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Gas-Phase Pyrolysis in Heterocyclic Synthesis. Gas-Phase Elimination Reactions of Some Substituted Aminoazoles

Nouria A. Al-Awadi* and Mohamed H. Elnagdi

Chemistry Department, Kuwait University, P.O. Box 5969, 13060 Safat, Kuwait

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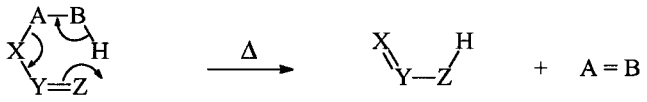
ABSTRACT

*Gas-phase pyrolyses of ethyl N-(5-cyanomethyl-1,3,4-thiadiazol-3-yl)carbamate (**1**), 1-benzoyl-3-(3-methyl-pyrazol-5-yl)thiourea (**2**), 1-benzoyl-3-(5-methylisoxazol-3-yl)thiourea (**3**), and 1-acetyl-3-(3-phenyl-pyrazol-5-yl)thiourea (**4**) have been studied. These reactions were homogeneous and unimolecular. The kinetics obeyed the first-order rate equation. Utilization of this pyrolytic reaction in heterocyclic synthesis is considered, and mechanistic information has been obtained from kinetic data and product analysis using an on-line pyrolysis GC-MS technique. The physical constants of four new substituted aminoazoles are also described. © 1997 John Wiley & Sons, Inc.*

INTRODUCTION

The synthesis of complex organic compounds from simple molecules is one of the major challenges in organic synthesis. Simple and efficient procedures for such syntheses continue to be needed to meet the demand for less expensive and neat synthetic approaches. In this aspect, one of us has reported the synthesis of thiadiazolylacetonitrile (**1**) [1] and azolylthioureas [2,3]. Our interest in gas-phase pyrolytic reactions, together with our most recent investigations on the synthesis of thiazolidines [4], drew our attention to the synthetic potential of heteroretroene pathways to the mechanism involving the six-membered transition state depicted in Equation 1:



EQUATION 1 Cyclic Transition State Formulation of Elimination Pathway

This article reports our investigation on the utility of the gas-phase pyrolytic reaction of (**1**) in the synthesis of the otherwise not readily obtainable 5-aminothiadiazol-2-ylacetonitrile. It also reports the synthesis, characterization, and pyrolysis of azolylthioureas (**2–4**). Gas-phase pyrolysis of compound (**2**) produced azolylisothiocyanates. It is of value to report here that synthetic approaches to azolylisothiocyanates are rather limited.

RESULTS AND DISCUSSION

Each compound gave excellent first-order kinetics, linear to >95% of reaction. Rate coefficients were very reproducible, and there were no deviations on the Arrhenius plots. The rate data are given in Table 1. An on-line pyrolysis utilizing the gas chromatography mass spectroscopy (GC-MS) method of analysis has greatly aided in the investigation of the mechanisms of these reactions.

*To whom correspondence should be addressed.

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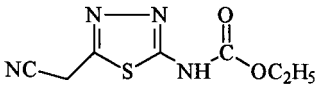
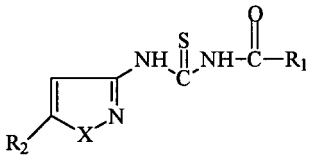
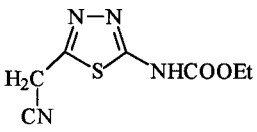
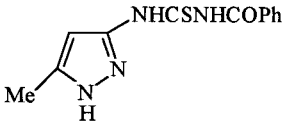
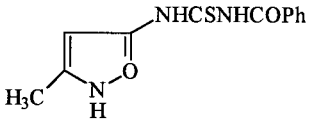
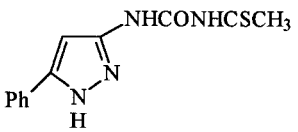


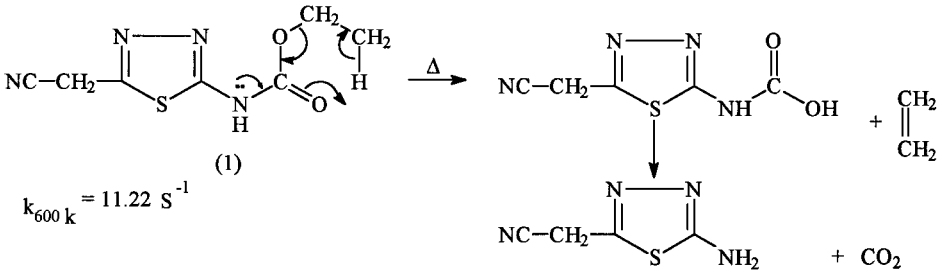
(1)



(2) X = NH ; R_1 = Ph ; R_2 = CH_3
(3) X = O ; R_1 = Ph ; R_2 = CH_3
(4) X = NH ; R_1 = CH_3 ; R_2 = Ph

TABLE 1 Rate Data

Compound	*T/K*	*k* s^{-1}	*log A* s^{-1}	E_a *kJ* mol^{-1}
 (1)	405.0	7.91×10^{-5}	11.75 ± 0.02	130.28 ± 0.13
	420.0	2.91×10^{-4}		
	428.0	5.62×10^{-4}		
	437.0	11.45×10^{-4}		
	448.0	2.63×10^{-3}		
	452.0	3.52×10^{-3}		
	458.0	5.40×10^{-3}		
 (2)	410.0	6.99×10^{-5}	12.44 ± 0.00	130.28 ± 0.01
	427.0	3.21×10^{-4}		
	435.0	6.23×10^{-4}		
	440.0	9.47×10^{-4}		
	447.0	1.66×10^{-3}		
	454.0	2.84×10^{-3}		
	460.0	4.46×10^{-3}		
 (3)	415.4	1.49×10^{-4}	10.77 ± 0.00	116.296 ± 0.00
	426.2	3.25×10^{-4}		
	437.5	7.56×10^{-4}		
	439.5	8.76×10^{-4}		
	444.5	1.2×10^{-3}		
	450.6	2.33×10^{-3}		
	456.7	2.99×10^{-3}		
	461.5	4.11×10^{-3}		
 (4)	422.8	9.75×10^{-5}	11.60 ± 0.26	126.30 ± 2.23
	433.8	2.72×10^{-4}		
	443.8	5.02×10^{-4}		
	448.6	8.14×10^{-4}		
	457.9	1.53×10^{-3}		
	462.8	2.22×10^{-3}		
	468.6	3.40×10^{-3}		

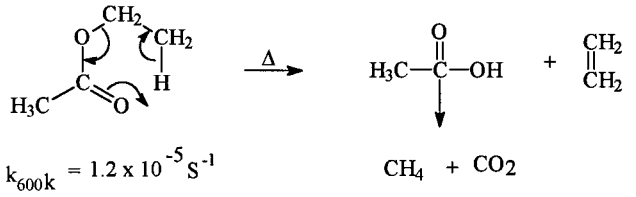


EQUATION 2 Thermolysis of Ethyl N-(5-cyanomethyl-1,3,4-thiadiazol-3-yl)carbamate

Ethyl N-(5-cyanomethyl-1,3,4-thiadiazol-3-yl)carbamate (**1**)

The pyrolysis reaction proceeds via a six-membered transition state to give ethene and 5-aminothiadiazol-2-ylacetonitrile, shown in Equation 2 above.

The transition state of this reaction could best be compared with that of the gas-phase pyrolysis of ethyl acetate shown in Equation 3 [5]:



EQUATION 3 Gas-phase pyrolysis of ethyl acetate

The enhanced reactivity of (**1**) over that of ethyl acetate may be derived from the −I effect of the N atom, which makes easier the C–O bond cleavage and also the +M effect that increases the nucleophilicity of the C=0 group.

1-Benzoyl-3-(3-methylpyrazol-5-yl)thiourea (**2**) *and 1-Benzoyl-3-(5-methylisoxazol-3-yl)thiourea* (**3**)

Two different mechanisms could conceivably operate in the pyrolysis reactions of (**2**) and (**3**). Scheme 1 shows that pyrolysis of (**2**) proceeds exclusively via pathway (**A**), producing 5-methyl-1H-3-pyrazolylisothiocyanate and benzamide, whereas pyrolysis of (**3**) proceeds via pathway (**B**), producing benzoylisothiocyanate and 3-amino-5-methylisoxazole.

1-Acetyl-3-(3-phenylpyrazol-5-yl)thiourea (**4**)

Three possible pathways for the thermal decomposition of this compound could be postulated and are shown as Scheme 2.

Product analysis reveals the formation of the azolylthiourea, and this is in accord with transition state (**C**) in (Scheme 2). No trace of either the aminoazolyl or the azolylisothiocyanate was detected.

This pathway could be supported by the fact that the reactivity of this compound in this particular reaction is determined by the protophilicity of the attacking group upon the hydrogen atom involved in the transition state. C=S is more protophilic and less thermodynamically stable than C=O in pathway (**A**) and C=N in pathway (**B**).

EXPERIMENTAL

Kinetic Studies

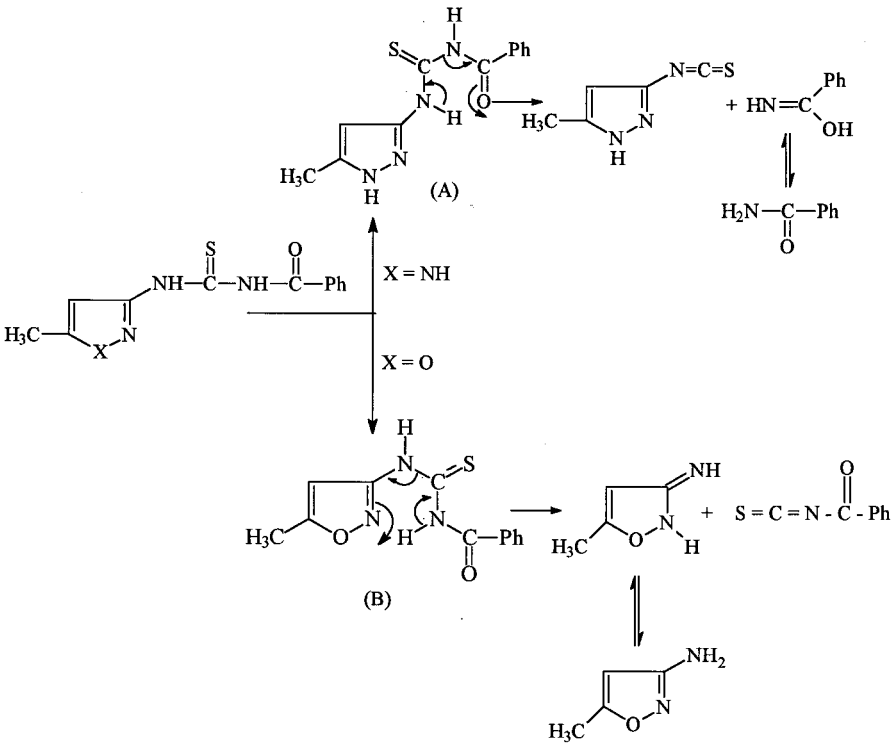
The experimental setup consists of (1) HPLC (Bio-rad model 2700) with UV-VIS detector (Bio-rad model 1740), HPLC column LC-8, 25 cm, 4.6 mm, 5.0 μm (Suppelco); and (2) CDS custom-made pyrolysis unit where the reaction takes place. The pyrolysis unit consists of an insulated aluminum block, a platinum resistance thermometer, and a thermocouple connected to a Comark microprocessor thermometer.

A detailed description of the kinetic procedure has been given elsewhere [6].

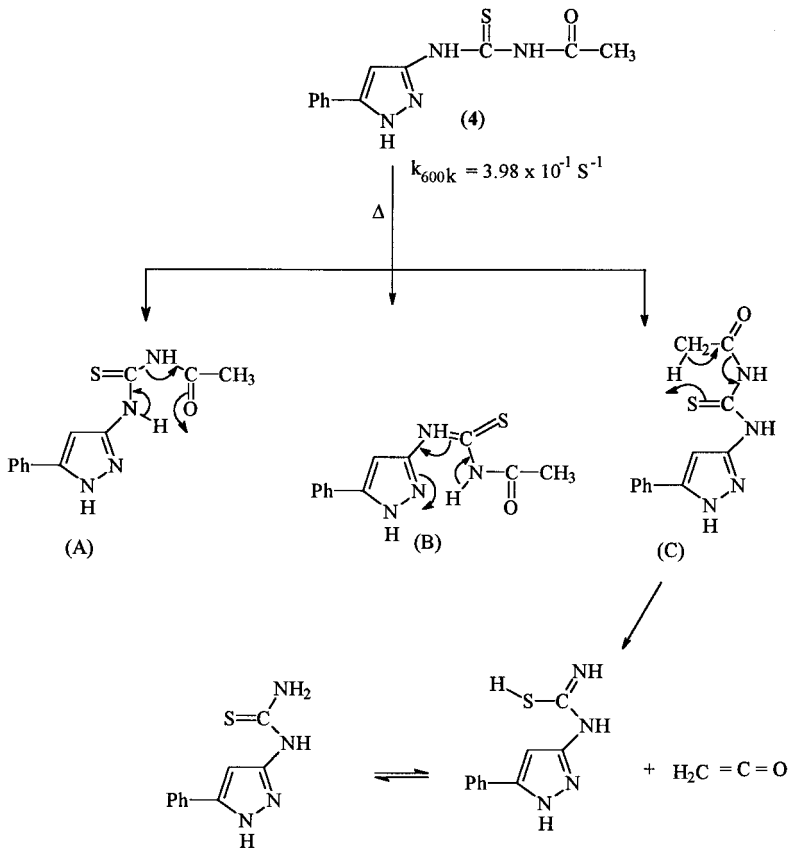
The procedure and the instrumentation for product analysis have been described elsewhere [6].

Synthesis

Ethyl N-(5-cyanomethyl-1,3,4-thiadiazol-3-yl)-carbamate (**1**). This was prepared by following the procedure described by Elmoghayar et al. [1]. To a solution of ethoxycarbonylisothiocyanate (prepared from 0.012 mole of ammonium isothiocyanate and 0.01 mole ethyl chloroformate as described earlier) in dioxane, cyanoethanoic hydrazide (0.01 mol) was added. The reaction mixture was stirred for 60 minutes, then subjected to filtration, the filtrate dissolved in acetic acid (20 mL), and the solution refluxed for 20 minute. The reaction mixture was then evaporated in vacuo and the remaining solid product was triturated with water. The solid product so formed



SCHEME 1 Pyrolysis of 1-benzoyl-3-(3-methylpyrazol-5-yl)thiourea (**2**) and 1-benzoyl-3-(5-methylisoxazol-3-yl)thiourea (**3**).



SCHEME 2 Thermolysis of 1-acetyl-3-(3-phenylpyrazol-5-yl)thiourea (**4**).

was collected by filtration and crystallized from ethanol. Mp 166–167°C, ^{1}H NMR ($CDCl_3$, 80 MHz), δ 1.3 (t, 3H), 3.8 (s, 2H), 4.3 (q, 2H), and 10.1 (bs, 1H). Calcd for $C_7H_8N_4O_2S$: C, 39.62; H, 3.77; N, 26.42; and S, 15.09%. Found: C, 39.67; H, 3.79; N, 26.37; and S, 15.18%.

Azolylthioureas (**2–4**)

These were prepared by the following procedure reported by Elnagdi et al. [2] for the reaction of benzoylisothiocyanate with 3-phenyl-1-H-pyrazoleamine. Thus, a suspension of ammonium thiocyanate (0.012 mol) in dioxane (20 mL) is treated with the appropriate acid chloride (0.01 mol) and then refluxed for 15 minutes. The reaction mixture was cooled to room temperature and then treated with solution of the appropriate heterocyclic amine (0.01 mol) in dioxane (10 mL). The reaction mixture was refluxed for 10 minutes and then evaporated in vacuo. The residual product was triturated with water, and the solid product, so formed, was collected by filtration and crystallized from the appropriate solvent.

1-Benzoyl-3-(3-methylpyrazol-5-yl)thiourea (**2**). Mp 220°C, ^{1}H NMR ($CDCl_3$, 80 MHz), δ 2.2 (s, 3H), 6.9 (s, 1H), 7.8 (m, 5H), 11.5 (bs, 1H), 12.5 (bs, 1H), and 13.1 (bs, 1H). Calcd for $C_{12}H_{12}ON_4S$: C, 55.38; H, 4.65; N, 21.53; and S, 12.31%. Found: C, 55.32; H, 4.72; N, 21.66; and S, 15.29%.

1-Benzoyl-3-(5-methylisoxazol-3-yl)thiourea (**3**). Mp 155°C, ^{1}H NMR ($CDCl_3$, 80 MHz), δ 2.2 (s, 3H), 8 (m, 5H), and 13.4 (bs, 2H). Calcd for $C_{12}H_{11}O_2N_3S$: C, 55.17; H, 4.24; N, 16.09; and S, 12.25%. Found: C, 54.99; H, 4.26; N, 15.96; and S, 12.38%.

1-Acetyl-3-(3-methylpyrazol-5-yl)thiourea (**4**). Mp 206–207°C, ^{1}H NMR ($CDCl_3$, 80 MHz), δ 2.2 (s, 3H), 7.6 (m, 5H), 11.4 (bs, 1H), 12.2 (bs, 1H), and 12.8 (bs, 1H). Calcd for $C_{12}H_{12}ON_4S$: C, 55.38; H, 4.65; N, 21.53; and S, 12.29%. Found: C, 55.42; H, 4.72; N, 21.66; and S, 12.34%.

ACKNOWLEDGMENT

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