THERMOLYSIS OF trans-3-CHLORO-4,4,5-TRIMETHYL-3,5-DIPHENYL-4,5-DIHYDRO-3*H*-PYRAZOLE

Nebiyou Desalegn, Pedro C. Vasquez, Paul J. Franklin, G. Davon Kennedy* and A.L. Baumstark*
Department of Chemistry, Center for Biotech and Drug Design
Georgia State University, Atlanta, Georgia 30303-3083, USA
E-mail: chealb@langate.gsu.edu; Fax : 404-651-1416

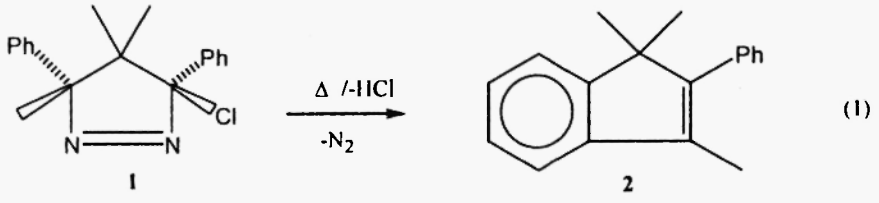
Abstract: The thermal decomposition of trans-3-chloro-4,4,5-trimethyl-2,5-diphenyl-4,5-dihydro-3*H*-pyrazole (**1**) produced 1,1,3-trimethyl-2-phenylindene (**2**) in excellent yield. A kinetic analysis showed that the reaction involved isolable diene intermediate(s) and yielded activation parameters for thermolysis of **1** of: $\Delta H^{\ddagger}$= 32.9 kcal/mole; $\Delta S^{\ddagger}$= -2.4 eu; $\Delta G^{\ddagger}$= 33.9 kcal/mole; k_1 (180 °C) = $1.3 \times 10^{-3} s^{-1}$.

Introduction

Previously as a result of our interest in new oxygen-atom transfer reagents,[1] we developed methodology[2] for the synthesis of highly substituted pyrazolines via 3,4-dihydro-2*H*-pyrazole intermediates. Subsequently, thermolytic decomposition of highly substituted hydroperoxy and acetoxy/alkoxy pyrazolines was shown to provide synthetically useful routes to β,γ-unsaturated ketones[3a] and highly substituted cyclopropanes,[3b] respectively. Recently, we have achieved[4] the synthesis of trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl-3*H*-pyrazole via the unexpected C-halogenation of lithio 3,4,4-trimethyl-3,4-dihydro-3,5-diphenyl-2*H*-pyrazole by tosyl chloride. Limited studies on the thermolysis of halosubstituted pyrazolines have been carried out.[5] We report here a product and kinetics study of the thermal decomposition of trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl-3*H*-pyrazole, **1**.

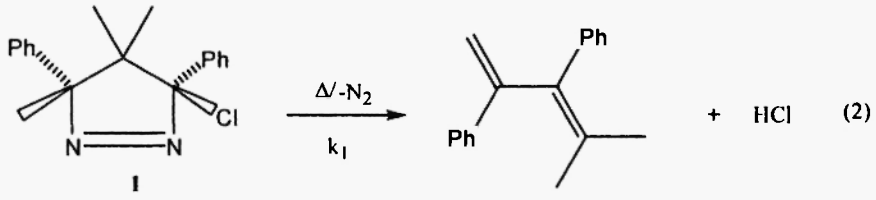
Results and Discussions

The thermal decomposition of trans-3-chloro-4,4,5-trimethyl-3,5-diphenyl-3*H*-pyrazole,**1**, either neat or in 1,3-dibromobenzene was carried out from 150 °C to 200 °C. Evolution of gas (N_2) was observed. Upon complete decomposition, no cyclopropane products were observable; instead, the final product was determined to be 1,1,3-trimethyl-2-phenylindene (**2**), isolated in 96% yield (rxn 1). Compound **2** was identified by comparison of physical and spectroscopic data with published results.[6]



1 **2** (1)

Analysis of reaction mixtures at 150 °C and for those with partial decomposition of **1** at higher temperatures revealed that **2** was not the initial product. Formation of olefinic material was noted which slowly converted to the stable final product (**2**). The initial intermediate major product was isolated in 51% yield and identified[7] as 2,3-diphenyl-4-methyl-1,3-pentadiene **3** (rxn 2). Reaction mixtures containing **3** or isolated samples of **3** treated with HCl gas slowly rearranged upon prolonged heating to indene **2**.



1

3 (major product)

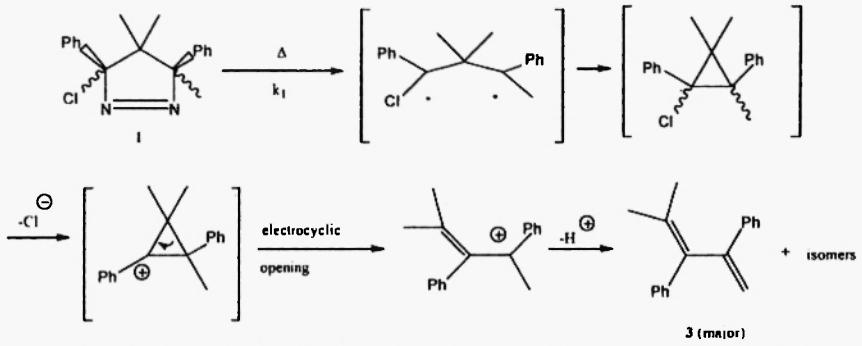
The thermolysis of chloropyrazoline **1** in 1,3-dibromobenzene (monitored by ^{1}H NMR spectroscopy) was carried out at constant temperature (oil bath ± 1 °C from 150 °C to 180 °C). Evolution of (N_2) gas and discoloration of the solution were observed. The rate of disappearance of signals for the starting material was found to be identical to the rate of appearance of product signals. The disappearance of **1** was found to be of the first order. Values of k_1 ranged from 7.3 ± 0.8 x $10^{-5}s^{-1}$ at 150 °C to 1.3 ± 0.1 x $10^{-3}s^{-1}$ at 180 °C. After complete destruction of **1**, the diene intermediate was observed to undergo a slow conversion (days) to indene **2** under the reaction conditions. A thermolysis reaction carried out in the presence of excess added quinoline (base) yielded k_1 values essentially unchanged from those in which the HCl was not neutralized.[8] The activation parameters for thermolysis of **1** were determined by the Arrhenius method. The results were $\Delta H^{\ddagger}$= 32.9 ± 1.0 kcal/mole; $\Delta S^{\ddagger}$= -2.4 eu; $\Delta G^{\ddagger}$= 33.9 kcal/mol and k_1 (150 °C) = 7.3x$10^{-5}s^{-1}$. The results are very similar to those for 5-acetoxy and 5-methoxy pentasubstituted pyrazolines.[3b] The results are summarized in Table-1.

Table-1 : Summary of first order rate constants for the thermal decomposition of pyrazoline **1** in 1,3-dibromobenzene at various temperatures.

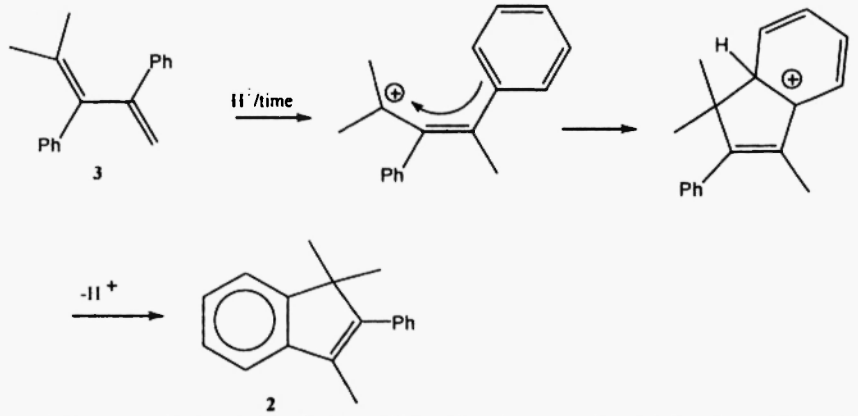
Temp ± 1 °C	k_1 s^{-1} x 10^{+5}	k_{rel}
150	7.3 ± 0.8	1.0
150[a]	7.9 ± 0.4[a]	--
155	19 ± 2	2.6
160	21.2 ± 0.7	2.9
165	32 ± 1	4.4
170	50 ± 3	6.8
180	130 ± 6	17.8

a) in presence of excess added quinoline

Although no direct evidence for cyclopropane formation was obtained, the results can be interpreted assuming the initial formation of thermally unstable chlorocyclopropane intermediate via normal pyrazoline bond scission processes. Subsequent ionic cleavage of the chlorocyclopropane bond followed by electrocyclic ring opening would yield diene **3** (Scheme-1). A straightforward acid catalyzed process can be envisioned from the diene to the final product, indene **2**. Reprotonization of the diene would regenerate the allylic cation which could undergo a straightforward slow intramolecular cyclization (Scheme-2) to yield the acid stable indene.



Scheme-1: Postulated mechanism for formation of isolable diene intermediate(s) via an unstable chlorocyclopropane intermediate.



Scheme-2: Suggested mechanism for the acid-catalyzed conversion of diene **3** to indene **2**.

In conclusion, mechanistically the results are indicative of normal pyrazoline bond scission (loss of N_2) to a diradical, closure of which presumably would yield a thermally labile chlorocyclopropane. The high thermal stability of this type of pyrazoline seems to preclude the isolation of chlorocyclopropanes under thermolytic conditions. Therefore, photolytic processes need to be explored.

Experimental

The synthesis of **1** with an X-ray structure has been previously reported.[4]

Product Studies: After complete decomposition of 25 mg of **1** at 150 °C, ^{1}H NMR analysis showed the products to be 68% diene **3**, 20% indene **2** and several minor olefinic compounds (not isolated, appeared to be isomeric dienes). From thermolysis of a 100 mg sample of **1**, diene **3** was isolated in 51% yield via chromatotron (petroleum ether as eluant). Diene **3** (oil) was identified by MS and NMR data: ^{1}H NMR ($CDCl_3$); 1.82 (s, 3H), 1.84 (s, 3H), 5.15 (d, J=1.5 Hz, 1H), 5.68 (d, J=1.5 Hz, 1H), 7.20-7.60 (m, 10H).[7]

Indene **2** was the only observable product after complete decomposition of 100 mg of **1** at high temperatures (200 °C) neat or in solution or by prolonged heating at lower temperatures. The indene (oil) was isolated in 96% yield (chromatotron). Indene **2** was identified by MS and NMR data: ^{1}H NMR ($CDCl_3$); 1.29 (s, 6H), 1.95 (s, 6H), 7.22-7.55 (m, 9H) and ^{13}C NMR ($CDCl_3$): 11.04, 24.35, 50.95, 119.13, 121.10, 125.09, 126.48, 126.91, 128.11, 129.45, 132.48, 137.05, 143.99, 151.84, 153.09.[6]

Kinetic Studies: A 25 mg sample of **1** was placed in a 5 mm NMR sample tube, followed by an equal molar amount of 2-bromoanisole (internal standard) and 0.500 mL of 1,3-dibromobenzene (Aldrich) as solvent. The

sample tube was capped and sealed with parafilm®. After obtaining an initial NMR spectrum, the sample was placed in a constant temperature silicone oil bath (± 1 °C). The sample was removed from the oil bath at varying intervals depending on the experimental temperature, and was immediately cooled by placing it in a water/ice bath. The progress of the reaction was monitored by ^{1}H NMR integration of the upfield-most signal (Me group) for **1** vs that for the internal standard. The sample was returned to the oil bath to continue the decomposition. Time was taken as the total spent in the oil bath for each point.

Acknowledgments

Acknowledgment is made to the Georgia State University Research Foundation for support of this work.

References and Notes

1. P.C. Vasquez and A.L. Baumstark "The Chemistry of Cyclic α-Azohydroperoxides" in Advances in Oxygenated Processes, Vol. 4, pp 107-129, Ed.: A.L. Baumstark, JAI Press (1995).

2. A.L. Baumstark, M. Dotrong and P.C. Vasquez, *Tetrahedron Lett.* **28**, 1963 (1987).

3. (a) A.L. Baumstark and P.C. Vasquez, *J. Heterocycl. Chem.*, **28**, 113 (1991); (b) G.D. Kennedy, A.L. Baumstark, M. Dotrong, T. Thomas, and N. Narayanan, *J. Heterocycl. Chem.* **28**, 1773 (1991).

4. J. Szwec, P.C. Vasquez, P.J. Franklin, G.D. Kennedy and A.L. Baumstark, *Heterocycl. Comm.* **10**, 133 (2004).

5. (a) For a review please see: P.S. Engel, *Chem. Rev.* **80**, 99 (1980); (b) N. Yoshihiko, M. Hamaguchi and T. Nagai, *J. Org. Chem.* **54**, 1153 (1989).

6. L. Anke and P. Weyerston, *Chem. Ber.* **118**, 617 (1985).

7. (a) J. Böhmer and R. Grigg, *Tetrahedron* **55**, 13463 (1999); (b) A. Padwa, T. Kumagai and M. Tohidi, *J. Org. Chem.* **48**, 1834 (1983).

8. The presence of excess quinoline appeared to stop the conversion of **3** to **2**.

Received on June 2, 2005