DYE-SENSITIZED PHOTOOXIDATION OF 2,4-DISUBSTITUTED IMIDAZOLES: THE FORMATION OF ISOMERIC IMIDAZOLINONES

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Abstract- The photooxidation of 2,4-disubstituted imidazoles (**1**) in MeOH using hematoporphyrin as a sensitizer afforded isomeric 3-imidazolin-5-ones (**2**) and 2-imidazolin-4-ones (**3**).

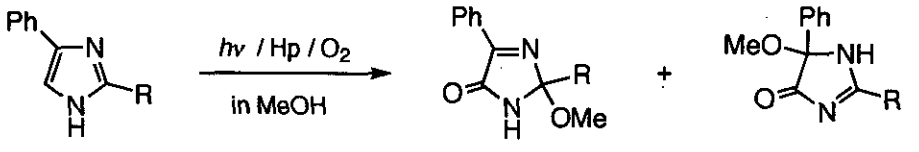
Particular attention has been paid to the sensitized photooxidation of imidazoles because of the correlation of photodynamic enzyme deactivation by air, dye and light with the destruction of histidine residues in proteins.[1] Mechanistic studies strongly indicate that the reaction of histidine in this destruction involves singlet oxygen[2] which would attack the imidazole ring of the histidine residue.[3] However, the initial product of oxidation still remains to be identified because of its high susceptibility to the attack by nucleophiles.[4]

Upon applying an aprotic solvent, we have observed a facile formation of nitrile in the sensitized photooxidation of 2-substituted imidazoles (including a histidine derivative), whereas the photooxidation of imidazoles in protic solvents gave a variety of products depending on the nature of substrate, the solvent, and other reaction conditions.[3a,4,5] The solvent employed may play an important role in governing the outcome of singlet oxygen reaction with imidazoles. We now describe the photooxidation of 2,4-disubstituted-imidazoles (**1**) in MeOH using hematoporphyrin (Hp) as a sensitizer,[6] resulting in the formation of isomeric imidazolinones (**2**) and (**3**).

As a typical procedure, a solution of 2,4-diphenylimidazole (**1a**) (10 mM) and Hp (0.25 mM) in MeOH was irradiated with a 100 W high-pressure mercury lamp through a Pyrex filter under oxygen at 25°C for 3 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel using chloroform as an eluant to afford 2-methoxy-2,4-diphenyl-3-imidazolin-5-one (**2a**) and 5-methoxy-2,5-diphenyl-2-imidazolin-4-one (**3a**) in 2.6% and 12.2% yields respectively. **2a** thus obtained is a new type of product in the photooxidation of 2,4-diphenylimidazole, while **3a** had been already isolated.[5b] A similar irradiation of 2,4-disubstituted imidazoles (**1**) gave the corresponding imidazolinones (**2**) and (**3**)[7] (Table 1). Although the yields of **2** were still not optimized, the present results provide a useful synthetic method for 3-imidazolin-5-ones since only the synthesis of 1,2,2,4-tetramethyl-3-imidazolin-5-one[8a] and 2,2-*bis*(trifluoromethyl)-3-imidazolin-5-one[8b] has been reported.

The uv and ^{1}H-nmr spectral data (Table 1) can be used to distinguish clearly between 3-imidazolin-5-ones (**2**) and 2-imidazolin-4-ones (**3**). In the uv spectra, **2** exhibited a single absorption maximum around 264 nm with essentially the same molar extinction coefficient (log ε) because of their common chromophore [-N=C(Ph)-CO-NH-] which is independent of the substituent (R) at C_2-position.

Table 1 Yields, and the uv and ^{1}H-nmr spectral data for 3-imidazolin-5-ones (**2**) and 2-imidazolin-4-ones (**3**).



1 **2** **3**

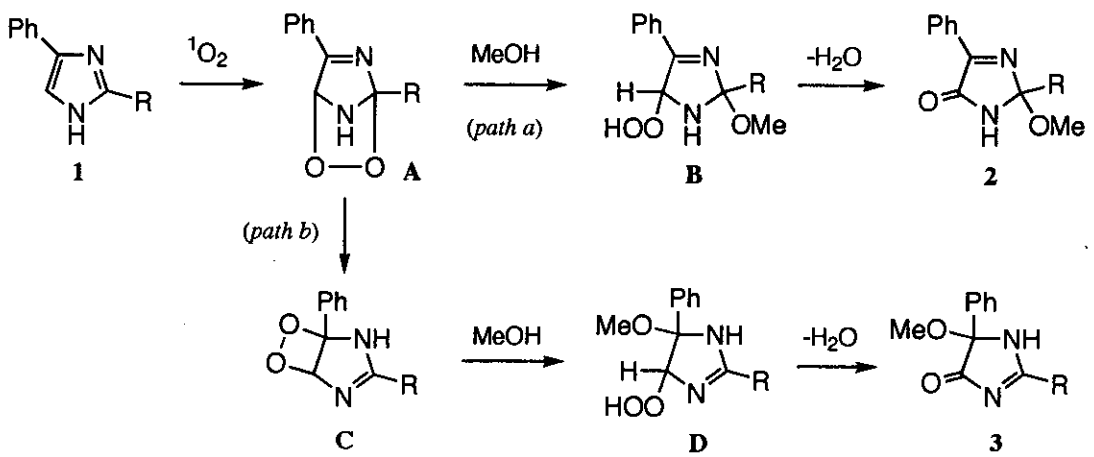
a: R = Ph, b: R = Me, c: R = *p*-$NO_2C_6H_4$, d: R = *p*-MeC_6H_4

	Yields (%)[a]	Uv[b] λ_{max}/nm (log ε)		^{1}H-Nmr[c] δ_{OCH_3} / ppm	
2a	2.6	264 (4.11)			3.27
2b	9.8	260 (4.08)		1.79[d]	3.15
2c	1.8	267 (4.26)			3.36
2d	12.4	264 (4.12)			3.31
3a	12.2	238 (4.21)	256 (4.02, sh)		3.42
3b	3.8	225 (3.65)	261 (3.12, sh)	2.44[e]	3.29
3c	10.7	259 (4.21)	287 (4.00, sh)		3.44
3d	23.2	252 (4.19)	269 (4.17)		3.42

[a] Yields were not optimized. [b] Uv spectra were recorded in ethanol. [c] ^{1}H-Nmr spectra were recorded in $CDCl_3$. [d] Tertiary CH_3 signal at C_2-position. [e] CH_3 signal at azomethine C_2-position.

On the contrary, the uv spectra of **3** showed a couple of absorption maxima to be different from each other in λ_{max} and log ε because the chromophore in **3** [-CO-N=C(**R**)-NH-] involves the substituent (R) at C_2-position and is not identical. In the ^{1}H-nmr spectra, the signal assigned to *O*-methyl group in **2** was always observed in slightly upper field in comparison with that in **3**.

The reaction mechanism for the formation of **2** and **3** is pictured in Scheme 1. The Diels-Alder type addition of singlet oxygen[9] to the imidazole ring of **1** forms initially the 2,5-endoperoxide[10] **A** as a key intermediate. Subsequent nucleophilic attack of methanol on **A** (*path a*) with the formation of 5-hydroperoxide **B** followed by dehydration of **B** gives **2**. On the other hand, the formation of **3**, as discussed by Wasserman *et al.*,[5b] is interpreted in terms of rearrangement of **A** to dioxetane intermediate[11] **C** (*path b*), nucleophilic attack of methanol on **C** affording 4-hydroperoxide **D**, and dehydration of **D**. Only in the case of the photooxidation of **1b**, the yield of **2b** (9.8%) was superior to that of **3b** (3.8%). This fact can be explained by assuming that the nucleophilic attack of methanol preferred on the less hindered C_2-position bearing methyl group in **A**, compared with the C_5-position bearing phenyl group in **C**.



Scheme 1

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