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Synthesis of aziridines from imines and ethyl diazoacetate in room temperature ionic liquids

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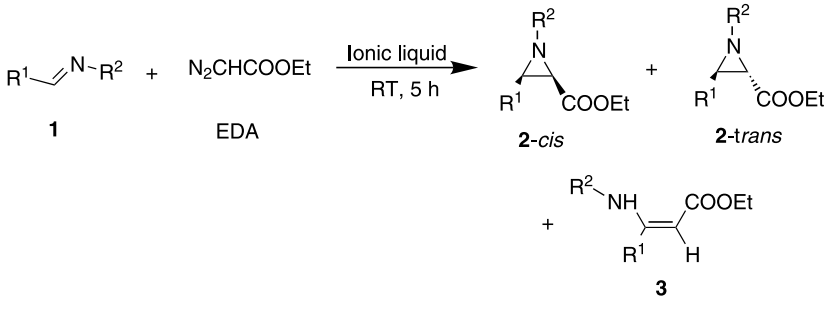
Abstract—The synthesis of aziridines from imines and ethyl diazoacetate in room temperature ionic liquids is reported. The reactions proceed readily under mild conditions with high *cis* selectivities and high yields.

Due to their highly regio- and stereoselective ring-opening reactions, aziridines are valued as building blocks for the synthesis of a wide range of nitrogen-containing compounds.[1] Therefore, a general methodology for one-step formation of aziridines would be very useful. Recently, several groups have developed transition metal catalyzed aziridinations based on [*N*-(-*p*-toluenesulfonyl)imino] phenyliodinane (PhI=NTs) as the nitrene source[2] and transition metal-catalyzed aziridination processes using chloramine-T (Ts-N-ClNa) and bromamine-T (Ts-N-BrNa).[3] Routes to aziridines starting from imines have also been reported. For example, Jorgensen has reported reactions of imines with ethyl diazoacetate (EDA) catalyzed by $Cu(OTf)_2$.[4] The same reaction was also effectively catalyzed by methylrhenium trioxide[5] and Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$[6] and $InCl_3$.[7] A recent report demonstrated that $Ln(OTf)_3$ also catalyzed the synthesis of aziridines from imines and EDA.[8] Wulff has disclosed an extremely exciting result in the chiral arylborate (derived from VAPOL and VANOL) catalyzed reaction of ethyl diazoacetate and imines.[9]

Recent exploration of the industrial potential of green chemistry using room-temperature ionic liquids, particularly those based on 1,3-dialkylimidazolium cations such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($bmimBF_4$) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($bmimPF_6$), as novel reaction media has become an exciting area of research. Their utility in alkylation, esterification, acylation, hydroformylation, alkoxycarbonylation, hydrogenation, the Beckmann rearrangement, Baylis–Hillman, Biginelli, Diels–Alder and Heck reactions as well as in other organic transformations has been demonstrated.[10] Herein, we wish to report a convenient synthesis of aziridines from imines and EDA in ionic liquids at room temperature (Scheme 1).



Scheme 1.

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Table 1. Formation of azridines **2a–h** from imines **1a–h** and EDA in room temperature ionic liquids[a]

Entry	Ionic liquid	Imine	R^1	R^2	Product (yield%)[b]	
1[c]	$bmimBF_4$	**1a**	Ph	Ph	**2a** (82, *cis*:*trans* = 29.6:1)	**3a** (3)
2[c]	$bmimPF_6$	**1a**	Ph	Ph	**2a** (95, *cis* only)	**3a** (2)
3	$bmimPF_6$	**1a**	Ph	Ph	**2a** (93, *cis* only)	**3a** (3)
4[d]	$bmimPF_6$	**1a**	Ph	Ph	0	0
5[e]	$bmimPF_6$	**1a**	Ph	Ph	0	0
6	$bmimPF_6$	**1b**	*p*-Me-Ph	Ph	**2b** (83, *cis* only)	**3b** (8)
7	$bmimPF_6$	**1c**	*p*-Me-Ph	*p*-Me-Ph	**2c** (91, *cis* only)	
8	$bmimPF_6$	**1d**	*o*-MeO-Ph	Ph	**2d** (85, *cis* only)	
9	$bmimPF_6$	**1e**	*p*-Cl-Ph	Ph	**2e** (98, *cis* only)	
10	$bmimPF_6$	**1f**	*o*-Cl-Ph	Ph	**2f** (97, *cis* only)	
11	$bmimPF_6$	**1g**	*p*-NO_2-Ph	Ph	**2g** (98, *cis*:*trans* = 33.7:1)	
12	$bmimPF_6$	**1h**	*p*-Br-Ph	Ph	**2h** (98, *cis* only)	

[a] All reactions were carried out using 0.5 mmol of imine and 0.5 mmol of EDA in 1.5 ml of ionic liquid at room temperature for 5 h.
[b] Isolated yield, the ratio of *cis* and *trans* isomers was determined by GC–MS and ^1H NMR.
[c] 1 mmol of imine and 0.5 mmol of EDA.
[d] 0.5 mmol of imine, 0.5 mmol of EDA and 0.1 mmol of $bmimPF_6$ in 3 ml of CH_2Cl_2 at room temperature for 7 h.
[e] 0.5 mmol of imine, 0.5 mmol of EDA and 0.1 mmol of $bmimPF_6$ in 3 ml of hexane at room temperature for 7 h.

Table 2. Formation of azridines **2a** from imine **1a** and EDA in $bmimPF_6$ recycling[a]

Entry	Recycle no.	Product (yield%)[b]	
1	1	**2a** (93, *cis* only)	**3a** (3)
2	2	**2a** (93, *cis* only)	**3a** (3)
3	3	**2a** (93, *cis* only)	**3a** (3)
4	4	**2a** (94, *cis* only)	**3a** (2)
5	5	**2a** (91, *cis* only)	**3a** (4)

[a] 0.5 mmol of imine and 0.5 mmol of EDA in 1.5 ml of $bmimPF_6$ at room temperature for 5 h.
[b] Isolated yield, the ratio of *cis* and *trans* isomers was determined by GC–MS and ^1H NMR.

$BmimBF_4$ and $bmimPF_6$ ionic liquids were synthesized according to the procedures reported in the literature.[11] Entry 1 in Table 1 shows that $bmimBF_4$ produces an 82% yield of the aziridines **2a** with a diastereoselectivity of about 30:1, from 1 equiv. of imine **1a** and 0.5 equiv. of ethyl diazoacetate in $bmimBF_4$ for 5 h. When $bmimPF_6$ is used, a 95% yield of *cis*-**2a**[12] was obtained as a single product (Table 1, entry 2). With equimolar amounts of imine **1a** and EDA in $bmimPF_6$ for 5 h at the room temperature, a 93% yield of *cis*-**2a** was obtained (Table 1, entry 3). However, when a catalytic amount of $bmimPF_6$ was used, no aziridine was observed. As summarized in Table 1, arylimines with either electron donating or electron withdrawing groups react readily with EDA in $bmimPF_6$, affording the corresponding aziridines with high *cis* selectivities. In fact, for most of the reactions examined, only the *cis* aziridines were isolated. No carbene-coupling product was detected under these reaction conditions, however a small amount of **3** was obtained in some cases. It has been suggested that the formation of aziridines in ionic liquids proceeds in a similar manner to that previously proposed for typical Lewis acids.[6,8] A typical procedure was as follows: A mixture of the imine (0.5 mmol) and EDA (0.5 mmol) was stirred in 1.5 ml of the ionic liquid ($bmimPF_6$) at room temperature for 5 h. The products were extracted with petroleum ether and ethyl acetate (5:1) and purified by column chromatography on silica gel with petroleum ether and ethyl acetate (5:1) as eluent. The room temperature ionic liquid ($bmimPF_6$) was dried under vacuum for the next run. The resulting products were analyzed by NMR and GC–MS.

Being composed entirely of ions, ionic liquids are immiscible with some organic solvents. When the reaction is over, the products are easily extracted from the ionic liquids with petroleum ether and ethyl acetate (5:1). The ionic liquid ($bmimPF_6$) could be dried under vacuum for further use. The procedure was repeated five times and the results are shown in Table 2. It is obvious that the ionic liquid ($bmimPF_6$) still retains high conversion and *cis* selectivities during the fifth cycle. In addition, these reactions proceed readily at room temperature and do not need another Lewis acid promoter, such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$, etc.

In summary, we have demonstrated an aziridine synthesis in ionic liquids at room temperature. The reactions proceed readily under mild conditions and show high yields and *cis* selectivity. Further study regarding the mechanism is underway.

Acknowledgements

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12. Data of representative products: *cis*-ethyl 1,3-diphenylaziridine-2-carboxylate (*cis*-**2a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H), 3.22 (d, $J=6.7$ Hz, 1H), 3.61 (d, $J=6.8$ Hz, 1H), 3.91–4.12 (m, 2H), 7.05–7.40 (m, 10H); MS m/z 267 (M+, 25), 194 (100).