

The Lilly Research Laboratories

Thermal Fragmentation of 3,5-Diaryl-1,2,4-oxadiazoles

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3,5-Diaryl-1,2,4-oxadiazoles have been shown to undergo thermal fragmentation, and the pathway for the transformation is discussed.

3,5-Diaryl-1,2,4-oxadiazoles, since the early work of Tiemann, have been renowned for their stability and unreactiveness (1). It was claimed (2) that 3,5-diphenyl-1,2,4-oxadiazole could be distilled without decomposition at atmospheric pressure.

We have investigated the thermal stability of 3,5-diaryl-1,2,4-oxadiazoles and have found that slow distillation at atmospheric pressure of 3,5-diphenyl-1,2,4-oxadiazole gave phenyl isocyanate. In order to follow the course of the fragmentation, two unsymmetrically-substituted diaryl 1,2,4-oxadiazoles were thermolyzed.

3-(*p*-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole heated in a vessel at 250° with a flame (3) yielded benzonitrile, *p*-chlorophenyl isocyanate, and a solid (4) melting at 312°. In a similar fashion thermolysis of 3-(*p*-chlorophenyl)-5-(*p*-methoxyphenyl)-1,2,4-oxadiazole gave *p*-methoxybenzonitrile, *p*-chlorophenyl isocyanate, and the same solid (4), m.p. 312°. It is proposed that the reaction follows the sequence given below (5). The fragmentation is visualized as a reversal of the 1,3-dipolar addition of benzonitrile oxides and aryl cyanides to give 3,5-diaryl-1,2,4-oxadiazole (6). The rearrangement of the nitrile oxide to the isocyanate (7) seemingly displaced the equilibrium away from the oxadiazole ring system.

We recently examined a sample of 3-phenyl-1,2,4-oxadiazole that had been stored at room temperature for ten years. This material had been prepared by the reaction of benziminohydroxamic acid and triethyl orthoformate (8) which were heated under

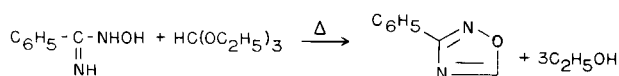
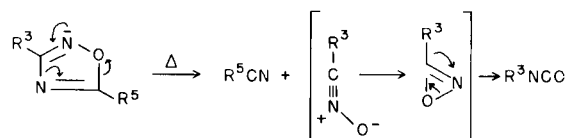
reflux for two hours. The yield was decreased by long heating, and benzonitrile was formed. The material that was placed in storage was very pure with no indication of nitrile in its infrared spectrum. On examination a decade later the product contained benzonitrile.

A sample of 3-phenyl-1,2,4-oxadiazole was heated at atmospheric pressure, while a stream of nitrogen was passed through the system and bubbled into concentrated ammonium hydroxide. Rapid decomposition took place at an internal temperature of 200°. A liquid and a solid remained, and these were identified as benzonitrile and cyanuric acid (9). The ammonia solution was evaporated on a steam bath, and the product was shown to be urea. Most of the cyanic acid was trimerized to cyanuric acid, but that which was swept into the ammonia formed ammonium cyanate that was rearranged to urea according to the classical findings of Woehler in 1826.

The thermolysis of 3-phenyl-1,2,4-oxadiazole seemingly involved a cleavage of different bonds of the 1,2,4-oxadiazole system than were cleaved in the fragmentation of the 3,5-diaryl-1,2,4-oxadiazoles that were studied (10).

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EXPERIMENTAL

3-Phenyl-1,2,4-oxadiazole.

A solution of 13.6 g. (0.1 mole) of benziminohydroxamic acid (11) and 100 ml. of triethyl orthoformate was heated under reflux for two hours. Distillation under reduced pressure gave 3-phenyl-1,2,4-oxadiazole (8,9), b.p. 100°/10 mm., yield 60%. Longer heating of the reactants resulted in a decrease in the yield of oxadiazole and formation of benzonitrile. A pure sample of 10 g. of 3-phenyl-1,2,4-oxadiazole, after being stored in a stoppered bottle for 10 years, contained about 1 g. of benzonitrile.

3-(*p*-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole.

This compound was prepared according to the general procedure of Clarke (12) starting with *p*-chlorobenziminohydroxamic acid (11) and benzoyl chloride. The product melted at 110°.

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.53. Found: C, 65.80; H, 3.48.

3-(*p*-Chlorophenyl)-5-*p*-methoxyphenyl-1,2,4-oxadiazole.

The compound was prepared from *p*-chlorophenylbenziminohydroxamic acid (11) and anisoyl chloride according to the general procedure of Clarke (12). The product melted at 155-157°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.87; N, 9.77. Found: C, 62.59; H, 3.96; N, 9.56.

Thermolysis of Aryl-1,2,4-oxadiazoles.

1. A sample of 3,5-diphenyl-1,2,4-oxadiazole (12) was distilled very slowly at atmospheric pressure. In addition to starting material in the distillate, phenyl isocyanate was also identified.

2. A 14 g. sample of 3-(*p*-chlorophenyl)-5-phenyl-1,2,4-oxadiazole was heated at atmospheric pressure to about 250° by means of a flame. After the exothermic reaction had subsided, the residue was distilled. About 5 g. each of benzonitrile and *p*-chlorophenyl isocyanate were obtained in addition to a solid that was identified as *N,N*-bis(*p*-chlorophenyl)urea (13), m.p. 312°.

3. A 10 g. sample of 3-(*p*-chlorophenyl)-5-(*p*-methoxyphenyl)-1,2,4-oxadiazole was heated to about 250°, and an exothermic reaction resulted. Distillation under reduced pressure gave about 2 g. each of *p*-methoxybenzonitrile and *p*-chlorophenyl isocyanate. The residue yielded 1 g. each of *N,N*-bis(*p*-chlorophenyl)urea (13) and starting material.

4. A 12 g. sample of pure 3-phenyl-1,2,4-oxadiazole was placed in a flask equipped with a nitrogen inlet tube and an air condenser connected to a trap containing concentrated ammonium hydroxide. As nitrogen was passed through the system, the flask was heated to about 200°, by means of a flame, and an exothermic reaction ensued. A solid was formed in the condenser and vigorous bubbling occurred in the ammonia. The solid residue was identified as cyanuric acid and the liquid residue was distilled to give 6 g. of benzonitrile. The ammonium hydroxide solution was evaporated on a steam bath, and the residual product was urea.

REFERENCES

(1) For a recent excellent review of the chemistry of 1,2,4-oxa-

diazoles, see F. Eloy, *Fortschr. Chem. Forsch.*, **4**, 807 (1965).

(2) F. Tiemann and P. Kruger, *Ber.*, **17**, 1685 (1884).

(3) When a sample was heated in a sealed vessel in an oil bath at 250° for five minutes, it was shown by gas chromatography to be unchanged.

(4) The solid was identified as *N,N*'-bis(*p*-chlorophenyl)urea. Its formation is explained by the addition of moisture, contained in the reaction system, to *p*-chlorophenyl isocyanate to form the corresponding carbamic acid that lost carbon dioxide and yielded *p*-chloroaniline. Addition of *p*-chloroaniline to the isocyanate gave the urea.

(5) In a recent publication on the pyrolysis of 3,5-diphenyl-1,2,4-oxadiazole, J. L. Cotter and G. J. Knight, *Chem. Commun.*, 336 (1966), proposed a concerted cleavage-phenyl migration.

(6a) R. Huisgen, W. Mack, and E. Anneser, *Tetrahedron Letters*, 587 (1961); F. Eloy, *Bull. Soc. Chim. Belges*, **73**, 793 (1964). (b) F. D. Dodge, *Ann. Chem.*, **264**, 178 (1891), in a very interesting study of the thermolysis of 3,4-diphenyl-1,2,5-oxadiazole, found that slow distillation of this compound gave the isomeric 3,5-diphenyl-1,2,4-oxadiazole, benzonitrile, and phenyl isocyanate, thus implicating benzonitrile oxide as an intermediate in the cleavage.

(7a) H. Wieland, *Ber.*, **40**, 1667 (1907); *ibid.*, **42**, 803 (1909), studied the conversion of nitrile oxides to isocyanates and furoxans. (b) G. Grundmann and J. M. Dean, *Angew. Chem.*, **76**, 682 (1964).

(8) M. Arbasino and P. Gruenanger, *Chim. Ind. (Milan)*, **45**, 1238 (1963); *Chem. Abstr.*, **60**, 10672 (1964).

(9) F. Eloy, R. Lenaers, and C. Moussebois, *Chem. Ind. (London)*, 292 (1961).

(10) A referee suggested that the cleavage might be similar to that of the 3,5-diaryl-1,2,4-oxadiazoles followed by the reaction $HCN + R^3CNO \rightarrow R^3CN + HOCN$. This proposal is analogous with the reaction of nitrile oxides and isonitriles reported by P. V. Finzi and M. Arbasino, *Tetrahedron Letters*, 4645 (1965).

(11) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962), general procedure A.

(12) K. Clarke, *J. Chem. Soc.*, 4251 (1954).

(13) F. D. Chattaway and K. J. P. Orton, *Ber.*, **34**, 1073 (1901), reported m.p. 310°.

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