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Synthesis and Photochemical Behaviour of 4-Nitroimidazoles in the Presence of Oxygen

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Abstract: Synthesis and photochemical properties of 1-aryl-4-nitroimidazoles are described. These compounds are good sensitizers of superoxide ion. Only 1-phenyl-2-methyl-4-nitroimidazole is a photosensitizer of singlet oxygen.

During the last three decades nitroimidazoles as a class of compounds have attracted much attention. They have been used in therapy against amoebic, trichomonal, giardial, and anaerobic bacterial infections, as antabuse agents,[1] and as hypoxic cell radiosensitizers in cancer therapy.[2] Demonstrations of the mutagenic and carcinogenic properties of certain nitroimidazoles have diminished interest in synthesis of new 2- and 5-nitroimidazoles[3] and have increased interest in less mutagenic 4-nitro isomers.[4]

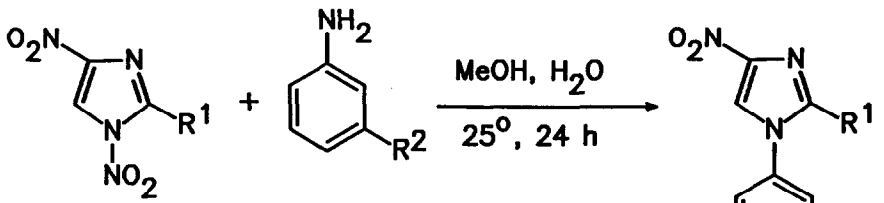
The interaction between nitroimidazoles and oxygen has been studied showing that several nitroimidazoles can inhibit cellular oxygen utilization.[5] Nevertheless, some other compounds stimulate cellular oxygen utilization and some have no effect.[6] The interaction of nitroimidazoles with oxygen has been explained assuming that nitrocompounds are catalysts of superoxide production.[7] This effect can involve the formation of nitro radical anion of the substrate. The compounds which have the greatest therapeutic effect as hypoxic cell radiosensitizers in animals are those which least interfere with cell respiration.[8] In fact

modification of cell respiration by nitroimidazoles can be involved in the mechanism of their cytotoxicity in well oxygenated cells.

In this context we have studied the interaction between 4-nitroimidazoles and oxygen under photochemical conditions. This study could give useful information to understand the behaviour of nitroimidazoles in the presence of oxygen.

The photochemical behaviour of nitroimidazoles has not been widely investigated. It is known the replacement of nitro group with cyano, while the behaviour in the presence of singlet oxygen has been studied only with simple imidazole derivatives.[9]

1-Aryl-4-nitroimidazoles **3** with a free five position in imidazole ring have been obtained from appropriate 1,4-dinitroimidazoles **1** and anilines **2** by the novel degenerated imidazole ring transformation reaction described earlier by one of us.[4,10] Amination of 2-methyl-4-nitro-1-phenylimidazole (**3c**) with 4-amino-1,2,4-triazole (**4**) in dimethylsulfoxide in the presence of sodium methanolate has yielded 5-amino-



1a: $R^1 = H$ **2a**: $R^2 = H$

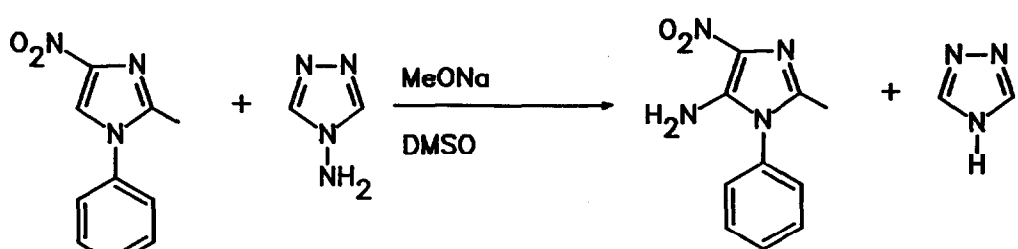
1b: $R^1 = CH_3$ **2b**: $R^2 = Cl$

3a: $R^1 = R^2 = H$

3b: $R^1 = H, R^2 = Cl$

3c: $R^1 = CH_3, R^2 = H$

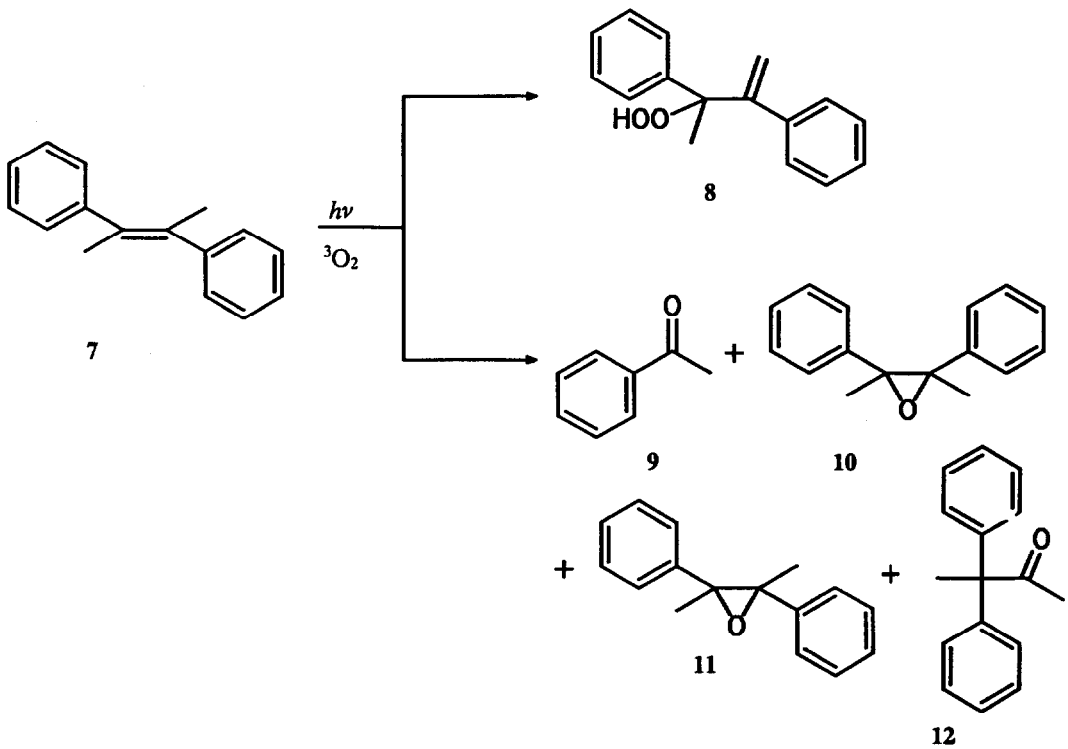
3d: $R^1 = CH_3, R^2 = Cl$



3c **4** **5** **6**

2-methyl-4-nitro-1-phenylimidazole (**5**) in a process being a modification of the known method used for amination of nitroarenes.[11,12]

Compounds **3a-d** and **5** were used as substrate in the following experiments. It was reported that the irradiation of *trans*-α,α'-dimethylstilbene (**7**) in acetonitrile in the presence of both oxygen and a suitable sensitizer gave only compound **8** when the sensitizer can produce singlet oxygen *via* an energy transfer process, while, if the sensitizer can give an electron transfer process, superoxide ion can be produced and then a completely different product mixture was obtained.[13]



This type of reaction allows us to distinguish between type I and type II photooxidation (Scheme 1).[14] Clearly type I photooxidation is very similar to the proposed mechanism for the interaction between nitroimidazoles and oxygen in the cells.

The irradiation of a 5 x 10^{-2} *M* solution of **7** containing 2 x 10^{-4} *M* **3a-d** and **5** in acetonitrile in a Pyrex tube at 13°C for 2 h with a high pressure mercury arc furnished a mixture which was analyzed by both ^{1}H-NMR and GC-MS. The results are reported in the Table.

Scheme 1

Type I

$$\text{Sens} + h\nu \longrightarrow {}^1\text{Sens}$$
$${}^1\text{Sens} + \text{S} \longrightarrow {}^1(\text{Sens}^{\cdot-}/\text{S}^{+\cdot})$$
$${}^1(\text{Sens}^{\cdot-}/\text{S}^{+\cdot}) \longrightarrow \text{Sens}^{\cdot} + \text{S}^{+\cdot}$$
$$\text{Sens}^{\cdot-} + {}^3\text{O}_2 \longrightarrow \text{Sens} + \text{O}_2^{\cdot-}$$
$$\text{S}^{+\cdot} + \text{O}_2^{\cdot-} \longrightarrow \text{Oxidation products}$$

Type II

$$\text{Sens} + h\nu \longrightarrow {}^1\text{Sens}$$
$${}^1\text{Sens} + {}^3\text{O}_2 \longrightarrow {}^3\text{Sens} + {}^1\text{O}_2$$
$${}^3\text{Sens} + {}^3\text{O}_2 \longrightarrow \text{Sens} + {}^1\text{O}_2$$
$${}^1\text{O}_2 + \text{S} \longrightarrow \text{Oxidation products}$$

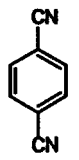
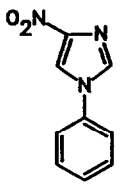
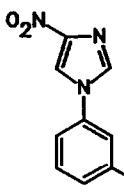
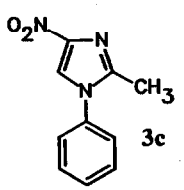
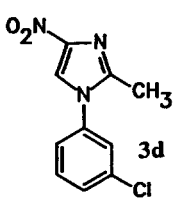
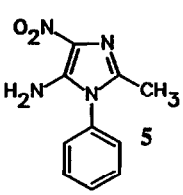
Sens = sensitizer
S = substrate

We used 1,4-dicyanobenzene as reference: in this case, in agreement with the behaviour shown by DCA,[13] most of the product derived from singlet oxygen oxidation of the substrate. By using **3a, 3b, 3d,** and **5** as substrate we observed a net increase of superoxide ion mediated oxidation of **7**. Compounds **3a** and **3b** gave almost the same distribution product. Compound **5** gave only superoxide ion mediated oxidation products. Surprisingly **3c** did not follow the same behaviour. This compound gave almost quantitative yields of compound **8** deriving from singlet oxygen oxidation of **7**.

The preferential formation of compounds **9 - 12** in the photochemical oxidation of **7** sensitized by compounds **3a, 3b, 3d,** and **5** is in agreement with the low value of reduction potential reported for these type of compounds.[15-17] In particular the reduction potential for **3a** and **3d** was - 0.32 and - 0.33 V respectively. These compounds are very good sensitizers of superoxide ion and this behaviour is in full agreement with the observation that radiosensitizing efficiency of nitroimidazoles increased with the rise of their reduction potential.[16]

However several cases of nitroimidazoles with both high radiosensitizing ability and low value of reduction potential were reported.[16] In this case **3c** seems to behave in the same manner. In fact, this compound is a singlet oxygen sensitizer in spite of a reduction potential of - 0.39 V. Furthermore, electron transfer process can be estimated by using the Weller equation.[18] In this equation ΔE_{exc} and $E_{1/2}^{Red}$ represent

Table

Substrate	λ_{max} (nm)	E^{Red} (V)	A:B [a]
		– 2 [b]	71:29
 3a	292	– 0·32	20:80
 3b	297	-----	23:76
 3c	299	– 0·39	95:5
 3d	306	– 0·33	30:70
 5	364	----	0:100

a) A: percent of products deriving from singlet oxygen oxidation of 7; B = percent of products deriving from superoxide ion oxidation of 7; b) Mariano, P. S.; Stavinoha, J. L. in *Synthetic Photochemistry*, Ed. by W. H. Horspool, Plenum Press, New York, 1984, p. 145.

the variables when we change the sensitizer. Nevertheless, both the variables estimated by the UV spectrum and the voltammetric peak value respectively did not show any significant variation.

Clearly the different reactivity can not be ascribed to the thermodynamics of the process. The difference must be due to a kinetic effect. The only remarkable difference found in the properties of the substrates was the little difference in the reduction potential. This difference can be due to a conformational one. On the basis of molecular mechanics calculations (Alchemy II, Tripos Associates) we have found that, while in the most stable conformation compounds **3a** and **3b** were planar, the most stable conformations in **3c** was obtained in the presence of a dihedral angle between the two aromatic rings of 21.2°. This situation can inhibit the participation of the phenyl ring in the stabilization of the radical ion and then induce the observed kinetic effect.

Finally, we have observed during the photoreaction of *trans*-α,α'-dimethylstilbene with our sensitizers an extensive *cis-trans* isomerization of the substrate. Probably this effect, not reported when DCA was used as sensitizer,[13] was due to an exciplex formation. This behaviour using DCA was observed in carbon tetrachloride, while we observed this effect in acetonitrile. Clearly, this behaviour must be due to the different stability of the exciplexes in this solvent.

In conclusion, we have found that, in spite to previous reported data on the reactivity of imidazoles towards singlet oxygen, 4-nitroimidazoles can be used as sensitizers in photochemical oxidations. Furthermore, we have found that little changes in the structure can dramatically modify the type of the reactivity of the substrate.

Experimental

1,4-Dinitroimidazole and 1,4-dinitro-2-methylimidazole were prepared as described elsewhere.[19] Other chemicals were of commercial grade. α,α'-Dimethylstilbene was synthetized by reductive coupling of acetophenone according to the method described by Lenoir.[20] Crystallization from ethanol yielded pure trans-α,α'-dimethylstilbene (m.p. 102 - 103°C).

Synthesis of 1-aryl-4-nitroimidazoles (general procedure)

Amine (0.01 mole) was added to a stirred suspension of dinitroimidazole (0.01 mole) in aqueous methanol 1:1 (40 ml) at 20°C. Stirring was continued for 2 h and the resulting mixture was left overnight in the darkness. The colored deposit was collected and heated for 1 h in boiling methanol (10 ml). Colorless crystals, which had precipitated on cooling were recrystallized from acetone, methanol, or aqueous methanol.

1-Phenyl-4-nitroimidazole **3a**. M.p. 187 - 188°C (MeOH - acetone). UV (methanol): λ_{max} (ε_{max}) 292 (11600); ^{1}H NMR (acetone-d_6) δ: 8.53 (1 H, d, J = 1.6 Hz, C_5-H), 8.14 (1 H, d, J = 1.6 Hz, C_2-H), 7.46 - 7.83 (5 H, m, phenyl).

1-(3-Chlorophenyl)-4-nitroimidazole **3b**. M.p. 121 - 122°C (aqueous methanol); UV (methanol): λ_{max} (ε_{max}) 297 (11500); ^{1}H NMR (acetone-d_6) δ: 8.61 (1 H, d, J = 1.6 Hz, C_5-H), 8.21 (1 H, d, J = 1.6 Hz, C_2-H), 7.50 - 7.89 (4 H, m).

1-Phenyl-2-methyl-4-nitroimidazole **3c**. M.p. 142 - 143°C (aqueous methanol); UV (methanol): λ_{max} (ε_{max}) 299 (10800); ^{1}H NMR (acetone-d_6) δ: 8.13 (1 H, s, C_5-H), 7.5 - 7.61 (5 H, m), 2.32 (3 H, s, CH_3).

1-(3-Chlorophenyl)-2-methyl-4-nitroimidazole **3d**. M.p. 136 - 137°C (aqueous methanol); UV (methanol): λ_{max} (ε_{max}) 306 (8700); ^{1}H NMR (acetone-d_6) δ: 8.26 (1 H, s, C_5-H), 7.56 - 7.80 (4 H, m), 2.37 (3 H, s, CH_3).

1-Phenyl-2-methyl-4-nitro-5-aminoimidazole **5**.

A suspension of sodium methanolate (2.8 g, 52 mmol) in DMSO (300 ml) was poured into a solution of 1-phenyl-2-methyl-4-nitroimidazole (1 g, 4.9 mmol) and 4-amino-1,2,4-triazole (2 g, 24 mmol) in DMSO (10 ml) at 25°C. The prepared red suspension was stirred for 2 h at 25°C and then poured into saturated ammonium chloride aqueous solution. The precipitated sediment was filtered off, rinsed with water and dried to yield crude product (0.48 g, 45%). M.p. 260 - 263°C (dec., DMF - EtOH). Elemental Analysis Found: C 54.74, H 4.67, N 25.67%. $C_{10}H_{10}N_4O_2$ requires: C 55.04, H 4.62, N 25.68%. UV (methanol): λ_{max} (ε_{max}) 365 (15700); ^{1}H NMR (DMSO-d_6) δ: 7.40 - 7.60 (5 H, m), 7.25 (2 H, bs, NH), 1.97 (3 H, s, CH_3).

Photooxidation of trans-α,α'-dimethylstilbene.

A solution (50 ml) containing 2 x 10^{-4} *M* **3a-d** or **5** and 5 x 10^{-2} *M trans*-α,α'-dimethylstilbene in acetonitrile was irradiated in a Pyrex tube surrounded by a Pyrex water jacket connected to a Haake F3 thermostat to maintain the temperature at 13.0 ± 0.1°C with a high pressure mercury arc (Helios Italquartz) surrounded by a Pyrex water jacket, in the presence of oxygen. After 2 h, the solvent was removed at room temperature on a rotary evaporator; residual oil was analyzed via ^{1}H NMR and GC-MS. Compound **8**: ^{1}H NMR ($CDCl_3$) δ: 1.84 (3 H, s, CH_3), 5.49 (2 H, dd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, C = CH_2), 7.0-7.5 (10 H, m); MS (*m/z*): 239 (3 %, M + - 1), 238 (18), 237 (10), 223 (6), 222 (25), 221 (12), 209 (13), 208 (20), 194 (7), 193 (19), 181 (8), 179 (11), 178 (15), 167 (7), 144 (25), 131 (10), 129 (26), 128 (100), 127 (28), 118 (16), 117 (50), 116 (17), 115 (21), 105 (40), 104 (21), 102 (13), 94 (45), 91 (24), 78 (14), 77 (43), 51 (24). Compound **9**: the identification of this compound was made by ^{1}H NMR ($CDCl_3$) by using the peak at δ 2.30 (3 H, s, CH_3); MS (*m/z*): 120 (42 %), 106 (7), 105 (100), 78 (9), 77 (91), 51 (27). Compounds **10** and **11** were determined by ^{1}H NMR spectra of the reaction mixture in benzene-d_6 by using peaks at δ 1.23 (3 H, s, CH_3) and 1.62 (3 H, s, CH_3) respectively; MS (*m/z*): 224 (1 %), 223 (13), 222 (75), 120 (22), 105 (96), 104 (12), 103 (100), 102 (15), 91 (7), 78 (19), 77 (67), 51 (29). Compound **12** was determined by ^{1}H NMR spectra of the reaction mixture in benzene-d_6 by using the peak at δ 1.70 (3 H, s, CH_3); MS (*m/z*): 224 (2 %), 208 (4), 121 (66), 105 (15), 104 (100), 103 (13), 91 (4), 78 (5), 77 (18).

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