Heteroatom Chemistry
Volume 11, Number 4, 2000

Thermolysis of Hexasubstituted-4,5-Dihydro-3H-Pyrazoles: Kinetics and Activation Parameters

Pedro C. Vasquez, Derrick C. Bennett, Kishia K. Towns, G. Davon Kennedy, and A. L. Baumstark

Department of Chemistry, Center for Biotechnology and Drug Design, Georgia State University, Atlanta, GA 30303-3083

Received 18 October 1999; revised 1 March 2000

ABSTRACT: *A kinetics study of the thermolysis of a series of hexasubstituted-4,5-dihydro-3H-pyrazoles (pyrazolines* **1a:** *3,3,4,4-tetramethyl-5-phenyl-5-acetoxy;* **1b:** *cis-3,5-diphenyl-3,3,4-trimethyl-5-acetoxy;* **1c:** *cis-3,5-diphenyl-3,4,4-trimethyl-5-methoxy;* **1d:** *3,3,5-triphenyl-4,4-dimethyl-5-acetoxy), which produced the corresponding hexasubstituted cyclopropanes* **2a–d** *in quantitative yields was carried out. The first order rate constants (k_1) for thermal decomposition and activation parameters were determined. The relative reactivity series was found to be* **1d** $\gg$ **1b** $\sim$ **1c** $>$ **1a.** *The activation parameters for thermolysis were found to be: for* **1a** $\Delta H‡ = 39.8$ *kcal/mol,* $\Delta S‡ =$ *14 eu,* $k_{150^\circ} = 6.8 \times 10^{-5}\, s^{-1}$*; for* **1b** $\Delta H‡ = 33.5$ *kcal/mol,* $\Delta S‡ = 0.2$ *eu,* $k_{150^\circ} = 1.7 \times 10^{-4} s^{-1}$*; for* **1c** $\Delta H‡ = 32.7$ *kcal/mol,* $\Delta S‡ = -1.8$ *eu,* $k_{150^\circ} = 1.2 \times 10^{-4} s^{-1}$*; for* **1d** $\Delta H‡ = 30.1$ *kcal/mol,* $\Delta S‡ = -1.6$ *eu,* $k_{150^\circ} = 8.8 \times 10^{-3} s^{-1}$*. The effect of variation of C3 substituents on the activation parameters for thermolysis paralleled the trend reported for acyclic analogs. The results are consistent with the formation of a (singlet) 1,3-diradical intermediate with subsequent closure to yield the cyclopropanes. The mechanism of diradical formation appears to involve N_2-C_3 bond cleavage as the rate determining step rather than simultaneous two bond scission.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:299–302, 2000

Correspondence to: A. L. Baumstark.
Contract Grant Sponsor: National Science Foundation (NSF).
Contract Grant Number: CHE-9017230.
Contract Grant Sponsor: National Science Foundation (NSF).
Contract Grant Number: CHE-9414136.
Contract Grant Sponsor: GAANN.
Contract Grant Sponsor: GSU Research Fund

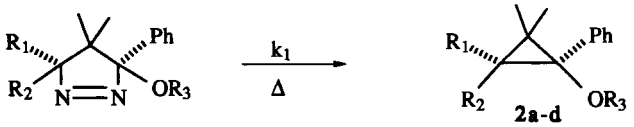
INTRODUCTION

The preparation of acetoxy cyclopropanes plays an important role in organic synthesis [1]. Historically, several general methods for cyclopropane synthesis have been developed. Two of the more common methods involve either "carbene" addition to alkenes [2a] or 1,3-dipolar addition to alkenes to produce pyrazolines which upon thermolysis or photolysis extrude nitrogen to yield cyclopropanes [2b]. These approaches generally are limited to the synthesis of cyclopropanes with four or less substituents [2–3]. Recently, we developed a method for the synthesis of alkoxy or acetoxy hexasubstituted cyclopropanes via thermolysis [4] of hexasubstituted-4,5-dihydro-3H-pyrazoles (pyrazolines). Although substantial investigations of the mechanism of the thermolysis of azo compounds have been carried out, the data on pyrazolines are limited [5–6]. We report here the results of a kinetics study of the thermal decomposition of a series of hexasubstituted-4,5-dihydro-3H-pyrazoles to yield hexasubstituted cyclopropanes.

RESULTS AND DISCUSSION

A series of hexasubstituted-4,5-dihydro-3H-pyrazoles **(1a–d)** were prepared in good yield employing the

procedures developed in our laboratories [4]. Thermolysis of pyrazolines **1a–d** in toluene (under reflux) produced the corresponding hexasubstituted cyclopropanes **2a–d** in essentially quantitative yields (reaction 1) as previously reported under slightly different conditions [4]. For *cis* pyrazolines **1b–c,** no isomerization to the *trans* pyrazolines was detectable during the thermolysis. The cyclopropanes were isolated in good yield and characterized by spectroscopic and physical methods.



1a $R_1 = R_2 = Me, R_3 = Ac$
1b $R_1 = Ph, R_2 = Me, R_3 = Ac$
1c $R_1 = Ph, R_2 = Me, R_3 = Me$
1d $R_1 = R_2 = Ph, R_3 = Ac$

(1)

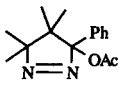
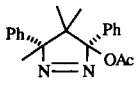
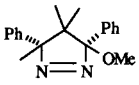
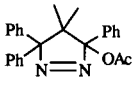
As previously noted [4], the reactions are not stereospecific. The thermolysis of the *cis* compounds, **1b** and **1c,** yielded mixtures of *cis/trans* cyclopropanes **2b** and **2c** with the major product corresponding to retention of stereochemistry (with *cis/trans* ratios of 68/32 and 85/15, respectively).

The thermolysis of **1a–d,** followed by ^{1}H NMR spectroscopy, was carried out in 1,2-dichlorobenzene or diphenyl ether. The reaction was found to be of the first order. The rate of disappearance of pyrazoline was found to be identical to the rate of appearance of cyclopropane. The first order rate constants were determined by monitoring the reaction at constant temperature for at least 2 half-lives. No discoloration was noted during the thermolyses. The only observable products were the cyclopropanes, formed in quantitative yields. The products were confirmed by GC-MS analysis. The relative reactivity series for thermolysis was found to be **1d** $\gg$ **1b** $\sim$ **1c** $>$ **1a.** The rate constants are summarized in Table 1.

The activation parameters for the thermolysis of **1a–d** were determined by the Arrhenius method. As expected from the k_1 data, compound **1d** was found to be the least stable. Compounds **1b** and **1c** were essentially of equal stability and both considerably more stable than **1d.** Pyrazoline **1a** was the most stable of the series. However, the high $\Delta H‡$ value for **1a** is balanced by the relatively large positive $\Delta S‡$ value to yield a $\Delta G‡$ value only slightly higher than that for **1b.** This relative stability series is in agreement with that for pentasubstituted pyrazolines [6d]. The results are summarized in Table 2.

The activation parameters for **1a** are similar to those for the 3,3-dimethyl pyrazoline [7a] ($\Delta H‡$ = 39.1 kcal/mol, $\Delta S‡$ = 11.1 eu). Interestingly, the activation parameters for trans-3,5-diphenylpyrazoline [7b] ($\Delta H‡$ = 27.0 kcal/mol; $\Delta S‡$ = 3.4 eu) are lower than those for the more highly substituted pyrazolines in the present study. This is consistent with previous observations [6b] that 4,4-dimethyl groups increase stability. The magnitude of $\Delta H‡$ (Table 2) seems to be dependent on substitution at C_3 (R_1, R_2). The trend in the $\Delta H‡$'s and $\Delta S‡$'s parallel those found for structurally similar acyclic symmetric azo compounds [5]. The first formal phenyl for methyl substitution results in a decrease in $\Delta H‡$ value. A second formal phenyl for methyl substitution follows the same pattern but with lesser magnitude. The trend noted in $\Delta S‡$ values (decrease) upon increased formal phenyl for methyl substitution also is similar to that noted for acyclic systems [5]. Interpretation of $\Delta S‡$ is always difficult especially considering cor-

TABLE 1 First-Order Rate Constants (k_1) for the Thermolysis of Pyrazolines **1a–d**

Compound	*Structure*	$k_1 s^{-1}$ (10^{+5})	*T ± 1 °C*	*Solvent*[a]
1a		4.8 ± 0.6	149	DPE
		6.8 ± 0.7	150	DCB
		11.8 ± 1.2	157	DPE
		37 ± 1	165	DPE
		47 ± 2	170	DCB
		51 ± 4	170	DPE
		134 ± 15	180	DCB
1b		14.9 ± 1.7	148	DPE
		16.7 ± 1.2	150	DCB
		33 ± 2	157	DPE
		46 ± 3	160	DCB
		79 ± 4	165	DPE
1c		1.8 ± 0.1	132	DCB
		4.1 ± 0.2	139	DCB
		12.4 ± 0.2	150	DCB
		16.3 ± 0.5	152	DCB
		35 ± 2	161	DCB
		56 ± 4	167	DCB
1d		2.2 ± 0.2	91	DCB
		20 ± 1	108	DCB
		43 ± 2	117	DCB
		125 ± 7	128	DCB
		330 ± 15	140	DCB

[a]DPE, Diphenyl Ether; DCB, 1,2-Dichlorobenzene.

TABLE 2 Activation Parameters for the Thermolysis of Pyrazolines **1a,b,d** *at 150°C*

Compound	*ΔH‡ kcal/mol*	*ΔS‡ eu*	*ΔG‡ kcal/mol*	$k_1 s^{-1}$ (*150°C*)
1a	39.8 ± 0.6	14	33.9	6.8×10^{-5}
1b	33.5 ± 1.0	0.2	33.5	1.7×10^{-4}
1c	32.7 ± 0.6	−1.8	33.5	1.2×10^{-4}
1d	30.1 ± 0.3	−1.6	30.8	8.8×10^{-3}[a]

[a]Extrapolated.

responding errors in ΔH‡. However, the lower ΔS‡'s noted for **1b–d** as compared to that of **1a** suggest the loss of degrees of freedom possibly from delocalization into the phenyl group.

The mechanistic interpretation of azo compound/pyrazoline thermolysis data has proven to be complex and difficult. The historical perspective can be obtained from an excellent review by Engel [5]. The classic question of the mechanism for the loss of nitrogen from pyrazolines by either simultaneous breakage of both C–N bonds (one-step) or consecutive breakage of the two C–N bonds (two-step) remains controversial [5,6]. Because pyrazolines **1a–d** are unsymmetrical, one simultaneous two bond cleavage and two consecutive one bond cleavage pathways are possible (Scheme 1).

The product studies are consistent with the formation of a singlet 1,3-diradical intermediate. The preference for retention of configuration in the cyclopropanes is consistent with rapid closure of the diradical. The small quantities of products with loss of configuration could be due to rotation around one of the single bonds in the diradical or could result from rotation of the diazenyl diradical with backside displacement of nitrogen [6d]. The kinetics results clearly show that the thermolytic reaction is sensitive to substitution at C_3 (R_1, R_2). In contrast, the reaction is relatively unaffected by substitution of an alkoxy for an acetoxy group at C_5. It is assumed that differences in ground-state energies are negligible. These results indicate that N_2–C_3 bond scission may be rate determining or at least leading if simultaneous cleavage is operative.

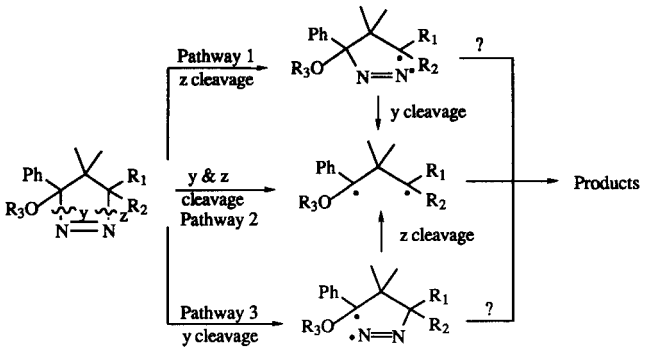
In the present case, additional insight can be gained by analysis of the relative bond energies of N_2–C_3 and N_1–C_5 estimated by a group additivity approach [8] combined with analysis in regard to the activation parameter data. Table 3 contains the calculated bond energies for pathways 1, 2, and 3 (Scheme 1). The calculations for pathway 1 predict the N_2–C_3 bond (z in Scheme 1) to be considerably weaker than the N_1–C_5 bond (y). For Pathway 2 (simultaneous two-bond scission), the calculated bond energies are larger than the observed ΔH‡'s. The results for Pathway 3 suggest that once the y bond is cleaved, the remaining "bond" (z) is extremely weak. In addition, for Pathway 3 two of the calculated bond energies (y) are larger than the observed ΔH‡'s. Pathways 2 and 3 do not seem to fit the data. Pathway 1 appears to be the best description assuming that z cleavage is rate-determining with large ΔH‡ values that mirror that variation in N_2–C_3 bond strength. This requires barrier of y cleavage to be essentially the bond energy for N_1–C_5.

In conclusion, the stability of the pyrazolines parallels that of the N_2–C_3 bond energy suggested of consecutive cleavage of the two NC bonds rather than simultaneous cleavage.

EXPERIMENTAL

All solvents were commercially available and of reagent grade. The syntheses of 5-acetoxy and 5-methoxy-4,4-dimethyl-3,3,5-trisubstituted-4,5-dihydro-3H-pyrazoles **1b–d** and cyclopropanes **2b–d** have been reported [4]. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300-NMR spectrometer in deuteriochloroform unless otherwise specified. Melting points were taken in a Thomas Hoover Unimelt apparatus. The IR spectra were recorded on a Perkin Elmer Paragon 1000 FT spectrometer. MS data were recorded on a Shimadzu QP-500 mass spectrometer coupled to a Shimadzu GC-17A gas chromatograph. Kinetic experiments were carried out on a Varian EM-360 60 MHz NMR spectrometer.

3,3,4,4-Tetramethyl-5-phenyl-5-acetoxy-4,5-dihydro-3H pyrazole, **1a:** m.p. 102–104 (d): yield 63%; ^{1}H NMR: 0.20 (s, 3H), 1.17 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 2.02 (s, 3H), 7.43 (m, 5H); ^{13}C: 16.7, 21.4, 21.5, 23.6, 24.2, 44.2, 92.3, 114.1, 124.4, 128.2, 128.2,



SCHEME 1

TABLE 3 Calculated Bond Energies[a] for Formation of Diradical Intermediates in the Thermolysis of **1a–d**

Compound	*Pathway 1*[b]		*Pathway 3*[b]		*Pathway 2*[b]
	z	y	y	z	overall (both y and z)
1a	17	28	39	6	45
1b	15	28	39	4	43
1c	15	20	31	4	35
1d	13	28	39	2	41

[a]kcals; rounded to nearest whole number;
[b]See Scheme 1.

137.5, 166.4; Anal. Calc for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 68.95; H, 7.70; N, 10.73.

PRODUCT STUDY

The following general procedure is representative. A solution of pure pyrazoline (~0.6 mmol; weight via 4-place balance) in toluene (~5 mL) was heated under reflux (inert atmosphere) for up to 24 hrs. NMR analysis showed the cyclopropanes to be the only observable product. Upon completion the solvent was removed under reduced pressure. The crude cyclopropanes were purified by chromatographic methods or by crystallization from petroleum ether/acetone in good yield. The data for cyclopropanes **2b–d** have been reported [4]. Compounds **2b–d** were isolated in 80+% yields employing this approach.

1-Acetoxy-2,2,3,3-tetramethyl-1-phenylcyclopropane (**2a**) oil: yield 76%; ^{1}H NMR: 1.01 (s, 6H), 1.18 (s, 6H), 1.91 (s, 3H), 7.4 (br, 5H); ^{13}C: 17.5, 20.8, 21.1, 25.2, 70.3, 127.50, 127.54, 132.8, 135.9, 170.7; Anal. Calc for $C_{15}H_{20}O$: C, 77.55; H, 8.68. Found: C, 77.54; H, 8.68; MS *m+/z* 232.

THERMOLYSIS PROCEDURE

The kinetic experiments were performed utilizing the following general procedure. A 14–16 mg sample of pure 3,3,4,4,5,5-hexasubstituted-3H-pyrazole derivative was weighed into a 5 mm NMR sample tube followed by the addition of 6 μL of *p*-bromoanisole (internal standard) and 0.70 mL of diphenyl ether or 1,2-dichlorobenzene. The ^{1}H NMR spectrum was recorded and the signals integrated. The NMR tube was heated at a constant temperature in a silicon oil bath (T $\pm$ 1.0°C). The reaction progress was observed by monitoring the disappearance (^{1}H NMR electronic integration) of the most upfield methyl group signal of the 3-H pyrazole derivative versus that of the methoxy group of the internal standard. For **1b–c,** no isomerization to the *trans* analogs was detected. The NMR sample was placed in an ice bath after removal from the constant temperature bath before and after NMR analysis. The reaction time was taken as the combination of time spent in the constant temperature bath. No discoloration of the solution in the NMR tube was noted during the thermolysis. The cyclopropanes (quantitative yield) were the only observable products (NMR, GC-MS). First-order plots obtained from the data were linear for at least two half lives (correlation coefficients of greater than 0.98). Plot of appearance of product or disappearance of pyrazoline yielded identical k_1 values. Variation between duplicate runs was less than 20% of the value of k_1, and were due to difficulties in maintaining temperature control over extended time periods.

REFERENCES

[1] Wenkert, E. Acc Chem Res 1980, 13, 27.
[2] (a) Maas, G. Top Curr Chem 1987, 137, 75; (b) Padwa, A., Ed. 1,3-Dipolar Cycloaddition Chemistry; John Wiley and Sons: New York, 1984; Vol. 1, p 394.
[3] (a) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. J Am Chem Soc 1990, 112, 1906; (b) Scott, L. T.; Brunsvold, W. R.; Kirms, M. A.; Erden, I. J Am Chem Soc 1981, 103, 5216; (c) Doyle, M. P.; van Leusen, D. J Org Chem 1982, 47, 5326.
[4] Kennedy, G. D.; Baumstark, A. L.; Dotrong, M.; Thomas, T.; Narayanan, N., J Heterocyc Chem 1991, 28, 1773.
[5] For a general review of the mechanism of the thermal decomposition of acyclic and cyclic azoalkenes see: Engel, P. S. Chem Rev 1980, 80, 99.
[6] (a) Recent examples of mechanistic studies on acyclic and cyclic compounds include: Engel, P. S.; Wang, C.; Chen, Y.-Q.; He, S. L.; Andrews, B. K.; Weisman, R. B., J Org Chem 1994, 59, 6257; (b) Adam, W.; Harrer, H. M.; Nau, W. M.; Peters, K. J Org Chem 1994, 59, 3786; (c) Engel, P. S.; Wu, W.-X. J Org Chem 1990, 55, 2720; (d) Nakano, Y.; Hamaguchi, M.; Nagai, T. J Org Chem 1989, 54, 1135; (e) Engel, P. S.; Wang, C.; Chen, Y.; Rüchardt, C.; Beckhaus, H.-D., J Am Chem Soc 1993, 115, 65; (f) Adam, W.; Reinhard, G.; Platsch, H.; Wirz, J., J Am Chem Soc 1990, 112, 4570.
[7] (a) Roth, W. R.; Martin, M. J Liebigs Ann Chem 1966, 88, 3963; (b) Bandish, B. K.; Garner, A. W.; Hodges, M. L.; Timberlake, J. W. J Am Chem Soc 1975, 97, 5856.
[8] (a) Eigenmann, H. K.; Golden, D. M.; Benson, S. W. J Phys Chem 1973, 77, 1687; (b) Benson, S. W. Chem Rev 1978, 78, 23.