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Thermolysis of 3-Phenyl-5-Arylamino-1,2,4-Oxadiazole and Thiadiazole Derivatives*

Abd El-Aal M. Gaber† and Talaat I. El-Emary

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

Ahmed A. Atalla

Chemistry Department, Faculty of Science, Al-Azhar University, Assiut, Egypt

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ABSTRACT

Thermal reactions of 3-phenyl-5-arylamino-1,2,4-oxadiazoles **I** *and* **II** *were investigated. Neat heating at ca. 250°C for 6 hours afforded H_2O, benzonitrile, arylcyanamides, arylamines, azobenzene, benzimidazole derivatives, and 3,3′-diphenyl-5,5′-bis[1,2,4-oxadiazolyl]. Analogous results were obtained by the thermolysis of 3-phenyl-5-anilino-1,2,4-thiadiazole* **III** *at ca. 200°C for 2 hours. In addition to H_2S, NH_3, and HNCS, phenyl isothiocyanate and thiocarbanilide were obtained. Thermolysis of* **III** *in quinoline as a radical trap gave analogous results but also 2-anilinoquinoline. A free-radical mechanism has been suggested to account for the identified products.* © *1997 John Wiley & Sons, Inc.*

DISCUSSION

During the past 15 years, numerous patents have been issued on the use of 1,2,4-thiadiazole derivatives as fungicides [1], herbicides [2], bactericides [3], and dyes [4]. Also, several 1,2,4-oxadiazoles have been found to be useful as chemotherapeutic agents [5]. Following our interest [6] in pyrolysis reactions of mercapto-1,3,4-oxadiazole derivatives, we have recently reported [7] some examples of pyrolyses of substituted-1,3,4-thiadiazole derivatives. Moreover, the photochemical behavior at 254 nm of some 1,2,4-oxadiazole derivatives in methanol have been reported [8,9]. Thus, the biological effects of 1,2,4-oxadiazole and thiadiazole derivatives have prompted us to investigate the thermolysis of these compounds in order to gain further insight into the scope and mechanism of these reactions. Formation of the various products can be assumed to follow the series of reactions shown in Scheme 1, which involves preliminary homolysis of the N–O bond [10] to form the biradical (ia) through the route (a). The site of bond rupture is also influenced by the resonance stabilization of the resulting radicals.

As shown in Scheme 1, the biradical (ia) may fragment into benzonitrile and an arylaminoamidyl radical. The latter may abstract a hydrogen atom from a suitable source to give an arylurea, which ultimately decomposes under the same conditions to give NH_3, H_2O, and arylcyanamide and benzimidazole derivatives as shown experimentally, or undergo tautomerism to the enol form with subsequent loss of water to form an arylcyanamide. This proceeds in a manner similar to that reported for arylthioureas [11]. The formation of benzimidazole derivatives may be rationalized through heating of the arylcyanamide, possibly with an initial hydrogen shift occurring, with a subsequent intramolecular cyclization as suggested previously [12] (Scheme 1).

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†To whom correspondence should be addressed.

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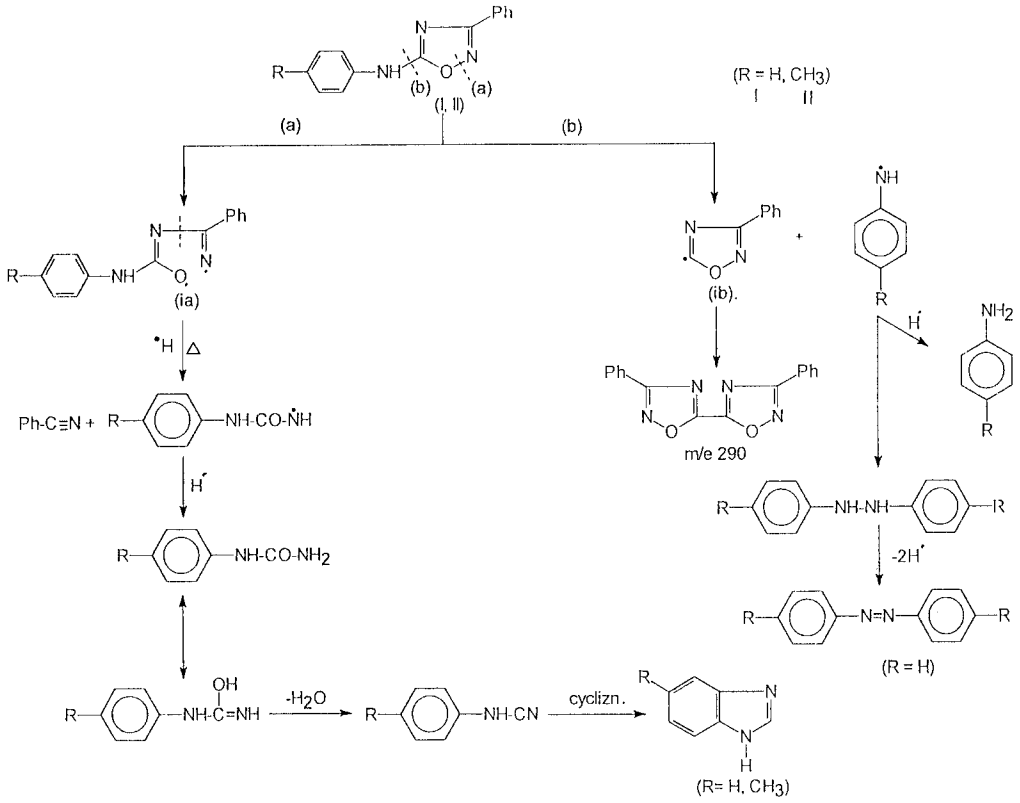


SCHEME 1

Another competing pathway for the thermolysis of 3-phenyl-5-arylamino-1,2,4-oxadiazoles **I** and **II** is the homolysis of the C–N bond by route (b) leading to the formation of arylamino and 3-phenyl-1,2,4-oxadiazolyl (ib) radical pairs. The former may abstract hydrogen from a suitable source to form arylamines. N,N-dimerization of the anilino radicals leads to the formation of hydrazobenzenes that ultimately undergo dehydrogenation into azobenzenes [13], these being thermally stable under the present conditions, as shown experimentally. The 3-phenyl-1,2,4-oxadiazolyl radical (ib) undergoes dimerization to form 3,3′-diphenyl-5,5′-bis[1,2,4-oxadiazolyl] [6], as shown in Scheme 1 and Table 1.

However, we cannot presently account for the formation of another observed product, as detected by the GC/MS analysis, where a compound showing a molecular ion peak at 147 was noted in the pyrolysate of **1**. Its elemental analysis implies the formula (C_9H_9NO); C, 73.47; H, 6.12; N, 9.52%.

Similar results have been obtained on thermolysis of 3-phenyl-5-anilino-1,2,4-thiadiazole **III** at ca. 200°C for 2 hours. This reaction gave H_2S, HNCS, NH_3, benzonitrile as a major product, phenyl isothiocyanate, phenylcyanamide, aniline, thiocarbanilide, and benzimidazole, as shown in Scheme 2 and Table 2.

The formation of NH_3 and phenyl isothiocyanate can be assumed to proceed through the homolysis of the N–S bond via biradical (iia). This forms benzonitrile and the phenylaminothioamidyl radical that can be considered to be the precursor of H_2S, phenyl cyanamide, and benzimidazole. Such products can be interpreted to arise as mentioned for the pyrolysis of **I**.

Another possible pathway for further reaction of the phenylaminothioamidyl radical involves decomposition into ammonia and phenyl isothiocyanate [14] through disproportionation.

Scheme 2 also includes homolysis of the C–N bond by route (b) to give 3-phenyl-1,2,4-thiadiazolyl (iib) and anilino radical pairs. The former may abstract hydrogen from a suitable source to form 3-phenyl-1,2,4-thiadiazole that, under the present conditions, as shown experimentally, gave HNCS and benzonitrile as major products. The formation of benzonitrile by both routes (a) and (b) may be correlated with its high yield among the observed products. A possible pathway for the formation of thiocarbanilide is the interaction of the anilino rad-

TABLE 1 Thermolysis of 3-phenyl-5-arylamino-1,2,4-oxadiazoles **I** and **II**

Decomposition Products	**I** (%)	**II** (%)
H_2O	trace	trace
NH_3	evolved	evolved
Benzonitrile[a]	(20)	(24)
Arylamines	(18)[b]	(22)[c]
Azobenzene[d]	(10)	—
Arylcyanamide	(16)[e]	(20)[f]
Benzimidazole derivatives	(14)[g]	(16)[h]
3,3′-Diphenyl-5,5′-bis[1,2,4-oxadiazolyl][i]	(12)	—
Other product	—	(10)[j]
Unchanged 1,2,4-oxadiazole	(10)	(8)

Expt. **I**: neat thermolysis of 3-phenyl-5-anilino-1,2,4-oxadiazole.
Expt. **II**: neat thermolysis of 3-phenyl-5-toluidino-1,2,4-oxadiazole.
[a]Bp 140–145°C/10 Torr; $_Dn^{20}$: 1.5271; on hydrolysis gave benzoic acid mp and mmp 120°C.
[b]Aniline; bp 75–80°C/10 Torr; acetyl derivative mp and mmp 113°C.
[c]p-Toluidine, bp 70–75°C/3 Torr, mp and mmp 45–46°C; benzoyl derivative mp and mmp 144–145°C.
[d]Bp 180–190°C/5 Torr; mp and mmp 65–67°C.
[e]Phenylcyanamide, mp and mmp 44–46°C.
[f]p-Tolylcyanamide, mp and mmp 70°C.
[g]Benzimidazole, mp 172–174°C; N-acetyl derivative, mp and mmp 113–114°C; N-benzoyl derivative, mp and mmp 93°C; picrate derivative mp and mmp 226–228°C.
[h]5-Methylbenzimidazole, mp 114–116°C; bp 180–185°C/5 Torr; on oxidation with $KMNO_4$ gave benzimidazole-5-carboxylic acid [23], mp $>$ 300°C.
[i]Mixed mp 140–142°C; IR coincident with an authentic sample.
[j]Solid, crystallized from ethanol. Mp 89–70°C, m/e 147; analysis (corresponding to C_9H_9NO): C, 73.47; H, 6.12; N, 9.52%.

ical and phenyl isothiocyanate [15] as shown in Scheme 2. However, it was noted that by the GC-MS analysis, in addition to the previous products, an unidentified compound showing a molecular ion peak at m/e 211 is detected from compound **III**. Its elemental analysis implies the formula ($C_{13}H_9NS$); C, 73.93; H, 4.26; N, 6.64, 15.17%.

Analogous results were also obtained when thermolysis of 3-phenyl-5-anilino-1,2,4-thiadiazole **III** was carried out in the presence of quinoline as a radical scavenger to give, in addition to the previously mentioned products, 2-anilinoquinoline, as shown in Scheme 2 and Table 2. Trapping of the anilino radical by quinoline as a radical trap may be considered as additional evidence for the free-radical reactions.

Preferential homolysis of the N–S bond (Scheme 2) and the N–O bond (Scheme 1) rather than the C–N bond accords with bond dissociation energies being of the order of 115, 150, and 180 Kcal mol^{-1}, respectively [10].

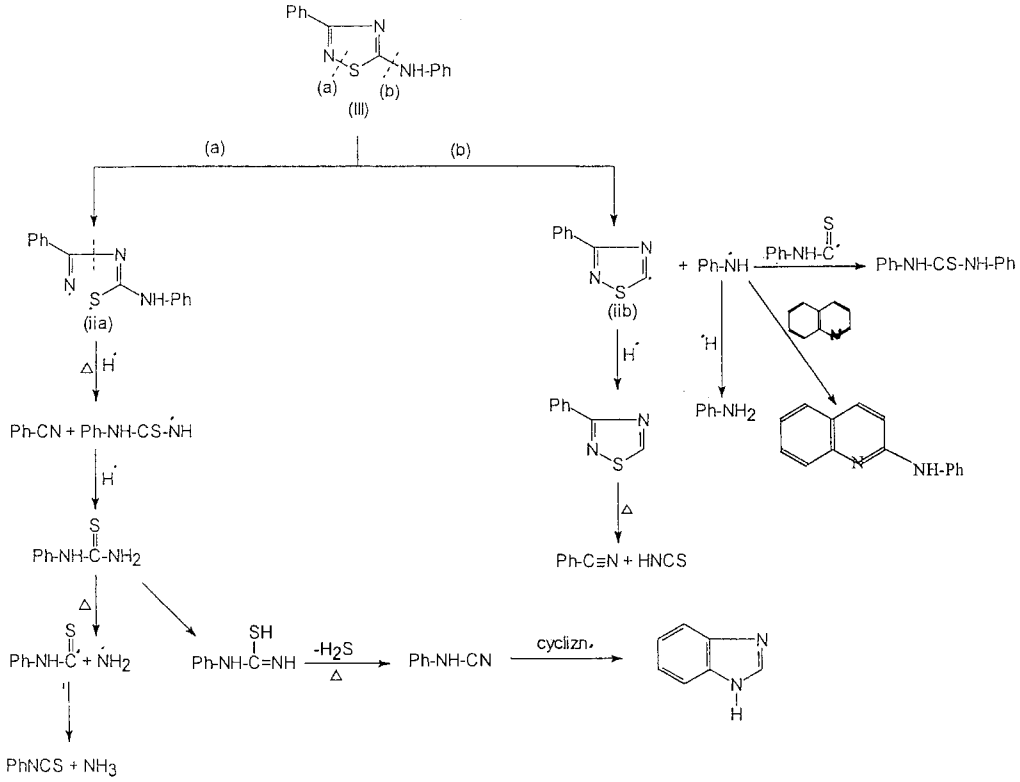
EXPERIMENTAL

All melting points are uncorrected. The IR spectroscopic data were obtained by use of KBr discs on a Pye-Unicam SP 3-100 instrument. TLC was performed using 10 $\times$ 3 cm glass plates coated with silica gel (60–80 mesh) and eluting with ether-pentane (1:9 v/v). Column chromatographic separations were carried out using a 150 $\times$ 2.5 cm glass column packed with Kieselgel 60 (0.040–0.063 mm) using the eluent gradient technique with $CHCl_3$-*n*-hexane, benzene-pet.ether (60–80°C), then ether–pentane mixtures. GLC was carried out on a Perkin-Elmer, Model Sigma 3B apparatus, using a 4 ft $\times$ 4 mm column packed with SE 30 over Chromosorb W (35–80 mesh) or 10% SE on Celite (60–80 mesh) at 200°C, using nitrogen as a carrier gas. Microanalyses were performed using a Perkin-Elmer 240°C microanalyzer. GC-MS analyses were carried out at the National Research Center in Cairo using a Finnigan Mat SSQ7000 spectrophotometer with (5% phenyl)-Methylpolysiloxane with a capillary column length of 30 m.

The following compounds in this study had melting points in accord with literature values: 3-phenyl-5-anilino-1,2,4-oxadiazole **I**, mp 175–177°C, Ref. [19], mp 177°C; 3-phenyl-5-toluidino-1,2,4-oxadiazole **II**, mp 135°C, Ref. [16], mp 136°C; 3-phenyl-5-anilino-1,2,4-oxadiazole **III,** mp 172°C, Ref. [16], mp 174°C.

Thermolysis of 3-Phenyl-5-arylamino-1,2,4-oxadiazoles **I,II**

General Procedure. In a 50 mL round flask equipped with an efficient reflux condenser was placed 5 g (0.02 mol) of each of the 1,2,4-oxadiazole derivatives. The flask was heated for 6 hours at ca. 250°C using a temperature-controlled heating mantle adjusted to the required temperature. The temperature was measured using a thermometer immersed in the reaction flask. The gases evolved were detected by standard means (NH_3 by Nessler's reagent). The pyrolysate was extracted with ether (twice) and benzene (twice), and the whole extract was evaporated on a water bath. The pyrolysate was separated into its constituents by fractional distillation under reduced pressure, whereupon the following compounds were obtained: aniline, p-toluidine, benzonitrile, and phenyl isothiocyanate (in the case of the 1,2,4-thiadiazole decomposition). The residue was treated by silica gel column chromatography to separate the charred materials that remained on the column. The eluents were collected and evaporated, and the products were analyzed by IR, GLC, TLC, elemental analyses, and GC-MS as compared with authentic samples.



SCHEME 2

TABLE 2 Thermolysis of 3-phenyl-5-anilino-1,2,4-thiadiazole **III**

Decomposition Products	**III** (%)	**IV** (%)
HNCS[k]	evolved	evolved
H_2S	evolved	evolved
NH_3	evolved	evolved
Benzonitrile	(24)	(18)
Aniline	(14)	(12)
Phenyl isothiocyanate[l]	(10)	(11)
Thiocarbanilide[m]	(12)	(10)
Phenylcyanamide	(14)	(16)
Benzimidazole	(12)	(11)
2-Anilinoquinoline	—	(13)[n]
Other product	(8)[o]	—
Unchanged 1,2,4-thiadazole(g)	1.4	1.6

See footnotes Table 1.
Expt. **III**: Neat thermolysis of 3-phenyl-5-anilino-1,2,4-thiadiazole.
Expt. **IV**: Heating of compound **III** in the presence of quinoline as a radical scavenger.
[k]HNCS detected by chemical test [17].
[l]Bp 110–115°C/10 Torr; $_D n^{20}$: 1.6265.
[m]Mixed mp 150–154°C.
[n]Eluted by column chromatography using pet ether(60–80°C)-benzene (2:1 v/v), mp and mixed mp 97°C.
[o]Solid, crystallized from methanol, mp 110–113°C; analysis (corresponding to $C_{13}H_9NS$): C, 73.93; H, 4.27; N, 6.64; S, 15.17%; m/e 211.

Thermolysis of 3-Phenyl-5-anilino-1,2,4-thiadiazole **III.** Compound **III** (5 g, 0.02 mol) was heated under reflux at ca. 200°C for 2 hours, wherein H_2S gas was detected by lead acetate. The pyrolysate was separated into its constituents as discussed previously. The results are summarized in Table 2.

Thermolysis of 3-Phenyl-1,2,4-thiadiazole. 3-Phenyl-1,2,4-thiadiazole (0.031 mol) was heated under reflux at ca. 200°C for 2 hours wherein HNCS was detected by chemical means [17]. The products, in the form of dark red viscous oils, were subjected to fractional distillation under reduced pressure to give a colorless oil, bp 41–46°C/3 Torr (3 g, 60%) (benzonitrile and unchanged starting material) (1.5 g).

Thermolysis of 3-Phenyl-5-anilino-1,2,4-thiadiazole **III** *in Quinoline.* Compound **III** (5 g, 0.02 mol) was added to anhydrous boiling quinoline and refluxed for 2 hours. The gases evolved were detected by standard means (NH_3 by Nessler's reagent). The solvent was removed by reduced pressure distillation, and the residue was chromatographed on silica gel with ethyl acetate/benzene (2:8 v/v) as eluent. The

separated products were identified as indicated in a previous work [7] by physical constants, including boiling points, melting points, IR, and GC-MS, and comparison with authentic samples whenever possible. Results are listed in Table 2.

Thermolysis of Phenylurea. Phenylurea (5 g) was heated under reflux at ca. 250°C for 6 hours, wherein NH_3 was detected by Nessler's reagent and H_2O was separated under reduced pressure. The residue was purified by column chromatography using 2% ether-pentane to give a 45% yield of phenylcyanamide and a 12% yield of benzimidazole.

Preparation of Reference Compounds. Thiocarbanilide [18], crystallized from ethanol, mp 154–156°C; 5-methylbenzimidazole [19], crystallized from water, mp 114°C; phenylcyanamide [20], mp 44.46°C; p-tolylcyanamide [20], crystallized from ethanol, mp 69–70°C; 3,3′-diphenyl-5,5′-bis[1,2,4-oxadiazoyl] [21], crystallized from ethanol, mp 142°C; 2-anilinoquinoline [22], mp 96–98°C.

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