Flash Vacuum Pyrolysis of Some 4-Nitroisoxazoles

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Flash vacuum pyrolysis (FVP) of some 5-alkyl-3-methyl-4-nitroisoxazoles affords 1-nitro-1-cyanoacetone as the only product. A general mechanism is suggested which involves isomerization of the isoxazole to a 1-azirine. A nonclassical reaction of 3-methyl-4-nitroisoxazoles is assumed as a consequence of the electron-withdrawing ability of the nitro group, which precludes ring closure of the nitrile ylide intermediate to the oxazole isomer. The formation of 1-nitro-1-cyanoacetone by FVP of the 3-unsubstituted 5-methyl-4-nitroisoxazole suggests that the activation barrier for a 1,2-hydrogen shift from a 1-azirine or a vinylnitrene is lower than that for the formation of nitrile ylide. The FVP of 5-ethyl-3-methylisoxazole affords 5-ethyl-2-methyloxazole.

Introduction

Thermal and photochemical isomerizations of isoxazoles into azirines, oxazoles, and α-carbonyl derivatives of acetonitrile have been widely investigated.[1] However, most of this research has been concerned with isoxazoles substituted with electron-releasing groups such as amino, alkyl, and alkoxy. We have reported on the gas-phase thermal isomerization of some amino- and alkylisoxazoles[2,3] and have proposed a general reactivity pattern (Scheme I).

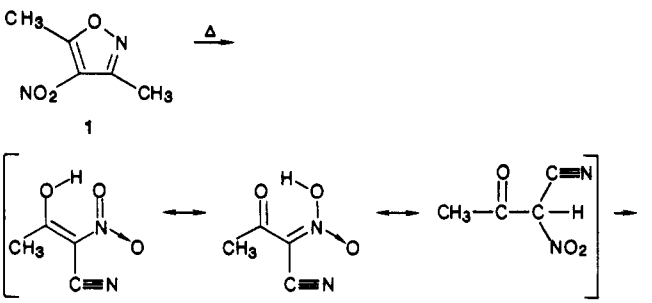
This pattern gives a satisfactory explanation of the reported experimental results and can be used to predict the expected isomer in the flash vacuum pyrolysis (FVP) of a given isoxazole based on the kind and position of its substituents. In addition, kinetic studies suggest that the step isoxazole → 1-azirine is rate-determining in all the derivatives studies.

In order to explore the gas-phase thermal behavior of isoxazoles substituted with an electron-withdrawing group we have carried out the FVP of the following 4-nitroisoxazoles: 3,5-dimethyl- (**1**), 5-ethyl-3-methyl- (**2**), 5-methyl- (**3**), and 5-(deuteriomethyl)-3-methyl-4-nitroisoxazoles (**4**). We also report on the FVP of 5-ethyl-3-methylisoxazole (**5**).

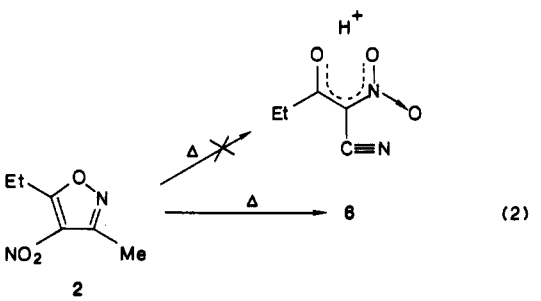
Results and Discussion

The FVP of **1** at 400 °C and 0.1 torr leads quantitatively to 1-cyano-1-nitroacetone (**6**, eq 1).

This result could be rationalized by a reaction pathway involving C–C bond scission at position 3 in the isoxazole ring with subsequent rearrangement and hydrogen abstraction to give **6**. If this pathway is correct, the FVP of asymmetrically substituted **2** should afford 1-cyano-1-nitro-2-butanone. However, the FVP of **2** under the same experimental conditions gave **6** quantitatively, thus precluding the suggested bond rupture at position 3 (eq 2).

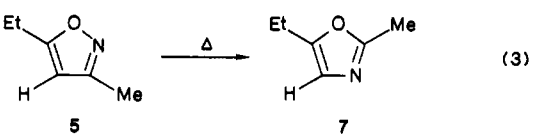


(1)



(2)

Since **2** bears an ethyl group at position 5 instead of the methyl of **1**, we wanted to know whether this difference was enough to change the reaction course. Therefore we carried out the FVP of 5-ethyl-3-methylisoxazole (**5**), which afforded quantitatively 5-ethyl-2-methyloxazole (**7**, eq 3) in good agreement with the mechanism of Scheme I.



(3)

It seems clear that isoxazoles **1** and **2** undergo a thermal reaction that involves loss of the alkyl group from position 5 and further intramolecular rearrangement to give **6**. Since this pathway requires migration of the 3-methyl group in some step of the reaction, we decided to explore the behavior of a 4-nitroisoxazole unsubstituted at position 3; therefore, we carried out the FVP of **3**. If **3** follows a reaction pathway analogous to that of **1** and **2**, 2-cyano-

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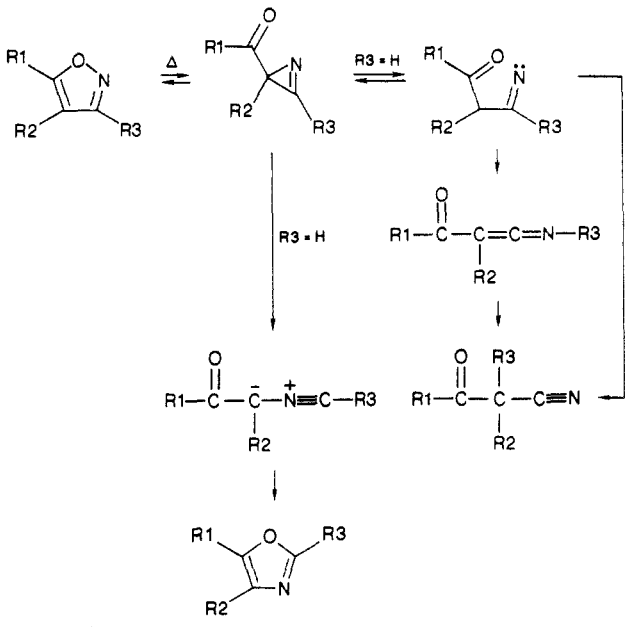
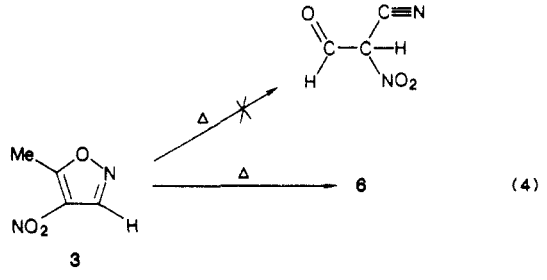
Scheme I



2-nitroacetaldehyde should be formed, but **6** was once again obtained in quantitative yield (eq 4).

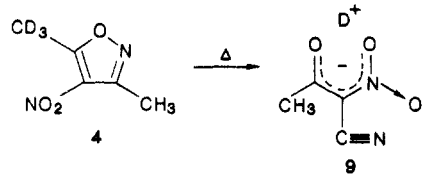


(4)

3

Although the FVP of **3** gives a different result from those observed with **1** and **2**, it is consistent with the general reactivity pattern of Scheme I.

Finally, we carried out the FVP of 5-(deuteriomethyl)-3-methyl-4-nitroisoxazole (**4**) in order to obtain experimental evidence on the way in which the 5-alkyl substituent is lost in **1** and **2**. The two possible routes involve either a C–C homolytic scission at position 5 followed by methyl migration and hydrogen abstraction or intramolecular hydrogen migration with extrusion of methylene and subsequent rearrangement of the 3-methyl group. The FVP of **4** affords quantitatively 1-cyano-1-nitroacetone-*1*-d_1 (**9**, eq 5), confirming the second reaction route.



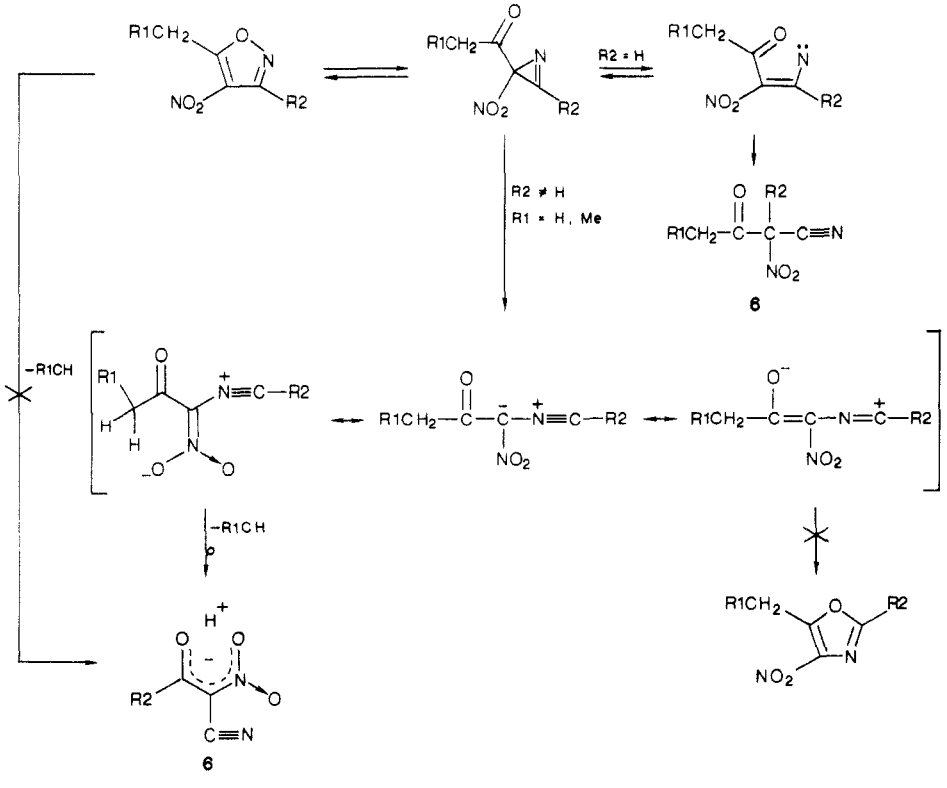
(5)

4 **9**

We conclude that the thermal reactions of **1**, **2**, and **4** to give **6** proceeds through a common pathway which involves hydrogen migration, methylene extrusion, and rearrangement. The possibility of direct loss of the substituent from position 5 of the isoxazole ring is rejected because this path does not explain the FVP of **3** to give **6**, the isomer predicted by Scheme I.

We propose the reaction pattern of Scheme II as the most satisfactory explanation for the experimental facts. We suggest that the thermolysis of these 4-nitroisoxazoles involves the intermediacy of 1-azirines. The nitro group attached to the carbon that supports part of the negative charge in the nitrile ylide intermediate prevents cyclization to the oxazole isomer and causes an intramolecular hydrogen migration followed by loss of methylene and subsequent rearrangement of the 3-methyl group. The result obtained with **3** indicates that the energy barrier for a 1,2-hydrogen shift from a 1-azirine or a vinylnitrene is

Scheme II



6

lower than that required by the step 1-azirine → nitrile ylide.

Experimental Section

^1H NMR spectra were recorded on a Varian T-60 or a Bruker FT-80 spectrometer; the latter was also used for ^{13}C NMR spectra. Chemical shifts are given in δ (ppm) downfield from Me_4Si. IR spectra were recorded on a Beckman IR-12 spectrometer, and mass spectra were recorded on a Finnigan 3300 with a 1500 INCOS data system. Solvents were analytical grade reagents. Melting points were determined by the capillary method on a Buchi-510 instrument and are uncorrected.

General Procedure for FVP. FVP was carried out in a Vycor glass reactor (30 cm long and 1.2 cm i.d.). The reactor was "seasoned" by the thermal decomposition of allyl bromide at 500 °C. All the 4-nitroisoxazoles were pyrolyzed between 300 and 400 °C. The system pressure was 10^{-3} torr without carrier and sample and 10^{-1} torr with carrier and sample; the time of residence in the reactor was about 10^{-2} s. Heating was performed with a tubular furnace (2 cm i.d.) equipped with a type k (Fe–Co) thermocouple covered with stainless steel and placed in the middle of the reactor to measure the gas temperature. The furnace was equipped with an electronic proportional controller (GAYNOR PRDH).

After the reactor reached reaction temperature, it was allowed to stand for at least 4 h under a nitrogen atmosphere in order to keep the temperature within ±0.5 °C (homogeneity along the reactor ≤2 °C).

Products were collected in a liquid–air-cooled trap beyond the reaction tube. In all runs the mass balance between the weight of sample used and the quantitative analysis of the reaction products was higher than 97%.

In a typical run, 0.5 mmol of the purified isoxazole was placed 10 cm before the oven inlet and cooled to liquid–air temperature; then the system was evacuated to 10^{-3} torr, and a stream of carrier gas was allowed to pass through the reactor. The sample was introduced into the carrier stream by heating with an external water bath at 40 °C during 30 min (time necessary to pass all the sample through the reactor at the appropriate dilution). Condensation of the sample before the oven inlet was prevented by placing an electrical resistance between bands of asbestos around the reactor which ensured temperatures between 80 and 100 °C.

The carrier gas used was oxygen-free dry nitrogen. The carrier flow rate was determined by a flow meter calibrated at room temperature and pressure and then corrected to the temperature and pressure of the reactor.

In some reactions we used either butadiene or cyclohexene as a carbene or radical scavenger, but no trapped products were found. Contact time, determined by neglecting the sample contribution to the overall flow rate, proved that $u(\text{carrier})/u(\text{sample}) \geq 50$.

Nitration of Isoxazoles. We used a slight modification of the techniques described in the literature.[4,5] The isoxazole (15.5 mmol) was placed in a 100-mL Erlenmeyer flask cooled with an ice/NaCl bath, and then 3.2 mL of concentrated → H_2SO_4 and 1.4 mL of concentrated HNO_3 were added dropwise, the temperature being kept near 0 °C. An additional 6.4 mL of Concentrated H_2SO_4 was then added dropwise, and the solution was allowed to stand without stirring at room temperature for 72–96 h. The solution was then heated in a water bath for 10 min (**1**), 1 h (**2**), or not at all (**3**). The solution was then diluted with cooled distilled water, and the product was extracted with diethyl ether, dried over $CaCl_2$, and condentrated in vacuo.

4-Nitro-3,5-dimethylisoxazole (1): from 3,5-dimethylisoxazole;[6] purified by sublimation at 35 °C (10^{-3} torr) (86% yield); white crystals; mp 63–64 °C; ^1H NMR (CCl_4) δ 2.5 (s, 3 H), 2.77 (s, 3 H); ^{13}C NMR (Me_2SO-d_6) δ 11.0 (q, J_1 = 131.5 Hz, 3-CH_3), 13.5 (q, J_1 = 132.7 Hz, 5-CH_3), 155.4 (q, J_2 = 7.1 Hz, C-3), 172.5 (q, J_2 = 7.13 Hz C-5), 129.9 (br, C-4); mass spectrum (70 eV), m/z (relative intensity) 142 (50), 83 (85), 43 (100), 42 (55); IR (KBr) 2930, 1608, 1592, 1505, 1412, 1371, 1352, 1275, 1165, 1043, 980, 830, 765 cm^{-1} (in agreement with lit.[5,6] and INCOS library).

5-Ethyl-3-methyl-4-nitroisoxazole (2): from 5-ethyl-3-methylisoxazole (**5**); purified by distillation at 50 °C (0.7 mm) (56% yield); ^1H NMR (CCl_4) δ 1.4 (t, 3 H, J_3 = 7 Hz), 2.5 (s, 3 H, 3-CH_3), 3.1 (q, 2 H, J_3 = 7 Hz, 5-CH_2); mass spectrum (30 eV), m/z (relative intensity) 156 (40), 139 (100), 57 (70). Anal. Calcd for $C_6H_8N_2O_3$: C, 46.16; H, 5.16; N, 17.94. Found: C 46.23; H, 5.17; N, 17.89.

5-Methyl-4-nitroisoxazole (3): from 5-methylisoxazole, commercially available; purified by distillation at 40 °C (0.4 mm) (80% yield); ^1H NMR ($CDCl_3$) δ 2.87 (s, 3 H), 8.75 (s, 1 H); mass spectrum (70 eV), m/z (relative intensity) 128 (25), 43 (100); IR (KBr) 3120, 2940, 1610, 1525, 1410, 1330, 1250, 1155, 985, 925, 895, 828, 760 cm^{-1}. Anal. Calcd for $C_4H_4N_2O_3$: C, 37.51; H, 3.15; N, 21.87. Found: C, 37.54; H, 3.15; N, 21.87. Found: C, 37.59; H, 3.15; N, 21.85.

5-(Deuteriomethyl)-3-methyl-4-nitroisoxazole (4): prepared according to the literature[8] by reaction of **1** (224 mg) with Me_2SO-d_6 (1 mL) and NaOD (0.1 mL, 30% in D_2O); another method[6] did not give good results.

The amount of deuteriation was checked by ^1H NMR using acetone as internal standard to confirm that no deuteriation of the C-3 methyl had occurred. After 4 h at room temperature the reaction was stopped by neutralization with DCl, the solution filtered to remove NaCl, and **4** isolated from Me_2SO-d_6 by column chromatography over silica gel, 35–70 mesh (ASTM), and with CCl_4 as eluting solvent. The product was purified by sublimation [35 °C (10^{-2} torr)] to give 148 mg (65%) of **4**: white crystals; mp 61–62 °C; [deuteriation ≥75% by] ^1H NMR (CCl_4) δ 2.5 (s, 3 H), 2.8 (m, deuteriated 5-CH_3); mass spectrum (70 eV), m/z (relative intensity) 145 (20), 144 (42), 143 (50), 142 (25), 98 (12), 97 (15), 83 (70), 46 (30), 45 (85), 44 (100), 43 (60).

5-Ethyl-3-methylisoxazole (5): prepared according to the literature[7] by reaction of 3,5-dimethylisoxazole with *n*-butyllithium in THF at −78 °C and quenching with MeI; isolated by distillation at 55 °C (30 mm) (45%); ^1H NMR (CCl_4) δ 1.25 (t, 3 H, J_3 = 7 Hz), 2.15 (s, 3 H, 3-CH_3), 2.65 (q, 2 H, J_3 = 7 Hz, 5-CH_2), 5.6 (s, 1 H, Ar); mass spectrum (30 eV), m/z (relative intensity) 111 (65), 96 (20), 82 (100), 57 (15), 54 (30). Anal. Calcd for C_6H_9NO: C, 64.84; H, 8.16; N, 12.6. Found: C, 64.75; H, 8.15; N, 12.62.

FVP of 1–4. FVP was carried out by the general procedure at 300–400 °C. The product **6** was identified in the reaction mixture because the isolated compound decomposed. Compound **6**: light yellow liquid; strongly acidic; polymerizes readily in the absence of solvent; ^1H NMR (Me_2SO-d_6) δ 2.01 (s, 3 H), 8.68 (br s); ^{13}C NMR (Me_2SO-d_6) δ 21.15 (s, broad band inverted in APT), 113.5 (s, broad band not inverted in APT), 128 (br, broad band not inverted in APT), 172.7 (s, broad band not inverted in APT); IR (5% in CCl_4, NaCl cells) 3200–3600 (br), 2930, 2260, 1710, 1410, 1285 cm^{-1}; mass spectrum (20 eV), m/z (relative intensity) 128 (10) 43 (100).

In the FVP of **4** the mass spectrum of the product shows a peak at m/z 43 instead of the scrambling of m/z 43–46 that would be expected if the deuteriomethyl group had been retained. Moreover, ^1H NMR ($CDCl_3$, CH_3NO_2 internal standard) showed quantitative retention of the CH_3 group [δ 2.01 (s)] and the disappearance of the broad signal at δ 8.68.

FVP of 5. FVP was carried out at 500–600 °C according to the general procedure. The only product was a light yellow liquid, which was identified in the reaction mixture as 5-ethyl-2-methyloxazole (**7**): ^1H NMR (CCl_4) δ 1.22 (t, 3 H, J_3 = 7 Hz), 2.32 (s, 3 H), 2.57 (q, 2 H, J_3 = 7 Hz), 6.37 (s, 1 H); mass spectrum (30 eV), m/z (relative intensity) 111 (10), 96 (30), 82 (15), 71 (50), 59 (100), 44 (55), 43 (70). The compound decomposes readily in the presence of light or in the absence of a solvent.

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Registry No. **1**, 1123-49-5; **2**, 108418-33-3; **3**, 1122-06-1; **4**, 108418-34-4; **5**, 31301-34-5; **6**, 97925-51-4; **7**, 53833-29-7; 3,5-dimethylisoxazole, 300-87-8; 5-methylisoxazole, 5765-44-6.

^{17}O NMR Study of Steric Interactions in Hindered N-Substituted Imides

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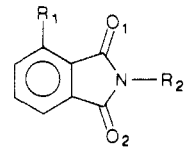
^{17}O NMR spectroscopic data (natural abundance in acetonitrile at 75 °C) were obtained for a series of N-substituted phthalmides (1–11), a series of N-substituted succinimides and maleimides (**12–19**), and N-substituted phthalamides (**20–22**). The ^{17}O NMR data showed large deshielding effects as the steric bulk of the N-substituent increased; introduction of a 3-substituent in the phthalimide series produced additional deshielding. The deshielding effects of 3-substitution and N-substitution in the phthalimides were found to be roughly additive. The results correlated with in-plane bond angle distortions (X-ray results and molecular mechanics calculations). The results for *N*-arylphthalimides showed that the aromatic ring was rotated out of the plane (torsion angle effect) in those cases.

^{17}O NMR spectroscopy is rapidly developing into an important method for examining a wide variety of structural problems[1] and may provide new insights into the understanding of chemical reactivity.[2] A number of ^{17}O NMR studies have focused on electronic effects,[3] while others have investigated conformational effects.[4] Recent work has shown that quantitative relationships can be formulated between ^{17}O NMR data and torsion angles for aromatic nitro compounds,[5] acetophenones,[6] aryl ketones,[7] and aromatic carboxylic acids and derivatives.[8] Thus structural information relating to torsion angle relationships is accessible readily by ^{17}O NMR methodology. ^{17}O studies on anhydrides have shown sensitivity to structural variations.[9] Recently, ^{17}O NMR data[2] on a series of hindered 3-substituted phthalic anhydrides and corresponding phthalides have been shown to correlate with in-plane bond angle distortions. The nontorsional ^{17}O chemical shift effects observed for the anhydrides, thought to be indicative of repulsive van der Waals interactions, could be used[2] to explain the regiospecificity of reduction reactions. We report here ^{17}O NMR data for a series of N-substituted phthalimides, N-substituted phthalamides, and a series of N-substituted succinimides and maleimides which show that the ^{17}O NMR chemical shift data provide new insights into structure and reactivity in relation to steric phenomena.

Table I. ^{17}O Chemical Shift Data[a] for Substituted Phthalimides in CH_3CN at 75 °C



compd	R_1	R_2	$\delta(C{=}O)_1$	$\delta(C{=}O)_2$	$\delta(R)$
1	H	H	379.0	379.0	
2	H	Me	374.0	374.0	
3	H	*i*-Pr	383.0	383.0	
4	H	*t*-Bu	394.0	394.0	
5	*t*-Bu	H	407.3	370.6	
6	*t*-Bu	*t*-Bu	423.3	385.3	
7	H	Ph	378.3	378.3	
8	H	2-MeC_6H_4	381.3	381.3	
9	H	2,6-$Me_2C_6H_3$	384.0	384.0	
10	H	4-$MeOC_6H_4$	377.5	377.5	50.7
11	H	2-Me-4-$MeOC_6H_3$	380.0	380.0	51.0

[a] Natural abundance with 2-butanone internal standard; data point resolution ±0.2 ppm; reproducibility ≤±1 ppm.

Results

^{17}O NMR data were obtained (natural abundance) for a series of N-substituted phthalimides (1–11), a series of

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