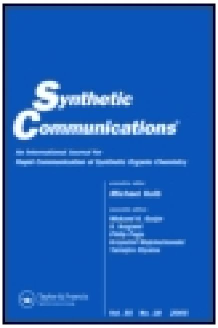

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Aminolysis of Epoxides in Ionic Liquid 1-Ethylpyridinium Trifluoroacetate as Green and Efficient Reaction Medium

Sanjay V. Malhotra [a] , Richard P. Andal [a] & Vineet Kumar [a]

[a] Department of Chemical and Environmental Science, New Jersey Institute of Technology, University Heights, Newark, New Jersey, USA

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Aminolysis of Epoxides in Ionic Liquid 1-Ethylpyridinium Trifluoroacetate as Green and Efficient Reaction Medium

Sanjay V. Malhotra, Richard P. Andal, and Vineet Kumar
Department of Chemical and Environmental Science, New Jersey Institute
of Technology, University Heights, Newark, New Jersey, USA

Abstract: Aminolysis of epoxides has been carried out using the ionic liquid 1-ethylpyridinium trifluoroacetate ([EtPy][TFA]) as reaction medium. The reactions went smoothly under mild conditions without any catalyst to afford corresponding β-aminoalcohols in high conversions. Moreover, further enhancement in the conversions was observed when $AlCl_3$ was used as Lewis acid catalyst.

Keywords: β-Amino alcohols, aminolysis, epoxides, ionic liquids

INTRODUCTION

β-Amino alcohols are important class of organic compounds obtained by nucleophilic ring opening of epoxides with amines. These compounds are used as building blocks for the synthesis of large number of medicinally and pharmaceutically important products[1] including synthetic amino acids.[2] They have also been used as chiral ligands in asymmetric synthesis.[3] The classical methods to synthesize β-amino alcohols require high temperatures and the use of excess amine.[4] Most often these reactions are slow and result in incomplete conversions. Also, the high reaction

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Address correspondence to Sanjay V. Malhotra, Laboratory of Synthetic Chemistry, SAIC Frederick Inc., National Cancer Institute at Frederick, 1050 Boyles Street, Frederick, MD 21702, USA (current address). E-mail: malhotrasa@mail.nih.gov

temperature is unfavorable to the control of selectivity and also harsh for certain functional groups. Subsequently, a wide range of methods have been developed for epoxide ring opening such as the use of enzymes,[5] alumina,[6] metal amides,[7] metal alkoxides,[8] metal triflates,[9] metal halides,[10] alkali metal perchlorates,[11] silica,[12] and montmorillonite clay[13] as catalysts or activators. However, most of these catalysts are moisture sensitive, difficult to handle, expensive, and required in stoichiometric amounts. Furthermore, with these catalysts, deactivated aromatic amines and some sterically hindered amines fail to open up epoxides or still require high temperature or pressure. In some cases, rearrangement of the oxiranes to allyl alcohols under the basic conditions[14] or polymerization in strongly acidic conditions has also been reported as side reactions.

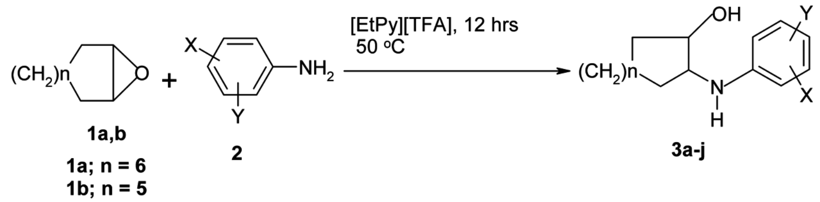
In the last decade, room-temperature ionic liquids (RTILs) have emerged as attractive alternatives to conventional organic solvents because of their advantageous properties (viz., negligible vapor pressure, nonflammability, recyclability, high thermal stability) and their ability to dissolve a wide range of organic and inorganic compounds. Most important, their properties can be adjusted to the reaction needs by proper manipulation of cations and anions.[15] Apart from tunable physical and chemical properties of ionic liquids, their immiscibility with various organic solvents enables the biphasic separation of the desired products and recyclability of expensive catalysts.[16] Despite such great properties and their applications in organic synthesis, there are very few examples of aminolysis of epoxide in ionic liquid medium. In on such report, tetrabutylammonium bromide has been utilized as reaction medium for these reactions, which is solid at room temperature and require high reaction temperatures.[16] In another report, 1-butyl-4-methyl imidazolium tetrafluoroborate has been used for synthesis of β-amino alcohols from epoxides.[17] But there are serious toxicity concern about imidazolium-based ILs. The studies show that toxicity of ILs increases with the number of nitrogen atoms in an aromatic cation ring and imidazolium-based ILs are reported to be more highly toxic than their pyridinium counterparts.[18] In our recent studies, we have proved that pyridinium-based ILs are not only nontoxic but also biodegradable.[19] In our attempts to develop cleaner methodologies for organic synthesis, we have reported the use of pyridinium-based ILs in a variety of reactions like Diels–Alder reactions,[20] Friedel–Craft alkylation,[21] Friedel–Craft acylation,[22] and asymmetric reductions of aromatic ketones.[23] Considering the importance of ionic liquids as an efficient new generation of reaction media, we report the application of ionic liquid 1-ethylpyridinium trifluoroacetate ([EtPy][TFA]) in the ring opening of epoxides by various aromatic amines.

RESULTS AND DISCUSSION

In a typical reaction, equimolar amounts of epoxide and amine were stirred with ionic liquid [EtPy][TFA] at 50 °C. It is important to note that no inert atmosphere was required for this reaction. After completion of the reaction, the product was extracted by diethyl ether, and ILs were recycled. Cyclohexenoxide (**1a**) and cyclopentenoxides (**1b**) were used as the epoxide in combination with different amines **2** to give corresponding β-amino alcohols **3a–j** with very high conversions (Scheme 1, Table 1). All the products were characterized by comparing their IR and ^{1}H NMR data with those reported in the literature. When the same reactions were carried out using 10 mol% of anhydrous $AlCl_3$, a further increase in conversions was observed in all the reactions. Moreover, in both the cases (i.e., in presence or absence of $AlCl_3$), the IL [EtPy][TFA] could easily be recovered and reused up to five cycles without loss of any activity. We also performed the same set of reactions in bulk using anhydrous $AlCl_3$ without any solvent or IL, but there was no significant conversion observed. These observations indicate that IL [EtPy][TFA] has a profound effect on the nucleophillic attack of amines on the epoxides.

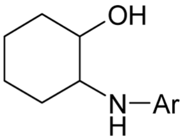
It is well reported in the literature that ILs can increase the nucleophilicity of amines,[30] which could be a reason for the reaction in the absence of any catalyst. With the addition of anhydrous $AlCl_3$, the acidity of the reaction medium further increased and the coordination of Al(III) with epoxide oxygen can further enhance the reaction, which is reflected by the higher conversions of β-amino alcohols in the [EtPy][TFA]-$AlCl_3$ system.

In conclusion, we have synthesized β-amino alcohols using IL liquid [EtPy][TFA] as reaction medium under mild and simple reaction conditions with easy work up. The IL [EtPy][TFA] is playing here the dual role of solvent as well as catalyst and could be easily recycled to make the protocol more economical and green. The conversions of products were further enhanced by using the [EtPy][TFA]-$AlCl_3$ system.



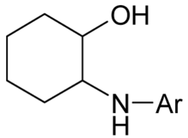
Scheme 1. Aminolysis of epoxides in ionic liquid.

Table 1. Catalytic ring opening of epoxides in [EtPy][TFA]

β-Amino alcohol	Yields (%)			
	$AlCl_3$ (no solvent)	[EtPy][TFA] (no catalyst)	[EtPy][TFA] + $AlCl_3$	Literature[a]
				
3a Ar = *o*-methoxyphenyl	5	78	90	70/7–11,[10a] 75/18[24] 95/3.5,[25] 80/12[26] 92, 94/20–30[9a] 70–85/18[27]
3b Ar = *m*-methoxyphenyl	10	83	99	94/2.5[25]
3c Ar = *o*,*o*′-dimethylphenyl	11	75	84	23/24,[28] 72/7[29] 50, 46/20–30[9a]

(*Continued*)

Table 1. Continued

β-Amino alcohol	Yields (%)			
	$AlCl_3$ (no solvent)	[EtPy][TFA] (no catalyst)	[EtPy][TFA] + $AlCl_3$	Literature[a]
3d Ar = *o*-methyl-*p*-chlorophenyl	12	77	88	—
3e Ar = *m*-bromophenyl	10	82	95	88, 93/20–30[9a] 92/12[26]
				
3f Ar = *o*-methoxyphenyl	5	70	85	56/20–24[10a] 61/18,[24] 80/12[26]
3g Ar = *m*-methoxyphenyl	10	80	98	—
3h Ar = *o*,*o*′-dimethylphenyl	8	74	82	72/15[29]
3i Ar = *o*-methyl-*p*-chlorophenyl	14	74	89	—
3j Ar = *m*-bromophenyl	8	75	92	—

[a] Yield (%)/time (h).

EXPERIMENTAL

The IL [EtPy][TFA] was synthesized following the procedure reported in the literature.[31] All other chemicals and reagents were of analytical grade and were used as obtained commercially.

General Procedure for Aminolysis of Epoxides in [EtPy][TFA] and Recovery of Ionic Liquid

The epoxide (2 mmol) was dissolved in the IL [EtPy][TFA] (2 ml) in a round-bottomed flask followed by the addition of aromatic amine (2.2 mmol). The reaction mixture was stirred for 12 h and the conversion was monitored by high performance liquid chromatography (HPLC) using C 18 column and isopropanol-hexane solvent mixure. After completion, the product was extracted with diethyl ether (3 × 15 ml) and further purified with silica-gel column chromatography using ethyl acetate/hexanes as solvent system. The ionic liquid left after product extraction was further washed with diethyl ether, dried in a vacuum oven at 60 °C for 8–12 h and used further for the same reaction. Some of the compounds synthesized are already known in literature and were characterized by matching their IR and ^{1}H NMR spectral data with those reported in the literature.

General Procedure for Aminolysis of Epoxides in [EtPy][TFA]-AlC$_3$ and Recovery of Ionic Liquid

The epoxide (2 mmol) was dissolved in the mixture of IL [EtPy][TFA] (2 ml) and anhydrous AlCl$_3$ (0.2 mmol) in a round-bottomed flask followed by addition of aromatic amine (2.2 mmol). The reaction mixture was stirred for 12 h, and the conversion was monitored by HPLC. After completion, the product was extracted with diethyl ether (3 × 15 ml) and further purified with silica-gel column chromatography using ethyl acetate/hexanes as solvent system. The viscous liquid left after product extraction was washed with diethyl ether, dissolved in 20 ml of dichloromethane, and passed through a silica-gel column to get the recovered IL, which was dried in a vacuum oven at 60 °C for 8–12 h and used further for the same reaction. ^{1}H and ^{13}C NMR spectra of new compounds are given here.

Data

Compound 3d

^{1}H (300 MHz, $CDCl_3$) δ7.09 (m, 1H), 6.43–6.73 (m, 2H), 4.84 (m, 1H), 3.70 (brs, 2H), 2.84 (m, 1H), 2.30 (s, 3H), 1.53–1.59 (m, 4H), 1.39 (m, 2H), 1.27 (m, 2H); ^{13}C (75.5 MHz, $CDCl_3$) δ145.96, 129.85, 127.65, 127.15, 116.88, 74.74, 61.71, 32.50, 28.10, 24.40, 20.90, 17.80.

Compound 3g

^{1}H (300 MHz, $CDCl_3$) δ6.82 (m, 1H), 6.02–6.35 (m, 3H), 4.54 (m, 1H), 4.27 (brs, 2H), 3.37 (m, 1H), 2.09 (m, 1H), 1.76 (m, 1H), 1.42–1.62 (m, 4H), 1.40 (s, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ160.96, 147.25, 129.22, 107.51, 106.41, 105.36, 76.99, 60.54, 32.67, 29.38, 20.19, 14.77.

Compound 3i

^{1}H (300 MHz, $CDCl_3$) δ7.09 (m, 1H), 6.44–6.73 (m, 2H), 4.53 (m, 1H), 3.62 (brs, 2H), 3.40 (m, 1H), 2.30 (s, 3H), 2.11 (m, 1H), 1.77 (m, 1H), 1.62 (m, 2H), 1.50 (m, 2H); ^{13}C (75.5 MHz, $CDCl_3$) δ145.96, 129.86, 129.22, 127.65, 127.15, 116.89, 76.99, 62.09, 32.67, 29.38, 20.19, 17.80.

Compound 3j

^{1}H (300 MHz, $CDCl_3$) δ7.18 (m, 3H), 6.52 (m, 1H), 4.53 (m, 1H), 3.36 (m, 1H), 2.93 (brs, 2H), 2.11 (m, 1H), 1.77 (m, 1H), 1.62 (m, 2H), 1.50 (m, 2H); ^{13}C (75.5 MHz, $CDCl_3$) δ148.60, 126.81, 124.57, 118.91, 117.58, 112.53, 76.99, 60.54, 32.67, 29.38, 20.19.

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