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SENSITIZED PHOTOREDUCTION OF NITROSOAZOLES ON TITANIUM DIOXIDE

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Abstract - The photosensitized reduction of some 4-nitrosopyrazoles and 4-nitrosoimidazoles using titanium dioxide as a photocatalyst has been investigated. The photoreaction produces the corresponding 4-aminoazoles and assumes an initial electron transfer from the conduction band of the excited titanium dioxide to the nitroso compound, followed by hydrogen transfer from the solvent. The photoreduction reaction takes also place by irradiating nitrosoazoles in the presence of triethylamine in acetonitrile, pointing out the electron transfer also to occur from a ground state donor to the excited nitrosoazole.

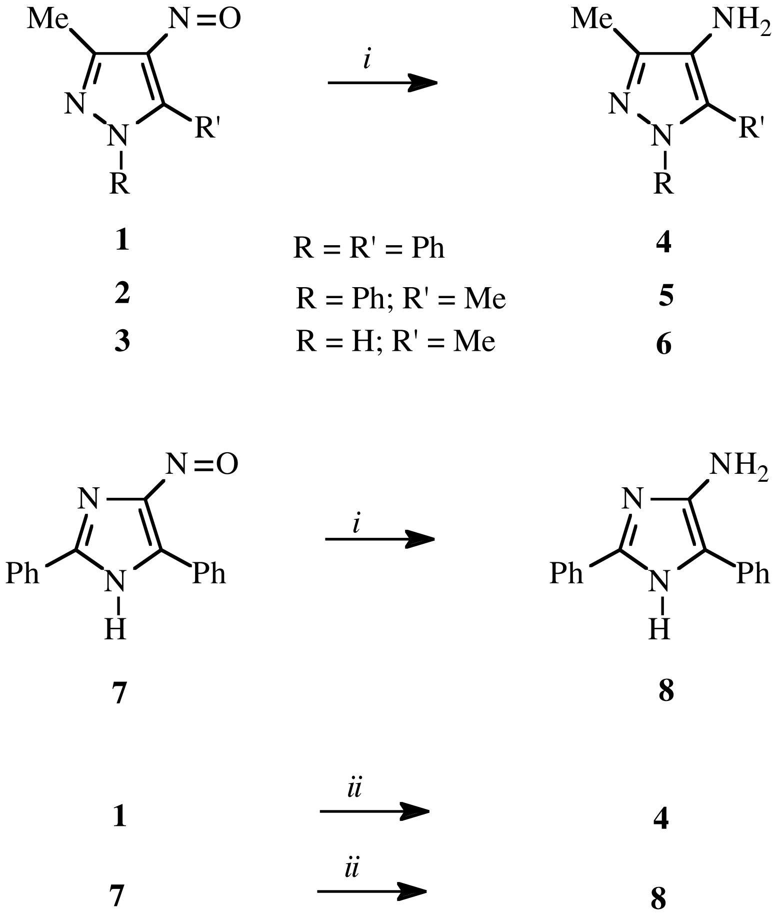
The photocatalytic reactions at semiconductor particles have been receiving increasing attention for synthetic projects: their use in processes involving functional group modifications constitutes a new tool for the organic chemist.[1-8] On the other hand, an interesting point of view regards the question of photodegradation of organic substrates,[3] particularly heterocyclic compounds which are widely used in medicinal and agricultural chemistry. In the frame of our researches regarding the photochemical behavior of five-membered heterocycles,[9] we became interested in the photochemistry of nitrosoazoles, namely nitrosopyrazoles for which an antifungal activity is recognised[10] and nitrosoimidazoles which are considered active form of nitroimidazole drugs used therapeutically.[11] In particular, aiming to exploit semiconductor catalysts in heterocyclic chemistry that is oxidation, reduction, functionalization, we looked at the behavior of these nitrosoazoles toward a semiconductor-assisted photoreduction. As for non-photochemical methods, it is worthy noting that the reduction of 4-nitrosopyrazoles into the corresponding amino compounds is reported to occur by using hydrazine in ethanolic solution,[12] or, in some case, tin and hydrochloric acid;[13] in turn, the reduction of the nitroso-diphenylimidazole (**7**) into the amino compound (**8**) is easily accomplished by using stannous chloride in hydrochloric acid, or ammonium sulfide in ethanol.[14]

The use of a semiconductor catalyst in a photoreduction reaction has been reported for aliphatic and aromatic nitro compounds which were transformed into the amino compounds.[7] The reaction is accomplished by using titanium dioxide (TiO_2; anatase) in alcoholic solvent, and has been interpreted as proceeding through the corresponding nitroso and hydroxylamino derivatives as intermediates. In a generalized pattern of the photoreduction process, irradiation of titanium dioxide promotes one electron from the valence band to the conduction band.[7,8] The electron in the conduction band is readily available for transference and then the acceptor will be reduced, while the electron hole in the valence band is open for donation and then the donor will be oxidized. In the above cited case, the photoreduction of the nitro compound is coupled with the oxidation of the alcoholic solvent, while concomitant formation of molecular hydrogen takes place.[7] In this note we report preliminary results concerning with the photoreduction of 4-nitrosopyrazoles (**1-3**) and 4-nitroso-diphenylimidazole (**7**) on semiconductor photocatalyst (TiO_2). In addition, a preliminary assay of the photoreduction of nitrosoazoles by using ground state electron donor (e.g. triethylamine) is also presented.

RESULTS AND DISCUSSION

Irradiation (with RPR-3500Å Hg lamps) of a suspension of titanium dioxide in ethanol containing the 1,5-diphenyl-3-methyl-4-nitrosopyrazole (**1**) produces the corresponding 1,5-diphenyl-3-methyl-4-aminopyrazole (**4**). Similarly, the 1-phenyl-3,5-dimethyl- (**2**) and the 3,5-dimethyl-4-nitrosopyrazole (**3**) give the corresponding 4-aminopyrazoles (**5**) and (**6**), respectively. When comparatively irradiated in the absence of TiO_2, compounds (**1-3**) remained unchanged, thus indicating that the semiconductor really acts as a photosensitizer in the photoreduction reaction.

Scheme



Reaction Conditions

i : hν/(RPR-3500Å Hg lamps)/EtOH/TiO$_2$; *ii* : hν/(RPR-2537Å Hg lamps)/MeCN/TEA

In some cases, during the irradiation of compounds (**1-3**) in the presence of titanium dioxide, the fast consumption of the starting substrate is not coupled with a comparable increase of the amine formed. TLC and HPLC analyses of the first-stage photolysate showed the formation of intermediate species developing into the final amino compounds by continuing irradiation. However, because of photodegradation processes, or interferences by a greatly-absorbing intermediate, preparative-scale photoreactions allowed to isolate the reduced amino compounds (**4-6**) in low yelds (about 40-50%) largely depending on experimental conditions such as concentration of starting material and irradiation time. Similar results have been observed in the semiconductor-assisted photoreduction of the nitrosoimidazole (**7**) from which the amino derivative (**8**) was isolated in about 40% yield.

To obtain informations on the efficiency of the photoreduction, irradiations on analytical scale were carried out and photolysates have been analized by HPLC. Since the efficiency for the reduction is generally increased when the concentration of the starting substrate decreases, a 10^{-3} M concentration of the nitroso compound has been chosen for all substrates, while an excess of titanium dioxide was used to ensure that light is absorbed by the semiconductor. The results are shown in Figure 1. In all the cases the concentration of the amine reaches a maximum value, and then decreases. Significantly, the structure of the nitroso compound affects the efficiency of the process, likely affecting the reduction potential of the substrate or of a resulting key-intermediate; in turn, the photoreactivity of the resulting amino compound will depend on its structure.

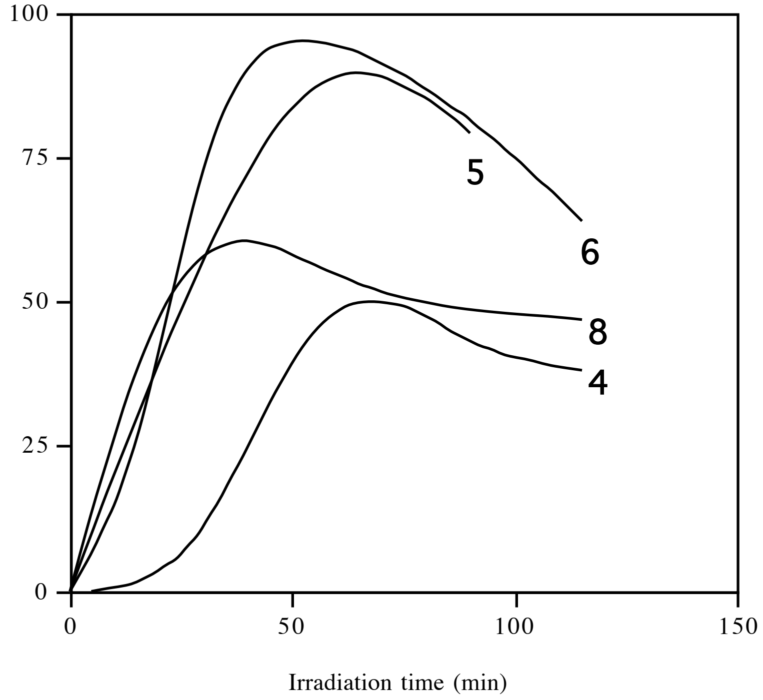


Figure 1 - Change in the concentration of amino compounds (**4**), (**5**), (**6**), and (**8**) (% values referred to starting material), with irradiation time in the titanium dioxide-sensitized photolysis of nitrosoazoles (**1**), (**2**), (**3**), and (**7**), respectively.

As anticipated, the formation of aminoazoles may be explained by assuming an electron transfer from the conduction band of the excited semiconductor toward the nitroso substrate, followed by hydrogen transfer from the solvent. The fact that the mechanism may occur through an electron transfer from a suitable donor was checked irradiating nitrosoazoles in the presence of triethylamine as a ground state donor.[15] To this aim we tested irradiation of the representative nitrosopyrazole (**1**) which shows an intense absorption at the $\lambda = 254$ nm. As expected, irradiation of compound (**1**) with RPR-2537Å Hg lamps in the acetonitrile and in the presence of an excess of triethylamine gave the aminopyrazole (**4**). Clearly, in the reduction pathway, the hydrogen transfer could take place from the resulting triethylamine-radical-cation. Again, preparative scale experiments gave low yields (31%) of the amino compound, while analytical irradiations showed the formation of **4** in 70% yield by HPLC. Similarly, analytical irradiation (at $\lambda = 254$ nm) of the nitrosoimidazole (**7**) in acetonitrile containing triethylamine, and HPLC analyses of photolysate, besides starting material (40%), gave the amino compound (**8**) (60%). However, isolation of **8** from a preparative-scale irradiation was frustrating probably because of its higher decomposition in the MeCN/TEA photoreaction medium and in the work-up of such reaction mixture. Further studies might be useful to a complete understanding of the role of different parameters in the photoreaction.

EXPERIMENTAL

Irradiations were carried out by using a Rayonet RPR-100 photoreactor equipped with 16 RPR-2537Å (quartz vessels) or RPR-3500Å (pyrex vessels) Hg lamps. HPLC analyses were performed by using a Shimadzu LC-10APVP instrument and a Nucleosil 120-5-C_{18} Macherey-Nagel column. Ethanol (95%), anhydrous acetonitrile, and triethylamine were obtained from Aldrich Chemical Co. Titanium dioxide (anatase) was obtained from Merck. Flash chromatography was performed on Macherey-Nagel silica gel 60 (230-400 mesh).

Nitroso compounds (**1**),[16] (**2**),[17] (**3**),[17] and (**7**)[18] which were used for irradiations, and amino compounds (**4**),[12] (**5**),[12] (**6**),[12] and (**8**)[14] which were used for comparison, were prepared as reported.

General Procedure for Irradiations of Nitroso Compounds with Titanium Dioxide : Analytical Scale

In a 50 mL Pyrex tube equipped with a magnetic stir bar were mixed 0.04 mmol of the nitroso compound (**1-3,** or **7**) and 40 mL of a suspension of 2.5 g/L of TiO in 95% ethanol. The mixture was purged with nitrogen and then irradiated with RPR-3500Å Hg lamps under continuous nitrogen bubbling and stirring. At different interval time, 0.4 mL of samples of the reaction mixture were taken, filtered with an 0.2 μm HPLC syringe filter and analyzed by HPLC. Results are presented in the Figure 1.

General Procedure for Irradiations of Nitroso Compounds with Titanium Dioxide : Preparative Scale

In an appropriate Pyrex flask equipped with a magnetic stir bar were mixed a sample of the nitroso compound (**1-3,** or **7**) and an excess of a suspension of 2.5 g/L of TiO_2 in 95% ethanol. The mixture was purged with nitrogen and then irradiated with RPR-3500Å Hg lamps under continuous nitrogen bubbling and stirring. After the irradiation, the mixture was centrifuged, filtered to remove TiO_2 particles, and then the solvent was removed under reduced pressure and the residue chromatographed.

Irradiation of compound (1)

Irradiation of compound (**1**) (0.16 g, 0.6 mmol) in 600 mL of the TiO_2 suspension for 3 h, and chromatography by using light petroleum-ethyl acetate mixtures gave **4** (60 mg, 40%), mp 104°C (from water) (lit[12] mp 104°C).

Irradiation of compound (2)

Irradiation of compound (**2**) (0.16 g, 0.8 mmol) in 600 mL of the TiO_2 suspension for 4 h, and chromatography by using light petroleum-ethyl acetate mixtures gave **5** (75 mg, 50%), mp 65°C (from light petroleum) (lit[12] mp 68°C).

Irradiation of compound (3)

Irradiation of compound (**3**) (0.25 g, 2.0 mmol) in 400 mL of the TiO_2 suspension for 4.5 h, and chromatography by using ethyl acetate and ethyl acetate-methanol mixtures gave **6** (110 mg (50%), mp 203°C (from ethanol) (lit[12] mp 203-204°C).

Irradiation of compound (7)

Irradiation of compound (**7**) (0.15 g, 0.6 mmol) in 600 mL of the TiO_2 suspension for 3 h**,** and chromatography by using light petroleum-ethyl acetate mixtures gave **8** (56 mg, 40%), mp 160°C (from benzene) (lit[14] mp 162°C).

Irradiations in the Presence of Triethylamine (TEA)

To a sample of the nitroso compound (**1**) (20 mg, 0.08 mmol) in 40 mL of anhydrous acetonitrile, purged with nitrogen, a large excess of TEA (0.22 mL, 1.6 mmol) was added and then the mixture was irradiated with RPR-2537Å Hg lamps for 30 min. HPLC analyses of the photolysate gave starting material (30%)

and the amino compound (**4**) (70%). Similar irradiation of the nitroso compound (**7**), and HPLC analyses of the photolysate gave starting material (40%) and the amino compound (**8**) (60%). A preparative-scale irradiation [200 mg of **1**, in 160 mL of acetonitrile and 2 mL of TEA, apportioned in 4 quartz tubes, irradiated for 1 h] and chromatography allowed to isolate 60 mg (31%) of the amino compound (**4**).

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