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Gas-Phase Elimination Reactions of 4-Substituted-2-alkoxythiazoline-5-ones

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ABSTRACT

Gas-phase eliminations of 4-substituted-2-alkoxythiazoline-5-ones have been studied. These compounds eliminate via a six-membered transition state to produce 4-substituted-thiazolidine-2,5-diones. These eliminations are unimolecular first-order reactions. Utilization of this thermolysis reaction in the synthesis of new 4-substituted-thiazolidine-2,5-diones is considered. Additional mechanistic information was obtained by comparing the kinetic data for thermal elimination reactions of these compounds with that of 1-ethoxythiazole. © *1996 John Wiley & Sons, Inc.*

INTRODUCTION

Interest in thiazolidinedione has recently been revived [1,2]. The activity of 5-arylidenethiazolidine-2,4-diones as antidiabetics is behind this interest [3,4]. Several 5-substituted-2,4-thiazolidinediones have been shown to be active antifungal and antibacterial agents [5]. Isomeric 2,5-thiazolidinediones also seem to be biologically active; however, their chemistry is very limited due to the absence of a general synthetic approach for these compounds.

In connection with our interest in gas-phase reactions [6], it occurred to us that it is quite possible that 4-phenylhydrazono-2-ethoxythiazoline-5-one (**1**), 4-furfurylidene-2-ethoxythiazoline-5-one (**2**), 4-phenylhydrazono-2-isopropoxythiazoline-5-one (**3**), and 4-furfurylidene-2-isopropoxythiazoline-5-one (**4**) would undergo gas-phase elimination reactions to yield 4-substituted-2,5-thiazolinediones according to a mechanism that involves the six-membered transition state described in Scheme (1).

RESULTS AND DISCUSSION

Table 1 summarizes the first-order rate coefficients of the gas-phase pyrolytic reactions of 4-substituted-2-alkoxythiazoline-5-ones (**1–4**). Each rate coefficient represents an average of three kinetic runs, in agreement to within a ±2% rate spread. The kinetic runs showed no adverse reactor-surface effects. The kinetic rate using an empty carbonized reaction vessel was compared with that found by use of a similar vessel packed with glass helices. This increase in the surface to volume of approximate ninefold did not affect the kinetic rate. Since a sixfold change in the amount of substrate used per kinetic run gave no significant change in rate coefficient, these reactions were deemed to be first-order processes. The Arrhenius parameters seem to be in agreement with the pathways proposed for these reactions.

It occurred to us that it was also possible for **1** and **3** to undergo simultaneous rearrangement into azoenols (cf. Scheme 2).

The recent introduction of an on-line pyrolysis gas chromatography-mass spectroscopy (GC-MS) method of analysis in our laboratory has greatly aided in the investigation of the mechanism by permitting the analysis of the products from these reactions. This, together with the NMR analysis of the products that clearly shows the disappearance of the alkoxy groups, reveals the formation of 4-substituted-2,5-thiazolidinediones, which is consistent with the reaction pathway of Scheme 1. The results

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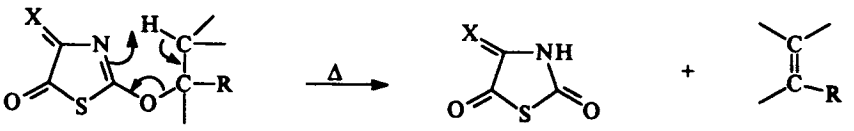
TABLE 1 Rate Coefficients and Arrhenius Parameters for the Thermolysis of

Compound Number	*TK*	10^4 *k/s*$^{-1}$	log A/s^{-1}	E_aKJ/mol^{-1}	10^3k(*500 K*)
1	443.2	1.43	12.77 ± 0.30	152.86 ± 2.9	10.6
	453.1	2.94			
	463.1	7.21			
	468.6	11.45			
	473.1	15.10			
	485.1	38.10			
2	455.5	3.37	10.54 ± 0.45	132.4 ± 4.4	5.9
	465.4	6.88			
	469.0	8.47			
	473.6	10.40			
	478.5	14.50			
	483.4	22.40			
	488.0	29.60			
3	433.0	1.00	13.05 ± 0.0	156.8 ± 0.01	8.5
	456.1	2.86			
	463.2	5.46			
	468.1	7.78			
	473.2	11.20			
	479.2	20.90			
	483.7	26.70			
4	488.1	2.48	11.72 ± 0.38	155.2 ± 4.0	0.57
	493.1	3.75			
	502.1	5.92			
	506.8	8.58			
	515.1	16.70			
	523.2	26.50			



SCHEME 1

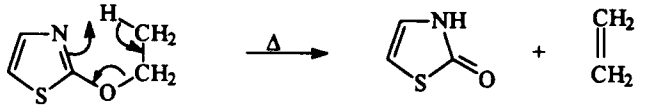
X	R
1) Ph-NH-N=	H
2) 2-furylmethylene	H
3) Ph-NH-N=	CH_3
4) 2-furylmethylene	CH_3

indicated that 1 and 3 are much more reactive than 2 and 4. This could be explained in terms of a greater -I effect of the phenylhydrazone group over that of the furyl-methylene group, since C–O bond breakage is aided by electron withdrawal [7].

Previously, one of us [8] showed that 2-ethoxythiazole undergoes unimolecular first-order thermal elimination into ethylene and 2-thiazolone (cf. Scheme 3). The ability of alkoxyheterocycles to undergo elimination is, at first consideration, surprising since the aromaticity of the ring is interrupted. However, because of the concerted nature of the reaction, this interruption is only marginal.

Electron supply to the C=N bond raises the nucleophilicity of the nitrogen, thereby increasing the rate. This effect is more pronounced in the compounds under consideration than in the case of 2-ethoxythiazole (cf. Table 2). This factor contributes to the higher reactivity of 1 and 2 over that of 2-ethoxythiazole. The ease of reaction is related to the ease of delocalization of an electron pair onto nitrogen in these compounds. (cf. Scheme 4).

SCHEME 2



SCHEME 3

SCHEME 4

EXPERIMENTAL

All melting points are uncorrected. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. The IR spectra were obtained on a Pye-Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were measured in DMSO on a Varian EM-360 MHz, using TMS as internal standard, and chemical shifts are expressed as δ. Mass spectra were recorded on a Varian 311A spectrometer. Compounds 1 and 2 have been prepared utilizing literature procedures [9,10].

Kinetic Studies

The experimental setup consists of (1) high-pressure liquid chromatography (HPLC) (Bio-rad model 2700) with UV-VIS detector (Bio-rad model 1740), HPLC column LC-8, 25 cm, 4.6 mm, 54 μm (Supelco); (2) CDS custom-made pyrolysis unit in which the reaction takes place. The pyrolysis unit consists of an insulated aluminum block, a platinum resistance thermometer, and a thermocouple connected to a Comark microprocessor thermometer.

Kinetic Procedure

A 0.2 mL sample of a very dilute solution of the pure reactant (in ppm level) in acetonitrile containing an internal standard was pipetted into the reaction tube that was then sealed under vacuum and kept inside the pyrolyzer for 600 seconds at a temperature at which 10–20% pyrolysis occurred. The content of the tube was then analyzed by HPLC.

This process was repeated for every 5–10 degree rise in temperature of the pyrolyzer and for the same time period until around 80–90% of pyrolysis had occurred. The kinetic rate was obtained from the first-order expression, $kt = ln\ (a_0/a)$. The Arrhenius parameters were obtained from a plot of log k vs. $1/TK$.

TABLE 2 Relative Rate of Pyrolysis of **1** and **2** as against that of 2-Ethoxythiazole at 600 K.

Compound	$10^2\ k(s^{-1})$	k_{rel}
2-Ethoxythiazole	1.6	1.0
1	307	192
2	81	51

Product Analysis

Using Flow Technique. A solution of substrates in chlorobenzene was passed down a reactor column (length of 1 m) packed with helices [11]. The column was heated to a temperature comparable to that used in the appropriate kinetic investigation. The products of pyrolysis were swept out using a stream of nitrogen gas, and the effluents were trapped in a glass coil surrounded by a jacket of Dry Ice.

The material collected on the walls of the trap was crystallized and analyzed by gas-liquid chromatography (GLC) and by NMR spectroscopy.

Using On-line Pyroprobe GC-MS. Pyroprobe (CDS Analytical Model 2000), which is a multiple-step platinum filament pyrolysis instrument, interfaced to the GC-MS system by means of a heated chamber that houses the filament rod during pyrolysis. A minute amount of the compound to be pyrolyzed was placed in a quartz tube inside the coil probe. The probe was placed inside the interface and sealed into the interface using a septum with a 1/4" hole. The temperature programming of the interface and probe were so adjusted as to make an efficient pyrolysis of the compound. The pyrolysates were swept into the GC-MS system by the carrier gas. The conditions of the GC and the MS were adjusted to get a good separation of the pyrolysates and for their proper identification.

Synthesis of 3 *and* 4

N-(isopropoxythiocarbonylglycine) [12]. A mixture of ethyl O-isopropyldithiocarbonate 1.7 g (0.01 mol) and glycine 0.7 g (0.01 mol) was refluxed in 10% aqueous potassium hydroxide (20 mL) for 2 hours.

The reaction mixture was neutralized, and the solid that had formed was filtered off, washed with water, then crystallized from dilute ethanol to yield 1 g. (56%) of N-(isopropoxythiocarbonylglycine), mp 125°C; IR (KBr) ν3480–3320 (COOH and NH), 2950 (CH_3), 1700 (C=O) cm^{-1}; ^1H NMR δ 1.35 (d, 6H, $2CH_3$), 4.42 (s, 2H, CH_2), 5.60 (m, 1H, CH), 6.22 (s, 1H, NH), 10.70 (s, 1H, COOH); MS: m/z = 177 (M^+). Anal. calcd for $C_6H_{11}NO_3S$: C, 40.7; H, 6.3; N, 7.9; S, 18.1. Found: C, 40.7; H, 6.2; N, 7.9; S, 18.2%.

4-Phenyldrazono-2-isopropoxy-2-thiazoline-5-ones (**3**). N-isopropoxythiocarbonyl(glycine) was heated with acetic anhydride, then treated with the appropriate aromatic diazonium chloride as previously described for the preparation of 4-aryl-hydrazono-2-benzyloxy-2-thiazoline-5-ones.

3: Yellow crystals; yield 2 g (76%); mp 165°C, IR (KBr) ν 3380 (NH), 3700 (aromatic CH); 2980–2900 (CH and CH_3); 1710 (C=O) cm^{-1}. ^1H NMR δ 1.50 (d, 6H, $2CH_3$), 5.59 (m, 1H, CH), 7.20–7.45 (m, 3H, ArH), 7.61–7.89 (m, 2H, ArH), 10.30 (br, 1H, NH). MS: m/z = 263 (M^+). Anal. calcd for $C_{12}H_{13}N_3O_2S$: C, 54.7; H, 5.0; N, 16.0; S, 12.2. Found: C, 54.8; H, 5.1; N, 15.8; S, 12.1%.

2-Furylidene-2-isopropoxy-2-thiazoline-5-ones (**4**). N-(isopropoxythiocarbonyl)glycine (0.01 mol) was treated with 2-furanal (0.01 mol), then with acetic anhydride (30 mL) and sodium acetate (1.0 g). The reaction mixture was then refluxed for 30 minutes, and left to cool. The solid product, so formed, was collected by filtration and crystallized from ethanol.

4: Pale yellow crystals; mp 120; yield 65%. IR: 3100 (aromatic CH); 2980–2920 (CH and CH_3). ^1H NMR δ 1.52 (d, 6H, $2CH_3$); 5.59 (m, 1H, CH), 6.6–6.8 (furyl and CH = protons), MS: m/z = 237. Anal. calcd for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7; N, 5.9; S, 13.5%. Found: C, 55.7; H, 4.3; N, 5.8; S, 13.4%.

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