Thermolysis of Some 4- and 5-Substituted Isothiazoles in the Gas Phase

By **Guillermo E. Castillo** and **Héctor E. Bertorello,**[*] Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Estafeta 32, Córdoba 5000, Argentina

A new synthesis of thioketens is described by the gas-phase thermolysis of the 4- or 5-substituted isothiazoles (1)—(3). It is believed that the reactions may involve thioxocarbenes (8) or thiirens (9) as short-lived intermediates. A scheme for the reaction mechanism is proposed in the light of results of chemical trapping experiments and the activation parameters found.

OUR comparison of the mass spectra, thermolyses,[1] and photolyses[2] of heterocycles has led us to examine the thermolysis of the isothiazoles (1), (2), and (3). The stability of isothiazoles is well known,[3] but few kinetic and thermodynamic data are available. Photore-arrangements[4] of thiazoles and isothiazoles are rational-ized by the participation of bicyclic and zwitterionic intermediates and such fragmentations could provide a route to thiirens. Recently, the thermolysis of 5-

phenyl-1,3,4-oxathiazol-2-one[5] has been shown to give carbon dioxide, benzonitrile, and sulphur, together with a benzonitrile sulphide the identity of which was pro-posed on isolation of its 1,3-dipolar adducts. Matrix photolysis of 1,2,3-thiadiazole by one group[6] was considered to involve a cyclic thiiren but e.s.r. studied by others[7] indicated that the photochemically induced evolution of nitrogen involved a diradical species. From chemical-trapping experiments, Strausz et al.[8] postulated thiiren intermediates in the photodecom-position of 1,2,3-thiadiazole and its 5-methyl derivative.

Thiiren possesses 4π electrons and should be anti-aromatic. MO calculations for thiiren,[9] $1H$-azirine,[9]

[1] H. E. Bertorello and M. Martínez de Bertorello, *Boletín de la Academia Nacional de Ciencias*, Córdoba, Argentina, in the press, 1977; G. E. Castillo and H. E. Bertorello, Abstracts, VI Congreso Argentino de Farmacia y Bioquímica, Mar del Plata, Argentina, April 1975.

[2] D. A. Murature, J. D. Pérez, M. Martínez de Bertorello, and H. E. Bertorello, *Anales Asoc. quim, argentina*, in the press.

[3] F. Kurzer, *Org. Compounds Sulphur, Selenium, Tellurium*, 1973, **2**, 556

[4] M. Kojima and M. Maeda, *J.C.S. Chem. Comm.*, 1970, 386; M. Ohashi, A. Iio, and T. Yonezawa, *ibid.*, p. 1148; A. Lablache-Combier and A. Pollet, *Tetrahedron*, 1972, **28**, 3141; G. Vernin, C. Riou, H. J. M. Dou, L. Boucasse, J. Metzger, and G. Loridan, *Bull. Soc. chim. France*, 1973, 1743; M. Maeda, A. Kawahara, M. Kai and M. Kojima, *Heterocycles*, 1975, **3**, 389.

[5] J. E. Franz and L. L. Black, *Tetrahedron Letters*, 1970, 1381.

[6] A. Krantz and J. Laureni, *J. Amer. Chem. Soc.*, 1974, **96**, 6768.

[7] P. Krauss, K.-P. Zeller, H. Meier, and E. Müller, *Tetrahedron*, 1971, **27**, 5953.

[8] O. P. Strausz, J. Font, E. L. Dedio, P. Kerbale, and H. E. Gunning, *J. Amer. Chem. Soc.* 1967, **89**, 4805.
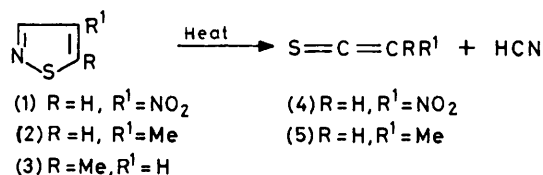
[9] M. J. S. Dewar and C. A. Ramsden, *J.C.S. Chem. Comm.*, 1973, 688.

and oxiren [10] give conflicting results depending on the methods used. Although the i.r. spectrum of a thiiren has been recorded at low temperatures [11] no synthesis of a stable derivative has yet been achieved.

We now describe the thermolyses of some isothiazoles in the gas-phase which, we believe, involve thiirens (9), or the isomeric thioxocarbenes (8).

RESULTS AND DISCUSSION

Gas-phase thermolysis of 4-nitro-(1), 4-methyl-(2), and 5-methyl-isothiazole (3), afforded hydrogen cyanide and nitro-(4) and methyl-(5) thioketens (Scheme 1). The

$$ \underset{\text{(1) R=H, R}^1\text{=NO}_2}{\underset{\text{(2) R=H, R}^1\text{=Me}}{\underset{\text{(3) R=Me, R}^1\text{=H}}{}}} \xrightarrow{\text{Heat}} S{=}C{=}CRR^1 + HCN $$

(4) R=H, R¹=NO₂
(5) R=H, R¹=Me

SCHEME 1

temperatures and contact times for the thermolysis of compounds (1)—(3) are recorded in Tables 1—3. The

$$ S{=}C{=}CRR^1 + NHMe_2 \longrightarrow RR^1CH{\cdot}CS{\cdot}NMe_2 $$

(4) R=H, R¹=NO₂
(5) R=H, R¹=Me
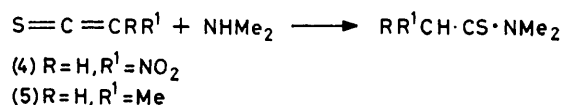
SCHEME 2

product compositions were constants over the temperature ranges studied. The thioketens were characterized by i.r. (strong bands in the 1 800 cm⁻¹ region), n.m.r.

considered for the reaction. Path (i) involves a diradical intermediate (6) whereas the intermediate in path (ii) is a thioxocarbene (8), with an important dipolar canonical form (7) in equilibrium with the thiiren (9). Wolff rearrangement [14] of (8) would form the thioketen products.

Reactions in the presence of radical scavengers (toluene carrier technique) gave identical product compositions for each isothiazole. Kinetic first-order rate constants for the thermolysis of the isothiazoles (1)—(3) (Tables 1—3) gave excellent Arrhenius plots;

TABLE 1

Rate constants and product distribution for the thermolysis of compound (1) in the gas-phase at different temperatures

$\theta_c/°C$	$10^3\ t_c/s^{-1}$ *	% Recovered reactant	% (4) †	% HCN †	$10^{-2}\ k/s^{-1}$ ‡
530.0	0.8	82.6	13.4	3.4	2.39
540.0	1.0	67.3	25.9	6.6	3.96
550.0	1.0	59.8	32.1	8.0	5.14
560.0	1.0	49.5	40.2	10.1	7.03
570.0	1.1	34.5	52.1	13.2	9.67
570.0 ¶	0.9	42.0	46.0	11.5	9.64
580.0	1.0	22.0	62.0	16.7	15.14
590.0	1.0	14.0	68.7	17.4	19.66

* N₂ as carrier gas; t_c = contact time. † Yield expressed in % (w/w). ‡ N.m.r. spectrometric analysis of the reaction mixture. ¶ Dry air as carrier gas.

activation parameters were obtained by a least-squares analysis. In the presence of radical scavengers (dry air or oxygen), the rates were identical within ±5%. The simplest conclusion from these results is that the
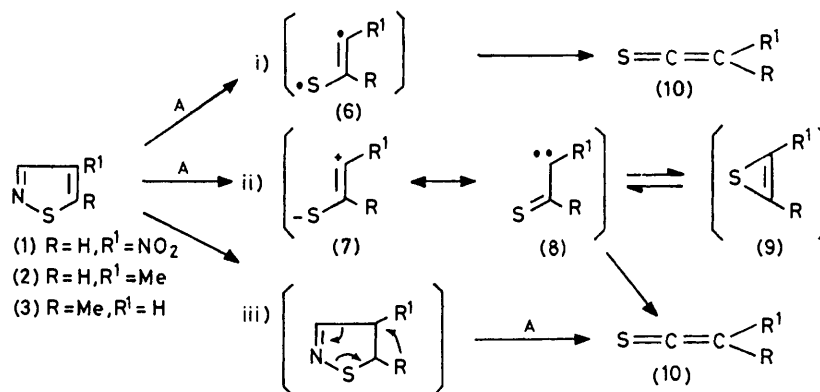
SCHEME 3 Alternative paths of the reaction mechanism for thermolysis of the isothiazoles (1), (2), and (3). A = −HCN

spectra (cf. ref 12), and by reaction with NN-dimethylamine at −78 °C. The NN-dimethylthioamides obtained were identified by their physical properties. The i.r. spectral bands were similar to other known NN-dimethylthioamides (cf. ref. 13). Three paths were

thermal decompositions of isothiazoles (1)—(3) does not possess a predominant radical-chain path.

[10] I. G. Csizmadia, H. E. Gunning, R. K. Gosavi, and O. P. Strausz, J. Amer. Chem. Soc., 1973, 96, 133; A. C. Hopkinson, J.C.S. Perkin II, 1973, 794; O. P. Strausz, R. K. Gosavi, A. S. Denes, and I. G. Csizmadia, J. Amer. Chem. Soc., 1976, 98, 4784.

[11] J. Laureni, A. Krantz, and R. Hajdu, J. Amer. Chem. Soc., 1976, 98, 7872.

[12] E. G. Howard, jun., U.S.P. 3,035,030/1962 (Chem. Abs., 1962, 57, 13617 f); E. U. Elam, F. H. Rasch, J. T. Dougherty, V. W. Goodhett, and K. C. Brannock, J. Org. Chem., 1968, 33, 2738; M. S. Raasch, ibid., 1972, 37, 1347; G. Seybold and Ch. Heibl, Angew. Chem. Internat. Edn., 1975, 14, 248.

[13] C. Collard-Charon and M. Renson, Bull. Soc. chim. belges, 1963, 72, 304.

[14] K.-P. Zeller, H. Meier, and E. Müller, Annalen., 1972, 766, 32; Tetrahedron Letters, 1971, 537.

Runs in an unpacked reactor (surface-to-volume ratio 1 : 17 times of the packed vessel) gave the following rate constants: for (1)/550 °C, $k = 5.12 \times 10^2$ s^{-1}; for (2)/

TABLE 2

Rate constants and product distribution for the thermolysis of (2) in the gas-phase at different temperatures

θ/°C	$10^3\ t_c$/s^{-1} *	% Recovered reactant †	% (4) †	%HCN †	$10^{-2}\ k$/s^{-1} ‡
530.0	1.0	69.5	22.0	8.0	3.63
540.0	1.0	56.0	31.2	12.0	5.80
550.0	0.9	52.2	34.5	12.8	7.22
550.0 ¶	1.0	49.0	37.2	13.0	7.13
560.0	1.1	29.5	50.1	19.6	11.10
570.0	1.3	15.1	60.6	23.6	14.54
580.0	1.0	10.6	64.3	24.8	22.44
590.0	1.0	7.0	67.3	25.6	26.59

* N$_2$ as carrier gas; t_c = contact time. † Yield expressed in % (w/w). ‡ N.m.r. spectrometric analysis of the reaction mixture. ¶ 1% Oxygen as carrier gas.

550 °C, $k = 7.20 \times 10^2$ s^{-1}; for (3)/650 °C, $k = 4.55 \times 10^2$ s^{-1}. Comparison with Tables 1—3 showed the absence of surface catalysis.

Efforts to trap a possible zwitterionic species by using benzonitrile or furan as vapour carriers failed, thus suggesting that any zwitterionic transients are short-

TABLE 3

Rate constants and product distribution for the thermolysis of (3) in the gas-phase at different temperatures

θ_c/°C	$10^3\ t_c$/s^{-1} *	% Recovered reactant †	% (5) †	% HCN †	$10^{-2}\ k$/s^{-1} ‡
640.0	1.0	76.0	17.2	6.5	2.74
650.0	0.9	66.1	24.4	9.2	4.60
660.0	1.0	55.6	32.4	12.1	5.87
670.0	1.0	50.0	36.3	13.5	6.93
680.0	0.7	47.8	37.9	14.2	10.54
690.0	1.0	28.0	52.3	19.6	12.73
690.0 ¶	1.3	19.2	58.0	22.0	12.69
700.0	1.0	16.3	59.6	22.5	18.14
710.0	1.0	11.7	63.8	24.0	21.45

* N$_2$ as carrier gas; t_c = contact time. † Yield expressed in % (w/w). ‡ N.m.r. spectrometric analysis of the reaction mixture. ¶ Dry air as carrier gas.

lived. The E_a magnitudes and ΔS * values for the thermolysis of isothiazoles (1)—(3) (Table 4) suggests that the symmetry-controlled retrocycloaddition ($\pi^2 + \pi^2$) and 1,2-R shift (hydrogen or methyl) by path (iii) (Scheme 3) is unlikely. The thermodynamic parameters are compatible with ring cleavage and a transition state with many rotational degrees of freedom, thus supporting the formation of a thioxocarbene (8) in the rate-determining step of the thermolyses, followed by rapid unimolecular rearrangement of (8) ⟶ (10). The different migrational ability of hydrogen and methyl reflected by the difference in E_a for the isothiazoles (2), and (3) is partially attributed to steric hindrance by the 5-methyl group in (3).

The absence of intermolecular insertion products expected for the thioxocarbene (8), suggests a short life

time for this intermediate, *i.e.* that the competitive intramolecular rearrangement is the faster process. In

TABLE 4

Activation parameters, E_a (kcal mol^{-1}), ΔS* (cal K^{-1} mol^{-1}), and $\log_{10} A$ (s^{-1}) for the thermolysis of (1), (2), and (3) in the gas-phase.

Compound	E_a	$\log_{10} A$	ΔS*	θ_c/°C
(1)	47.4 ± 1.6	15.3 ± 0.4	+7.5	530—590
(2)	46.2 ± 1.7	15.1 ± 0.5	+6.5	530—590
(3)	51.0 ± 1.9	14.7 ± 0.5	+4.3	640—710

agreement, MINDO/3 and NDDO calculations [9] suggest that a thioxocarbene rearranges into thioketen with a zero activation energy. This fact supports the assumption that the rate-determining step is the formation of (8).

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Varian T-60 high-resolution instrument and chemical shifts are quoted in δ (p.p.m.) downfield from tetramethylsilane which was used as internal reference. Absorbances were determined on a Beckman DBG spectrophotometer. I.r. spectra were recorded either on a Beckman IR8 or IR12 spectrometers, in sodium chloride cells or potassium bromide pellets. M.p.s are uncorrected, and were determined, by the capillary method on a Büchi apparatus, model Dr. Tottoli. G.l.c. analyses were performed on a Varian S-202 gas chromatograph, equipped with a Gow-Mac gas density detector using a 2.5-m stainless-steel column packed with 30% (w/w) of dinolyl phthalate on Chromosorb P or a 3.5-m copper column packed with 22% (w/w) of $\beta\beta'$-oxydipropionitrile on Chromosorb P. All isothiazole derivatives were from K & K laboratories, and their purities were checked by g.l.c. analyses [F & M 776 apparatus, using a 1.3 m copper column packed with 3% (w/w) of SE30 on Chromosorb P or a 4.7 m stainless-steel column packed with 15% (w/w) of Carbowax 20 M on Chromosorb A] and n.m.r. analyses, which indicated that they were always better than 99.5%. Solvents were analytical reagents or otherwise purified by standard methods. Elemental analyses were carried out with a Hewlett–Packard F & M 185 elemental analyzer.

Thermolysis in a Flow System.—Flow thermolyses were carried out using a Vycor glass tube (300 mm length × 15 mm o.d.) filled with Vycor tubes (15 mm length × 5 mm o.d.) heated by a Lindberg Hevi Duty ' Mini-Mite ' electric furnace equipped with a thermocouple of Platinell II and a pyrometer, and connected to a conventional vacuum system. A stream of dry oxygen-free nitrogen was monitored by a calibrated flowmeter. In a typical experiment 1 mmol of the isothiazole derivative was placed at 10 cm from the furnace in a trap cooled with liquid air. The system was evacuated to 1 × 10^{-3} Torr measured with a McLeod gauge. To prevent back condensation the sample was heated smoothly by using a Nichrome wire connected to a Varivolt at 25—30 V. The Vycor glass reactor had previously been seasoned by pyrolysis of n-butyl bromide at 450s °C; this prevented non-homogeneous reactions. Products were trapped in collectors cooled with liquid air, or in appropriate solutions, *i.e.* hydrogen cyanide by a 5%

potassium carbonate solution (aq.) and thioketens (4) and (5) by a 25—30% (w/v) of NN-dimethylamine solution (aq.), or otherwise dissolved *in vacuo* with chloroform or carbon tetrachloride for spectral analyses. Mass balance of each run confirmed that the products obtained accounted for all the starting material.

Analysis of Reaction Mixtures.—(a) *Determination of hydrogen cyanide.* HCN was identified by comparison (g.l.c.) with an authentic sample prepared according to a general method of synthesis,[15] and estimated by a slightly modified literature technique:[16] to a known amount of sample dissolved in 5% potassium carbonate solution (5 ml), a 1% picric acid solution (5 ml) was added. This mixture was heated on a boiling water-bath for 5 min and then diluted (to 100 ml). The colour was analysed at 520 nm against a standard prepared with pure distilled hydrogen cyanide.

(b) *Determination of nitrothioketen* (4). The reaction mixture trapped at the furnace outlet in a suitable collector, was cooled with liquid air. It was then dissolved in chloroform, and a ^1H n.m.r. spectral analysis was carried out, using a standard (toluene) for the quantitative determinations. The yield expressed in % for (4) was obtained by measuring the integrated signal for the hydrogen of (4) and comparing with the methyl signal of toluene. The experimental method has an error of $\pm 0.6\%$. Results of the yields for the thermolysis of (4) at several temperatures are compiled in Table 1, and represent a sample of analytical data for a total of 30 runs. The spectral absorptions for (4) are: ^1H n.m.r. (CHCl$_3$), δ 4.65; i.r. (CHCl$_3$) 1820s cm^{-1}, assigned to C:C stretching vibration.[12]

(c) *Determination of methylthioketen* (5). The reaction mixture was dissolved in carbon tetrachloride, and ^1H n.m.r. spectral analysis was carried out using chloroform as internal standard. The yield expressed in % for (5) was obtained by measuring the integrated signal of the hydrogen of (5) and comparing with the hydrogen signal of chloroform. Results of the yields for the thermolysis of (2) and (3) are summarized in Tables 2 and 3, and represent a

sample of analytical data for a total of 30 runs for each isothiazole. The spectral absorptions for (5) are:[12] ^1H n.m.r. (CHCl$_3$) δ 2.10 (d, 3 H, $J = 7$ Hz) and 4.10 (q, 1 H, $J = 14$ Hz); i.r. (CHCl$_3$) 1724w and 1 767s cm^{-1}.

Reaction of Compound (4) *or* (5) *with* NN-*Dimethylamine.* —The thioketens (4) or (5) were bubbled through a trap containing a 25—30% (w/v) NN-dimethylamine solution (B.D.H.) (5 ml) at -78 °C. When (4) was mixed with the reagent following addition of hexane, crystals were obtained. Filtration and recrystallization from hexane afforded NN-dimethylthio-2-nitroacetamide (11), m.p. 92—93 °C; i.r. (KBr) 1 536s, 1 420m, 1 383s, 1 285m, and 1 123m cm^{-1} (Found: C, 32.4; H, 5.5; N, 18.95. C$_4$H$_8$N$_2$SO$_2$ requires C, 32.42; H, 5.44, N, 18.90%). The thioketen (5) reacted similarly at the same temperature. Once the reaction was complete, the mixture was distilled under reduced pressure (in a nitrogen atmosphere) at 80 °C/1 Torr (lit. 72 °C/0.1 Torr)[17] yielding a colourless liquid whose i.r. spectrum (KBr, neat) showed similar bands to those previously reported.[13]

Polymerization of Compounds (4) *and* (5).—Sealed tubes containing the thioketen (4) or (5), *in vacuo*, afforded light brown tars either upon exposure to light or when heated. Solubility essays in almost all common organic solvents gave negative results; i.r. (KBr) showed bands at 1 585 cm^{-1} for the polymerized thioketen (4), and 1 563 cm^{-1} for the polymerized thioketen (5), which are in accordance with the values assigned to C:C.[18]

The polymerization process is slow at room temperature in the dark, since samples of (4) or (5) in sealed tubes showed i.r. bands characteristic of the monomers even when stored up to 30 days.

[15] A. I. Vogel, 'A Textbook of Practical Organic Chemistry', Longmans, London, 1959, p. 182.

[16] F. D. Snell and C. T. Snell, ' Colorimetric Methods of Analysis ', Van Nostrand, New York, 1959, vol II A, p. 719.

[17] P. Reynaud, R. C. Moreau, and J. P. Samama, *Bull. Soc. chim. France*, 1965, 3623.

[18] M. S. Raasch, *J. Org. Chem.*, 1970, **35**, 3470.