The First I_2-Promoted Efficient Aminoacetylation of Activated Aziridines in Ionic Liquid

Vijai K. Rai,*[a,b] Nihar Sharma,[b] Anil Kumar[b]

[a] Department of Applied Chemistry, Institute of Technology, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh 495 009, India

[b] School of Biology and Chemistry, Shri Mata Vaishno Devi University, Katra, Jammu & Kashmir 182 320, India
Fax +91(7752)260148; E-mail: vijaikrai@hotmail.com

Received: 27.10.2012; Accepted after revision: 29.10.2012

Abstract: A novel and efficient aminoacetylation of aziridines is reported. Herein, 2-phenyl-1,3-oxazolan-5-one with tosylaziridines affords 3-(N-substituted)aminopyrrolidin-2-ones via regioselective terminal aziridine opening–aminoacetylative cyclization cascades. The reaction is performed using [bmim]OH/molecular iodine as a new catalyst system where ionic liquid [bmim]OH also works as reaction media and proceeds via an isolable intermediate. After isolation of the product, the ionic liquid, [bmim]OH can be easily recycled for further use without any loss of efficiency. No byproduct formation, operational simplicity, ambient temperature, high yield, and excellent diastereoselectivity are salient features of the present synthetic protocol.

Key words: pyrrolidine-2-ones, ionic liquid, aziridines, diastereoselectivity, molecular iodine

Aziridines are an elite class of compounds present in various natural products and have been useful intermediates as well as building blocks in organic synthesis.[1] In terms of synthetic transformations, the utility of aziridines derives from their selective ring-opening reactions with various nucleophiles, which often form the basis for more complex target syntheses, especially N-containing compounds.[2,3] γ-Butyrolactams (pyrrolidin-2-ones) are a class of versatile core structures present in various natural products such as isocynamatrine[4a,b] and clausenamide[4c–f] and are also important intermediates in the synthesis of a variety of nitrogenated heterocycles with interesting biological activities (Figure 1).[4–8]

Due to their versatile applications in organic and medicinal chemistry, the development of new synthetic routes for the preparation of pyrrolidin-2-ones is an important endeavor and has been well documented in the literature.[10–21] However, most of the reactions suffer from one or more disadvantages, such as expensive reagents, long reaction times, low yields, tedious workup, and, most importantly, none of these methods cater a direct process for the synthesis of 3-(N-substituted)aminopyrrolidin-2-ones and tend to be lengthy and cumbersome if the lactam contains any sort of substitution. Recently, Ghorai et al. have reported the synthesis of pyrrolidin-2-one via a nucleophilic ring opening with a methylene group[22a] in addition to other literature reports on the synthesis of 4-(N-substituted)aminopyrroildin-2-ones.[22b,c] Very recently, we have reported the synthesis of 3-mercapto-pyrrolidin-2-one starting via ring opening of aziridines with masked mercaptoacid.[22d] To date, there is no report on the direct synthesis of 3-aminopyrrolidin-2-ones.

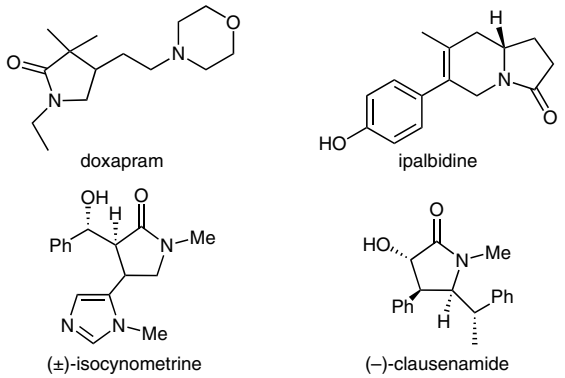


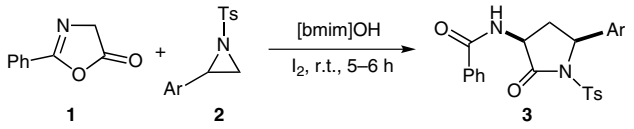
Figure 1 Pyrrolidin-2-one ring-containing natural products and pharmaceutical molecules

Ionic liquids (IL) have attracted much attention as environmentally friendly reaction media,[23–25] catalysts,[26–28] and reagents[29,30] and are also easy to recycle.[29,30] Moreover, the synthesis of amides is important in many areas of chemistry, including peptide, polymer, and complex molecule synthesis.[31] Inspired by these valid points and keeping the synthetic and pharmacological importance of the amide group in mind we turned our attention to utilize masked amino acids as substrates viz. 2-phenyl-1,3-oxazolan-5-one, which can introduce an amide group at the α position into γ-lactam, which is the target molecule in the present investigation.

In this Letter, we report a new molecular-iodine-catalyzed one-pot atom efficient method for the preparation of 3-(N-substituted)aminopyrrolidin-2-ones **3** in a single step using [bmim]OH as a green reaction promoter. This one-pot synthetic protocol is highly atom efficient as there is no byproduct formation and involves novel utilization of the masked amino acid 2-phenyl-1,3-oxazolan-5-one (**1**) with terminal aziridines **2** affording 3-(N-substituted)aminopyrrolidin-2-ones **3** in high yield and excellent diastereoselectivity, in favor of the *cis* isomer (Scheme 1). Furthermore, the present synthesis of 3-(N-substituted)amino functionalized γ-lactam **3** is an outcome of our

SYNLETT 2013, 24, 0097–0101
Advanced online publication: 04.12.2012
DOI: 10.1055/s-0032-1317675; Art ID: ST-2012-B0924-L

quest for developing new synthetic routes employing green chemistry protocols.[32]



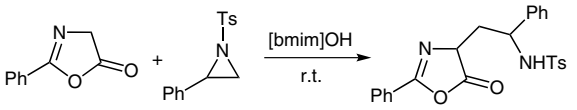
1 2 3

Scheme 1 One-pot aminoacetylation of aziridines **2** in ionic liquid [bmim]OH

In a preliminary experimentation, a controlled reaction was carried out using 2-phenyl-1,3-oxazolan-5-one (**1**) and aziridine **2a** (Ar = Ph) in [bmim]OH but the reaction did not afford the desired γ-lactam **3a** (Table 1, entry 1) even after 48 hours, rather conversion of tosylaziridines **2a** into the corresponding amine **4a** was observed (Scheme 2). Then, we turned our attention to use molecular iodine as catalyst in conjunction with different room-temperature ionic liquid (RTIL). For this purpose, 2-phenyl-1,3-oxazolan-5-one (**1**) and aziridine **2a** (R = Ph) were chosen as model substrates for the synthesis of representative compound **3a** (Table 1) wherein molecular iodine evidenced its catalytic efficacy in conjunction with RTIL, affording **3a** in excellent yield (Table 1, entry 1). A variety of RTIL were screened for the present reaction and amongst [bmim]BF_4, [bmim]OH, [bmim]PF_6, and [bmim]Br, [bmim]OH was found to be the most effective RTIL for the conversion of the tosyl aziridine **2a** to the corresponding γ-lactam **3a** (Table 1, entries 2–4).

In order to elucidate the role of other solvents in lieu of RTIL as reaction medium, various solvents were used under the present reaction conditions. The results validate our premise that the reaction would not only be faster but also result in higher yield using RTIL as compared to other conventional solvents (Table 1, entries 2, 5–9). Interestingly, yield of the target compound **3a** is poor using polar aprotic solvents (Table 1, entries 8 and 9). Thus, RTIL [bmim]OH stands out as the choice, with its fast conversion and quantitative yield in conjunction with molecular iodine, as an inexpensive and versatile catalyst in the present envisaged synthetic protocol. The optimum catalyst loading for molecular iodine was found to be 10 mol%. When the amount of catalyst decreased from 10 mol% to 5 mol% relative to the substrates, the yield of product **3a** was reduced (Table 2, entries 2 and 10). However, the use of 15 mol% of the catalyst showed the same yield, and the same time was required (Table 1, entries 2 and 11). It was noted that a higher reaction temperature (up to 60 °C) instead of room temperature had no appreciable effect on the yield.

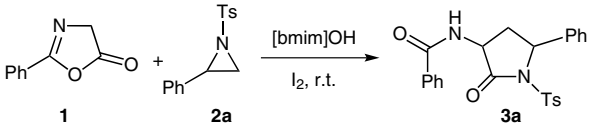
Next, in order to investigate the substrate scope for the general validity of the present investigation, a variety of tosyl aziridines **2** were used under the optimized reaction conditions, and different 3-(N-substituted)aminopyrrolidin-2-ones **3** were synthesized. The yields were consistently good (Table 2), and the highest yield was 96% (Table 2, entry 3). Thus, the present optimized synthesis is accomplished by stirring a mixture of 2-phenyl-1,3-oxazolan-5-one (**1**), aziridine **2**, and molecular iodine in [bmim]OH at room temperature for 5–6 hours.[33]



1 2a 4a

Scheme 2 Reaction of masked amino acid **1** and aziridines **2** in [bmim]OH

Table 1 Optimization of Reaction Conditions for the Formation of **3a**[a]



1 2a 3a

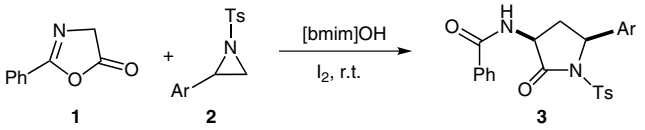
Entry	RTIL/solvent	I_2 (mol%)	Time (h)[b]	Yield (%)[c]
1	[bmim]OH	–	48	–
2	[bmim]OH	10	5	94
3	[bmim]PF_6	10	10	86
4	[bmim]Br	10	10	88
5	1,4-dioxane	10	17	74
6	MeCN	10	15	78
7	CH_2Cl_2	10	18	75
8	DMF	10	16	41
9	DMSO	10	16	46
10	[bmim]OH	5	5	88
11	[bmim]OH	15	5	94

[a] Reaction conditions: **1** (2 mmol), **2a** (2 mmol), I_2 (0.2 mmol), [bmim]OH (5 mL).
[b] Stirring time at r.t.
[c] Yield of isolated and purified product **3a**.

Isolation and purification by recrystallization afforded the target compound **3** in 85–96% yield with 96–98% diastereoselectivity (Table 2) in favor of the *cis* isomer. Product **3** was extracted with EtOAc leaving the [bmim]OH behind, which can be recycled easily for further use without loss of efficiency (Table 3). The diastereomeric ratios in the crude isolates were checked by ^{1}H NMR spectroscopy to note any alteration of these ratios during subsequent purification. The crude isolates of **3** were found to be a diastereomeric mixture containing 96–98% of the *cis* isomer.

On the basis of ^{1}H NMR spectroscopy and the literature precedent,[34] the *cis* stereochemistry was conclusively assigned to **3**, as their coupling constants ($J_{5H,4Ha}$ = 7.0–7.6 Hz, $J_{5H,4Hb}$ = 6.3–6.7 Hz) was lower than that for the minor *trans* isomer ($J_{5H,4Ha}$ = 10.5–10.8 Hz, $J_{5H,4Hb}$ = 11.5–11.9 Hz). Furthermore, the assigned *cis* stereochemistry of lac-

Table 2 One-Pot Synthesis of 3-(N-Substituted)aminopyrrolidin-2-ones **3**



1 **2** **3**

Entry	Aziridine **2**	Ar	Time (h)[a,b]	Product **3**	Yield (%)[c,d]	*cis*/*trans*[e]
1	**2a**	Ph	5	**3a**	94	96:4
2	**2b**	4-$MeOC_6H_4$	5	**3b**	89	96:4
3	**2c**	4-$O_2NC_6H_4$	5	**3c**	96	98:2
4	**2d**	4-BrC_6H_4	5	**3d**	93	96:4
5	**2e**	4-ClC_6H_4	5	**3e**	92	98:2
6	**2f**	3-ClC_6H_4	5	**3f**	95	98:2
7	**2g**	4-MeC_6H_4	6	**3g**	88	97:3
8	**2h**	4-AcC_6H_4	6	**3h**	91	97:3
9	**2i**	4-FC_6H_4	5	**3i**	85	96:4
10	**2j**	3-MeC_6H_4	6	**3j**	91	97:3
11	**2k**	3-BrC_6H_4	5	**3k**	94	98:2
12	**2l**	1-naphthyl	5	**3l**	89	98:2

[a] Reaction conditions: **1** (2 mmol), **2a** (2 mmol), I_2 (0.2 mmol), [bmim]OH (5 mL).
[b] Stirring time at r.t.
[c] Yield of isolated and purified product.
[d] All compounds gave C, H, and N analyses ± 0.39% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR] and MS (EI) data.
[e] As determined by ^{1}H NMR spectroscopy of the crude products.

tams **3** was also established by NOE observations (Figure 2). For example, 7.8% NOE was observed by between 5-H and 4-H_a; 8.1% between 3-H and 4-H_a of product **3a**. This indicates that 3-H, 4-H_a, and 5-H are located on the same face of the molecule, that is, *cis* to one another.

The formation of 3-(N-substituted)aminopyrrolidin-2-ones **3** can be rationalized by nucleophilic attack of the methylene carbon (C-4) of the masked amino acid **1** to the less substituted carbon of tosyl aziridine **2** regioselectively, followed by protonation of aziridine nitrogen leading to the intermediate **4** (Scheme 3). The adduct **4** undergoes intramolecular nucleophilic attack of the nitrogen atom of the NHTs group at the carbonyl carbon (C-5) of the 1,3-oxazolan-5-one moiety to yield the target compounds **3** (Scheme 3). This conclusion is based on the observation that the representative intermediate compounds **4a** (Ar = Ph), **4e** (Ar = 4-ClC_6H_4), and **4i** (Ar = 4-FC_6H_4) could be isolated in 41–49% yield, these could be converted into the corresponding lactams **3a**, **3e**, and **3i** in quantitative yields.[35]

Presumably, in the ring-transformation step, iodine plays a key role in the reaction by polarizing the carbonyl group of the substrate **1**, thereby enhancing the electrophilicity of the carbonyl carbon, which facilitates the nucleophilic attack of the NHTs of aziridine **2**. Usually, the electronic factor favors the aziridine ring opening by a nucleophilic attack at the benzylic carbon. However, when the steric factor predominates over the electronic factor, the nucleophile prefers to attack at the terminal carbon rather than the benzylic carbon.[36] Here, presumably due to bulky nature of the attacking nucleophile, the steric factor predominates over the electronic effect to afford products **3**.

Table 3 Recyclability of [bmim]OH in the Synthesis of **3a**

Run	1	2	3	4	5
Yield (%)	96	96	95	95	92

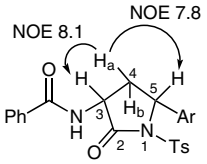
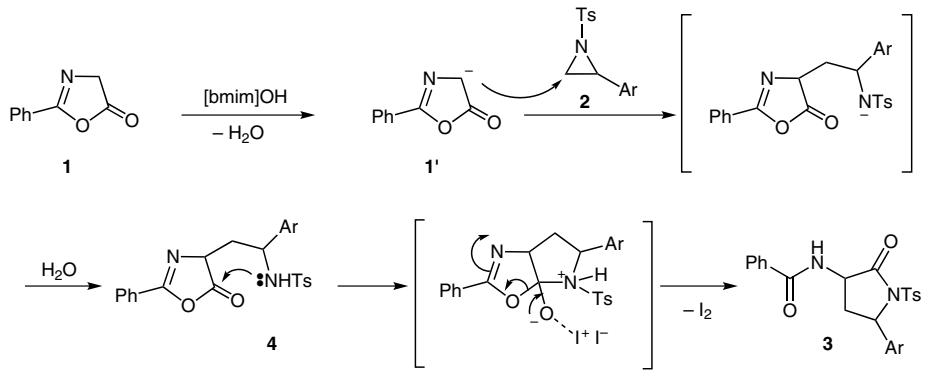


Figure 2 NOE observations of pyrrolidin-2-ones **3**

In conclusion, we have documented an original and practical regio- and diastereoselective route to synthetically and pharmaceutically important 3-(N-substituted)aminopyrrolidin-2-ones via nucleophilic aziridine ring opening with a novel substrate viz. 2-phenyl-1,3-oxazolan-5-one.



Scheme 3 Plausible mechanism for the formation of 3-(N-substituted)aminopyrrolidin-2-ones **3**

The efficacy of the reaction lies in its high yield, no by-product formation, ambient temperature, and recyclability of the ionoc liquid [bmim]OH. Thus, this simple methodology would be a practical alternative to the existing procedures for the production of this kind of fine chemicals to cater to the need of academia as well as of industry.

Acknowledgment

We sincerely thank the CSIR, New Delhi (01(2441)/10/EMR-II) and UGC, New Delhi [F. No. 39-764/2010 (SR)] for financial support. We are also thankful to IIIM Jammu and SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra.

References and Notes

(1) (a) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 1049. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (c) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, **2006**. (d) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (e) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(2) (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (c) Grahm, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966. (d) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (e) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160.

(3) (a) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270. (b) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471. (c) Lu, P. *Tetrahedron* **2010**, *66*, 2549. (d) Garima, V. P. S.; Yadav, L. D. S. *Green Chem.* **2010**, *12*, 1460. (e) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 79. (f) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.

(4) (a) Khuong-Huu, F.; Monseur, X.; Ratle, G.; Lukacs, G.; Goutarel, R. *Tetrahedron Lett.* **1973**, *14*, 1757. (b) Chiaroni, A.; Riche, C.; Tchissambou, L.; Khuong-Huu, F. *J. Chem. Res., Synop.* **1981**, 182. (c) Yang, M.-H.; Cao, Y.-H.; Li, W.-X. *Yaoxue Xuebao* **1987**, *22*, 33. (d) Xu, L.; Liu, S.-L.; Zhang, J.-T. *Chirality* **2005**, *17*, 239. (e) Yu, L.; Liu, G. *Zhongguo Yaoxue Zazhi* **2000**, *35*, 446. (f) Liu, Y.; Shi, C. Z.; Zhang, J. T. *Yaoxue Xuebao* **1991**, *26*, 166.

(5) (a) Yang, D.; Lian, G.-Y.; Yang, H.-F.; Yu, J.-D.; Zhang, D.-W.; Gao, X. *J. Org. Chem.* **2009**, *74*, 8610. (b) Duan, X. J.; Li, X. M.; Wang, B. G. *J. Nat. Prod.* **2007**, *70*, 1210. (c) Donohue, S. R.; Krushinski, J. H.; Pike, V. W.; Chernet, E.; Phebus, L.; Chesterfield, A. K.; Felder, C. C.; Halldin, C.; Schaus, J. M. *J. Med. Chem.* **2008**, *51*, 5833. (d) Kulig, K.; Sapa, J.; Nowaczyk, A.; Filipek, B.; Malawska, B. *Eur. J. Med. Chem.* **2009**, 3994. (e) Chang, T.; Hattori, M.; Sheu, C. WO 2009094807-A1, **2009**. (f) Ngo, V. X.; Old, D. W. WO 2009055289-A2, **2009**. (g) Hook, D.; Ruch, T.; Riss, B.; Wietfeld, B.; Sedelmeier, G.; Napp, M.; Baenziger, M.; Hawker, S.; Ciszewski, L.; Waykole, L. M. WO 2008083967-A2, **2008**. (h) Bush, J. K.; Hansen, M. M.; Li, R.; Mabry, T. E.; Snyder, N. J.; Wallace, O. B.; Xu, Y. WO 2007127688-A2, **2007**. (i) Kenda, B.; Quesnel, Y.; Ates, A.; Michel, P.; Turet, L.; Mercier, J. WO 2006128692-A2, **2006**.

(6) (a) Kralj, D.; Novak, A.; Dahmann, G.; Grošelj, U.; Meden, A.; Svete, J. *J. Comb. Chem.* **2008**, *10*, 664. (b) Bagnoli, L.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Scarponi, C.; Tiecco, M. *J. Org. Chem.* **2010**, *75*, 2134.

(7) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149; and references cited therein.

(8) (a) Biggs-Houck, J. E.; Davis, R. L.; Wei, J.; Mercado, B. Q.; Olmstead, M. M.; Tantillo, D. J.; Shaw, J. T. *J. Org. Chem.* **2012**, *77*, 160. (b) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.

(9) Elford, T. G.; Lesanko, A. U.-L.; Pascale, G. D.; Wright, G. D.; Hall, D. G. *J. Comb. Chem.* **2009**, *11*, 155.

(10) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981.

(11) Yang, L.; Zheng, Q.-Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Org. Lett.* **2008**, *10*, 2461.

(12) Pelletier, S. M.-C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2009**, *11*, 4512.

(13) Mapes, C. M.; Mani, N. S. *Org. Process Res. Dev.* **2007**, *11*, 482.

(14) Sell, M. S.; Klein, W. R.; Rieke, R. D. *J. Org. Chem.* **1995**, *60*, 1077.

(15) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2000**, *65*, 6688.

(16) Garcia, A. L. L.; Carpes, M. J. S.; de Oca, A. C. B. M.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050.

(17) Krawczyk, H.; Albrecht, Ł.; Wojciechowski, J.; Wolf, W. M.; Krajewska, U.; Różalski, M. *Tetrahedron* **2008**, *64*, 6307.

(18) Xie, C.; Han, D.; Hu, Y.; Liu, J.; Xie, T. *Tetrahedron Lett.* **2010**, *51*, 5238.

(19) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621.

(20) Leśniak, S.; Pasternak, B. *Tetrahedron Lett.* **2005**, *46*, 3093.

(21) Leśniak, S.; Nazarski, R. B.; Pasternak, B. *Tetrahedron* **2009**, *65*, 6364.

(22) (a) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 6173. (b) Bisol, T. B.; Bortoluzzi, A. J.; Sá, M. M. *J. Org. Chem.* **2011**, 948. (c) Hoang, C. T.; Bouillére, F.; Johannesen, S.; Zulauf, A.; Panel, C.; Pouilhés, A.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Org. Chem.* **2009**, *74*, 4177. (d) Rai, V. K.; Rai, P. K.; Bajaj, S.; Kumar, A. *Green Chem.* **2011**, *13*, 1217.

(23) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363.

(24) Bao, W.; Wang, Z. *Green Chem.* **2006**, *8*, 1028.

(25) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157.

(26) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667.

(27) Qiao, K.; Yakoyama, C. *Chem. Lett.* **2004**, *33*, 472.

(28) Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* **2003**, *44*, 2409.

(29) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2005**, *46*, 1489.

(30) Earle, M. J.; Ktdare, S. P.; Seddon, K. R. *Org. Lett.* **2004**, *6*, 707.

(31) (a) Benz, G. In *Comprehensive Organic Synthesis*; Vol. 6; Trost, B. M.; Fleming, I., Eds.; Chap. 2.3; Pergamon Press: Oxford, **1991**. (b) Albericio, F.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. *Org. Prep. Proced. Int.* **2001**, *33*, 203.

(32) (a) Rai, V. K.; Tiku, P.; Kumar, A. *Synth. Commun.* **2012**, *42*, 1489. (b) Rai, V. K.; Singh, S.; Singh, P.; Yadav, L. D. S. *Synthesis* **2010**, 4051. (c) Yadav, L. D. S.; Singh, S.; Rai, V. K. *Green Chem.* **2009**, *11*, 878. (d) Yadav, L. D. S.; Rai, V. K. *Tetrahedron Lett.* **2006**, *47*, 395.

(33) **General Procedure for the Synthesis of γ-Lactams 3**
A mixture of 2-phenyl-1,3-oxazol-5-one (**1**, 2.0 mmol), tosylaziridine **2** (2.0 mmol), and a catalytic amount of I_2 (0.2 mmol) in [bmim]OH (5 mL) was stirred at r.t. for 5–6 h. After completion of the reaction as indicated by TLC, H_2O (10 mL) was added, and the mixture was extracted thrice

with EtOAc (10 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure to afford an analytically pure sample of a single diastereomers **3** (Table 2). After isolation of the products, the remaining aqueous layer containing the ionic liquid was washed with hexane and dried in vacuum resulting in recycled ionic liquid, [bmim]OH (Table 3). The structure of the product **3** was confirmed by their elemental and spectral analyses.

Characterization Data of Representative Compounds 3

Compound **3a**: colorless solid, mp 103–104 °C. IR (KBr): ν_{max} = 3348, 3031, 2938, 1746, 1701, 1605, 1583, 1451 cm^{-1}. ^1H NMR (400 MHz, $_3$): d = 2.31 (s, 3 H), 2.81 (ddd, *J* = 10.8, 7.1, 4.3 Hz, 1 H), 2.90 (ddd, *J* = 10.8, 8.9, 6.5 Hz, 1 H), 4.61 (ddd, *J* = 8.9, 7.5, 4.3 Hz, 1 H), 4.89 (dd, *J* = 7.1, 6.5 Hz, 1 H), 7.21–7.49 (m, 10 H), 7.85–7.98 (m, 4 H), 8.12 (br, exch, 1 H). ^{13}C NMR (100 MHz $_3$): d = 25.1, 33.7, 43.3, 53.5, 127.1, 127.9, 128.6, 129.3, 130.0, 130.7, 132.5, 133.2, 133.8, 134.7, 139.2, 140.1, 171.0, 178.3. MS (EI): *m/z* = 434 [M^+]. Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.59; H, 5.31; N, 6.27

Compound **3e**: colorless solid, mp 151–153 °C. IR (KBr): ν_{max} = 3355, 3032, 2925, 1741, 1701, 1596, 1577, 1451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d = 2.28 (s, 3 H), 2.78 (ddd, *J* = 10.7, 7.4, 4.8 Hz, 1 H), 2.90 (ddd, *J* = 10.7, 9.0, 6.6 Hz, 1 H), 4.63 (ddd, *J* = 9.0, 7.5, 4.8 Hz, 1 H), 4.85 (dd, *J* = 7.4, 6.6 Hz, 1 H), 7.26–7.53 (m, 9 H), 7.88–7.91 (m, 4 H), 8.15 (br, exch, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): d = 25.5, 33.2, 43.8, 54.0, 127.2, 127.9, 128.7, 129.5, 130.1, 130.8, 131.4, 132.0, 132.7, 133.3, 134.0, 138.9, 171.2, 178.2. MS (EI): *m/z* = 468, 470 [M^+, $M^+ + 2$]. Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$: C, 61.47; H, 4.51; N, 5.97. Found: C, 61.69; H, 4.13; N, 6.19.

Compound **3i**: colorless solid, mp 135–137 °C. IR (KBr): ν_{max} = 3350, 3029, 2932, 1743, 1702, 1601, 1578, 1445 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d = 2.28 (s, 3 H), 2.82 (ddd, *J* = 10.9, 7.1, 4.3 Hz, 1 H), 2.92 (ddd, *J* = 10.9, 8.9, 6.7 Hz, 1 H), 4.66 (ddd, *J* = 8.9, 7.5, 4.3 Hz, 1 H), 4.86 (dd, *J* = 7.1, 6.7 Hz, 1 H), 7.19–7.55 (m, 9 H), 7.79–7.92 (m, 4 H), 8.17 (br, exch, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): d = 25.6, 33.1, 43.5, 53.5, 127.7, 128.4, 129.0, 129.6, 130.3, 131.1, 131.8, 132.5, 133.2, 134.0, 134.8, 140.1, 171.0, 178.8. MS (EI): *m/z* = 452 [M^+]. Anal. Calcd for $C_{24}H_{21}FN_2O_4S$: C, 63.70; H, 4.68; N, 6.19. Found: C, 63.89; H, 4.91; N, 5.87.

(34) Brace, N. O. *J. Fluorine Chem.* **2003**, *123*, 237.

(35) Isolation of **4a** (Ar = Ph), **4e** (Ar = 4-ClC_6H_4), and **4i** (Ar = 4-FC_6H_4) and Their Conversion into the Corresponding Pyrrolidin-2-ones **3a**, **3e**, and **3i**

The procedure followed was the same as described above for the synthesis of **3**, except that the reaction time in this case was only 2 h instead of 5–6 h used for **3**. To obtain analytically pure samples of **3a**, **3e**, and **3i** and to assign stereochemistry the same procedure was adopted as described for **3a**, **3e**, and **3i**. Finally, these intermediates were stirred at r.t. for the next 3–4 h to give the corresponding cyclized products **3a**, **3e**, and **3i** respectively.

Characterization Data of Representative Compound

Compound 4a: IR (KBr): ν_{max} = 3345, 3030, 2930, 1708, 1605, 1581, 1455 cm^{-1}. ^1H NMR (400 MHz, $_3$): d = 2.23 (s, 3 H), 2.51–2.53 (m, 2 H), 3.81 (m, 1 H), 4.01 (dd, *J* = 7.9, 3.8 Hz, 1 H), 5.29 (br, exch, 1 H), 7.21–7.59 (m, 12 H), 7.85–7.81 (m, 2 H). ^{13}C NMR (100 MHz, $_3$): d = 25.1, 37.2, 45.5, 64.2, 126.7, 127.5, 128.2, 129.0, 129.7, 130.3, 132.0, 132.6, 133.3, 134.0, 135.2, 138.5, 169.8, 177.2. MS (EI): *m/z* = 434 [M^+]. Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.63; H, 4.88; N, 6.19.

(36) (a) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270. (b) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471. (c) Lu, P. *Tetrahedron* **2010**, *66*, 2549. (d) Garima, V. P. S.; Yadav, L. D. S. *Green Chem.* **2010**, *12*, 1460. (e) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 79.