ORGANIC LETTERS

2007
Vol. 9, No. 16
3005−3008

Thermal Decomposition of *meso*- and *d,l*-3,4-Diethyl-3,4-dimethyldiazetine *N,N′*-Dioxide

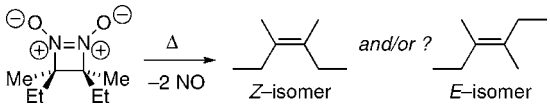
Gary W. Breton,* Justine E. Nickerson, Anna M. Greene, and Lindsey H. Oliver

Department of Chemistry, Berry College, P.O. Box 495016, Mount Berry, Georgia 30149

gbreton@berry.edu

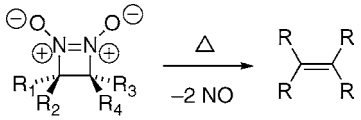
Received May 4, 2007

ABSTRACT



Two stereochemically defined diazetine *N,N′*-dioxides were synthesized. Thermal decomposition at 200 °C resulted in 95% retention of stereochemistry in the alkene product relative to the starting stereochemistry. These results suggest that decomposition occurs via cleavage of the two C–N bonds either simultaneously or in rapid succession.

1,2-Diazetine *N,N′*-dioxides (diazetine dioxides), **1** in Figure 1, are a class of strained four-membered ring azo dioxide



1

1a $R_1 = R_3 = H$. $R_2 = R_4 = Ph$
1b $R_1 = R_2 = R_3 = R_4 = Me$
1c $R_1 = R_3 = Me$. $R_2 = R_4 = Et$
1d $R_1 = R_4 = Me$. $R_2 = R_3 = Et$
1e $R_1 = R_2 = R_3 = R_4 = H$

Figure 1. Thermal decomposition of diazetine dioxides, **1**.

heterocycles.[1] They have been used as highly effective low-energy triplet quenchers in photochemical reactions,[2] and have recently been investigated for their pharmaceutical potential as vasorelaxants and antiaggregants.[1,3] Their biological activity can be attributed to the liberation of 2 equiv of nitric oxide (NO) upon thermal decomposition (Figure 1). However, the mechanism of decomposition is still in question.[1,4,5] To realize the full potential of diazetine dioxides as therapeutic agents it is imperative to have a clear understanding of their preferred mode of thermal decomposition.

We recently reported the thermal decomposition of *cis*-1,2-diphenyl-3,4-diazetine *N,N′*-dioxide (**1a**, Figure 2).[1] This compound decomposed at a rate much greater than that of alkyl-substituted diazetine dioxides (e.g., 1,1,2,2-tetramethyldiazetine dioxide, **1b**), and the product distribution was found to be solvent dependent. In boiling chloroform *trans*-stilbene (**2**) was the major product (indicating inversion of stereochemistry relative to the starting material) while in DMSO the major product was diphenyl glyoxime (**3**) (believed to result from direct isomerization of the diazetine dioxide via migration of the benzylic hydrogens). The route leading to *trans*-stilbene was attributed to cleavage of a C−N

(1) Breton, G. W.; Oliver, L. H.; Nickerson, J. E. *J. Org. Chem.* **2007**, *72*, 1412−1416 and references cited therein.
(2) (a) Ullman, E. F.; Singh, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 5077−5078. (b) Singh, P. J.; Ullman, E. F. *J. Am. Chem. Soc.* **1976**, *98*, 3018−3019.
(3) (a) Severina, I. S.; Belushkina, N. N.; Grigoryev, N. B. *Biochem. Mol. Biol. Int.* **1994**, *33*, 957−967. (b) Severina, I. S.; Ryaposova, I. K.; Volodarsky, L. B.; Mozhuchin, D. C.; Tichonov, A. Y.; Schwartz, G. Y.; Granik, V. G.; Grigoryev, D. A.; Grigoryev, N. B. *Biochem. Mol. Biol. Int.* **1993**, *30*, 357−366.
(4) (a) Greene, F. D.; Gilbert, K. E. *J. Org. Chem.* **1975**, *40*, 1409−1415. (b) Singh, P. *J. Org. Chem.* **1975**, *40*, 1405−1408.
(5) Snyder, J. P.; Heyman, M. L.; Suciu, E. N. *J. Org. Chem.* **1975**, *40*, 1395−1404.

10.1021/ol0710414 CCC: $37.00
Published on Web 07/14/2007

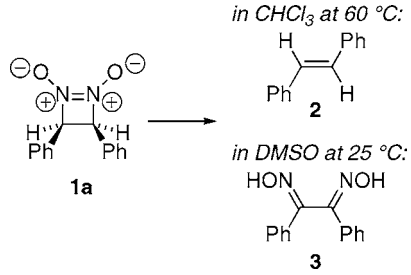
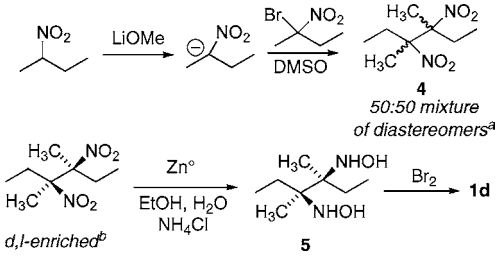


Figure 2. Solvent-dependent pathways for the decomposition of **1a**

bond in the diazetine dioxide to form a transient diradical followed by bond rotation and cleavage of the remaining C−N bond. We wondered whether simple alkyl-substituted diazetine dioxides might exhibit the same sort of scrambling of stereochemistry upon decomposition.

The stereochemically defined diazetine dioxides **1c** and **1d** have been briefly reported in the literature as synthetic intermediates, but their decomposition was apparently not investigated.[6] We synthesized compounds **1c** and **1d** according to literature procedures that generally mirrored the synthesis of the well-known tetramethyl derivative **1b** (Scheme 1).[7] Attempted synthesis of the dinitro intermediates

Scheme 1. Synthesis of Diazetine Dioxides **1c** and **1d**



[a] Separation of the diastereomers was effected via standard column chromatography to afford enriched *meso*- and *d*,*l*-isomers. [b]Reaction of the *meso*-enriched dinitro compound led to **1c**.

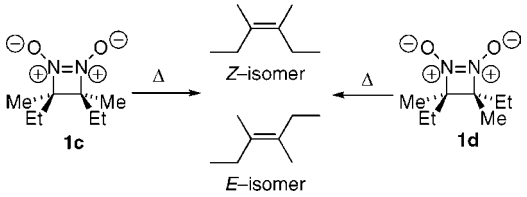
4 in aqueous solution according to methods reported in the literature were not successful in our hands.[7c,8] We were, however, able to synthesize **4** via coupling of the preformed lithium salt of nitrobutane with independently prepared 2-bromo-2-nitrobutane in DMSO.[9] Furthermore, we found that separation of the *meso*- and *d*,*l*-dinitro stereoisomers could be effected quite well with standard column chromatography rather than the laborious series of fractional crystallizations previously reported.[8,10]

According to the literature,[8] five recrystallizations of a 50/50 mixture of diastereomers afforded the *meso*-isomer in 95% purity, while a single column afforded the *meso*-isomer in 99% purity (by GC). A second column purification on the enriched *d*,*l*-isomer afforded the diastereomer in 94% purity while the literature reports it in only 65% purity. Zinc metal reduction of the stereochemically enriched dinitro compounds to bishydroxyl amines **5** followed by oxidation to the corresponding diazetine dioxides proceeded according to literature precedent.[7c]

We recently reported the kinetics of decomposition of compound **1b** as determined by ^{1}H NMR spectroscopy.[1] We desired to compare the rate of decomposition of compounds **1c**,**d** with that of **1b**, but ^{1}H NMR spectroscopy was not nearly as appealing a method because of the greater complexity of the NMR spectra of **1c**,**d** (and, hence, expected overlap of signals). We found that the decomposition of **1b** could be readily followed by UV−vis spectroscopy at 100 °C in high-boiling *n*-butanol as solvent by following loss of the absorption at 257 nm (corresponding to the azo dioxide functional group). Clean, first-order kinetics were observed. The rate determined ($k = [1.2 \pm 0.2] \times 10^{-4}$ s^{-1}) was consistent with the rate determined by NMR spectroscopy in DMSO-d_6 ($k = [8.9 \pm 0.1] \times 10^{-5}$ s^{-1}).[1] Compounds **1c** ($k = [2.2 \pm 0.1] \times 10^{-4}$ s^{-1}) and **1d** ($k = [1.7 \pm 0.2] \times 10^{-4}$ s^{-1}) exhibited marginally higher rates of decomposition, possibly attributable to the slightly greater steric interactions of the larger ethyl groups on these compounds relative to the four methyl groups of **1b** (the *cis*-oriented ethyl groups of **1c** affording the greatest steric interactions and therefore the highest reaction rate). Despite very subtle differences, all of the compounds (as would be expected) decomposed at similar rates.

For product analysis, decomposition of the diazetine dioxides was effected in the heated injector port (set at 200 °C) of a GCMS. In both cases, only NO and the corresponding alkenes were observed. Thermolysis of the enriched *d*,*l*-

Table 1. Thermal Decomposition of Diazetine Dioxides **1c** and **1d**



compd	temp (°C)	ratio *Z*:*E*	% stereoretention
1c[a]	200	94:6	95
1c[a]	350	83:17	83
1d[b]	200	10:90	95
1d[b]	350	15:85	89

[a] Enriched sample (99% *meso*: 1% *d*,*l*). [b] Enriched sample (94% *d*,*l*: 6% *meso*).

(6) White, D. K.; Greene, F. D. *J. Am. Chem. Soc.* **1978**, *100*, 6760−6761.
(7) (a) Singh, P.; Boocock, D. G. B. *Tetrahedron Lett.* **1971**, *42*, 3935−3938. (b) Greene, F. D.; Gilbert, K. E. *J. Org. Chem.* **1975**, *40*, 1409−1415. (c) Ullman E. F. Diazacyclobutanes. U.S. Patent 4,032,519, June 28, 1977.
(8) Shustov, G. V.; Tavakalyan, N. B.; Shustova, L. L.; Pleshkova, A. P.; Kostyanovskii, R. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 364−375.
(9) Kornblum, N.; Boyd, S. D.; Pinnick, H. W.; Smith, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 4316−4318.

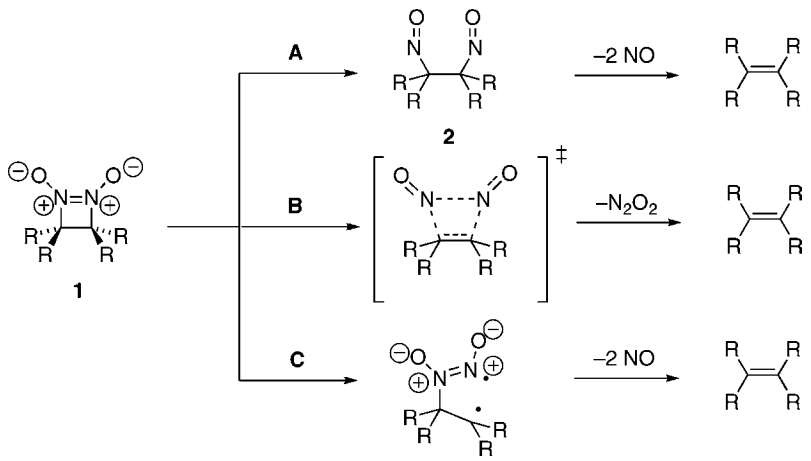


Figure 3. Possible mechanisms for the decomposition of diazetine dioxides.

isomer (94% *d*,*l* and 6% *meso*) led to a 90:10 mixture of *E*- and *Z*-3,4-dimethyl-3-hexene (confirmed with authentic samples) suggesting 95% retention of the initial stereochemistry (see Table 1). Similarly, injection of enriched *meso*-isomer (99% *meso*) led to a 6:94 mixture of *E*- and *Z*-alkenes suggesting the same percentage of stereochemical retention. Decomposition at higher temperatures (350 °C) led to greater amounts of stereochemical scrambling (see Table 1). Control experiments confirmed that the alkenes themselves did not isomerize under these conditions.

We have previously proposed three potential modes of decomposition for diazetine dioxides (Figure 3).[1] Mechanism A in Figure 3 results from initial breaking of the azo dioxide N═N bond to form a dinitroso intermediate (**2**), which could then release two molecules of NO to generate the alkene product. Mechanism B represents a concerted loss of two molecules of NO (or a molecule of N_2O_2) along with generation of the alkene. Both a symmetrical and an asymmetrical version of mechanism B could be envisioned. In support of the feasibility of this mechanism an asymmetrical, yet concerted, elimination of N_2 has been put forth as the likely mode of decomposition for the related 1,2-diazetine compounds.[11] Mechanism C depicts single bond scission to form a diradical intermediate, followed by loss of two molecules of NO (or a molecule of N_2O_2) and formation of the alkene product. Mechanisms A and C would conceivably lead to stereochemical scrambling due to C−C bond rotation of the bisnitroso or diradical intermediates, respectively, prior to C═C bond formation. Mechanism B, however, would lead to stereochemical retention.

Many cyclic azo dioxide compounds are in equilibrium with their bisnitroso counterparts when in solution.[7b] The bisnitroso compounds give rise to strongly colored blue or green solutions. We, and others,[7b] have observed that there is no coloration of solutions when diazetine dioxides are heated in solution, even to the point of decomposition. This observation, in conjunction with the retention of stereochemistry observed in the decomposition of **1c**,**d**, strongly argues against the involvement of mechanism A.

Decomposition of *cis*-diphenyl diazetine dioxide **1a** led to inversion of stereochemistry affording *trans*-stilbene rather than the stereochemically retained *cis* isomer.[1] This result is, of course, inconsistent with mechanism B, and mechanism A was excluded for the same reason cited above. Mechanism C is likely in this case since the phenyl group could act to stabilize the carbon radical center of the intermediate. This stabilization would enhance the lifetime of the intermediate and allow ample time for C−C bond rotation. Bond rotation would be further facilitated by the relief of steric strain caused by the proximate phenyl groups.

Predominant (95%) retention of the relative starting stereochemistry of both the *meso*- and *d*,*l*-isomers of diazetine dioxides **1c** and **1d** upon decomposition could be explained in two ways.

If mechanism C is operative, as it is with **1a**, stereochemical retention in this case could be explained by sufficiently rapid cleavage of the second C−N bond upon rupture of the first. Thus, if the lifetime of the intermediate diradical was exceptionally short relative to the phenyl-stabilized diradical of **1a**, the N_2O_2 fragment might be eliminated before substantial C−C bond rotation could take place. The small amount of stereochemical scrambling observed could be attributed to the small percentage of diradicals that have the opportunity to undergo C−C bond rotation prior to elimination of N_2O_2. The larger percentage of sterochemical scrambling at higher temperatures may be attributed to the greater energy content of the diradicals, thus promoting C−C bond rotation.

Alternatively, the results may be intepreted in terms of a competition between mechanisms B and C assuming they have similar, but different, activation barriers. If the activation barrier for mechanism C is greater than that of mechanism B, mechanism B would be preferentially followed (along

(10) Asaro, M. F.; Nakayama, I.; Wilson, R. B., Jr. *J. Org. Chem.* **1992**, *57*, 778−782.
(11) Breton, G. W.; Shugart, J. H. *J. Org. Chem.* **2003**, *68*, 8643−8649.

with predominant stereochemical retention), while minor competition by mechanism C would rationalize the small percentage of stereochemically scrambled alkene product. At higher temperatures, mechanism C would compete more effectively, and increased scrambling would be expected to occur (as observed).

To differentiate between the possible decomposition mechanisms, we have launched an intensive computational investigation of relevant intermediates and transition state structures, and intend to correlate these computational predictions with the experimentally determined results. These computations are currently underway, and will be presented in the near future.

Acknowledgment. This material is based upon work supported by the National Science Foundation under Grant No. 0405034

Supporting Information Available: All experimental procedures and ^{1}H NMR spectra for compounds **1c** and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0710414