

Methanol (10 mL) and *p*-toluenesulfonic acid monohydrate (6.96 mmol) were loaded into a 50 mL round flask. A solution of 1,1,3,3-tetramethylguanidine (6.96 mmol) in methanol (10 mL) was added dropwise and the reaction mixture was stirred for 9 h at room temperature. The solvent was removed under reduced pressure affording a white solid that was recrystallized from acetone to afford [TMG][TsO] as colorless crystals in a yield of 99% (1.98 g); mp 150.5–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm, δ): 7.86 (br s, 2H, NH_2), 7.69 (d, 2H, J = 8.0 Hz, ArH-2,2′), 7.08 (d, 2H, J = 8.0 Hz, ArH-3,3′), 2.83 (s, 12H, NCH_3), 2.27 (s, 3H, Ar-CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm, δ): 161.7, 143.1, 139.2, 128.4, 125.7, 39.5, 21.1. HRMS-ESI m/z (%): 690 $[(TMG)_3(TsO)_2]^+$ (5), 404 $[(TMG)_2(TsO)+1]^+$ (12), 403.24741 $[(TMG)_2(TsO)]^+$ ($C_{17}H_{35}N_6O_3S$ requires 403.24859, 100).

Acknowledgments

We thank the Spanish Ministry of Education and Science and the Xunta de Galicia for financial support under projects CTQ2007-61788, CTQ2007-61272, and PGIDIT04BTF301031PR.

References and notes

1. (a) Gawley, R. E. *Org. React.* **1988**, *35*, 1–30; (b) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 6th ed.; Wiley & Sons: New York, 2007. pp 1613–1616.
2. Dahlhoff, G.; Niederer, J. P. M.; Hoelderich, W. F. H. *Cat. Rev.* **2001**, *43*, 381–441.
3. Butler, R. N.; O'Donoghue, D. A. *J. Chem. Res. (S)* **1983**, 18–20.
4. De, S. K. *Synth. Commun.* **2004**, *34*, 3431–3435.
5. Li, Z.; Lu, Z. *Lett. Org. Chem.* **2008**, *5*, 495–498.
6. Li, Z.; Ding, R.; Lu, Z.; Xiao, S.; Ma, X. *J. Mol. Catal. A* **2006**, *250*, 100–103.
7. Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* **2005**, *46*, 671–674.
8. Ishida, M.; Suzuki, T.; Ichihashi, H.; Shiga, A. *Catal. Today* **2003**, *87*, 187–194.

9. (a) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2003**, *44*, 7437–7439; (b) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2003**, *44*, 755–756; (c) Banerjee, K.; Mitra, A. K. *Indian J. Chem., Sect. B* **2005**, *44*, 1876–1879.
10. Boero, M.; Ikeshoji, T.; Liew, C. C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* **2004**, *126*, 6280–6286.
11. Brown, R. F.; Van Gulick, N. M.; Schmid, G. H. *J. Am. Chem. Soc.* **1955**, *77*, 1094–1097.
12. Vaidya, S. P.; Nayak, U. R. *Indian J. Chem., Sect. B* **1986**, *25*, 581–585.
13. Pi, H. J.; Dong, J. D.; An, N.; Du, W.; Deng, W. P. *Tetrahedron* **2009**, *65*, 7790–7793.
14. Poole, C. F. *J. Chromatogr., A* **2004**, *1037*, 49–82.
15. Welton, T.; Wasserscheid, P.. In *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, 2008; Vol. 1. pp 265–268.
16. Ren, R. X.; Zueva, L. D.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8441–8443.
17. (a) Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 403–405; (b) Elango, Y.; Srirambalaji, R.; Anantharaman, G. *Tetrahedron Lett.* **2007**, *48*, 9059–9062.
18. Zicmanis, A.; Katkevica, S.; Mekss, P. *Catal. Commun.* **2009**, *10*, 614–619.
19. Guo, S.; Deng, Y. *Catal. Commun.* **2005**, *6*, 225–228.
20. Guo, S.; Du, Z.; Zhang, S.; Li, D.; Li, Z.; Deng, Y. *Green Chem.* **2006**, *8*, 296–300.
21. Du, Z.; Li, Z.; Gu, Y.; Zhang, J.; Deng, Y. *J. Mol. Catal. A: Chem.* **2005**, *237*, 80–85.
22. Paranthaman, S.; Gounder, K. P. *J. Mol. Model.* **2004**, *10*, 198–203.
23. Pan, X. Q. *Tetrahedron Lett.* **2009**, *50*, 347–349.
24. Stuart, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475.
25. Pereiro, A. B.; Santamarta, F.; Tojo, E.; Rodríguez, A.; Tojo, J. *J. Chem. Eng. Data* **2006**, *51*, 952–954.
26. Pereiro, A. B.; Tojo, E.; Rodríguez, A.; Canosa, J.; Tojo, J. *Green Chem.* **2006**, *8*, 307–310.
27. Park, S.; Kazlauskas, R. J. *J. Org. Chem.* **2001**, *66*, 8395–8401.
28. Gao, H.; Han, B.; Li, J.; Jiang, T.; Wu, W.; Chang, Y.; Zhang, J. *Synth. Commun.* **2004**, *34*, 3083–3086.
29. Laali, K. K.; Gettwert, V. J. *J. Org. Chem.* **2001**, *66*, 35–40.
30. Li, S.; Lin, Y.; Xie, H.; Zhang, S.; Xu, J. *Org. Lett.* **2006**, *8*, 391–394.
31. Stradling, S. S.; Hornick, D.; Lee, J.; Riley, J. *J. Chem. Educ.* **1983**, *60*, 502–503.