Gas-Phase Pyrolysis in Organic Synthesis. Part 3: Novel Cyclization of 2-Arylhydrazonopropanals into Cinnolines¹

AJITH KUMAR, NOURIA A. AL-AWADI, MOHAMED H. ELNAGDI, YEHIA A. IBRAHIM, KAMINI KAUL

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

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ABSTRACT: 3-oxo-3-aryl-2-arylhydrazonopropanals (1) have been converted under thermal gas-phase conditions cleanly into cinnolines (2). A plausible mechanism is suggested to account for this transformation based on the kinetics and products of reaction. © John Wiley & Sons, Inc. Int J Chem Kinet 33: 402–406, 2001

INTRODUCTION

This article describes an efficient synthesis of 3-aroylcinnolines via cyclization of 2-arylhydrazonopropanols under gas-phase conditions (Scheme I). Kinetic data were used to suggest a mechanism for this cyclization reaction based on the products of the reaction.

It is of value to report here that synthetic approaches to cinnolines are rather limited; cyclization of the monophenylhydrazones of benzil and 4,6-dimethyl-1,2-cyclohexanedione in sulfuric acid was reported more than half century ago and no further report for the application of this procedure to other derivatives was reported [2].

Two possible pathways for the gas-phase cyclization of (1) to (2) could be postulated (Scheme II). The first one involves a nucleophilic attack by the aromatic moiety of the hydrazone on the formyl carbonyl carbon, followed by elimination of water to produce cinnoline (2). Alternatively, one would assume initial thermal isomerization of 1 into 1', which will undergo $6-\pi$ -electrocyclization process to produce 1" via a quasi-aromatic six-membered transition state followed by elimination of water to yield cinnoline (2). According to mechanism (A), electron-donating substituent (X), which will increase the nucleophilicity of the ring, should significantly accelerate the reaction rate.

By contrast, mechanism (B) predicts that electronwithdrawing substituent (X) should enhance the reaction rate if the thermal isomerization of 1 to 1' is the rate-controlling factor since this will increase the acidity of the hydrogen atom of the hydrazono group involved in the isomerization process of 1 to 1'. While a negligible electronic effect of the substituent (X) on the rate of reaction would be observed if the 6- π -electrocyclization of 1' into 1" is the rate-controlling factor.

Correspondence to: N. A. Al-Awadi (chesc@kuc01.kuniv. edu.kw)

¹See [1].

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EXPERIMENTAL

Kinetic Procedure and Product Analysis

Experimental details of both kinetic and reaction product analysis have been described in an earlier communication [5].

Kinetic Studies.

Reaction Set-up. Preliminary kinetic results were obtained on a system featuring a Eurotherm 093 pyrolysis unit coupled to a Perkin Elmer Sigma 115 gas chromatograph. The kinetic data reported are from a reactor set-up including: (1) HPLC (Bio-rad Model 2700) fitted with a UV/VIS detector (Bio-rad Model 1740); HPLC: Column LC-8, 25 cm, 4.6 mm, 5 μ m (Supelco); and a CDS custom-made pyrolysis unit for the thermolysis reactions. The pyrolysis tube is jacketed by an insulating aluminium block fitted with a platinum resistance thermometer and a thermocouple connected to a Comark microprocessor thermometer.

Kinetic Runs and Data Analysis. Aliquot parts (0.2 ml) of very dilute solutions (ppm) of neat substrates in acetonitrile as solvent and chlorobenzene as internal

standard were pipetted into the reaction tube, which was then sealed under vacuum (0.28 mbar) and placed inside the pyrolyzer for 600 s at a temperature at which 10-20% pyrolysis is deemed to occur. The contents of the tube were analyzed using the HPLC probe.

At least three kinetic runs were repeated for each $5-10^{\circ}$ C rise in temperature of the pyrolyzer and for the same time interval until 90–95% pyrolysis was achieved. The rates were followed over a temperature range exceeding 55 K, and the rate coefficients were calculated using the expression for a first-order reaction: $kt = \ell na_0/a$. The Arrhenius parameters were obtained from a plot of log k vs. 1/T(K).

Product Analysis.

Flow Technique. Solutions of substrates in chlorobenzene were passed down a 1-m reactor column packed with helices. The column was heated to temperatures comparable to those used in the kinetic investigations. The products of pyrolysis were swept through the column 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



Scheme II Pathways for the gas-phase cyclization of 2-arylhydrazonopropanals into cinnolines (2).

on the walls of the trap (glass coil) was crystallized and analyzed by NMR spectroscopy.

RESULTS AND DISCUSSION

Kinetics

The rate coefficients $k/(s^{-1})$ are used to determine the $E_a(kJ \text{ mol}^{-1})$ values of compounds (Table I). Each rate coefficient represents the mean from three kinetic runs in agreement to within $\pm 2\%$. The reactions were ascertained to be homogeneous, unimolecular, and free of reactor surface effects. The Arrhenius plots were linear up to $\geq 95\%$ reaction. The homogeneous nature of the reaction was tested by comparing rates using a normal reactor with those obtained when the reactor vessel is packed with helices. Absence of a free radical pathway in the elimination reaction is confirmed using established procedures [3,4]. The relative rates of gas-phase pyrolysis of the substrates $1(\mathbf{a}-\mathbf{k})$ are recorded in Table II.

The relative rate values at 550 K (Table II) for the gas-phase cyclization of (1) to (2) show no significant effect of the subsistent on the reaction rate, so mechanism (A) is improbable. We therefore suggest that the cyclization reaction proceeds via mechanism (B), which is initiated by a thermal isomerization of (1) to (1') followed by a rate-determining step that involves $6-\pi$ -electrocyclization of (1') into (1"). The latter then dehydrates to produce cinnoline (2).

Product Analysis

The cyclization of compounds 1(a-k) into the corresponding cinnolines upon pyrolysis in the gas phase is remarkably straightforward. The product from this cyclization may be formulated as 3-aroyl derivatives (2) or the isomeric 3-carboxaldehyde derivatives (3) (Scheme I). However, based on careful spectral analysis, the former were proved to be the sole reaction product. Moreover, we found that the same cinnoline derivatives (2) could be made by acid-catalyzed cyclization of the corresponding hydrazones 1.

 Table I
 Kinetic Data for Gas-Phase Cyclization of



Cpd.(1)	Ar	Х	T(k)	$k(s^{-1})$	$E_{\rm a}~({\rm kJ}~{ m mol}^{-1})$
(a)	C_6H_5	Н	438.3	0.29	61.26 ± 0.76
			463.3	0.79	
			502.9	2.73	
			513.5	3.50	
			534.3	6.14	
			558.3	11.25	
(b)	$4-ClC_6H_4$	Н	434.8	0.27	53.79 ± 2.87
			462.8	0.80	
			493.8	2.34	
			508.5	3.01	
			522.5	3.73	
			544.4	6.33	
			564.8	9.36	
(c)	$4-MeC_6H_4$	Н	440.7	0.33	45.18 ± 1.34
	0 4		469.1	1.06	
			486.3	1.53	
			501.4	2.04	
			548.8	5.37	
			558.2	6.75	
(d)	4-MeOC_H	Н	446.3	0.42	54.94 ± 0.95
(4)	11100000114		459.7	0.62	0.000 = 0.000
			500.6	2.29	
			516.3	3 19	
			532.3	4 56	
			551.4	6.88	
			559.6	8.10	
(e)	2-Furvl	н	496.05	1 40	6260 ± 172
(0)	2-1 ury1	11	505.95	1.40	02.00 = 1.72
			518.95	2.56	
			532.05	3.67	
			543.85	5.09	
			553.65	6.83	
(f)	2-Thienvl	н	443.85	0.65	43.00 ± 1.11
(1)	2-Thichyi	11	460.25	0.01	45.00 = 1.11
			522 55	3.25	
			543.45	5.00	
			563 25	5.00 7.24	
(a)	СЧ	$4 \mathrm{OM}_{2}$	517.5	6.47	63.10 ± 0.48
(g)	$C_6 n_5$	4-0Me	522.25	0.47	03.19 ± 0.40
			519 15	0.55 12.56	
			540.45	15.50	
(h)	СЦ	4 NO	219.33 121 75	30.09	21.29 ± 0.67
(11)	C ₆ Π ₅	4-1NO ₂	454.75	3.00	51.58 ± 0.67
			440.93	4.80	
			403.13	9.00	
			524.15	15.90	
			537.05	19.91	
			548.25	22.10	/ .• ·
					(continues)

Cpd.(1)	Ar	Х	T(k)	$k(s^{-1})$	$E_{\rm a}$ (kJ mol ⁻¹)
(i)	C ₆ H ₅	4-Cl	518.45	1.98	74.94 ± 4.40
	0.5		548.35	4.90	
			563.55	7.12	
			578.35	12.53	
(j)	C_6H_5	3-OMe	526.75	1.83	84.96 ± 3.41
			540.85	2.38	
			554.95	4.08	
			583.35	11.10	
			605.05	18.93	
(k)	C_6H_5	3-Cl	539.95	4.63	74.93 ± 7.27
			552.25	7.01	
			564.05	10.96	
			576.55	12.1	
			588.25	19.6	

Table I Continued

In this communication, the mechanism of the gasphase pyrolysis of (1) as an interesting route toward cinnoline derivatives is described. Kinetic and mechanistic study of acid-catalyzed synthesis of (2) from (1), together with a detailed synthetic procedure of the

Table IIRate Coefficients and Relative Rates at 550 Kfor Gas-Phase Cyclization of 2-Arylhydrazonopropanals(1a-K)

Compound (1)	$10^4 k(s^{-1}) 550 \text{ K}$	k _{rel.}	
a	9.37	1	
b	7.48	0.8	
с	5.59	0.6	
d	6.83	0.7	
e	5.99	0.6	
f	5.90	0.6	
g	14.45	1.5	
h	23.03	2.4	
i	5.22	0.5	
j	3.57	0.4	
k	6.49	0.7	

substrates (propanals) and a detailed n.m.r. and m.s. spectra analysis of the formed cinnoline, is a subject of another publication.

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