Photoinduced Molecular Rearrangements. Some Comments on the Ring-Photoisomerization of 1,2,4-Oxadiazoles into 1,3,4-Oxadiazoles

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The ring-photoisomerization of 3-amino- and 3-methylamino-5-phenyl-1,2,4-oxadiazoles into the corresponding 2-amino- and 2-methylamino-5-phenyl-1,3,4-oxadiazoles has been reinvestigated by examining the effect of a base on the photoreaction. On irradiating at λ = 254 nm in methanol, yields of the ring-photoisomers were found to be significantly enhanced by the addition of triethylamine (TEA) in the photoreaction medium. By contrast, irradiation of the 3-amino-5-phenyloxadiazole in acetonitrile containing TEA gave an almost complete photoreduction into benzoylguanidine, while few percent of the ring photoisomer were detected. Furthermore, the pyrene-sensitized photolysis of 3-amino-5-phenyloxadiazole in acetonitrile containing triethylamine also gave benzoylguanidine but no traces of the ring photoisomer.

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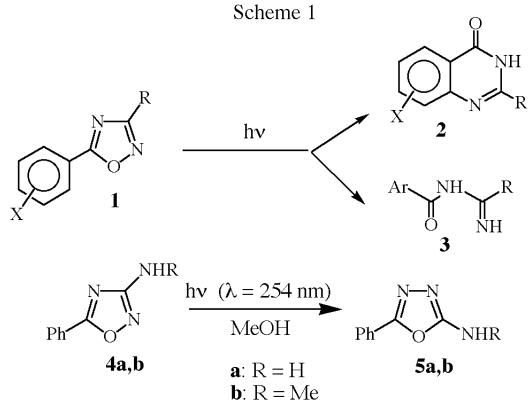
The photochemistry of the 1,2,4-oxadiazole heterocycle suggests that photolytic intermediates arising from the ring O-N bond breaking will develop into different final products depending on their structure and/or experimental conditions [1-6]. Thus, they can stabilize into open-chain compounds in a solvolytic [2,3] or reduction [4] pattern, or they can undergo subsequent heterocyclization reactions with or without involvement of an added reagent [4,5]. In this context, we recently reported [6] that irradiation of some 3-substituted 5-aryl-1,2,4-oxadiazoles **1** in methanol in the presence of different sensitizers or electron-donors such as triethylamine (TEA) gave both heterocyclization to yield **2** by involving the aryl moiety at C-5 of the oxadiazole nucleus and open-chain reduction products **3** in different ratios depending on the structure of intermediates and photoreaction conditions (Scheme 1). This photoreactivity has been explained by assuming a photoinduced electron transfer (either from the sensitizer in its excited state to the oxadiazole substrate or from the electron donor reagent to the excited oxadiazole) producing an oxadiazole radical anion from which breaking of the ring O-N bond takes place.

Scheme 1



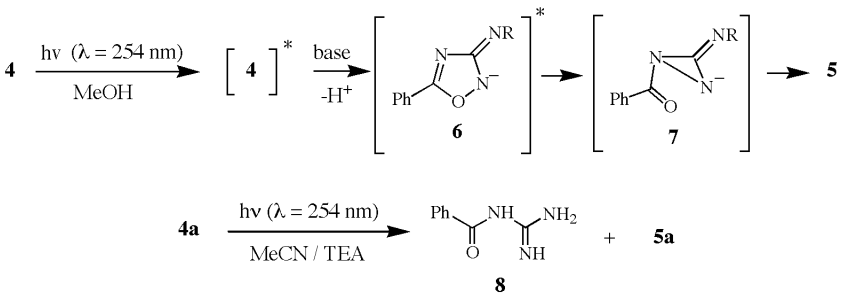
Besides the above photochemistry, ring-photoisomerization of the 1,2,4-oxadiazoles into the corresponding 1,3,4-oxadiazoles has been also reported [3,7] (Scheme 1) and claimed to occur (in low yields, however) only for some structurally defined substrates. In fact, this photoreaction, which has been related to the isoxazole to oxazole photorearrangement and interpreted according to the ring contraction-ring expansion route [8], was found to be dependent on the presence of an XH moiety such as NH_2, NHMe or OH at C(3) of the ring. This restriction suggested that the ring-photoisomerization reaction should involve tautomeric or deprotonated forms in the ground or excited state of the oxadiazole substrate, or in the outcoming three-membered ring intermediate [3].

To verify this hypothesis and get more insight into this peculiar photoreactivity of the 1,2,4-oxadiazole nucleus, we have now reinvestigated the ring-photoisomerization of 3-amino- (**4a**) and 3-methylamino-5-phenyloxadiazole (**4b**) by examining the effect of an added base (such as TEA) to the photoreaction medium [9]. Moreover, in view of results concerning photolysis of 3-substituted 5-aryl-oxadiazoles [6], we became also interested in checking the possibility of an electron-transfer mechanism in the ring-photoisomerization reaction.

Results and Discussion.

Irradiations of compounds **4a** or **4b** at λ = 254 nm in methanol and in the presence of triethylamine (TEA) or methylamine showed that both bases significantly enhance their photoconversion into the ring isomers **5a** or **5b**, respectively, by a comparable extent [10]. A typical experiment carried out on both oxadiazoles **4a** or **4b** showed that, after 1 hour of irradiation yields of the ring isomer (**5a** or **5b**) increase from a few percent in the absence of the base to about 20% when irradiations were carried out in the presence of TEA or methylamine. Analysis of photolysates after 1 hour of irradiation of

Scheme 2



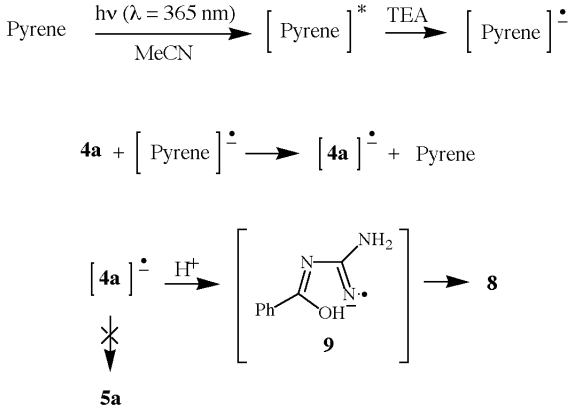
solutions of 3-aminooxadiazole **4a** containing different molar ratios of TEA showed that the photoconversion was markedly accelerated even by the presence of small amounts of the added base (0.1 TEA/oxadiazole molar ratio) and that the concentration of the ring-photoisomer **5a** reaches a maximun value of 20% at a TEA/oxadiazole molar ratio of about 1/2, and remains practically unchanged at higher ratios. Furthermore, upon more prolonged irradiation times, the yield of the ring-photoisomer increased. In fact, a preparative scale photolysis of the oxadiazole **4a** in the presence of methylamine (used instead of TEA to minimize photoreduction processes) gave **5a** in 40% yield. On the other hand, prolonged irradiations of compounds **4a,b** in methanol without added base did not give acceptable preparative results, since the photoreaction was complicated by the formation of side-products.

To explain the above results it is noteworthy to consider the role of the NHR group linked at C(3) of the ring, from which base-catalized tautomeric equilibrium may take place. It is well known [11] that amino-azoles exist predominantly in the amino-form tautomer (at least in the ground state). If one considers the excitation process, we may suppose that the NH moiety of 3-amino- (**4a**) or 3-methylamino-oxadiazole (**4b**) (in their amino or tautomeric imino forms) will show a higher acidity in the excited state than in the ground state; a proton transfer may then occur which would be markedly effected by the presence of a base. Our opinion is that the excited anion **6** could be the key-species collapsing into a diaziridine-type intermediate **7** from which the final ring-isomer would take place (Scheme 2). Involvement of an excited anion agrees with the observation that a high yield of photoconversion also takes place even at low molar ratio of the base. In the case of irradiations in the absence of base, methanol (as amphoteric solvent) can promote the photorearrangement reaction, but to a lesser extent.

Interestingly, it is worthy to note that the effect of the added base was found to be markedly dependent on the solvent used in the photoreaction. Thus, irradiation of **4a** in acetonitrile (MeCN) containing TEA gave an almost complete photoreduction into the benzoylguanidine (**8**), while only a few percent of the ring-isomer **5a** could be detected (Scheme 2). The highly efficient photoreduction observed upon photolysis of **4a** in MeCN/TEA clearly suggests an electron transfer between the electron-donor reagent (TEA) and the oxadiazole in its excited state. The main fate of the resulting oxadiazole radical anion, likely through its protonated form arising from the involvement of the coupled TEA radical-cation, will be the breaking of the ring O-N bond followed by reduction of open-chain intermediate species into the final product **8**. In protic solvent, one could suppose that hydrogen bond formation and solvation effects may change the mode of excited state collapse resulting in its interaction with TEA as a base rather than as a reducing agent.

To search a clear-cut electron transfer mechanism we then examined the pyrene-sensitized photolysis of **4a** in acetonitrile containing TEA. In this case, the pyrene radical-anion (which is formed by an electron transfer from TEA to the excited pyrene) [12] will be the electron-donor species toward the oxadiazole substrate in its ground state [13] (Scheme 3). As expected, this photoreaction gave an almost complete photoreduction to **8**, while no significant amounts of the ring-photoisomer **5a** were detected. Again, the resulting oxadiazole radical-anion will be the precursor of a ring-cleaved intermediate such as **9** which will be converted essentially to **8** in a reduction rather than in a heterocyclization reaction.

Scheme 3



As a conclusive comment, this investigation confirms that the ring-photoisomerization of the 1,2,4-oxadiazole nucleus into the 1,3,4-oxadiazole system can not be considered a general photoreaction since it appears strictly determined by structural features of substituent at C(3) of the 1,2,4-oxadiazole heterocycle as well as by experimental conditions. Further spectroscopic and theoretical investigations are in progress to provide greater understanding of different excited states involved in these reactions and how the electronic transitions depend on the structure of the oxadiazole substrate.

EXPERIMENTAL

For instruments and general procedures see our previous papers [3] [4] [6]. HPLC analyses were performed by using a C-18 SIL X-10 Perkin-Elmer column (25 cm x 4.6 mm diameter) eluting with water/acetonitrile (1/1 mixtures). Triethylamine and pyrene were obtained from Aldrich Chemical Co. Ethanolic (33%) methylamine was obtained from Fluka; anhydrous methanol and acetonitrile from Romil Co. Flash chromatography was performed on Macherey-Nagel silica gel 60 (230-400 mesh).

Photochemical reactions were carried out in anhydrous methanol or in acetonitrile (the solutions were purged by nitrogen bubbling before irradiation) by using a Rayonet RPR-100 photoreactor equipped with 16 Hg lamps irradiating, respectively, at λ = 254 nm (RPR-2537Å) (in quartz vessels) and at λ = 365 nm (RPR-3500Å) (in pyrex vessels), and a merry-go-round apparatus. Experimental conditions (irradiation time and concentration of solutions to be irradiated) have been chosen as to minimize the formation of side-products. However, in each series of experiments, all the parameters involved have been kept homogeneous. Since oxadiazole substrates do not absorb at λ = 365 nm, in the pyrene-sensitized photolysis the sensitizer was the only absorbing species. Quantitative analyses of photolisates were accomplished by HPLC.

Oxadiazoles **4a** [14] and **4b** [7] (which were used for irradiations), and compounds **5a** [15], **5b** [16] and **8** [17] which were used as authentic samples for comparison and HPLC determinations were obtained as reported in the above references.

Irradiations of 3-Amino- (**4a**) and 3-Methylamino-5-phenyl-1,2,4-oxadiazole (**4b**) in Methanol in the Presence of Bases.

A solution of the oxadiazole **4a** or **4b** (0.19 mmol) in methanol (30 ml) was apportioned into three quartz tubes (10 ml each). In two of these samples the appropriate base (methylamine or TEA) (0.13 mmol) was added and all three samples for each oxadiazole substrate were simultaneously irradiated at λ = 254 nm for 1 hour. HPLC analysis of samples irradiated without the base showed the unreacted starting material (about 95%) and few percent (3-5%) of the 1,3,4-oxadiazole **5a** or **5b**, respectively. HPLC analysis of samples irradiated in the presence of bases showed comparable results for both irradiations of **4a** or **4b** (recovered in 80 and 78 % yields, respectively) determining compounds **5a** (20%) or **5b** (22%), respectively.

A solution of compound **4a** (60 mg) in methanol (60 ml) was apportioned into six quartz tubes to which variable amounts of TEA were added as to have increasing molar ratios TEA/oxadiazole from 0.1 to 2. The samples were simultaneously irradiated at λ = 254 nm for 1 hour, and photolysates were analysed by HPLC. The concentration (%) of compound **5a** reaches the maximum value (20%) at the molar ratio TEA/oxadiazole of 0.5, and then remains practically invariated.

Preparative Scale Irradiation of the Oxadiazole (**4a**) in Methanol containing Methylamine.

A solution of compound **4a** (0.2 g) in methanol (200 ml) containing methylamine (0.2 ml) was apportioned in five quartz tubes and then irradiated at λ = 254 nm for 4 hours. After removal of the solvent under reduced pressure, chromatography of the residue (performed with light petroleum:ethyl acetate 1:1) returned starting material (80 mg, 40%), and gave **5a** (80 mg, 40%), mp 242 °C, lit [14] mp 242 °C and **8** (10 mg, 5%), mp 160 °C lit [17] mp 160 °C.

Irradiation of the Oxadiazole (**4a**) in Acetonitrile Containing TEA.

A sample of the oxadiazole **4a** (10 mg, 0.06 mmol) in acetonitrile (10 ml) containing TEA (0.13 mmol) was irradiated at λ = 254 nm for 1 hour. HPLC analysis of the photolysate gave starting material **4a** (10%), benzoylguanidine (**8**) (85%) and the oxadiazole **5a** (5%).

Irradiation of the Oxadiazole (**4a**) in the Presence of Pyrene.

Irradiation of the oxadiazole **4a** (10 mg, 0.062 mmol) in acetonitrile (10 ml) containing pyrene (25 mg, 0.12 mmol) and TEA (0.12 mmol) at λ = 365 nm for 1 hour gave **8** in higher than 95% yields.

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