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Strategies for the Design of Organic Aziridination Reagents and Catalysts: Transition Structures for Alkene Aziridinations by NH Transfer

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Received March 31, 2003

B3LYP/6-31G* transition structures for aziridination of various alkenes by substituted oxaziridines and diaziridinum salts were located. Oxaziridines substituted with electron-withdrawing groups have activation energies for nitrogen transfer similar to those calculated for epoxidation by various known organic oxidants. These transition states are relatively insensitive to alkene substituents, but highly electron deficient alkenes were calculated to have low activation energies. *N*-Trimethylsilyl-derived oxaziridines are predicted to be good targets for alkene aziridination reagents. Activation energies calculated for aziridination by diaziridinium salts are generally lower in energy. Aziridinations of electron-rich and highly electron deficient alkenes by diaziridinium salts are predicted to be rapid. *N*-Methyl, *N*-trifluoroacetyl, and *N*-trimethylsilyl derivatives showed reasonable activation energies for nitrogen transfer.

Introduction

Aziridines are versatile synthetic intermediates.[1] The preparation of N-protected aziridines from alkenes has been made with various inorganic catalysts,[2] but an efficient organocatalyzed method for the preparation of aziridines from alkenes has yet to be established. Subsequent deprotection to give the free aziridine is often a difficult and low-yielding step in existing methods.[3]

Several promising organic reagents have been reported: the oxaziridine **1**,[4] diaziridine **2**,[5] and bis(hydrazinium) **3**[6] react with alkenes to give N-unprotected aziridines directly (Scheme 1, eqs 1−3). Generally the yields of aziridine obtained by the reaction of **1** are around 50% at 100 °C, while **2** and **3** have only been shown to react with α,*β*-unsaturated amides and ketones, respectively. A one-step mechanism for aziridination by **1** has been proposed on the basis of the observation that *trans*-*β*-methylstyrene gives the *trans*-aziridine.[4a]

In view of promising results that have been obtained using chiral dioxiranes[7] and oxaziridinium salts[8] for catalytic asymmetric alkene epoxidations (Scheme 1, eq 4), we were attracted to the possibility that the nitrogen analogues of these (**4**[4,9] and **5**[10]) might act as efficient N-transfer reagents (Scheme 1, eq 5). The 3,3-dimethyloxaziridine, generated in situ, is used already as an industrial reagent in the production of hydrazine on a scale of 10 000 tons per year (Scheme 2, eq 6).[11] While a diaziridinium has yet to be isolated, the formation of such

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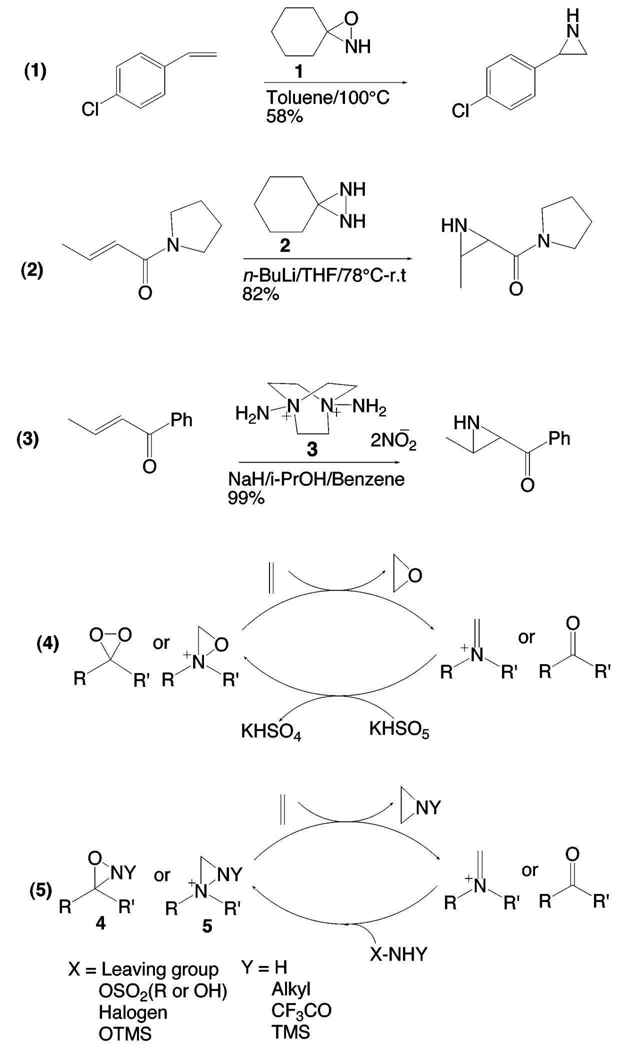
SCHEME 1



species has been proposed in the alkylations[12] and acylations[13] of various diaziridines (Scheme 2, eq 7). Under the conditions of the reaction, these diaziridinium salts fall apart to give the corresponding ketone, secondary amine, and ammonia for alkylation and an *N*-acyl hydrazone for acylation. However, diaziridines are reported to be stable for weeks in acid solutions, presumably as diaziridiniums.[10b] In a related reaction, the aziridination of olefins by oxidation of *N*-aminophthalimide[14] or 3-aminoquinazolinones[15] is believed to occur as shown in eq 8 (Scheme 2). Aziridination is believed to occur through a butterfly mechanism found for epoxidation by peracids.[15]

In an effort to understand how efficient NH transfer is achieved, the transition structures for reactions of various oxaziridines and diaziridinium salts with several alkenes have been located and examined. Implications for the design of organic aziridination reagents and catalyst are discussed.

Oxaziridines

The B3LYP/6-31G(d)[16] transition structures for the aziridination of ethylene and several substituted ethylenes by various oxaziridines are examined in Figure 1. The activation energy and transition-state geometry for **6a**, as well as those calculated for other C-substituted oxaziridines, are shown. Optimizations of **6a** with a larger basis set (6-311+G(d)) or with MP2/6-311G(d) gave nearly identical geometries and energies.[17] All transition states show concerted, but highly asynchronous, nitrogen transfer. This is in accord with the observation that the reaction of **1** with *trans*-β-methylstyrene gives the *trans*-aziridine.[4] In each case the plane of the forming aziridine ring and cleaving oxaziridine reagent are skewed about 20° from the spiro geometry (90°) found for epoxidations.[18] The preferred geometry allows for maximum overlap of the lone pair on N with the LUMO of the alkene. The frontier molecular orbital (FMO) interactions involved in the alkene aziridination transition structure are shown in Figure 2. In **8** the alkene LUMO interacts with the nitrogen lone pair orbital, which lies at a 60° angle[10b] to the plane of the oxaziridine ring. In **9** the alkene HOMO interacts with the N−O σ^* orbital.

Compound **6a** has an activation energy of 22.0 kcal/mol above separated reactants (24.8 kcal/mol from a reactant complex). Oxygen transfer from oxaziridine to ethylene, through a similar transition state, is calculated to be 11 kcal/mol higher in energy. The preference for nitrogen over oxygen transfer is a result of the better stabilization of the partial negative charge in the transition state by oxygen than by nitrogen. In **6a**, the charge on oxygen increases to −0.50 from −0.24 in the ground state, while the charge on the nitrogen decreases only slightly to −0.38 from −0.46. An activation energy of 12.9 kcal/mol is calculated for ethylene epoxidation by dioxirane at the same level of theory. The higher activation energy calculated for alkene aziridination by oxaziridines versus epoxidations by dioxiranes is reflected in the harsh reaction conditions necessary to bring about the aziridination.[4]

Introduction of methyl groups on the oxaziridine ring (**6b**,**c**) increases the activation energy by roughly 2 kcal/mol per methyl group. Trifluoromethyl groups (**6d**,**e**) each lower the activation energy by roughly 5 kcal/mol compared to **6c**. Attaching a fluorine (**6f**) directly to carbon

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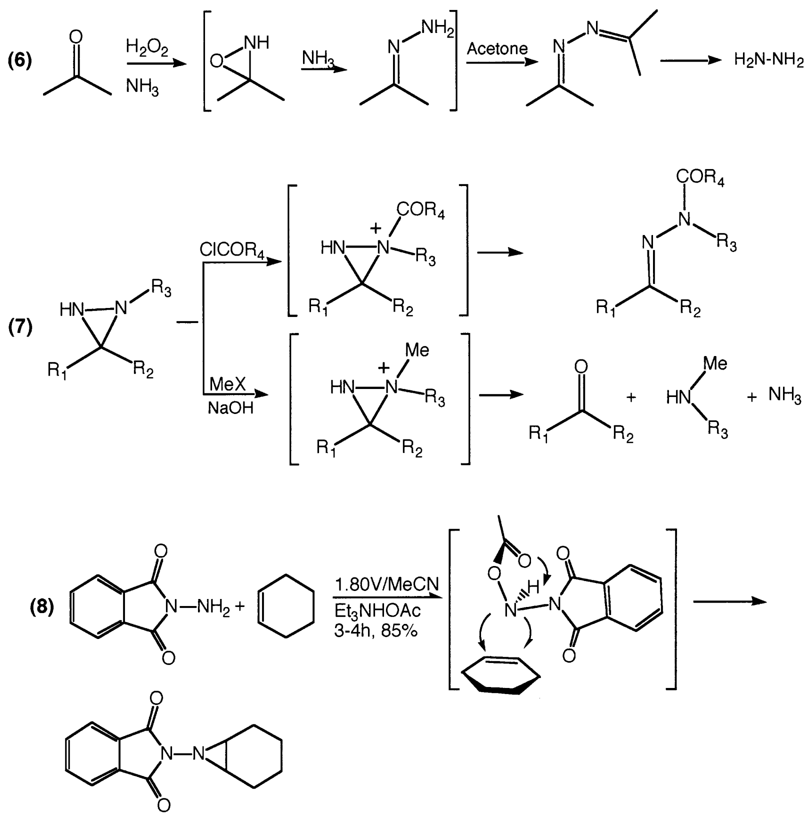
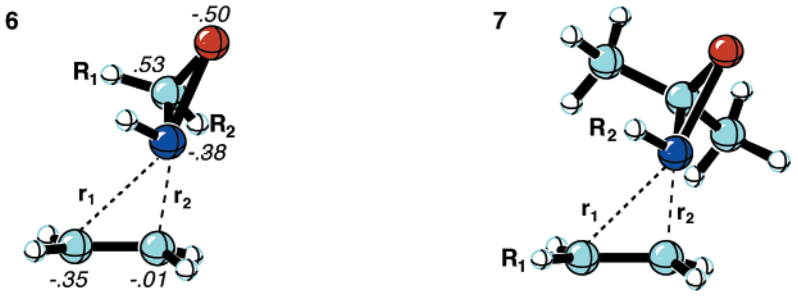
SCHEME 2



lowers the activation energy by 8.3 kcal/mol. A second fluorine atom (**6g**) lowers the activation energy even further. Activation energies calculated for **6e**−**g** are within the range of activation energies calculated for oxygen transfer to alkenes from dioxiranes,[18] oxaziridinium salts,[19] and peracids.[18]

B3LYP/6-31G(d) transition structures and energies for aziridination of substituted alkenes by 3,3-dimethyloxaziridine are given in structures **7a**−**c**. The cyano, methoxy, and methyl ester substituents slightly lower the activation energy compared to that for ethylene. Alkene substituents are calculated to have a small effect on transition-state energies. This is in accord with the observation that aziridinations of both α-methylstyrene and 4-methoxy-α-methylstyrene by **1** require similar reaction conditions and give similar yields.[4b]

Transition structures for the aziridination of vinylidene cyanide and methylenemalonate dimethyl ester by 3,3-dimethyloxaziridine, shown in Figure 3, are calculated to have activation energies of only 7.2 and 9.3 kcal/mol,



	R_1	R_2	E_{act}	r_1	r_2
a	H	H	22.0	2.35	1.77
b	Me	H	23.7	2.35	1.75
c	Me	Me	25.5	2.32	1.74
d	CF_3	Me	20.4	2.34	1.80
e	CF_3	CF_3	14.9	2.34	1.87
f	F	H	13.7	2.36	1.90
g	F	F	7.1	2.42	2.01

	R_1	R_2	E_{act}	r_1	r_2	E_{act} O
a	OMe	H	22.3	2.47	1.81	---
b	CN	H	20.7	2.38	1.70	---
c	CO_2Me	H	19.8	2.36	1.71	---
d	H	Me	32.8	2.40	1.77	39.6
e	H	$SiMe_3$	23.3	2.36	2.02	32.9
f	H	CF_3OC	32.8	2.30	1.88	27.5

FIGURE 1. B3LYP/6-31G(d) activation energies and transition-state geometries for (**6a**,**b**) aziridination of ethylene by oxaziridines, (**7a**,**b**) aziridination of (**7a**) methoxyethene and (**7b**) cyanoethene by 3,3-dimethyloxaziridine, and (**7d**−**f**) aziridination of ethylene by N-substituted 3,3-dimethyloxaziridines. Energies are in kcal/mol. Distances are in angstroms. Charges are derived from electrostatic potential, ChelpG.

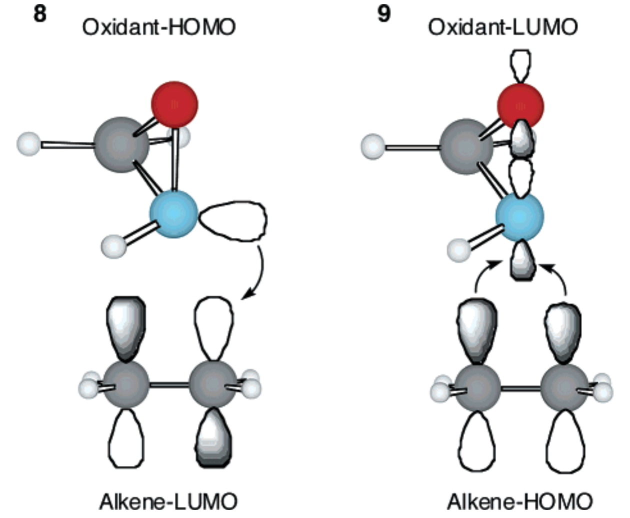


FIGURE 2. Frontier molecular orbital interactions governing alkene aziridination.

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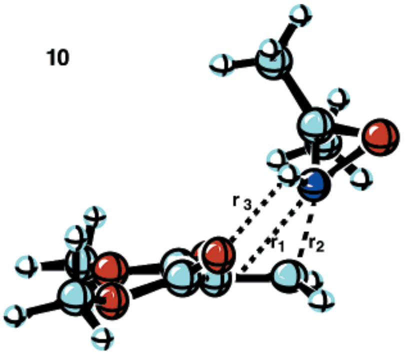

	1,1-	E_{act}	r_1	r_2	r_3
a	CO_2Me	7.2	2.57	1.83	2.17
b	CN	9.3	2.43	1.64	--

FIGURE 3. B3LYP/6-31G(d) transition states for aziridination of 1,1-disubstituted alkenes by 3,3-dimethyloxaziridine. The structure shown is for methylenemalonic acid dimethyl ester.

respectively. For these alkenes there is no longer a balance between FMO interactions **8** and **9.** Interaction **8** predominates, thus lowering the activation energy. In the transition state (**10a**) there is also hydrogen bonding between the transferring amine and an ester group, which further lowers the activation energy.

Transition structures were also located for nitrogen transfer from N-substituted oxaziridines. Results are listed for **7d**–**f**. Labile *N*-trimethylsilyl[20] and *N*-trifluoroacetyl groups can be easily removed to furnish the product aziridine. The *N*-methyl derivative was investigated as a possible method of transferring primary amines to alkenes. The *N*-trifluoroacetyl and *N*-methyl derivatives gave calculated activation energies that were considerably higher when compared to aziridination by the parent 1,1-dimethyloxaziridine (**6c**). For the *N*-trifluoroacetyl derivative oxygen transfer is preferred over nitrogen transfer, in accord with the analogous epoxidations by *N*-sulfonyloxaziridines.[9] The *N*-trimethylsilyl derivative was calculated to lower the activation energy by roughly 2 kcal/mol.

Diaziridiniums

The B3LYP/6-31G(d) calculated transition structures for aziridination of alkenes by protonated diaziridines are shown in Figure 4. The activation energy and transition-state geometry for **11**, as well as for substituted diaziridinium salts, are shown. Nitrogen transfers from diaziridinium ions are calculated to be more facile than from oxaziridines (activation energy for **11a** −0.3 kcal/mol from separated reactants and 11.7 kcal/mol from a reactant complex) and have earlier transition states. All transition states are also concerted and are slightly skewed from spiro (67° for **11a**). The protonated amine is a better leaving group than an alkoxide. An activation energy of 37.0 kcal/mol was calculated for nitrogen transfer from diaziridine to ethylene. Similar activation energies of 1.4 and 9.8 kcal/mol from the prereactant complex were calculated for ethylene epoxidation by oxaziridin-2-ium,[19] a potent class of oxidants, at the same level of theory.

Introduction of methyl groups on the diaziridinium ring increases the activation energy (**11b**–**f**). The activation energies and geometries calculated for reaction of 1,1,3-trimethyldiaziridinium in the gas phase and in a continuum solvation model for water ($\epsilon = 80$), are given in **11e**,**f**, respectively. Solvation increases the activation energy by 5 kcal/mol and shifts the transition state later along the reaction coordinate. Introduction of a trifluoromethyl group on nitrogen dramatically decreases the activation energy (**11g**).

The B3LYP/6-31G(d) transition structures and energies for aziridination of substituted alkenes by 1,1,3-trimethyldiaziridinium are also shown in Figure 4. Here, alkene substituents have a considerable effect on transition-state energies. Methoxy (**12a**) and methyl ester (**12c**) substituents lower the activation energy by 9 and 1.2 kcal/mol, respectively. In the transition state for **12c** there is hydrogen bonding between the between the transferring amine and an ester group (see **13a**). A cyano substituent (**12b**) increases the activation energy by 7 kcal/mol. Figure 5 shows aziridination of methylenemalonic acid dimethyl ester by 1,1,3-trimethyldiaziridinium and lists the activation energy for aziridination of vinylidene cyanide. For the diester, where there is hydrogen bonding, the activation energy for aziridination is only 5.3 kcal/mol. For the dicyano substituents the activation energy is considerably higher. Hydrogen bonding to the transferring amine substantially lowers the activation energy.

The preference for diaziridiniums to react with electron-rich species raises the possibility that the reagent diaziridinium might aminate the product aziridine to give an *N*-aminoaziridine. An activation energy of 2.3 kcal/mol was calculated for amination of the product aziridine by 1,1,3-trimethyldiaziridinium. For efficient alkene aziridination it may be necessary to mask the product aziridine. Figure 4 (**12d**–**f)** lists activation energies and geometries for nitrogen transfer from N-protected diaziridinium salts. The *N*-trifluoroacetyl derivative gave a slightly higher activation energy compared to the

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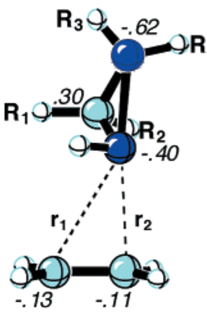

	R_1	R_2	R_3	R_4	E_{act}	r_1	r_2	
a	H	H	H	H	-0.3	2.62	2.30	
b	H	Me	H	H	3.0	2.52	2.22	
c	H	H	Me	H	4.0	2.54	2.18	
d	H	H	Me	Me	7.5	2.50	2.09	
e	H	Me	Me	Me	11.2	2.45	2.03	
f	H	Me	Me	Me	16.2	2.41	1.98	α=80
g	H	Me	CF_3	Me	4.0	2.55	2.22	

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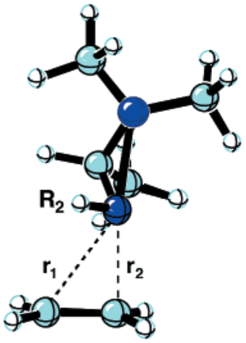

	R_1	R_2	E_{act}	r_1	r_2
a	OMe	H	2.1	3.24	2.79
b	CN	H	18.6	2.50	1.96
c	CO_2Me	H	10.0	2.43	1.93
d	H	Me	18.2	2.52	2.06
e	H	$SiMe_3$	23.9	2.52	2.19
f	H	CF_3OC	12.4	2.56	2.14

FIGURE 4. B3LYP/6-31G(d) activation energies and transition state geometries for (**10a**−**g**) aziridination of ethylene by diaziridinium ions, (**11a**,**b**) aziridination of methoxyethene (**11a**) and acrylonitrile (**11b**) by 1,1,3-trimethyldiaziridinium ion, and (**11c**−**e**) aziridination of ethylene by N-substituted 1,1,3-trimethyldiaziridinium ions.

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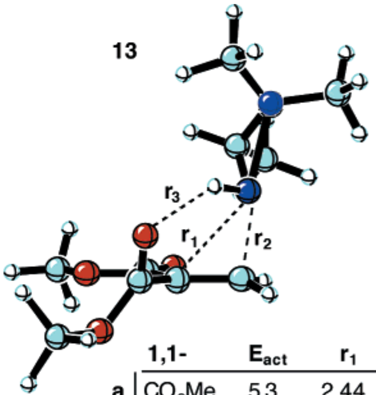

	1,1-	E_{act}	r_1	r_2	r_3
a	CO_2Me	5.3	2.44	1.91	1.99
b	CN	21.8	2.53	1.92	---

FIGURE 5. B3LYP/6-31G(d) transition states for aziridination of 1,1-substituted alkenes by 1,1,3-trimethyldiaziridinium. The structure shown is for methylenemalonic acid dimethyl ester.

parent 1,1,3-trimethyldiaziridinium, while the *N*-methyl group raised the TS energy by 7 kcal/mol. The higher activation energy calculated for the *N*-trimethylsilyl derivative is a result of steric interactions in the transition state. The range of calculated activation energies, 12.4−23.9 kcal/mol, is comparable to that calculated for aziridinations by oxaziridines, a process that has been observed.

Conclusion

Oxaziridines substituted with electron-withdrawing groups have activation energies for nitrogen transfer to ethylene similar to those calculated for epoxidation by various known organic oxidants, such as peracids, dioxiranes, and oxaziridinium salts. Activation energies for aziridinations by oxaziridines are relatively insensitive to alkene substituent, but highly electron deficient alkenes, such as diesters, are calculated to have considerably lower activation energies. *N*-Trimethylsilyl-derived oxaziridines are predicted to be good targets for alkene aziridination reagents. Oxaziridines derived from 1,1,1-trifluoroacetone are predicted to readily transfer nitrogen to both methylenemalonic acid dimethyl ester and vinylidene cyanide.

Activation energies calculated for aziridination by diaziridinium salts are generally lower in energy compared to oxaziridines. Aziridinations of electron-rich and highly electron deficient alkenes by diaziridinium salts are predicted to be rapid. Deactivation of the product aziridine toward electrophilic attack may be necessary. *N*-Methyl, *N*-trifluoroacetyl, and to a lesser extent *N*-trimethylsilyl derivatives show reasonable activation energies for nitrogen transfer. We predict that 1,1,3-trialkyl-*N*-(trimethylsilyl)diaziridinium salts will rapidly transfer nitrogen to vinyl ethers and methyl acrylate.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health, for financial support of this research. A.A. thanks the University of Nottingham for a travel grant and the EPSRC (GR/R54668) for support. We wish to thank Professor Andrei K. Yudin for helpful discussions.

Supporting Information Available: Tables giving Cartesian coordinates and energies for each structure computed. This material is available free of charge via the Internet at http://pubs.acs.org.

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