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Gas-phase elimination reactions of 4-arylideneimino-1,2,4-triazol-3(2*H*)-ones and their 3(2*H*)-thione analogues

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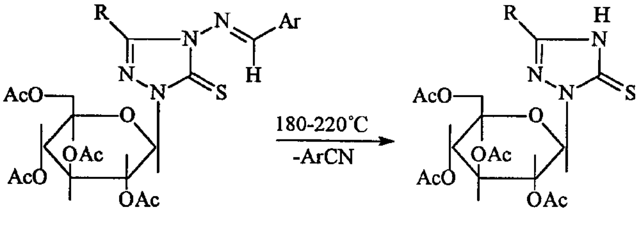
ABSTRACT: 4-Arylideneimino-1,2,4-triazol-3(2*H*)-ones (**1**–**4**) and their thio analogues (**5**–**8**) were pyrolysed in the gas phase. The reactions were homogeneous and free from catalytic and radical pathways. Analysis of the pyrolysate showed the elimination products to be substituted benzonitriles and the corresponding 3-hydroxy-1,2,4-triazoles and their thio analogues. The kinetic results and product analysis lend support to a reaction pathway involving a six-membered transition state. At 500 K, the thiooxotriazoles **5**–**8** were found to be 10^3-fold more reactive than the corresponding oxotriazoles **1**–**4**. The reactivities of the 2-oxotriazoles were compared with those of the substituted 2-oxopyridine-3-carbonitriles. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: arylideneiminotriazolones; arylidenetriazolethiones; gas-phase elimination

INTRODUCTION

We recently reported on the effective synthesis of 2-*N*- and 3-*S*-glucosyl-1,2,4-triazoles of potential biological interest.[1] Several attempts to synthesize the glucosyl derivatives of 1,2,4-triazoles either chemically[2] or enzymatically[3] resulted in a mixture of regioisomers, which makes structural analysis tedious. The key step to the selective synthesis of such compounds is via thermolysis of the arylideneimino derivatives at 180–220 °C to give the intermediate target 2-glucosyl derivatives and nitriles in almost quantitative yield (Scheme 1).



Scheme 1

A few years ago, we reported the results of our investigations on the thermolysis reactions of 1-arylmethyleneimino-1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carbonitriles and the utilization of this thermolysis reaction in the synthesis of functionally substituted nitriles which are unstable under basic and acidic conditions as an alternative approach for the conversion of aldehydes into nitriles[4] (Scheme 2).

In this paper, we report the results of kinetic studies on the gas-phase pyrolysis of 4-arylideneimino-1,2,4-triazol-3(2*H*)-ones and the corresponding 3(2*H*)-thiones.

RESULTS AND DISCUSSION

Kinetics

The rate constants *k* in Table 1 were used to determine the Arrhenius log *A* and E_a values for the gas-phase elimination reactions of compounds **1**–**8**. Each rate constant represents an average of three kinetic runs, in agreement to within ±1.5%. The reactions were ascertained to be homogeneous, unimolecular and free of reaction surface effects. The Arrhenius plots were strictly linear up to $\geq 95\%$ reaction. The rate constants of reaction at 500 K of these substrates are recorded in Table 2 along with relative rates. The homogeneous nature of the reactions was tested by comparing the rates using a normal reactor with those obtained when the reactor vessel was packed with helices. The absence of a radical pathway in the elimination reaction was confirmed using

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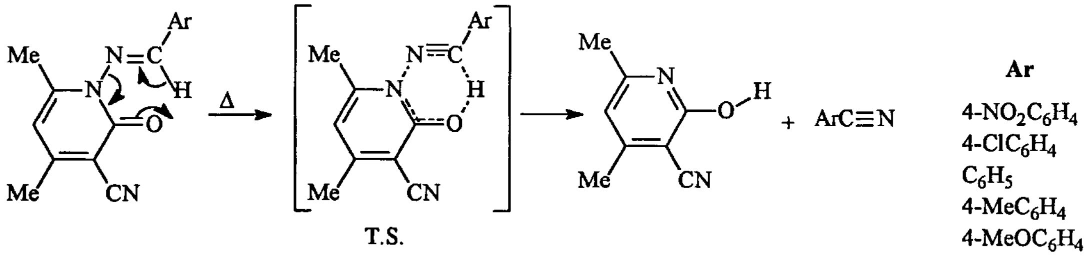
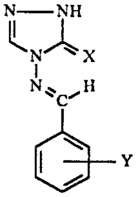


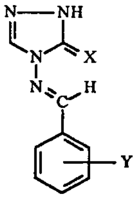
Scheme 2

Table 1. Kinetic parameters for pyrolysis of **1–8**



Compound	X	Y	Temperature (°C)	$10^4k(s^{-1})$	Log $[A\ (s^{-1})]$	E_a(kJ mol^{-1})
1	O	H	550.75	1.16	12.61 ± 0.23	174.63 ± 2.5
			561.05	2.30		
			570.85	4.18		
			580.85	7.79		
			590.95	14.96		
			600.55	27.90		
2	O	4-Cl	548.15	0.84	12.35 ± 0.19	172.42 ± 2.13
			568.45	3.32		
			578.75	5.82		
			588.45	11.14		
			597.45	20.50		
			605.75	29.58		
3	O	4-Me	563.85	2.94	12.32 ± 0.08	171.04 ± 0.90
			572.05	5.04		
			580.65	8.46		
			589.35	13.00		
			596.95	22.29		
4	O	4-OMe	538.75	0.98	9.78 ± 0.22	142.11 ± 2.38
			549.65	1.83		
			560.55	3.03		
			593.65	18.04		
			602.45	27.71		
5	S	H	446.55	1.34	10.67 ± 0.09	124.29 ± 0.77
			457.25	3.00		
			468.15	6.20		
			479.45	13.34		
			490.45	27.18		
6	S	4-Cl	447.15	1.37	11.03 ± 0.05	127.48 ± 0.42
			458.85	3.37		
			470.75	7.70		
			482.95	17.59		
			494.85	37.88		
7	S	4-Me	451.45	1.28	14.02 ± 0.01	154.83 ± 0.10
			458.95	2.52		
			470.75	9.72		
			482.05	17.60		
			488.75	29.88		
8	S	4-OMe	456.05	1.26	14.05 ± 0.02	156.72 ± 0.15
			463.85	2.52		
			471.35	4.81		
			489.05	20.44		
			497.35	38.87		

Table 2. Absolute and relative rate constants at 500 K for pyrolysis of **1–8**



Y	X		k_{rel}
	O $10^6\,k(\mathrm{s}^{-1})$	S $10^3\,k(\mathrm{s}^{-1})$	
H	2.35	4.83	2.1×10^3
4-Cl	2.19	5.20	2.4×10^3
4-Me	2.80	7.05	2.5×10^3
4-OMe	8.15	4.75	0.6×10^3

established procedures.[5,6] All the sulfur-containing triazoles **5**–**8** are $\sim 10^3$ times more reactive than their corresponding oxygen analogues **1**–**4**.

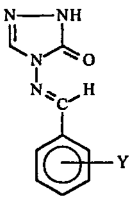
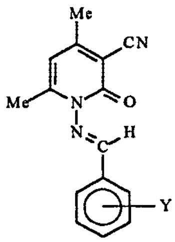
The pathway of the thermal gas-phase elimination reaction of comparable substrates was found to involve a concerted cyclic six-membered transition state.[7,8] The same mechanism is suggested to account for the present results. The only structural feature which distinguishes the 3-oxotriazoles **1**–**4** from their thio analogues **5**–**8** is the greater protophilicity and lability together with the relative thermodynamic stability and π-bond energy difference of the thio and carbonyl bonds. The change in relative rate constants in Table 3, although moderate, is nevertheless systematic and consistent with expected electron-withdrawing and electron-donating effects of substituents at the *para* position. This modest effect is due to the fact that transition state cyclization of 2-oxopyridines and 2-oxotriazoles is associated with H-bonding between O and the acid proton, whereas a much greater change in reactivity is observed when the protophilicity of X is reduced by replacing O with S.

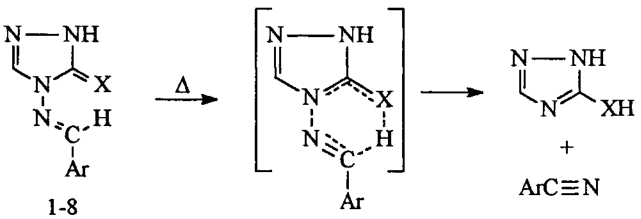
Mechanism

The reaction pathway shown in Scheme 3 is compatible with both the present results and the products of pyrolysis, and follows our earlier findings.[4] These reactions proceed via aromatization of the transition state which ultimately produces hydroxytriazoles or their thio analogues, which are more stable than the reactant, *N*-aminotriazoles **1**–**4**.

The reactivity of the substituted 2-oxopyridines is 10–100 times greater than that of the 3-oxotriazoles (Table 3). It is possible to rationalize this difference in reactivity in terms of the greater thermodynamic stability of the product formed, i.e. 2-hydroxypyridines, from the gas-phase elimination of the former compound relative to the

Table 3. Absolute and relative rate constants at 520 K for 3-oxotriazoles and 2-oxopyridines

Y	$10^4\,k\ (\mathrm{s}^{-1})$		k_{rel}
			
H	0.12	3.6	30
4-Cl	0.11	10.7	97
4-Me	0.14	3.0	21
4-OMe	0.32	2.2	9



	Ar
1,5	C_6H_5
2,6	$4\text{-}ClC_6H_4$
3,7	$4\text{-}MeC_6H_4$
4,8	$4\text{-}MeOC_6H_4$

1-4, X = O
5-8, X = S

Scheme 3

formation of 2-hydroxytriazoles, a product of the same reaction of the latter compounds.[9,10]

EXPERIMENTAL

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 an HPLC system (Bio-Rad Model 2700) fitted with a UV–VIS detector (Bio-Rad Model 1740) and an LC-8 column (25 cm × 4.6 mm i.d., 5 μm film thickness) (Supelco) and a CDS custom-made pyrolysis unit for the thermolysis reactions. The pyrolysis tube was 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. Aliquots (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 the tube was placed inside the pyrolyser for 600 s at a temperature where 10–20% pyrolysis was deemed to occur. The contents of the tube were analysed using the HPLC probe.

At least three kinetic runs were repeated for each 5–10 °C rise in temperature of the pyrolyser and for the same time interval until 90–95% pyrolysis was achieved. The rates were followed over a temperature range not less than 50 K, and the rate coefficients were calculated using the expression for a first-order reaction: $kt = \ln a_0/a$. 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 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 (glass coil) was crystallized and analysed by NMR spectroscopy.

Synthesis. *Preparation of 4-arylideneimino-1,2,4 triazol-3(2H)-ones.* To a stirred and heated solution of aminotriazole[11] (1 g, 10 mmol) in ethanol (10 ml) and a few millilitres of water was added a solution of benzaldehyde or substituted benzaldehyde (10 mmol) in ethanol (5 ml). The resulting solution was refluxed for 1–2 h and the precipitated product was filtered hot and recrystallized from ethanol or dioxane in 80–85% yield. The following compounds were thus prepared.

4-Benzylideneimino-1,2,4-triazol-3(2*H*)-one (**1**), white powder (m.p. 189–190 °C (EtOH), lit.[11] m.p. 182 °C. ^{1}H NMR (DMSO): δ 7.49–7.57 (m, 3H, Ar H), 7.78–7.83 (m, 2H, Ar H), 8.43 (s, 1H, triazole H), 9.44 (s, 1H, CH=N), 12.10 (s, 1H, NH). ^{13}C NMR: δ 128.6, 130.0, 132.4, 134.0, 136.6, 151.6, 155.1. Anal. Calcd for $C_9H_8N_4O$ (188): C 57.45, H 4.25, N 29.78. Found: C 57.90, H 4.36, N 29.39%. MS: *m/z* 188 (M^+). IR (cm^{-1}): 3215, 3126, 1720, 1700.

4-*p*-Chlorobenzylideneimino-1,2,4-triazol-3(2*H*)-one (**2**), white crystals, m.p. 225–226 °C (EtOH). ^{1}H NMR (DMSO): δ 7.58 (dd, 2H, Ar H), 7.84 (dd, 2H, Ar H), 8.40 (s, 1H, triazole H), 9.45 (s, 1H, CH=N), 12.10 (s, 1H, NH). ^{13}C NMR: δ 130.0, 130.3, 132.6, 135.9, 137.1, 151.6, 154.0. Anal. Calcd for $C_9H_7ClN_4O$ (222.5): C 48.54, H 3.15, N 25.16. Found: C 48.82, H 3.44, N 24.62%. MS: *m/z* 222, 224 (M^+). IR (cm^{-1}): 3144, 1717, 1700.

4-*p*-Methylbenzylideneimino-1,2,4-triazol-3(2*H*)-one (**3**), pale white powder, m.p. 222–223 °C (EtOH). ^{1}H NMR (DMSO): δ 2.37 (s, 3H, CH_3), 7.31 (d, 2H, Ar H), 7.68 (d, 2H, Ar H), 8.38 (s, 1H, triazole H), 9.38 (s, 1H, CH=N), 12.07 (s, 1H, NH). ^{13}C NMR: δ 22.0, 128.6, 130.1, 131.3, 136.7, 142.5, 151.7, 155.1. Anal. Calcd for $C_{10}H_{10}N_4O$ (202): C 59.41, H 4.95, N 27.72. Found: C 59.82, H 4.99, N 27.38%. MS: *m/z* 202 (M^+). IR (cm^{-1}): 3374, 3150, 1707.

4-*p*-Methoxybenzylideneimino-1,2,4-triazol-3(2*H*)-one (**4**), creamy white flakes, m.p. 221–222 °C (EtOH). ^{1}H NMR (DMSO): δ 3.83 (s, 3H, CH_3), 7.07 (d, 2H, Ar H), 7.76 (d, 2H, Ar H), 8.35 (s, 1H, triazole H), 9.34 (s, 1H, CH=N), 12.03 (s, 1H, NH). ^{13}C NMR: δ 56.3, 115.4, 126.4, 130.4, 136.6, 151.8, 155.2, 162.8. Anal. Calcd for $C_{10}H_{10}N_4O_2$ (218): C 55.05, H 4.59, N 25.68. Found: C 55.29, H 4.74, N 25.15%. MS: *m/z* 218 (M^+). IR (cm^{-1}): 3149, 3139, 1707, 1607.

Preparation of 4-arylideneimino-3-mercapto-1,2,4-triazoles. A mixture of the 4-amino-3-mercapto-1,2,4-triazole[12] (10 mmol) and benzaldehyde or its substituted analogues (10 mmol) in acetic acid (10 ml) was refluxed for 30 min. After cooling, the crystals of the products were filtered and recrystallized from ethanol to afford the title compounds in 80–90% yield. The following compounds were thus synthesized.

4-Benzylideneimino-3-mercapto-1,2,4-triazole (**5**), pale yellow crystals, m.p. 175–176 °C. ^{1}H NMR (DMSO): δ 7.48–7.71 (m, 3H, Ar H), 7.82–7.94 (m, 2H, Ar H), 8.91 (s, 1H, triazole H), 9.48 (s, 1H, CH=N), 13.95 (s, 1H, NH). ^{13}C NMR (DMSO): δ 129.4, 130.0, 133.0, 133.4, 139.0, 161.9, 163.8. Anal. Calcd for $C_9H_8N_4S$ (204): C 52.94, H 3.92, N 27.45, S 15.68. Found: C 52.98, H 4.06, N 26.94, S 16.25%. MS: *m/z* 204 (M^+). IR (cm^{-1}): 3445, 3106, 1596, 1286, 1228.

4-*p*-Chlorobenzylideneimino-3-mercapto-1,2,4-triazole (**6**), white crystals, m.p. 236–237 °C; lit.[13] m.p. 237 °C. ^{1}H NMR (DMSO): δ 7.63 (d, 2H, Ar H), 7.90 (d, 2H, Ar H), 8.91 (s, 1H, triazole H), 9.51 (s, 1H, CH=N), 14.01 (s, 1H, NH). ^{13}C NMR (DMSO): δ 130.8, 131.1, 131.9, 137.9, 138.8, 160.1, 163.9. Anal. Calcd for $C_9H_7ClN_4S$ (238.5): C 45.28, H 2.94, N 23.48, S 13.42. Found: C 45.54, H 3.13, N 23.44, S 13.40%. MS: *m/z* 238, 240 (M^+). IR (cm^{-1}): 3447, 3131, 1607, 1593, 1279, 1224.

4-*p*-Methylbenzylideneimino-3-mercapto-1,2,4-triazole (**7**), creamy white crystals, m.p. 199–201 °C. ^{1}H NMR (DMSO): δ 2.37 (s, 3H, CH_3), 7.34 (d, 2H, Ar H), 7.75 (d, 2H, Ar H), 8.91 (s, 1H, triazole H), 9.39 (s, 1H, CH=N), 14.01 (s, 1H, NH). ^{13}C NMR (DMSO): δ 22.1, 129.6, 130.2, 130.5, 139.0, 143.6, 161.6, 163.6. Anal. Calcd for $C_{10}H_{10}N_4S$ (218): C 55.05, H 4.59, N 25.68, S 14.67. Found: C 55.27, H 4.60, N 25.34 S, 14.66, MS: *m/z* 218 (M^+). IR (cm^{-1}): 3400, 3106, 1605, 1551, 1286, 1179.

4-*p*-Methoxybenzylideneimino-3-mercapto-1,2,4-triazole (**8**), pale white crystals, m.p. 230–232 °C; lit.[13] m.p. 224 °C. ^{1}H NMR (DMSO): δ 3.83 (s, 3H, CH_3), 7.08, (d, 2H, Ar H), 7.81 (d, 2H, Ar H), 8.86 (s, 1H, triazole H), 9.31 (s, 1H, CH=N), 14.01 (s, 1H, NH). ^{13}C NMR (DMSO): δ 56.4, 115.8, 125.4, 131.4, 131.7, 139.1, 162.2, 163.5. Anal. Calcd for $C_{10}H_{10}N_4OS$ (234): C 51.28 H 4.27, N 23.93, S 13.67. Found: C 51.27, H 4.27, N 23.55, S 13.41%. MS: *m/z* 234 (M^+). IR (cm^{-1}): 3405, 3133, 1602, 1548, 1293, 1253.

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