Facile One-Pot Preparation of 3-Chloro-2-(chloromethyl)propene and an ab Initio Study of the Deamination Reaction of Nitrosoaziridine

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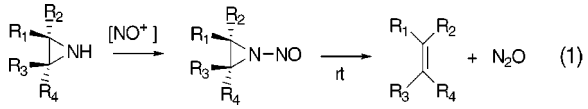
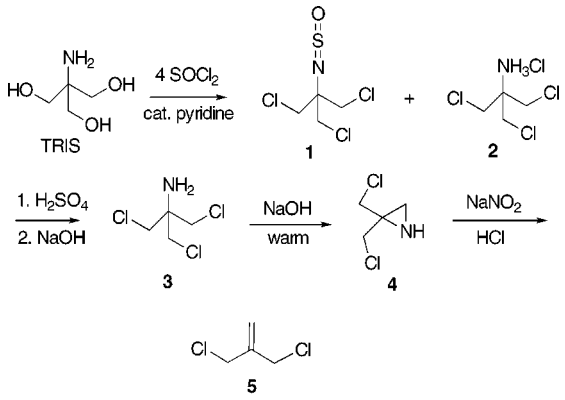
The facile stereospecific thermal conversion of *N*-nitrosoaziridines into alkenes is a well-known reaction[1] that has been studied mechanistically.[2,3] The labile *N*-nitrosoaziridines formed by nitrosation of N-unsubstituted aziridines (eq 1) have been observed spectroscopically[4] and have been isolated under low temperature conditions. While the deamination reaction has potential synthetic utility for the stereospecific synthesis of alkenes, especially the cis−trans interconversion of alkenes,[5] there are only a few reports of its application in organic synthesis.[6] Herein the utility of the deamination reaction is demonstrated by the convenient large scale one-pot preparation of 3-chloro-2-(chloromethyl)propene (**5**), a compound that is a useful starting material for many molecules including [1.1.1]propellane.[7] Additionally, high level ab initio molecular orbital calculations are presented for the deamination−fragmentation reaction, and these allow some insight into the mechanism of this cheletropic reaction.



Results and Discussion

The one-pot preparation of 3-chloro-2-(chloromethyl)propene (**5**) is shown in Scheme 1. By modification of a previously reported procedure,[8] commercially available tris(hydroxymethyl)aminomethane (TRIS) is converted to a mixture of the *N*-sulfinyl **1** and a smaller amount of the corresponding **2**.[9] A careful examination of this reaction revealed that a substoichiometric amount of pyridine is sufficient for full conversion, and about 4 equiv of thionyl chloride are required since 1 equiv converts the primary amino group to the *N*-sulfinylamino group.[10] The relative amounts of **1** and **2** are of no consequence since both compounds are converted to the same product in the next step. It was found that the sulfite anion generated on base-promoted hydrolysis of **1** causes much decreased yields in the last step of the reaction sequence. Therefore, acid-promoted hydrolysis was performed, and the liberated sulfur dioxide was removed by heating. Addition of base and gentle warming allow ring closure of crude **3** to 2,2-bis(chloromethyl)-aziridine (**4**). Further treatment of crude **4** with sodium nitrite and aqueous acid results in a vigorous evolution of gases. Steam distillation of the final product from the reaction mixture, separation from water, drying, and redistillation gives **5** in 55 to 60% overall yield. We believe that this one-pot procedure is now the method of choice for the preparation of this alkene on a laboratory scale.

Scheme 1



Theoretical and Computational Studies of the Denitrogenation Reaction. A theoretical examination of the cheletropic extrusion of nitrous oxide from *N*-nitrosoaziridine was presented by Woodward and Hoffmann.[11] They suggested two different symmetry allowed nonlinear pathways for the fragmentation reaction. The one which they favored involved a planar aziridine nitrogen conjugated with the N=O π system. This nonlinear mode of fragmentation is similar to that observed in the corresponding three-membered ring diazene derivatives.[11] The alternative suggestion involved a nonplanar aziridine nitrogen with a nonconjugating nitroso group. However, this possibility was considered to be unlikely due to the rotational energy required for typical nitrosamines. Based on the thermal stability of *N*-nitroso-9-azabicylo[4.2.1]nona-2,4,7-triene toward fragmentation, Mock and Isaac[3] proposed that the alternative mechanism was in fact the actual pathway.

To further probe the mechanism of the denitrogention reaction, ab initio calculations were carried out on the ground and transition states for the fragmentation reaction of *N*-nitrosoaziridine (**NA**) to ethene and nitrous oxide. The calculations were carried out using the Gaussian 94 package[12] and used the G2MP2 level of theory.[13]

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(9) If desired, compounds **1**, **3**, and **4** can be isolated and purified at the appropriate points of the preparation. See Experimental Section.

(10) For a review of the preparation and reactions of sulfinylamines and related compounds, see: Kresze, G.; Wucherpfennig, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 149 and references therein.

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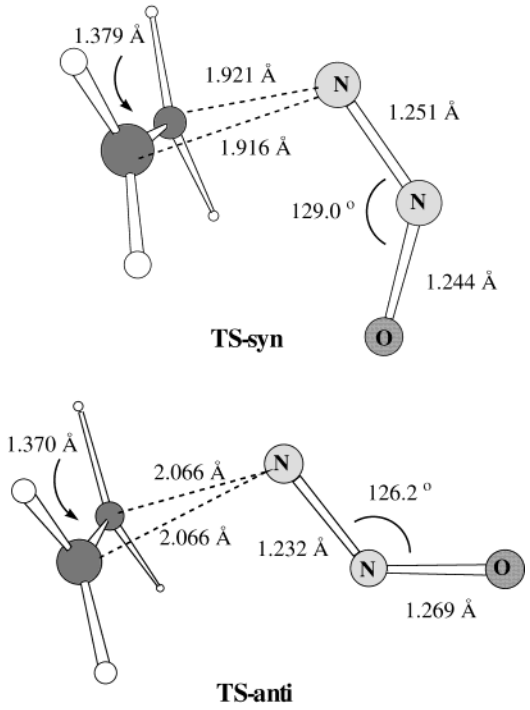

Figure 1. Selected (MP2/6-31G*) structural data for the two transition structures (**TS-syn** and **TS-anti**) leading to loss of nitrous oxide from *N*-nitrosoaziridine.

Previous computational work on these systems is limited to a study of their CD spectra and the rotational energy barrier of the *N*-nitroso group.[14] No electronic structure calculations on transition structures for fragmentation were found. An intensive search at the MP2/6-31G* level led to the discovery of two different transition structures for the fragmentation of nitrous oxide from **NA**. While no symmetry constraints were imposed during the search, both transition structures are very close to C_s symmetry with a strongly bent NNO bond angle. The two transition structures differ mainly by the orientation of the oxygen atom as either syn (**TS-syn**) or anti (**TS-anti**) to the cyclopropane ring.[15] Selected geometric parameters of the two different transition structures derived from MP2/6-31G* optimized geometries are shown in Figure 1. The total and relative energies of the structures of interest are given in Table 1.

Energetically, there is a huge difference between the two transition structures. **TS-syn** is much lower in energy than **TS-anti**. Based on G2MP2 energies, the transition structures are calculated to lie 21.4 and 47.6 kcal/mol above the ground state, while the overall reaction is predicted to be downhill by 27.9 kcal/mol.The magnitude of the difference in energy between the two transition structures (26.2 kcal/mol) is remarkable given

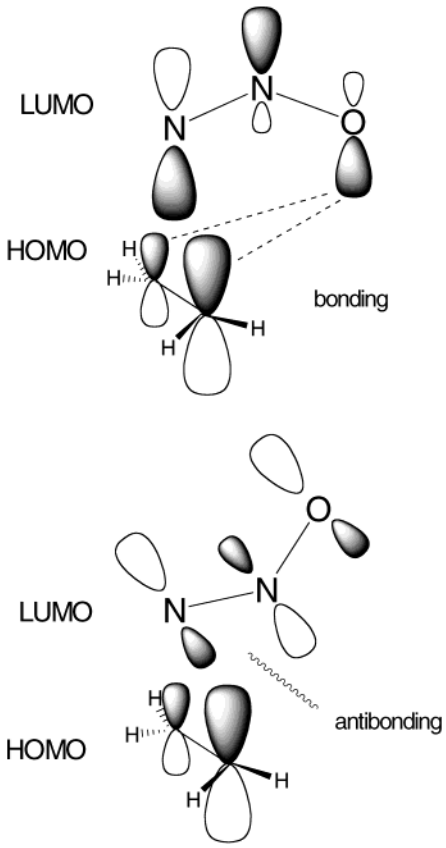

Figure 2. Simple frontier molecular orbital interaction between the LUMO of N_2O and HOMO of ethene showing the secondary orbital interactions proposed in the **TS-syn** and **TS-anti** transition structures.

Table 1. Total Energies (hartrees) and Relative Energies (kcal/mol using G2MP2 energies) of Selected Structures Based on G2MP2 Calculations

compound	MP2/6-31G*	G2MP2	relative *E*(kcal/mol)
NA	−262.456475	−262.802286	0.0
TS-syn	−262.408382	−262.768222	21.4
TS-anti	−262.359830	−262.726459	47.6
ethene	−78.2942862	−78.4143044	−27.9
nitrous oxide	−184.213683	−184.432465	

that the main difference between them is the orientation of the oxygen as syn or anti to the three-membered ring. It is tempting to speculate that the difference arises from secondary orbital interactions in the transition states between the bent nitrous oxide and the ethene that is forming. According to frontier molecular orbital theory,[16] the reaction can be approximated as the interaction between the HOMO of ethene and the LUMO of the bent nitrous oxide. Simple representations of these orbitals in **TS-syn** and **TS-anti** arrangements are shown in Figure 2. The **TS-syn** arrangement allows a stabilizing interaction between the orbitals of the carbon atoms and the orbital of the oxygen atom while the **TS-anti** arrangement will have a destabilizing secondary orbital interaction between the orbitals of the carbon atoms and the orbital of the middle nitrogen atom. That these secondary orbital effects would be so large is surprising and suggests further study of these systems is in order.

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(15) Both transition structures had one imaginary frequency. **TS-syn**: $\nu = -703$ i cm^{-1}; **TS-anti**: $\nu = -537$ i cm^{-1}.

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Experimental Section

Materials. Tris(hydroxymethyl)aminomethane (TRIS), thionyl chloride (97%), pyridine, and sodium nitrite (97%) were purchased from Aldrich. All other chemicals used were products of Fisher Scientific.

3-Chloro-2-(chloromethyl)propene (5). A 3 L four-necked round-bottomed flask was equipped with a mechanical stirrer, a thermometer reaching to the bottom, a pressure-equalizing dropping funnel, and a reflux condenser connected to a bubbler. The flask was filled with 150.0 g (1.24 mol) of TRIS and 390 mL (5.19 mol) of thionyl chloride. A large ice−water bath surrounded the flask. With good stirring, 50 mL (0.62 mol) of pyridine was cautiously added dropwise over the course of 10 min. After the addition was complete, the cooling bath was replaced with a heating mantle. The contents of the flask were allowed to stir without heating until gas evolution slowed (ca. 45 min) and then were slowly heated so that the final temperature reached 120 °C at the end of 6 h.[17] The brown mixture[18] was cooled in an ice−water bath to 20 °C, and 50 mL of water was added dropwise, slowly and very cautiously, over the course of 30 min with good stirring and cooling. An additional 250 mL of water was added. Then a solution of 70 mL (1.26 mol) of concentrated sulfuric acid in 300 mL of water was added over the course of 10 min. After the addition was complete, the contents of the flask were refluxed until gas evolution ceased. The clear orange solution was cooled to 10 °C using an ice−water bath and was made alkaline (pH∼13) by dropwise addition of a 30% (w/w) aqueous solution of sodium hydroxide (ca. 360 mL) while maintaining the reaction mixture below 30 °C. Once alkaline, the mixture was treated with a solution of 75.0 g (1.88 mol) of sodium hydroxide in 250 mL of water and was heated at 50 °C for 3 h with good stirring. After the mixture was cooled to room temperature,[19] a solution of 88.0 g (1.24 mol) of sodium nitrite in 200 mL of water was added. Then, a cold solution of 260 mL of concentrated hydrochloric acid in 260 mL of water was added dropwise into the vigorously stirred mixture over the course of 30 min. The temperature of the reaction mixture was allowed to rise above 50 °C, and colorless gases were smoothly generated throughout the addition. After the addition was complete, the reflux condenser was replaced with a distillation condenser. The green-brown mixture was heated with a heating mantle, and the product steam distilled into an ice-cooled receiver. After all the product had distilled, the two layers from the condensate were separated, the light blue organic layer was dried over magnesium sulfate and distilled with a short-path condenser to give 85.0 g (55% overall yield) of colorless liquid (bp 136−144 °C), >95% pure by GC (the major impurity being 1,3-dichloro-2-(chloromethyl)propene[20]). If desired, the product may be further purified by distillation through a 15 cm column packed with glass helices (bp 137 °C); ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.30 (s, 2H), 4.18 (s, 4H); ^{13}C NMR (91 MHz, $CDCl_3$): δ 141.17, 118.91, 44.66.

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Supporting Information Available: Complete G2MP2 geometries and energies for the structures in Table 1. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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(17) If the reaction is scaled down to 25 g of TRIS, the heating time may be reduced to 3 h.

(18) TRIS is converted to a mixture of **1** and **2** in a ca. 4:1 ratio. This was found by precipitation of salts with dichloromethane and analyzing solid and mother liquor separately. **Tris(chloromethyl)-*N*-sulfinylmethylamine** (**1**): bp 72−74 °C (0.02 mmHg); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.01 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.37, 44.95; MS (CI) 221.9 (M + H). **Tris(chloromethyl)methylammonium chloride** (**2**): mp 251−254 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.27 (bs, 3H), 4.04 (s, 6H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 59.11, 44.33; MS (CI) 176.0 (M − Cl).

(19) **2,2-Bis(chloromethyl)aziridine (4).** To the reaction mixture was added 400 mL of methylene chloride, and two layers were separated. Aqueous layer was extracted with 4 × 400 mL of dichloromethane. Combined organic layers were washed with 100 mL of water and dried over sodium sulfate. The solvent was removed by evaporation under water aspirator pressure at 35 °C, and pyridine was thoroughly removed by high-vacuum distillation (0.01 mmHg) at room temperature. The resulting brown liquid was distilled to give 121.1 g (70%) of clear colorless liquid, bp 42 °C (0.01 mmHg), which was first stirred with 1 g of sodium hydroxide pellets overnight at room temperature and then was kept refrigerated. ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.85 (d, J = 11.8 Hz, 1H), 3.65 (d, J = 11.5 Hz, 1H), 3.59 (d, J = 11.8 Hz, 1H), 3.36 (d, J = 11.5 Hz, 1H), 1.99 (d, J = 9.9 Hz, 1H), 1.70 (d, J = 8.0 Hz, 1H), 0.83 (bs, 1H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 47.61, 47.26, 39.22, 32.02. HRMS (CI): 140.0039 (M + H); calcd: 140.0034 for $C_4H_8Cl_2N$.

(20) **1,3-Dichloro-2-(chloromethyl)propene.** ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.39 (s, 1H), 4.35 (s, 2H), 4.21 (s, 2H); ^{13}C NMR (91 MHz, $CDCl_3$): δ 135.06, 122.49, 43.77, 38.28. Formation of trichloropropene under the employed reaction conditions is precedented by Boikov, Yu. A.; V'yunov, K. A.; Ginak, A. I. *J. Org. Chem. USSR* **1982**, *18*, 2010.