Lewis Acid-Catalyzed Synthesis of Aziridines

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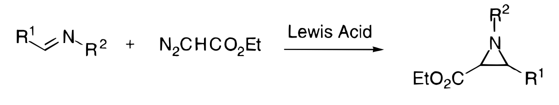
Aziridines are useful intermediates in organic synthesis.[1,2] Classical methods for the synthesis of aziridines are ring closure of amino alcohols,[3] ring opening of epoxides with sodium azide,[4] and addition of α-halo ester enolates to *N*-(trimethylsilyl)imines.[5]

Recently, methods for aziridine synthesis employing transition metal catalysts have been reported. For example, nitrene transfer to olefins from [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) in the presence of Cu(I) and Cu(II) salts has been demonstrated.[6] An alternative route, involving carbene transfer to imines, was reported by Jacobsen.[7] The reaction of imines with EDA catalyzed by chiral Cu(I)−bis(dihydrooxazole) complexes produces aziridines in moderate yields with ee's up to 67%. Jörgensen[8] was able to increase aziridine yields to 80−90% using $Cu(OTf)_2$ in combination with either (−)-menthyl diazoacetate or (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline), but enantioselectivities were moderate. More recently, Espenson[9] reported reaction of imines with EDA catalyzed by methylrhenium trioxide.

Two reports describe the formation of aziridines following activation of imines with Lewis acids, but these methods are not general. Thus, Bartnik[10a] reported the reaction of imines with phenyldiazomethane catalyzed by zinc iodide. Yields are moderate, and this method failed when ethyl diazoacetate was the carbene source. Aziridines have also been detected in the reaction of diazopenicillanates with imines in the presence of $BF_3{\cdot}Et_2O$.[11]

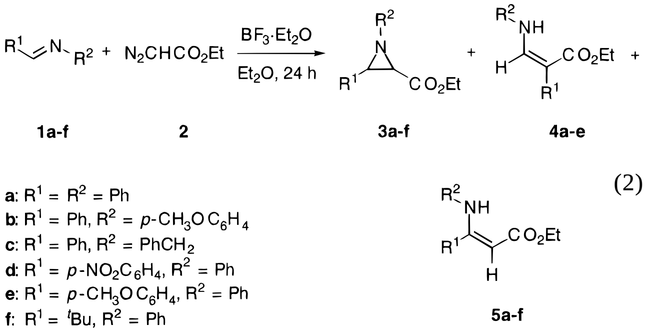
We report here a convenient synthesis of aziridines from various imines and ethyl diazoacetate catalyzed by readily available Lewis acids (eq 1).



1 **2** **3**

(1)

Treatment of an ethereal solution of *N*-benzilideneaniline (**1a**) with variable amounts of $BF_3{\cdot}Et_2O$ and 1.0 equiv of ethyl diazoacetate (EDA) resulted in the formation of aziridine **3a**. In the absence of $BF_3{\cdot}Et_2O$, no reaction was observed after a mixture of **1a** and EDA (1.0 equiv) was stirred for 48 h in ether at room temperature. With equimolar amounts of imine, $BF_3{\cdot}Et_2O$, and EDA, decomposition of the starting materials along with traces of aziridine **3a** were detected by ^1H NMR spectroscopy. When an ethereal solution of imine **1a** and a 10 mol % of $BF_3{\cdot}Et_2O$ was treated with 1.0 equiv of EDA, the ^1H NMR spectrum of the crude reaction showed a mixture of aziridine **3a**, plus **4a** and **5a** (eq 2).



a: $R^1 = R^2 = Ph$
b: $R^1 = Ph, R^2 = p\text{-}CH_3OC_6H_4$
c: $R^1 = Ph, R^2 = PhCH_2$
d: $R^1 = p\text{-}NO_2C_6H_4, R^2 = Ph$
e: $R^1 = p\text{-}CH_3OC_6H_4, R^2 = Ph$
f: $R^1 = {}^tBu, R^2 = Ph$

(2)

In an effort to minimize the formation of **4a** and **5a**, different solvents were tested (Table 1). After 1 h in the presence of 0.10 equiv of $BF_3{\cdot}Et_2O$, the ratio of products was determined by ^1H NMR analysis of the crude reaction mixtures. Our best results were obtained in hexane.[12] The reaction went to completion overnight, and 93% of pure *cis* aziridine **3a** was isolated by column chromatography (entry 1, Table 2).

Table 1[a]

solvent	**3a**:(**4a** + **5a**)	*cis*-**3a**: *trans*-**3a**	**3a**:**1a**
CH_2Cl_2	66:34	cis only	no imine
Et_2O	74:26	cis only	94:6
THF	69:31	cis only	97:3
toluene	57:43	cis only	95:5
hexane	94:6	90:10	75:25

[a] Reaction conditions: 25 °C, 1 h, 10 mL of solvent, 0.55 mmol of **1a**, 0.05 mmol of $BF_3{\cdot}Et_2O$.

Similar reactions were also performed with the imines **1b**−**1f**[13] and different Lewis acids. The conditions and results of this series of studies are listed in Table 2.

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(12) The following experimental procedure for the preparation of the aziridine **3a** is representative: Imine **1a** (2.00 g, 11.04 mmol) is dissolved in 100 mL of anhydrous hexane, and the solution is treated, under nitrogen, with 0.16 g (0.11 mmol) of $BF_3{\cdot}Et_2O$ and 1.20 g (11.04 mmol) of ethyl diazoacetate. The mixture is stirred at room temperature until the starting imine has been consumed (^1H NMR). Workup with water and chromatography on silica gel using hexane/ethyl acetate as eluent yields aziridine **3a** (2.73 g 93%).

(13) Imines **1d**−**f** were obtained as follows: The corresponding aldehyde (1.0 mmol) was dissolved in 20 mL of methylene chloride and treated with an equimolar amount of aniline in the presence of 10 g of $MgSO_4$. The resulting mixture was stirred overnight. Filtration and solvent removal yielded imines **1d**−**f** (pure by ^1H NMR), which were used without further purification.

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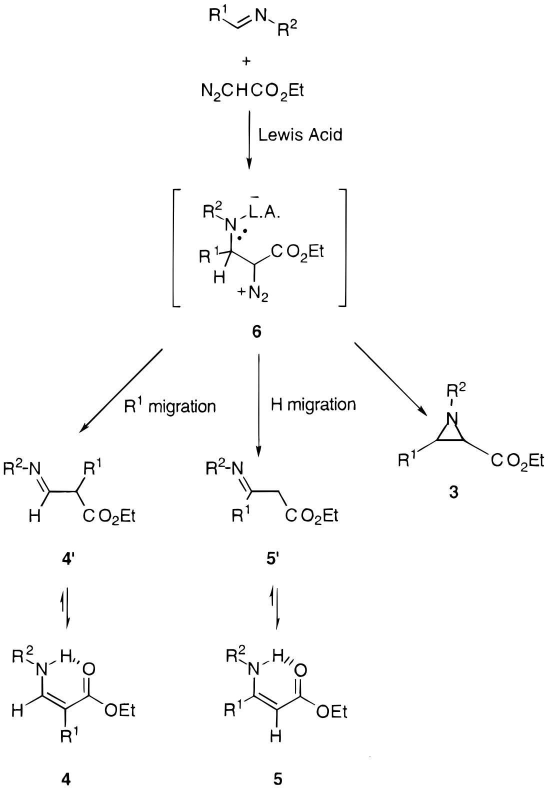
Table 2

entry	cat.	**1**	R^1	R^2	solvent	N$_2$CHE (equiv)	time	**3**:(**4** + **5**)	*cis*:*trans*	**3**^{a} (%)
1	BF$_3$	**a**	Ph	Ph	hexane	1.0	15 h	94:6	93:7	93
2	BF$_3$	**b**	Ph	*p*-CH$_3$OC$_6$H$_4$	hexane	1.0	48 h	95:5	cis only	53
3	BF$_3$	**c**	Ph	PhCH$_2$	Et$_2$O	2.0	15 h	73:24	cis only	51
4	BF$_3$	**d**	*p*-NO$_2$C$_6$H$_4$	Ph	Et$_2$O	1.0	1 h	88:12	82:18	80
5	BF$_3$	**e**	*p*-CH$_3$OC$_6$H$_4$	Ph	Et$_2$O	1.0	24 h	0:100		
6	BF$_3$	**f**	^{t}Bu	Ph	Et$_2$O	1.0	15 min	55:45	38:62	61
7	AlCl$_3$	**a**	Ph	Ph	CH$_2$Cl$_2$	1.0	2 h	65:35	98:2	56
8	AlCl$_3$	**b**	Ph	*p*-CH$_3$OC$_6$H$_4$	CH$_2$Cl$_2$	3.0	0.5 h	66:34	cis only	57
9	AlCl$_3$	**c**	Ph	PhCH$_2$	CH$_2$Cl$_2$	2.0	15 h	67:33	cis only	45
10	AlCl$_3$	**d**	*p*-NO$_2$C$_6$H$_4$	Ph	Et$_2$O	1.0	2 h	82:18	82:12	62
11	AlCl$_3$	**f**	^{t}Bu	Ph	Et$_2$O	1.0	15 min	88:12	28:72	58
12	TiCl$_4$	**a**	Ph	Ph	Et$_2$O	3.0	48 h	63:37	89:11	62
13	TiCl$_4$	**b**	Ph	*p*-CH$_3$OC$_6$H$_4$	CH$_2$Cl$_2$	2.0	15 h	52:48	cis only	44
14	TiCl$_4$	**c**	Ph	PhCH$_2$	hexane	1.5	48 h	76:24	cis only	42
15	TiCl$_4$	**d**	*p*-NO$_2$C$_6$H$_4$	Ph	Et$_2$O	1.0	3 h	79:21	74:26	83
16	TiCl$_4$	**f**	^{t}Bu	Ph	CH$_2$Cl$_2$	1.0	2 h	90:10	48:52	62

[a] Yields are of pure isolated product (best of at least two experiments). In the case of **1f** and **1a**, both isomers were isolated.

Scheme 1



In no case have products derived from carbene coupling (e.g., diethyl fumarate or maleate)[7] been detected. The absence of carbene coupling products suggests that no metal carbenoid species are involved in the transfer process.

Identification of **4** and **5** was possible on the basis of comparison of their NMR data with similar compounds.[14] Enamines **4** show a broad doublet ($\delta = 8.60-10.34$; $J = 12.0-13.0$ Hz) assigned as the NH resonance. This low-field shift is compatible with the existence of a hydrogen bond to the carbonyl group of the ester, and the large vicinal coupling is consistent with a trans periplanar relationship between the vicinal hydrogens.

Scheme 1 illustrates a mechanism consistent with the results in Table 2. Activation of the imine by complexation with the Lewis acid followed by nucleophilic addition of EDA results in formation of intermediate **6**.[15] Subsequent ring closure and loss of N$_2$ provides aziridines **3**. Byproducts **4** and **5** result from 1,2 migration of either the R^1 substituent or H to the incipient carbocation to yield initially **4′** and **5′**.[16] For aromatic imines, the ratio of aziridines to migration products is strongly dependent of the nature of the aryl ring. For Ar = $-C_6H_5$, the ratio of **3**:(**4** + **5**) is ca. 65:35, while for the electron-withdrawing *p*-NO$_2$C$_6$H$_4$ system the ratio increases to 82:18 and for the electron-donating substituent *p*-CH$_3$OC$_6$H$_4$ only traces of aziridine are observed, in keeping with the usual migratory aptitudes for these substituted aryl groups in electron-deficient rearrangements.

The conversion of imine **1f** (R^1 = ^{t}Bu) to aziridines is much faster than for *N*-aryl-substituted imines. This may be explained by the higher nucleophilicity of the imine nitrogen when R = alkyl. In this case, in addition to aziridines, only the hydride migration product in the iminic tautomeric form, **5f′**, is observed.

In summary, we have shown that simple Lewis acids catalyze the reaction of EDA with imines to form a variety of aziridines. The mechanism for aziridine formation shown in Scheme 1 may also apply to some transition metal-catalyzed additions[17] and must be considered when analyzing such results. We are currently investigating the use of chiral Lewis acids in these reactions.

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Supporting Information Available: Experimental procedures and characterization data for *cis*-**3a**, *trans*-**3a**, **4a**, **5a**, *cis*-**3b**, **4b**, *cis*-**3c**, **4c**, **5c**, *cis*-**3d**, **5d**, *cis*-**3f**, *trans*-**3f**, and **5f′** (5 pages).

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(15) Similar intermediates have been proposed; see refs 10a and 11.

(16) The possibility of an equilibrium between aziridines **3** and imines **4** and **5** was also tested. Pure *cis*-**3a** and pure *trans*-**3a** (R^1 = R^2 = Ph) were stirred separately for 15 h in hexanes in the presence of BF$_3$·Et$_2$O. After workup, no formation of **4** or **5** was detected.

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