

OZONOLYSIS OF SUBSTITUTED ISOXAZOLES<sup>†</sup>

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**Abstract** - The ozonolysis of substituted isoxazoles was investigated. The ozonolysis rates and the products were dependent on the site of the substituent group on isoxazole ring. The reaction mechanism of the ozonolysis of isoxazoles was also proposed.

We have reported the products and the reaction mechanism of the ozonolysis of five-membered heterocycles such as pyrroles, furans, pyrazoles, and oxazoles.<sup>1</sup> We also achieved the new peptide synthesis using the ozonolysis of oxazole derivatives which acted as both protection and activation of the carboxylic groups of an amino acid.<sup>2</sup>

Among various kinds of heterocycles, few papers concerning to the ozonolysis of isoxazoles have appeared in the literature.<sup>3</sup> As one of the typical heterocycles, the ozonolysis of isoxazoles should be of much interest as the useful functionalization reaction.

When 3,5-diphenylisoxazole (1a) was treated with ozone in CH<sub>2</sub>Cl<sub>2</sub> at -78°C, ozone attacked at C4-C5 bond of isoxazole ring to give the corresponding ozonide (2,5-diphenyl-3-aza-4,6,7,8-tetraoxa-bicyclo[3,2,1]-2-octene, 2a). Isolated 2a was characterized by iodometric titration, <sup>13</sup>C-nmr peak at δ 117.2 ppm of C5, no carbonyl absorption in ir spectrum, and elemental analysis. Under the thermal conditions, ozonide (2a) was decomposed to give benzonitrile, benzoic acid and carbon dioxide (eq. 1) *via* intermediate (3a), which was identified by comparison with the authentic

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<sup>†</sup> This paper is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday for his brilliant achievement in the field of heterocyclic chemistry.

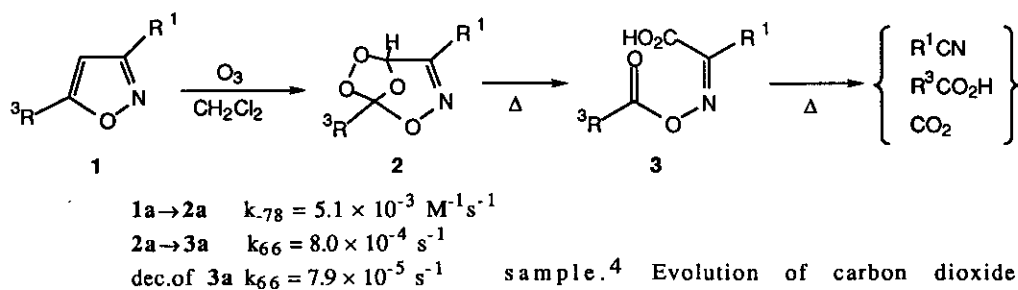


Table 1. Ozonolysis of 1

|     | R <sup>1</sup> | R <sup>3</sup> | yield (%)         |                                  |
|-----|----------------|----------------|-------------------|----------------------------------|
|     |                |                | R <sup>1</sup> CN | R <sup>3</sup> CO <sub>2</sub> H |
| 1 a | Ph             | Ph             | 96                | 80                               |
| 1 b | Me             | Ph             | —                 | 50                               |
| 1 c | Me             | Tol            | —                 | 64                               |
| 1 d | Ph             | Me             | 71                | —                                |
| 1 e | Tol            | Me             | 79                | —                                |
| 1 f | Tol            | Ph             | 82                | 100                              |
| 1 g | <i>t</i> -Bu   | Ph             | —                 | 87                               |
| 1 i | Ph             | H              | 76                | —                                |
| 1 j | Tol            | H              | 78                | —                                |
| 1 l | H              | Ph             | —                 | 81                               |
| 1 m | H              | Tol            | —                 | 59                               |

Evolution of carbon dioxide was detected by aqueous Ba(OH)<sub>2</sub>. Similarly various 4-unsubstituted isoxazoles gave nitriles and carboxylic acids in good yields (Table 1). In some cases, the isolation of ozonides (2) was succeeded even at room temperature. Reaction rate constants at each step of this reaction are evaluated with the kinetic parameters of 2a to 3a;  $E_a = 20 \text{ kcal mol}^{-1}$ ,  $\Delta S^\ddagger_{27} = -15 \text{ cal mol}^{-1}\text{K}^{-1}$ ,  $\Delta G^\ddagger_{27} = 24 \text{ kcal mol}^{-1}$ .

Criegee *et al.* previously reported the solvent effect of the thermal decomposition of the ozonides which had at least one hydrogen atom on the trioxirane ring.<sup>5</sup> The thermal decompo-

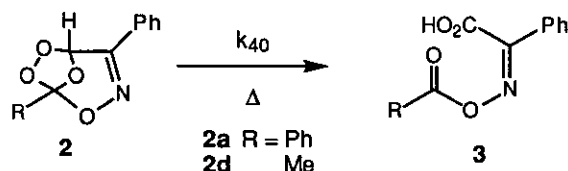


Table 2. Solvent Effect of Decomposition of Ozonides (2a and 2d)

| $k_{40} \times 10^4 (\text{s}^{-1})$ | 2a   | 2d   | $E_T^*$ |
|--------------------------------------|------|------|---------|
| Benzene                              | 0.02 | ~ 0  | 34.5    |
| THF                                  | 0.72 | 0.12 | 37.4    |
| MeCN                                 | 2.1  | 1.2  | 46.0    |
| MeOH                                 | > 8  | 6.1  | 55.5    |

\* ref 6

On the contrary, 4-substituted isoxazoles reacted with ozone in a different manner. 3,4-Disubstituted isoxazoles (**4**) were ozonolyzed to give  $\alpha$ -diketone monooxime (*s-cis*) (**5**) which isomerized to stable *s-trans* isomer (**6**) at reflux in MeOH (Table 3). The shift of the ir carbonyl absorption from 1771-1763  $\text{cm}^{-1}$  to 1677-1660  $\text{cm}^{-1}$  supported the formation of **6** in good agreement with the Kohler's results.<sup>6</sup>

When 4,5-diphenylisoxazole (7a) was treated with ozone followed by Me<sub>2</sub>S, benzoyl cyanide and benzoic acid were formed *via* unstable intermediate 8a (Table 4). Similarly 7b and 7c gave the corresponding acyl cyanides and carboxylic acids.

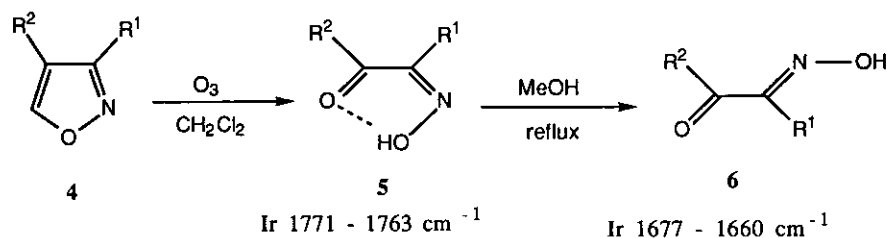


Table 3. Ozonolysis of 4

|            | R <sup>1</sup> | R <sup>2</sup> | yield of 6 (%) |
|------------|----------------|----------------|----------------|
| <b>4 a</b> | Ph             | Ph             | 48             |
| <b>4 b</b> | Ph             | Me             | 31             |
| <b>4 c</b> | Me             | Ph             | 31             |
| <b>4 d</b> | H              | Ph             | 24             |

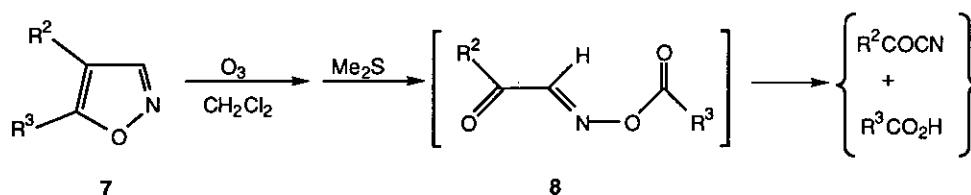


Table 4. Ozonolysis of 7

|           | R <sup>2</sup> | R <sup>3</sup> | yield (%)           |                                  |
|-----------|----------------|----------------|---------------------|----------------------------------|
|           |                |                | R <sup>2</sup> COCN | R <sup>3</sup> CO <sub>2</sub> H |
| <b>7a</b> | Ph             | Ph             | 51                  | 87                               |
| <b>7b</b> | Ph             | Tol            | 69                  | 61                               |
| <b>7c</b> | Me             | Ph             | —                   | 46                               |

Finally the reactivity of various isoxazoles toward ozone was compared by the competitive reactions summarized in Table 5. The ozonolysis was retarded by the introduction of substituent on C5, while it was accelerated by C3 substituent. The electron-donating effect of substituent on C5 was observed in the case of tolyl and methyl substituent. On the contrary, the obvious electronic effect of the substituent on C3 was not observed.

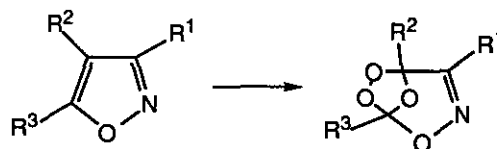
Ozonolysis of various types of isoxazoles is reasonably explained by Scheme 1. The reaction profile of ozonolysis is dependent on the nature of substituents on the isoxazole ring. In conclusion, isoxazoles easily react with ozone to form ozonides, which are thermally decomposed in polar solvent without the aid of oxidative/reductive post-treatment.

Table 5. Relative Reaction Rate of Ozonolysis of Various Types of Isoxazoles

|    | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | k <sub>78</sub> × 10 <sup>2</sup> M <sup>-1</sup> s <sup>-1</sup> |
|----|----------------|----------------|----------------|-------------------------------------------------------------------|
| 1a | Ph             | H              | Ph             | 0.51                                                              |
| 1b | Me             | H              | Ph             | 0.96                                                              |
| 1c | Me             | H              | Tol            | 1.3                                                               |
| 1d | Ph             | H              | Me             | 3.2                                                               |
| 1e | Tol            | H              | Me             | 0.98                                                              |
| 1f | Tol            | H              | Ph             | 0.43                                                              |
| 1g | <i>t</i> -Bu   | H              | Ph             | 0.52                                                              |
| 1h | <i>t</i> -Bu   | H              | <i>t</i> -Bu   | 0.88                                                              |
| 1i | Ph             | H              | H              | 2.4                                                               |
| 1j | Tol            | H              | H              | 1.5                                                               |
| 1k | <i>t</i> -Bu   | H              | H              | 3.1                                                               |
| 1l | H              | H              | Ph             | 0.32                                                              |
| 1m | H              | H              | Tol            | 0.53                                                              |
| 1n | H              | H              | Me             | 1.7                                                               |

|    | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | k <sub>78</sub> × 10 <sup>2</sup> M <sup>-1</sup> s <sup>-1</sup> |
|----|----------------|----------------|----------------|-------------------------------------------------------------------|
| 4a | Ph             | Ph             | H              | 7.2                                                               |
| 4b | Ph             | Me             | H              | 9.3                                                               |
| 4c | Me             | Ph             | H              | 14                                                                |
| 4d | H              | Ph             | H              | 18                                                                |
| 7a | H              | Ph             | Ph             | 0.30                                                              |
| 7b | H              | Ph             | Tol            | 0.70                                                              |
| 7c | H              | Me             | Ph             | 1.0                                                               |

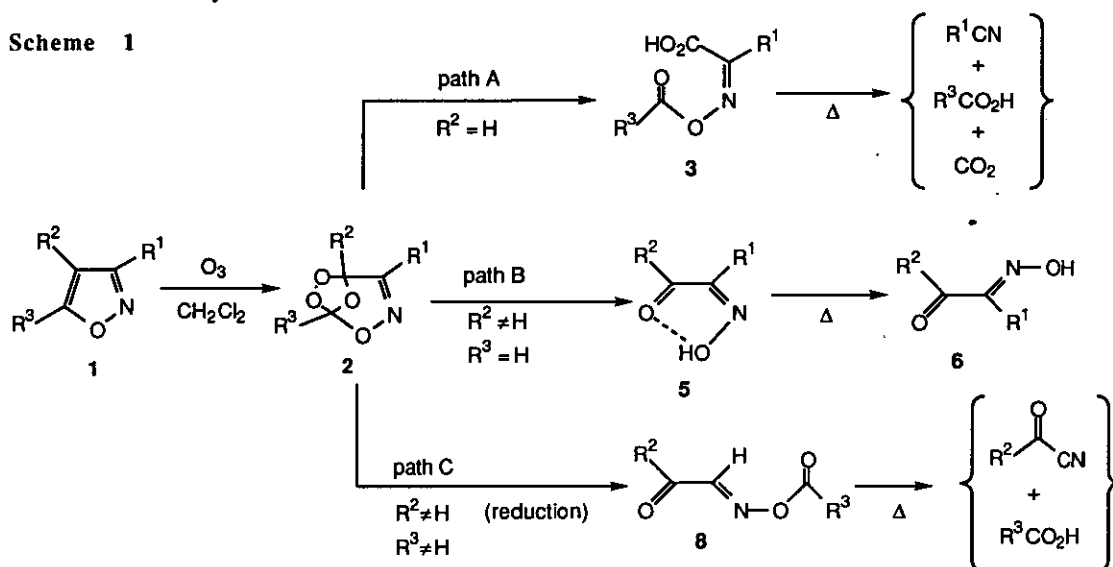


## EXPERIMENTAL

Melting points were measured on a Yanagimoto Melting Point Apparatus, and uncorrected. IR spectra were measured on a Shimadzu IR-460 spectrophotometer. <sup>1</sup>H-Nmr and <sup>13</sup>C-nmr spectra were recorded using JEOL JNM-EX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu QP-2000 spectrometer. Preparative

hplc was performed using JAI-LC20. Elemental analyses were performed by Perkin-Elmer Model 240 elemental analyzer.

Scheme 1



Isoxazoles (1a-e) were prepared by the method of Claisen<sup>7</sup> and the isomerization reaction through isoxazolium salts.<sup>8</sup> Isoxazoles (11-n and 7a-c) were synthesized from hydroxylamine and  $\alpha$ -formylketones,<sup>9</sup> and 4c-d were made according to Adembri's<sup>10</sup> and Arnold's<sup>11</sup> method. Compounds (1f-g, 1i-k, 4a and 4b) were prepared by 1,3-dipolar cycloaddition of nitrile oxide with the corresponding alkynes and enamines.<sup>12</sup>

#### Ozonolysis of 1

Isoxazole (1) (1.0 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and ozone-oxygen stream was bubbled through the solution at -78 °C (at -15 °C in the cases of 1a-b, 11-m, and 7a-c). The disappearance of isoxazole was monitored by hplc, and the solution was allowed to warm to room temperature with bubbling nitrogen gas to remove excess ozone. The solvent was removed under reduced pressure in cold water bath. All ozonides (2) were purified by preparative hplc, and were solidified after removal of solvent (CHCl<sub>3</sub>). For the isolation of 3, the crude ozonolysate from 1 was refluxed in THF (10 ml). The reaction was monitored by hplc. After removal of the solvent, the product was recrystallized from benzene - hexane - ethyl acetate mixture. 3a (yield 22%) and 3i

(yield 22%) were identified with authentic samples<sup>4</sup> by comparison of ir, <sup>1</sup>H and <sup>13</sup>C spectra, and retention time in hplc.

**3,5-Diphenylisoxazole-ozonide (2a)** : mp 135-140 °C; ir (KBr) 3080 (w), 3040 (w), 1750-1690 (broad, w), 1600 (w), 1450 (w) cm<sup>-1</sup>; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 6.46 (s, 1H), 7.35-8.13 (m, 10H); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 92.9 (CH), 117.2 (C), 125.8 (CH), 126.8 (CH), 128.5 (C), 128.5 (C), 128.6 (CH), 129.2 (CH), 131.2 (CH), 131.4 (CH), 154.5 (C). Anal. Calcd for C<sub>15</sub>H<sub>11</sub>NO<sub>4</sub>: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.86; H, 3.97; N, 4.93.

**5-Methyl-3-phenylisoxazole-ozonide (2d)** : mp 59 °C; ir (KBr) 3450 (broad, w), 3040 (m), 1780-1590 (broad, w) cm<sup>-1</sup>; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 1.94 (s, 3H), 6.24 (s, 1H), 7.41-7.62 (m, 5H); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 17.8, 92.4, 118.5, 126.4, 129.5, 130.8, 131.4, 154.5. Anal. Calcd for C<sub>10</sub>H<sub>9</sub>NO<sub>4</sub>: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.40; N, 6.70.

**5-Methyl-3-*p*-methylphenylisoxazole-ozonide (2e)** : mp 75-80 °C; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 1.89 (s, 3H), 2.32 (s, 3H), 6.26 (s, 1H), 7.16-7.47 (m, 4H); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 17.3, 21.3, 92.0, 118.1, 125.6, 127.5, 129.8, 141.5, 154.1; Anal. Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>4</sub>: C, 59.73; H, 5.01; N, 6.33. Found: C, 60.50; H, 5.13; N, 6.20.

**3-*p*-Methylphenyl-5-phenylisoxazole-ozonide (2f)** : mp 152-153 °C; ir (KBr) 3430 (broad, w), 3000 (w), 1600 (w), 1440(w), 1328(m), 1100(m), 974(m); <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 2.40 (s, 3H), 6.44 (s, 1H), 7.25-7.81 (m, 9H); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 21.5, 92.9, 117.2, 125.7, 126.8, 127.6, 128.6, 129.9, 131.3, 141.7, 154.4; Anal. Calcd for C<sub>16</sub>H<sub>13</sub>NO<sub>4</sub>: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.53; H, 4.66; N, 4.88.

**3-*tert*-Butyl-5-phenylisoxazole-ozonide (2g)** : mp 86-92 °C; ir (KBr) 3430 (broad, m), 2980 (s), 1728 (broad, w), 1440 (s), 1370 (s), 1330 (s); <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 1.25 (s, 9H), 6.06 (s, 1H), 7.42-7.75 (m, 5H); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 27.7 (CH<sub>3</sub>), 36.1 (C), 91.1 (CH), 116.7 (C), 126.7 (CH), 128.6 (CH), 128.8 (C), 131.2 (CH), 162.7 (C); Anal. Calcd for C<sub>13</sub>H<sub>15</sub>NO<sub>4</sub>: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.13; H, 6.03; N, 5.40.

**3-Phenylisoxazole-ozonide (2i)** : <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 6.28 (d, *J* = 1 Hz, 1H), 6.80 (d, *J* = 1 Hz, 1H), 7.40-7.62 (m, 5H); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 89.7, 108.9, 125.6, 129.2, 130.3, 131.3, 155.2; Anal. Calcd for C<sub>9</sub>H<sub>7</sub>NO<sub>4</sub>: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.18; H, 3.86; N, 7.34.

**Benzoyloximino-*p*-methylphenylacetic acid (3f)** : yield 51%; ir (KBr) 3105 (broad, s), 1744 (s), 1715 (s), 1597 (m), 1446 (m), 1321 (m), 1268 (s), 1204 (s), 1085 (s), 1010 (m) cm<sup>-1</sup>; <sup>1</sup>H-nmr

(DMSO- $d_6$ )  $\delta$  2.49 (s, 3H), 7.61-8.13 (m, 9H);  $^{13}\text{C}$ -nmr (DMSO- $d_6$ )  $\delta$  125.5, 128.0, 128.5, 128.8, 129.1, 129.4, 129.4, 130.1, 130.3, 143.0, 160.0, 162.6, 163.6; Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{NO}_4$ : C, 67.84; H, 4.63; N, 4.94. Found: C, 67.87; H, 4.64; N, 4.97.

#### Ozonolysis of 4

Isoxazole (4a) (1.0 mmol) was ozonolyzed by the method described above and the unstable intermediate (5a) was purified by the preparative hplc; yield 36 %; ir ( $\text{CH}_2\text{Cl}_2$ ) 3060 (w), 1766 (s), 1446 (w), 1127 (m), 908 (s);  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ )  $\delta$  7.17-7.62 (m), 8.44-8.60 (m);  $^{13}\text{C}$ -nmr ( $\text{CDCl}_3$ )  $\delta$  127.9 (CH), 128.1 (CH), 128.3 (C), 128.4 (CH), 128.6 (CH), 129.1 (C), 129.2 (CH), 130.4 (CH), 132.3 (CH), 161.9 (C); and isomerized to 6a by refluxing in methanol (10 ml) for 12 h. The product was identified by the comparison with the authentic sample.<sup>6,13</sup>

#### Ozonolysis of 7

Isoxazole (7a) (1.0 mmol) was ozonolyzed and excess ozone was removed by nitrogen bubbling. Dimethyl sulfide (7 mmol) was added, and the solution was allowed to warm to room temperature with stirring for 12 h. The solvent was removed to give crude 8a; yield 30 %; ir ( $\text{CH}_2\text{Cl}_2$ ) 3055 (w), 1756 (s), 1663 (m), 1596 (m), 1448 (m), 1234 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ )  $\delta$  7.46-8.29 (m);  $^{13}\text{C}$ -nmr ( $\text{CDCl}_3$ )  $\delta$  127.6 (C), 128.5 (CH), 128.8 (CH), 129.7 (CH), 130.6 (CH), 134.1 (CH), 134.4 (CH), 134.7 (C), 153.5 (CH), 163.2 (C), 187.5 (C). The crude 8a was decomposed by refluxing in THF for 12 h. Yields of the products were measured by hplc.

#### Reactivity of Isoxazoles with Ozone

The reaction rate was determined by the reaction of 1a (10 mg) with the saturated solution of ozone in  $\text{CH}_2\text{Cl}_2$  (10 ml) at  $-78^\circ\text{C}$  ( $[\text{O}_3] = 4.22 \times 10^{-2} \text{ mol/l}$ ) in the presence of nitrobenzene (15 mg) as an internal standard, and the reaction products were monitored by hplc. The relative ozonolysis rates were given by the action of the different isoxazole mixture (0.40 mmol each in  $\text{CH}_2\text{Cl}_2$ ). After the blue color of ozone was disappeared, unreacted isoxazoles were measured by gc. Kinetic parameters and solvent effects of ozonide (2a, 2d and 3a) were evaluated by hplc of the solution of 2a (15-30 mg) at  $66^\circ\text{C}$  using diphenyl ether as an internal standard.

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Received, 5th October, 1993