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$LiClO_4$-catalyzed highly diastereoselective synthesis of *cis*-aziridine carboxylates

J. S. Yadav,* B. V. S. Reddy, M. Shesha Rao and P. N. Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India

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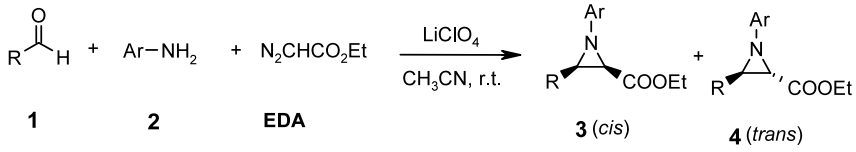
Abstract—Aldimines (generated in situ from aldehydes and amines) undergo ready addition with ethyl diazoacetate in the presence of a catalytic amount of lithium perchlorate in acetonitrile to afford the corresponding *cis*-aziridine carboxylates in high yields with high diastereoselectivity. 10 mol% $LiClO_4$ in acetonitrile provides a convenient catalytic media to perform the reactions under mild and neutral conditions.

Aziridines are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring opening contributes to their synthetic value.[1] The nucleophilic ring-opening of aziridines leads to many biologically active compounds such as α,β-unsaturated amino esters, β-lactam antibiotics and alkaloids.[2] Consequently, a variety of methods have been developed for the preparation of aziridines.[3] Among these methods, the nucleophilic addition of ethyl diazoacetate to imines is one of the most versatile methods for their synthesis.[4] Typically, copper salts are employed to promote the addition reactions of ethyl diazoacetate and imines to produce aziridine carboxylates.[5] Although, diazocarbonyl reactions are typically catalyzed by transition metal salts,[6] new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness. In this context, Lewis acids such as methylrhenium trioxide (MTO), $BF_3{\cdot}OEt_2$, $InCl_3$ and metal triflates including $Zn(OTf)_2$ and $Yb(OTf)_3$, have been reported for the addition of ethyl diazoacetate to imines.[7,8] In most cases, the products are obtained as a mixture of *cis*- and *trans*-aziridines and also the yields and selectivities reported are far from satisfactory. Furthermore, many of these reactions cannot be carried out in a one-pot operation with an aldehyde, amine and ethyl diazoacetate, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. In order to circumvent some of the problems associated with these methods, a one-pot procedure has recently been developed for this conversion using lanthanide triflate as a novel catalyst.[9] Even though, this method does not require the isolation of unstable imines, metal triflates are strongly acidic and are expensive. The development of mild and neutral alternatives such as lithium perchlorate would extend the scope and generality of this process.

In recent years, $LiClO_4$ in diethyl ether (LPDE) has emerged as a mild Lewis acid imparting high regio-, chemo- and stereoselectivity in various organic transformations.[10] Lithium perchlorate is found to retain its activity even in the presence of amines and has also been found to activate effectively nitrogen-containing compounds such as imines.[11]

In this report, we wish to describe a simple and convenient method for the synthesis of *cis*-aziridine carboxylates from imines and ethyl diazoacetate (EDA) using



Scheme 1.

* Corresponding author. Fax: +91-40-27160512; e-mail: yadav@iict.ap.nic.in

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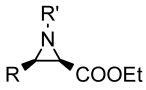
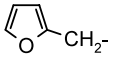
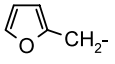
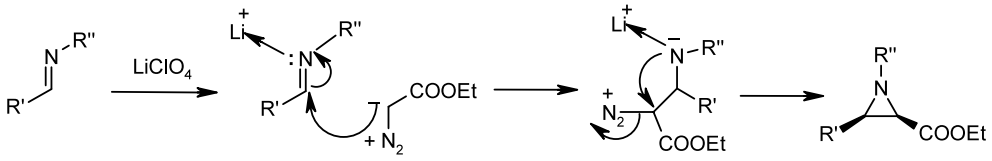
10 mol% lithium perchlorate in acetonitrile under mild reaction conditions[12] (Scheme 1).

A variety of aldimines (derived in situ from aldehydes and amines) reacted smoothly with ethyl diazoacetate to produce the corresponding aziridines in high yields (see Table 1). In all cases, the reactions proceed readily under mild conditions and are highly stereoselective, affording predominantly *cis*-aziridines, as evident from the ^{1}H NMR spectra of the crude products. The *cis*-stereochemistry of the aziridine **3a** was confirmed by the large coupling constant ($J=6.9$ Hz) of the aziridine

Table 1. $LiClO_4$-catalyzed synthesis of *cis*-aziridine carboxylates from imines

Entry	Aldehyde	Amine	Product[a]	Time (h)	Yield (%)[b]	*cis:trans*
	R-CHO	R'-NH_2				
a	R = Ph	R' = Ph	**3a**	4.5	89	*cis only*
b	R = 4-Me-Ph	R' = 4-Cl-Ph	**3b**	5.0	91	*cis only*
c	R = 2-Naphthyl	R' = Ph	**3c**	6.5	84	*cis only*
d	R = Ph	R' = 4-F-Ph	**3d**	5.5	87	*cis only*
e	R = 4-NO_2-Ph	R' = Ph	**3e**	6.0	75	85:15
f	R = 3-NO_2-Ph	R' = 4-Br-Ph	**3f**	6.5	79	82:18
g	R = 4-Cl-Ph	R' = 4-Cl-Ph	**3g**	5.0	86	*cis only*
h	R = 4-Me-Ph	R' = Ph	**3h**	4.5	90	*cis only*
i	R = 4-Me-Ph	R' = 4-Br-Ph	**3i**	5.5	85	*cis only*
j	R = 4-HO-Ph	R' = Ph	**3j**	6.0	80	*cis only*
k	R = Ph	R' = 	**3k**	5.0	87	97:3
l	R = 4-Cl-Ph	R' = 	**3l**	5.5	89	95:5
m	R = Ph	R' = $PhCH_2$-	**3m**	6.0	85	*cis only*
n	R = 4-Cl-Ph	R' = Ph	**3n**	4.5	90	*cis only*
o	R = 4-MeO-Ph	R' = Ph	**3o**	5.0	86	*cis only*
p	R = *n*-C_5H_{11}-	R' = Ph	**3p**	6.0	78	92:8
q	R = *n*-C_9H_{19}-	R' = Ph	**3q**	7.5	75	89:11
r	R = $PhCH_2CH_2$-	R' = Ph	**3r**	5.5	80	87:13

[a]All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b]Yield refers to pure products after column chromatography



Scheme 2.

ring hydrogens at δ 3.20 and 3.59 (the ring protons of *trans*-**3a** appear at δ 3.20 and 3.80 with a smaller coupling constant, $J=2.0$–3.0 Hz). The *cis*-stereochemistry of the products was further confirmed by comparing their spectral data with authentic compounds.[8] In the absence of catalyst, no reaction was observed after a mixture of imine and EDA was stirred in acetonitrile at room temperature for 12 h. The reaction probably proceeds through the activation of the imine by complexation with lithium perchlorate followed by nucleophilic addition of EDA on the C=N double bond and subsequent ring closing with loss of N_2 resulting in the formation of the aziridine **3** (Scheme 2).

It is of interest to mention that no side products such as an enamine or diethyl maleate were observed when acetonitrile or nitromethane were used as the solvent. However, treatment of an ethereal solution of *N*-benzylideneaniline with variable amounts of lithium perchlorate and 1 equiv. of ethyl diazoacetate also resulted in the formation of an aziridine. In other cases, the formation of aziridines was accompanied by the enamine as a side product when the reaction was performed using a stoichiometric amount of lithium perchlorate in diethyl ether. It has been suggested that the lithium perchlorate catalyzed aziridination in ether proceeds in the manner proposed previously for typical Lewis acids.[7] The use of 10 mol% of $LiClO_4$ in acetonitrile or in nitromethane was found to be the most ideal. A lower loading resulted in both a prolonged reaction time and lower yields. For instance, when using 5 mol% of $LiClO_4$, the reaction of benzaldehyde and aniline with EDA gave only a 65% yield even after 12 h. On the other hand, in the same reaction, a higher catalyst loading (a stoichiometric amount) reduced the reaction time (to 2.0 h) but increased the amount of enamine by-product (35%). Among various lithium salts such as lithium perchlorate, lithium triflate and lithium tetrafluoroborate, $LiClO_4$ was found to be the best catalyst of those tested for the aziridination. The influence of solvent in this reaction has also been investigated with the best results being obtained in acetonitrile or nitromethane. Aryl imines derived from aromatic amines and aromatic aldehydes and *N*-benzyl aryl imines and imines derived from aromatic amines and aliphatic aldehydes worked well. Aryl imines possessing either electron-donating or electron-withdrawing groups reacted readily with EDA in acetonitrile in the presence of lithium perchlorate affording the corresponding aziridines with high *cis*-selectivity. Not only aromatic aldehydes but also aliphatic aldehydes reacted smoothly under these reaction conditions to afford the corresponding aziridines in excellent yields with high diastereoselectivity. It is noteworthy that aziridine formation from aliphatic imines having α-hydrogens has also been achieved using this procedure whereas most *N*-alkyl aliphatic alidimines fail to give the desired product under most reported conditions.

In summary, acetonitrile solutions of lithium perchlorate were found to be a highly efficient and convenient catalytic media for the synthesis of *cis*-aziridine carboxylates from aldehydes, amines and ethyl diazoacetate in a single-step operation. In addition to its simplicity and milder reaction conditions, this method provides high yields of products with high *cis*-selectivity which makes it a useful and attractive strategy for the preparation of *cis*-aziridine carboxylates of synthetic importance.

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12. *Experimental procedure*: A mixture of the aldehyde (1 mmol), amine (1 mmol), ethyl diazoacetate (1.2 mmol) and $LiClO_4$ (10 mol%) in acetonitrile (10 mL) was stirred at 28°C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane 1:9) to afford pure *cis*-aziridine.

cis-Ethyl 1,3-diphenylaziridine-2-carboxylate (**3a**): Solid, mp 64–66°C; IR (KBr): *v* 3050, 2931, 2865, 1749, 1600, 1543, 1369, 1190; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99 (t, 3H, $J=7.0$ Hz), 3.20 (d, 1H, $J=6.8$ Hz), 3.60 (d, 1H, $J=6.8$ Hz), 3.99–4.05 (m, 2H), 7.06 (d, 2H, $J=8.4$ Hz), 7.20–7.40 (m, 6H), 7.55 (d, 2H, $J=8.1$ Hz); EIMS: *m*/*z* 335 M^+ 267, 194; ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 45.5, 47.1, 61.0, 119.9, 123.6, 127.7, 127.9, 128.0, 129.2, 134.6, 152.4, 167.8.

cis-Ethyl 1,3-di(*p*-chlorophenyl)aziridine-2-carboxylate (**3g**): Solid, mp 60–62°C; IR (KBr): *v* 3050, 2931, 2865, 1749, 1600, 1543, 1369, 1190; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.0 (t, 3H, $J=7.0$ Hz), 3.10 (d, 1H, $J=6.7$ Hz), 3.45 (d, 1H, $J=6.7$ Hz), 3.98–4.08 (m, 2H), 6.90 (d, 2H, $J=7.9$ Hz), 7.25 (d, 2H, $J=8.0$ Hz), 7.35 (d, 2H, $J=7.9$ Hz), 7.45 (d, 2H, $J=8.0$ Hz); EIMS: *m*/*z* 335 M^+, 267, 194; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 45.7, 46.6, 61.3, 121.2, 128.3, 128.5, 129.0, 129.2, 133.8, 136.3, 151.6, 166.9.

Ethyl 1-(2-furylmethyl)-3-phenyl-2-aziridine-2-carboxylate (**3k**): Liquid, IR (KBr): *v* 2982, 2930, 1745, 1667, 1610, 1500, 1374, 1189, 744; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, 3H, $J=6.9$ Hz), 2.60 (d, 1H, $J=6.7$ Hz), 3.05 (d, 1H, $J=6.7$ Hz), 3.75–3.87 (ABq, 2H, $J=13.7$ Hz), 3.90–4.0 (m, 2H), 6.25–6.30 (m, 2H), 7.20–7.40 (m, 6H); EIMS: *m*/*z* 271 M^+, 269, 188, 143, 116, 89, 53.

Ethyl 1-benzyl-3-phenyl-2-aziridine-2-carboxylate (**3m**): Liquid, IR (KBr): *v* 2925, 2865, 1747, 1655, 1505, 1453, 1173; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.0 (t, 3H, $J=7.0$ Hz), 2.60 (d, 1H, $J=6.8$ Hz), 3.0 (d, 1H, $J=6.8$ Hz), 3.65 (d, 1H, $J=13.9$ Hz), 3.85–4.0 (m, 3H), 7.20–7.45 (m, 10H); EIMS: *m*/*z* 281 M^+, 279, 235, 207, 189, 161, 143, 116, 91, 65.