JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Concomitant Nitrene and Carbene Insertion Accompanying Ring Expansion: Spectroscopic, X-ray, and Computational Studies

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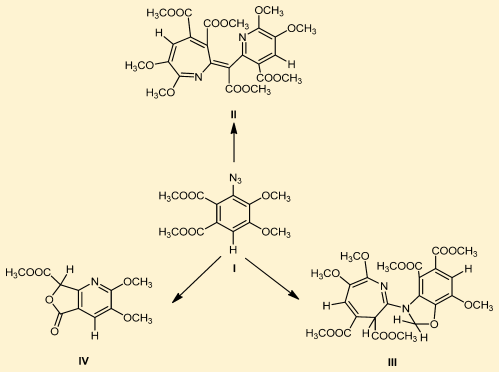
Supporting Information

ABSTRACT: Reinvestigation of the thermolysis of azido-meta-hemipinate (**I**) yielded, in addition to known **II**, unusual products **III** and **IV**. These products are formed via a rare intramolecular nitrene insertion into an adjacent methoxy C−H bond followed by an intermolecular reaction during a ring-expansion and a ring-extrusion reaction followed by a carbene insertion. The structures of the new compounds were confirmed using a battery of techniques, including HRMS (ESI-QTOF) and 2D NMR as well as X-ray crystallography for compound **IV**. Density functional theory methods were used to support the proposed mechanism of formation of the products.



INTRODUCTION

The chemistry of aryl azides is well-documented in the literature.[1] Arylnitrenes are known to generate a myriad of possible intermediates,[2] and substituents have been described as playing a mysterious role, especially in their most enigmatic reactions involving ring expansion to azepines.[3] In such reactions, a slippery potential-energy surface has been suggested.[4] Fluoro substituents on both of the ortho positions of arylnitrenes are known to yield long-lived singlet nitrenes[5] (true nitrenes[6]). Upon thermolysis or photolysis, aryl azides initially yield singlet nitrenes that can interconvert to the triplet state, thereby leading to the formation of the corresponding amine or azo compound. The singlet nitrene can rearrange to the corresponding benzazirine and heterocumulene. In substituted aryl azides, two different isomers of the benzazirine/heterocumulene could be involved in such reactions. Some of these reactions are regiospecific, whereas others are not,[7] and the presence of nucleophiles assists in the formation of 1H- and 3H-azepines. Alternatively, ring extrusion may lead to the formation of corresponding pyridylcarbenes.[8] The formation of cyano-substituted cyclopentadienes has also been documented (Scheme 1).

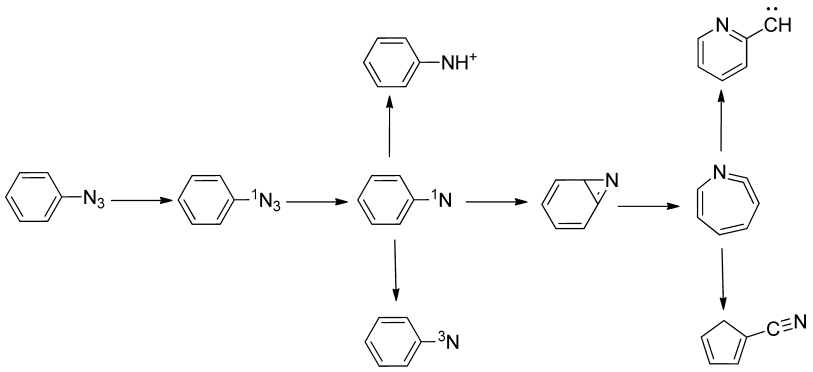
The pyrolysis of pentafluorophenyl azide constitutes an exceptional case in which a diazadecafluorofulvalene has been reported.[9] Increasing the rate of the intermolecular over the intramolecular reaction of arylnitrenes has remained a challenging problem.[10] On the basis of this example, it was predicted[11] that efficient photoaffinity labeling agents could be developed using this azide. Such reagents are now indeed commercially available.[12] It is known that the nitrile and methoxycarbonyl substituents alone do not provide any rate acceleration to the intramolecular cyclization of the corresponding aryl nitrenes and thus methyl *o*-azidobenzoate reacts in other ways.[13] Nitrenes derived from perfluorophenyl azide have found use in diverse areas such as materials science, functionalization of carbon materials (fullerenes, SWCNTs, and, more recently, for derivatizing graphene), and for the preparation of semiconducting devices and photovoltaics.[14]

We previously reported the formation of **II**[15] (methyl-2-(5,6-dimethoxycarbonyl-2,3-dimethoxy-azep-7-inylidine)-2-(5-methoxycarbonyl-2,3-dimethoxy-pyrid-6-yl) acetate) (Viswamayene).[16] during the thermolysis of 1-azido-5,6-dimethoxybenzene-2,3-dicarboxylic acid dimethyl ester (**I**, azido-meta-hemipinate). This reaction occurred presumably via a long-lived singlet nitrene involving a concomitant ring

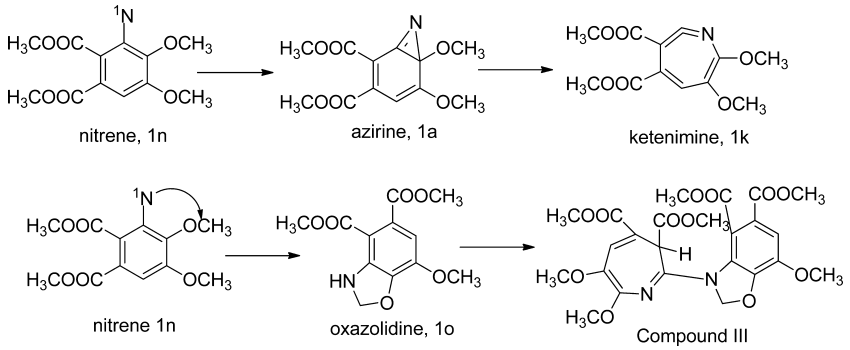
Received: November 26, 2013
Published: January 10, 2014

dx.doi.org/10.1021/jo402621w | J. Org. Chem. 2014, 79, 1199−1205

Scheme 1. Intermediates Formed during Photolysis and Thermolysis of an Aryl Azide



Scheme 2. Proposed Intermediates for the Formation of Compound III



expansion and ring extrusion.[17] This has been described as a most unusual reaction involving a series of rather involved rearrangement reactions.[18] We have used these for preparing photoresists for microlithography as well as for efficient functionalization of fullerenes and SWCNTs for photovoltaics.[19] Aryl azide-based heterobifunctional cross-linkers have been used for chemical cross-linking combined with mass spectrometry,[20] which has become an important tool for low-resolution mapping of interacting amino acids in proteins. Combined with the click reaction, this technique is important in studying transient protein−protein interactions with implications in proteomics/lipidomics, systems biology, and studies of the origin of diseases (e.g., cataractogenesis).[21]

RESULTS AND DISCUSSION

During a reinvestigation of the pyrolysis of azido-meta-hemipinate, further unusual products were obtained by us, and their characterization is given below. Thus, thermolysis of azido-meta-hemipinate (**I**) in chlorobenzene gave, in addition to **II**, two new compounds (**III** and **IV**). Column chromatography led to the elution of the unchanged azide followed by **IV**. Further elution yielded **II** and finally **III**. Compounds **III** and **IV** were analyzed by positive ion electrospray ionization quadrupole time-of-flight high-resolution mass spectrometry (ESI-QTOF-HRMS). The $[M + H]^+$ ion of compound **III** calculated for $C_{24}H_{27}N_2O_{12}$ was m/z 535.1564, and the $[M + H]^+$ ion of **IV** calculated for $C_{11}H_{12}NO_6$ was m/z 254.0664. The HRMS (ESI-QTOF) analysis of compounds **III** and **IV** showed the $[M + H]^+$ ion at m/z 535.1589 and 254.0656, respectively. The HRMS data of **III** and **IV** supported the proposed structures.

The molecular weight (534 Da) of **III** indicated that it could be a dimeric compound based on the nitrene intermediate obtained from **I**. Most unexpectedly, the ^{1}H NMR spectrum of **III** showed five different signals in the olefinic/aromatic chemical-shift region, and the broad signal expected from NH was not seen. Moreover, only seven methoxy signals were observed, not eight, as would be expected in the dimeric case. This ruled out the involvement of the triplet nitrene pathway that is known to lead to amines and azo compounds. In the ^{13}C NMR spectrum, the presence of four different methoxycarbonyl groups and a total of only seven methoxy signals again pointed to a missing methoxy group. Analysis of the ^{1}H−^{1}H COSY spectrum indicated that the two protons at δ 5.68 and 7.74 were closely related to each other through bonds. The HSQC spectrum further assisted the assignment of the aromatic and olefinic CH-bearing carbons at 132.58 and 111.62 ppm, respectively. The HMBC spectrum showed correlations between the peaks at δ 5.68 with the two carbonyl carbon signals at 166.11 and 167.05 ppm, indicating that this proton is closely associated through bonds to two different methoxycarbonyl groups. Thus, the reaction is regiospecific in nature, and the 3H-azepine alone is formed (toward the adjacent methoxycarbonyl group). In the HSQC spectrum, the peak resulting from the new carbon at 48.5 ppm showed a correlation with δ 5.68. The correlation between the two geminal protons of CH_2 in the NOESY spectrum established that these protons are magnetically nonequivalent and are within 5 Å of each other. The correlation of δ 5.68 with 5.91 and 6.4 ppm indicated that these three protons are close to each other in space.

The presence of three additional signals in the olefinic region combined with the negatively peaked CH_2 signal in the DEPT-135 spectrum gave the first clue to a possible insertion reaction. It is presumed that on thermolysis azido-meta-hemipinate leads to a long-lived singlet nitrene that subsequently undergoes an

dx.doi.org/10.1021/jo402621w | J. Org. Chem. 2014, 79, 1199−1205

intermolecular reaction regiospecifically. The initial nitrene intermediate could get converted to the benzazirine (i) and heterocumulene/azepinylidene (ii) intermediates. It is suggested that the generated nitrene simultaneously undergoes an insertion into the adjacent methoxy group intramolecularly, leading to the formation of an oxazolidine ring. The secondary amine intermediate then brings about a nucleophilic addition intermolecularly to the heterocumulene/azepinylidene intermediate, leading to **III** (Scheme 2). Only one of the two possible 3H-azepines is formed, showing that the reaction is regiospecific. The absence of any broad N−H signal rules out the formation of 1H-azepine.

The ^{1}H NMR spectrum of **IV** showed signals at δ 4.10, 3.92, and 3.80, which are ascribed to two methoxy and one methoxycarbonyl groups. It had one methoxy group less than that required for a monomeric structure. The MS (253 Da) analysis further confirmed its monomeric nature based on the nitrene intermediate corresponding to **I**. DEPT-135 studies confirmed the absence of any CH_2 group in **IV**.

Compound **IV** crystallizes in the noncentrosymmeric monoclinic space group *Cc* owing to the presence of a chiral center, but the molecule lacks any heavy atom (Z > 14) and hence determination of its absolute configuration from X-ray studies is difficult, particularly when using molybdenum as the X-ray source. Weak C-HPPPO hydrogen bonds hold the structure together in the unit cell (Figure 1). The relevant crystallographic information, bond distances, angles, and interaction geometry are listed in the Supporting Information.

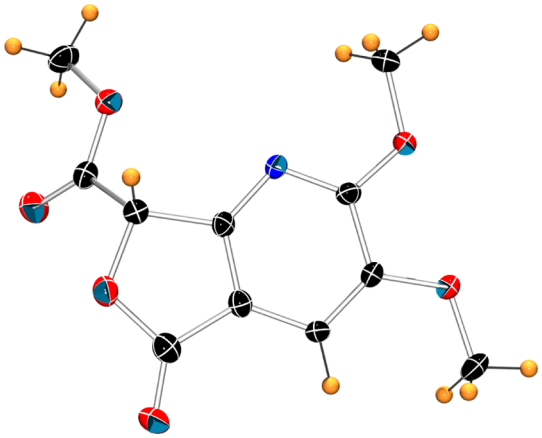


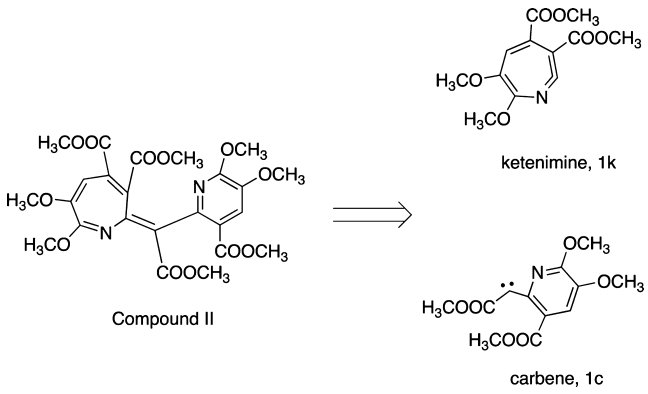
Figure 1. ORTEP diagram for **IV** with 30% ellipsoid probability.

COMPUTATIONAL STUDIES

To understand the formation of product **III** and **IV**, the potential-energy surfaces of the fate of the nitrenes were explored. We proposed that compound **II** is produced from the carbene and ketenimine shown in Scheme 3. Hence, we explored the potential-energy surface for the nitrene-to-carbene conversion.

Figure 2 shows the relative energy profile for this nitrene-to-carbene conversion (**1n** to **1c**) using computational methods described later (see Computational Methods). The nitrene (**1n**), which is formed from the precursor, would need to overcome an activation energy of 14.2 kcal/mol to convert to the azirine (**1a**). This process would be followed by a small energy barrier of 5.7 kcal/mol to expand the ring to form ketenimine (**1k**). Then, the nitrene (**1n**) has to overcome an

Scheme 3. Proposed Intermediates for Formation of Compound II



energy barrier of 17.5 kcal/mol in which a further slight expanding of the C=C=N angle from 154° to 161° in the transition state facilitates the contraction of the C−C bond to give **1a**. It further undergoes the three-membered ring opening to form the carbene. Under the experimental thermolysis conditions (130 °C), the formation of the carbene should be feasible.

Compound **III** is proposed to form via a nitrene insertion into the neighboring methoxy C−H to form the oxazolidine (**1o**) followed by the nucleophilic addition of the secondary amine to the ketenimine (Scheme 3). Results of our computation showed that there is a 10.1 kcal/mol activation-energy barrier for the formation of the oxazolidine (**1o**).

Compound **IV** is proposed to involve the formation of ylide (**1y**), for which the carbene interacts with the more basic carbonyl oxygen. This ylide intermediate can possibly undergo protonation and then demethylation to yield compound **IV**. To confirm the feasibility of the formation of this ylide, calculations were performed on this pathway, and these confirmed that the activation-energy barrier for such an ylide formation would only require 4.1 kcal/mol. Hence, the formation of the lactone structure is highly feasible. Moreover, we suggest that this intramolecular ylide formation would obviate the formation of any other isomers beyond observed lactone product **IV** (Scheme 4).

CONCLUSIONS

The thermolysis of azido-meta-hemipinate leads to the formation of three different compounds. The formation of **II** involves the reaction of a concomitant ring-expansion and ring-extrusion reaction. It is inferred that **III** is formed via a nitrene insertion into a neighboring methoxy C−H bond followed by the nucleophilic addition of the secondary nucleophilic amine to the ketenimine (Scheme 2).

It is suggested that **IV** is formed via ring extrusion to a pyridyl carbene and the possible involvement of an ylide intermediate, leading to the proposed lactone structure (Scheme 4). The formation of the above products is evidence of the presence of a wide range of intermediates that have been observed in the reactions of aryl azides. These are facilitated by the inability of the singlet nitrene to interconvert to the triplet state. The absence of externally added nucleophiles also assists in the formation of these products. Our results thus represent newer observations that add to the rich literature of this class of compounds.

dx.doi.org/10.1021/jo402621w | J. Org. Chem. 2014, 79, 1199−1205

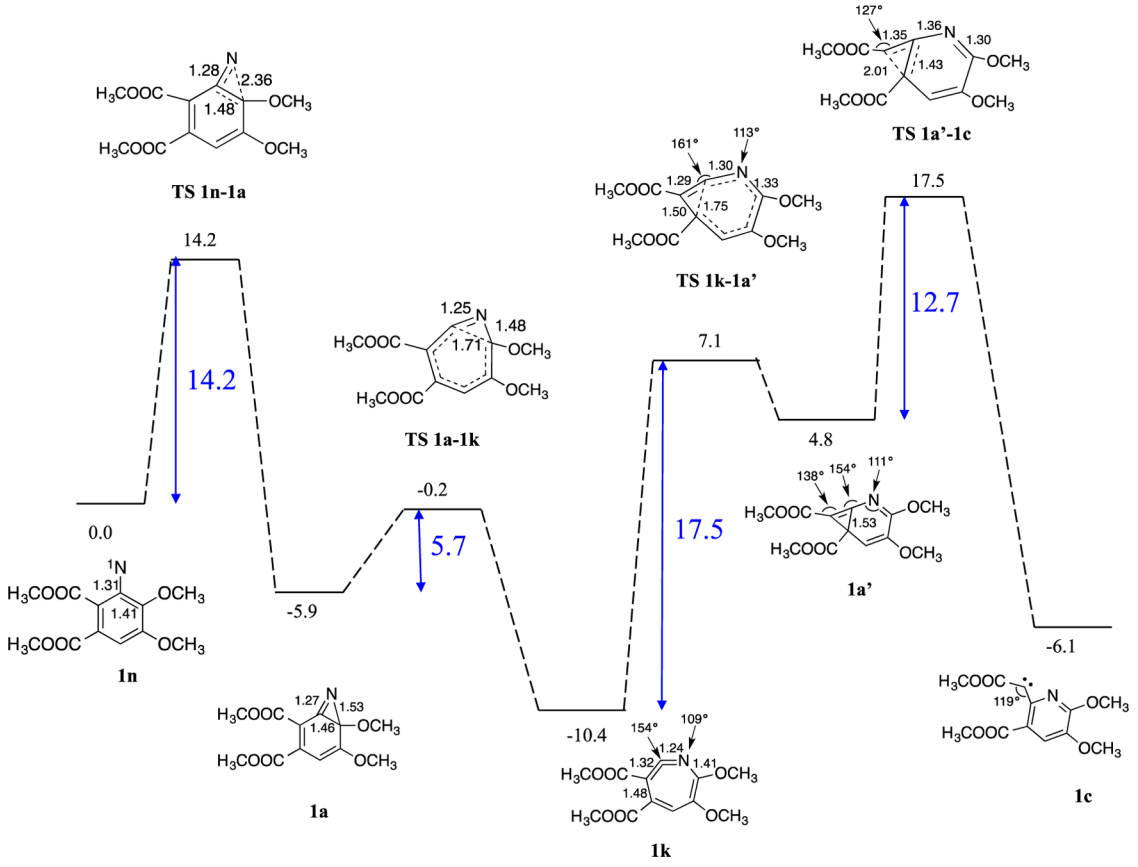


Figure 2. Relative energy profile (in kilocalories per mole) obtained from B3LYP/6-31+G(d,p) calculations for the nitrene-to-carbene interconversion. Selected distances are given in angstroms, and angles are given in degrees.

Scheme 4. Proposed Intermediates for Formation of Compound IV

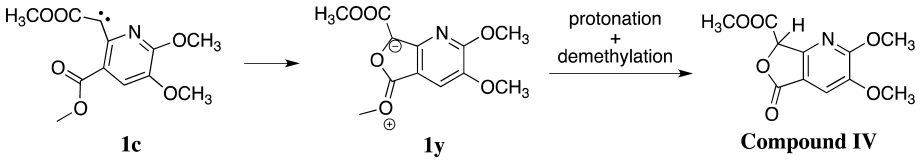
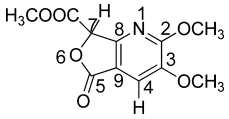


Table 1. NMR Assignment for Compound IV



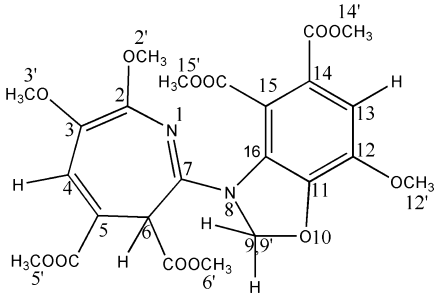
^{1}H NMR (δ)	assignment	^{13}C NMR (ppm)	assignment	DEPT-135	HSQC correlations
3.80 (s)	$COOCH_3$	53.1	$COOCH_3$	up	δ 3.80 with 53.1 ppm
3.92 (s)	OCH_3	55.3	OCH_3	up	δ 3.92 with 56.3 ppm
4.10 (s)	OCH_3	56.3	OCH_3	up	δ 4.10 with 55.3 ppm
5.67 (s)	H-7	111.6	C4	up	
7.35 (s)	H-4	112.2	C3	up	δ 7.35 with 111.6 ppm
		146.4	C8	QC	
		154.2	C7		
		160.03	C2	QC	
		166.4	carbonyl C	up	
		168.5	carbonyl C	QC	

EXPERIMENTAL SECTION

All of the chemicals used for synthesis were purchased and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60F254, 200 μm thick aluminum sheets, and the spots were visualized either under UV or by iodine vapor. The crude reaction mixture was analyzed by LCMS (binary LC with 500 MS) using a C-18 100 × 2.0 mm column followed by its purification using column chromatography silica gel (100−200 mesh, 8:2 petroleum ether/ethyl acetate) and preparative

dx.doi.org/10.1021/jo402621w | J. Org. Chem. 2014, 79, 1199−1205

Table 2. ^{1}H NMR, ^{13}C NMR, and DEPT-135 Data for Compound III with the Assignments of the Corresponding Protons and Carbon Atoms



^{1}H NMR (δ)	proton	^{13}C NMR (ppm)	carbon	DEPT-135	^{13}C NMR (ppm)	carbon	DEPT-135
3.538 (s)	H-6′	(1) 48.74	C-6	U	(13) 125.29	QC	QC
3.571 (s)	H-14′	(2) 51.91	C-14′	U	(14) 129.62	QC	QC
3.635 (s)	H-15′	(3) 52.41	C-6′	U	(15) 130.67	QC	QC
3.643 (s)	H-12′	(4) 52.53	C-5′	U	(16) 132.58	C-13	U
3.802 (s)	H-5′	(5) 52.62	C-2′	U	(17) 133.66	QC	QC
3.811 (s)	H-2′	(6) 54.34	C-15′	U	(18) 143.54	QC	QC
3.954 (s)	H-3′	(7) 56.56	C-3′	U	(19) 144.31	QC	QC
5.684 (s)	H-6	(8) 60.9	C-12′	U	(20) 152.24	QC	QC
5.9(d)	H-9	(9) 86.89	C-9	D	(21) 165.36	carbonyl on benzene ring	QC
6.4 (d)	H-9′	(10) 101.64	QC	QC	(22) 166.11	carbonyl on azepine ring	QC
7.141 (s)	H-4	(11) 111.62	C-4	U	(23) 167.05	carbonyl on azepine ring	QC
7.747 (s)	H-13	(12) 115.93	QC	QC	(24) 167.43	carbonyl on benzene ring	QC

Table 3. Two-Dimensional NMR Assignments for Compound III

COSY (δ)	HSQC (δ)	HMBC (δ)	NOESY (δ)
5.68 (H-6)−3.538 (H-6′)	5.68−48.5 (C-6)	5.68−101.64, 132.58, 166.11, 167.05	7.14−3.94 (H-3′)
7.14 (H-4)−3.95 (H-3′)	5.91, 6.4−86.89 (C-9)	5.91−133.66	7.79−3.571 (H-14′)
7.74 (H-13)−3.64 (H-12′)	7.14−111.62 (C-4)	6.4−133.66, 129.62, 144.31	7.79−3.635 (C-15′)
5.68−7.74 (H-13) and 6.4 (H-9′)	7.74−132.58 (C-13)	7.14−115. 93, 125.29, 143.54, 144.31, 167.05	7.79−3.643 (C-12′)
7.74−5.68	3.571−51.91 (C-14′)	7.74−48.5, 130.67, 152.24, 166.11	5.68−5.91 and 6.4
	3.538−52.41 (C-6′)		6.4−5.91 and 5.68
	3.635−54.34 (C-15′)		5.91−6.4 and 5.68
	3.643−60.94 (C-12′)		
	3.802−52.53 (C-5′)		
	3.811−52.62 (C-2′)		
	3.954−56.56 (C-3′)		

thin-layer chromatography (TLC). The purified compounds were analyzed by high-pressure liquid chromatography, nuclear magnetic resonance spectroscopy (NMR, 400 MHz) in $CDCl_3$ at 298 K, and positive ion electrospray ionization quadrupole time-of-flight high-resolution mass spectrometry (ESI-QTOF-HRMS). The UV−vis spectra and FT-IR were recorded.

A needle-shaped crystal of 0.3 × 0.08 × 0.06 in size was mounted on Xdiffractometer equipped with a Mo Kα microfocus sealed tube (λ = 0.71073). Data collection followed by subsequent data reduction was performed using CrysAlis Pro software.[22] The structure was solved by direct methods using SHELXS-97,[21] and the structure refinement was done with SHELXL-97[23] of the WinGx package.[24] The ORTEP figures were generated using ORTEP-3[25] and POV-Ray,[26] and the packing diagrams were generated by Mercury 3.0.[27] The crystallographic information file was prepared using PLATON.[28]

General Procedure for Thermolysis. Compound **I** (400 mg, 1.35 mmol) was dissolved in 20 mL of chlorobenzene and was heated at 130 °C for 4 h. Chlorobenzene was distilled off, and the crude reaction mixture was subjected to column chromatography (4:1 petroleum ether/ethyl acetate). The eluted compounds were recrystallized by petroleum ether/benzene.

2,3-Dimethoxy-5-oxo-5,7-dihydro-furo[3,4-*b*]pyridine-7-carboxylic Acid Methyl Ester, IV. From column chromatography on silica gel (using petroleum ether/ethyl acetate 90:10 as the eluent), the unchanged azide eluted out first followed by compound **IV**. Recrystallization gave shiny white crystals of compound **IV**. Yield = 12.5% (based on the percentage of the azide converted). R_f 0.7 (hexane/ethyl acetate 8:2). mp 80−82 °C. Anal. Calcd for $C_{11}H_{12}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.31; H, 4.394; N, 5.518. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3H), 3.92 (s, 3H), 4.10 (s, 3H), 5.67 (s, 1H), 7.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 52.4, 53.1, 55.3, 56.1, 111.2, 112.7, 146.3, 150.6, 154.2, 166.3, 167.9. DEPT-135: no downward peak (Table 1). HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{11}H_{12}NO_6$, 254.0664; m/z $[M + Na]^+$ calcd for $C_{11}H_{11}NO_6Na$, 276.0484; m/z $[M + K]^+$ calcd for $C_{11}H_{11}NO_6K$, 292.0223; found, 254.0656, 276.0493, 292.0237, respectively.

3-(6,7-Dimethoxy-3,4-bis-methoxy-3*H*-azepin-2-yl)-7-methoxy-2,3-dihydrobenzoxazolyl-4,5-dicarboxylic Acid Dimethyl Ester, III. Compound **III** was eluted after compounds **IV** and **II** (petroleum ether/ethyl acetate 70:30 eluent). The recrystallization with 1:1 benzene/petroleum ether gave compound **III** as a yellow solid. Yield = 7.5% (based on the percentage of the azide converted). R_f 0.4 (4:1 hexane/ethyl acetate). mp 202−203 °C. Anal. Calcd for $C_{24}H_{27}N2O_{12}$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.83; H, 4.912; N, 5.250. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.53 (s, 3H), 3.57 (s, 3H), 3.63 (s, 3H), 3.64 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 5.68 (s, 1H), 5.9 (d, 1H, J = 4 Hz), 6.4 (d, 1H, J = 4 Hz), 7.14 (s, 1H), 7.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 48.7, 51.9, 52.4,

dx.doi.org/10.1021/jo402621w | J. Org. Chem. 2014, 79, 1199−1205

52.5, 52.6, 54.3, 56.6, 60.9, 86.9, 101.6, 105.8, 111.6, 115.9, 125.3, 125.3, 129.6, 130.7, 132.6, 133.7, 143.5, 144.3, 152.2, 165.4, 166.1, 167.1, 167.4. DEPT-135 δ 86.8 (downward); COSY δ 7.74 correlating 5.68, δ 5.68, 7.14, 7.74 correlating 3.358, 3.95, and 3.64, respectively; HSQC δ 5.68 correlating δ 48.5, δ 7.14 correlating 111.62, δ 7.74 correlating 132.58, and δ 5.91 and 6.4 correlating 86.82; HMBC δ 5.68 correlating 101.6, δ 132.6 correlating 166.1 and 167.1; NOESY δ 5.91 correlating 6.4, δ 5.68 correlating 5.91 and 6.4 (Tables 2 and 3).

HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_{12}$, 535.1564; m/z $[M + Na]^+$ calcd for $C_{24}H_{26}N_2O_{12}Na$, 557.1383; found, 535.1589, 557.1401, respectively.

COMPUTATIONAL METHODS

Density functional theory calculations were performed with the Gaussian 09[29] suite of programs at the Ohio Supercomputer Center. Geometries were optimized with the 6-31+G(d,p)[30,31] basis set in conjunction with the B3LYP[32,33] density functional theory method. The nature of all stationary points, either minima or transition states, was determined by calculating the vibrational frequencies at the same level of theory. We have employed unrestricted B3LYP methods and found broken-symmetry solutions for the open-shell singlet nitrenes and the corresponding transition states for azirine formation, as has been described in the literature.[34]

ASSOCIATED CONTENT

Supporting Information

NMR spectra and HRMS (ESI-QTOF) for compounds **III** and **IV**; crystallographic data for compound **IV** along with bond distances and angles, ORTEP drawing, and X-ray data (CIF file); and geometries, vibrational frequencies, and energies for various transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

S.V.E thanks the Principal, St. Stephen's College, University of Delhi, Delhi for providing research facilities, OSDD−CSIR for research grants, and SIF, IISc Bangalore, and USIC, Delhi University for NMR spectra. C.M.H. and M.S.P. acknowledge financial support from the National Science Foundation (DMR-1212842). We thank the Ohio Supercomputer Center for providing generous allocations of computational resources to accomplish the results presented herein.

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