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Dye-Sensitized Photooxygenations of 1,3-Isoquinolinediones

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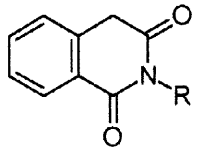
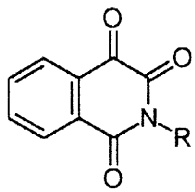
Abstract: Singlet oxygen reactions of 1,3-isoquinolinediones **1a-1e** could be sensitized by the anionic sensitizer Rose Bengal (RB) in methanol or by tetraphenylporphin (TPP) in the presence of pyridine as a base and a cosolvent in benzene. The products are the corresponding 1,3,4-isoquinolinetriones **2a-2e** and methyl 1-hydroxy-3-oxoisoindole-1-carboxylates **3b-3e** in methanol and the triketones **2a-2e** and the 3-hydroxy-3-alkyl (aryl)aminocarbonylbenzoisofuran-1-ones **4b-4e** in benzene-pyridine. TPP sensitized photooxygenations of the 4-alkylated 1,3-isoquinolinediones **5a-5c** yielded the 4-alkyl-4-hydroxy-1,3-isoquinolinediones **6a-6c**, the 4-alkyl-4-hydroperoxy-1,3-isoquinolinediones **7a-7c** and the 3-alkyl-3-hydroxybenzoisofuran-1-ones **8a-8b**. Reaction mechanisms have been proposed.

1,3-Isoquinolinedione and its derivatives have a wide range of biological activities and their structural modifications with the aim of finding new compounds of potential medical and other applications have drawn increasing research interest.[1] We report here the dye-sensitized photooxygenations of 1,3-isoquinolinediones **1a-1e** under different conditions.

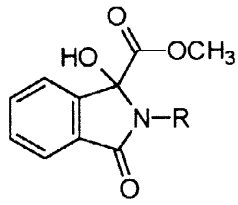
Dye-sensitized photooxygenations of enol compounds[2] are much less investigated than simple electron rich alkenes, enol ethers and enamines,[3] especially for the cyclic monoketones,[2e] since for these compounds the keto-enol tautomerism equilibrium usually lies heavily on the side of the keto form.[4] ^{1}HNMR measurements show that 1,3-isoquinolinediones **1** exist almost exclusively in the keto form in solutions of common



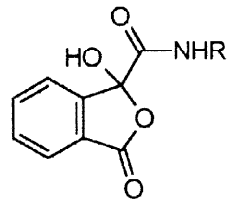
1a-1e



2a-2e



3b-3e



4b-4e

a: R = H, **b**: R = CH_3, **c**: R= C_6H_5, **d**: R = 4-$CH_3OC_6H_4$, **e**: R = 4-FC_6H_4

solvents such as methanol, benzene and chloroform. In accord with this, we found that, under typical singlet oxygen reaction conditions with tetraphenylporphin (TPP) as sensitizer in benzene solutions, **1** could not be photooxygenated even on prolonged irradiation with oxygen purging. However, when the photolysis of **1a** was carried out with Rose Bengal (RB) as sensitizer in methanol, photooxygenation proceeded promptly to lead to

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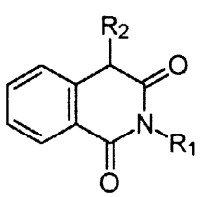
rapid consumption of the starting material and the formation of the 1,3,4-isoquinolinetrione **2a** as product. We believe that, the ability of RB to sensitize the reaction is associated with its anionic structure in which the carboxylic and the phenolic anions both act as basic sites and hydrogen bond acceptors to shift the keto-enol tautomerism equilibrium toward the enol side and significantly increase the electron density at the enolic C=C bond than in the unhydrogen-bonded enol. Photooxygenations of **1b-1e** in methanol with RB as sensitizer also proceeded smoothly. In these cases, the 1,3,4-isoquinolinetriones **2b-2e** and the methyl 1-hydroxy-3-oxoisoindole-1-carboxylates **3b-3e** were isolated as products. The results are summarized in Table 1.

Table 1 Dye-sensitized photooxygenations of 1,3-isoquinolinediones **1** and 4-alkyl-1,3-isoquinolinediones **5**[a]

Entry	Substrate	Sensitizer	Solvent	Irrd. time (h)	Products and yields (%)[b]
1	**1a**	RB	CH_3OH	4	**2a** (43)
2	**1a**	RB	CH_3CN	5	**2a** (53)
3	**1b**	RB	CH_3OH	2	**2b** (26), **3b** (28)
4	**1c**	RB	CH_3OH-CH_3CN (5:1 v/v)	2	**3c** (48)
5	**1c**	RB	CH_3CN	4	**2c** (47)
6	**1a**	TPP	PhH-Py (5:1 v/v)	10	**2a** (83)
7	**1b**	TPP	PhH-Py (5:1 v/v)	11	**2b** (76), **4b** (14)
8	**1c**	TPP	PhH-Py (5:1 v/v)	12	**2c** (65), **4c** (20)
9	**1d**	TPP	PhH-Py (5:1 v/v)	8	**2d** (75), **4d** (18)
10	**1e**	TPP	PhH-Py (5:1 v/v)	10	**2e** (63), **4e** (22)
11	**5a**	TPP	PhH-Py (5:1 v/v)	15	**6a** (10), **7a** (64), **8a** (19)
12	**5b**	TPP	PhH-Py (5:1 v/v)	15	**6b** (27), **7b** (50), **8b** (13)
13	**5c**	TPP	PhH-Py (5:1 v/v)	15	**6c** (30), **7c** (45), **8b** (15)

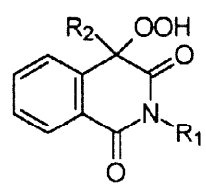
a: [Sens] 5×10^{-4} mol/L [Substrate] 5×10^{-2} mol/L b: Yields of isolated pure products based on consumed 1,3-isoquinolinediones

Control experiments showed that, products **3b-3e** were actually formed from the triketones in dark reactions. Therefore, treatment of **2b** in methanol in the dark in the presence of RB resulted in the formation of **3b** in 96% yield. This methanolysis reaction is a base catalysed reaction since RB or other base such as sodium methoxide or triethylamine was found necessary for the reaction and in the absence of a base, the triketones **2** were found stable in methanol at room temperature or at elevated temperatures.[5]

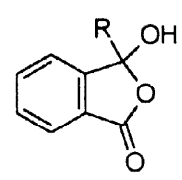


5a-5c

6a-6c



7a-7c



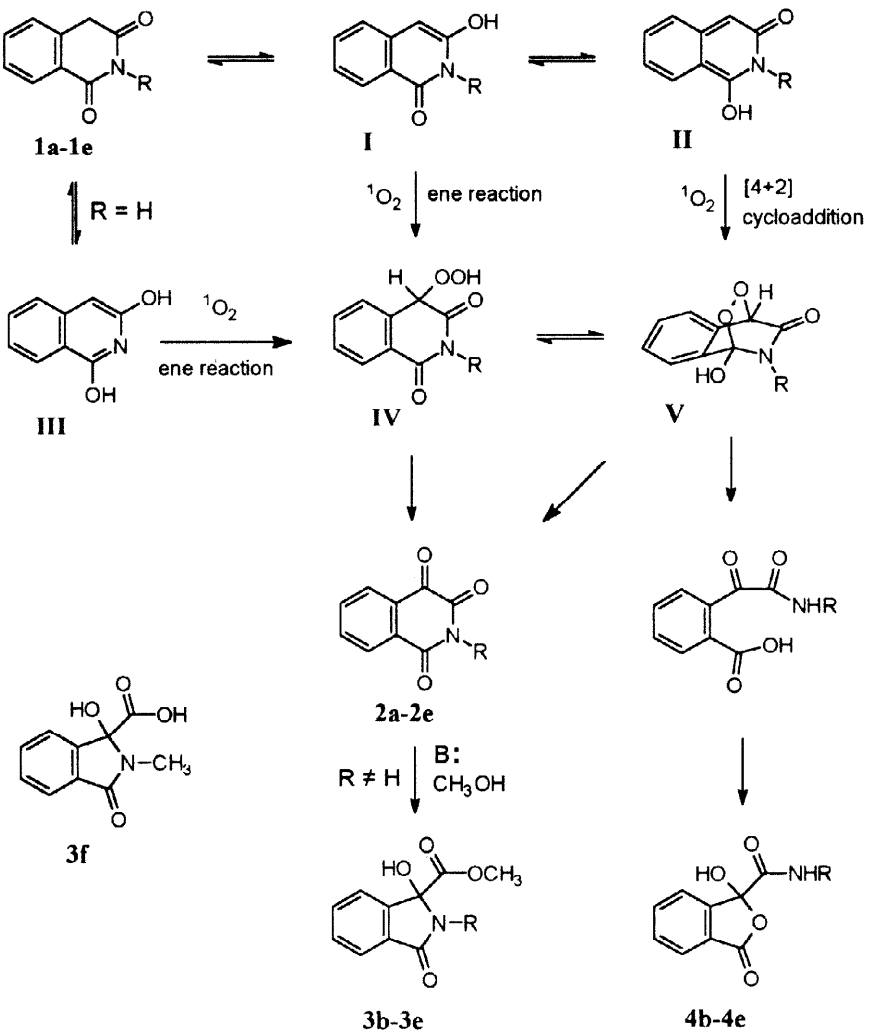
8a-8b

5-7: **a** $R_1 = R_2 = CH_3$, **b** $R_1 = CH_3$, $R_2 = C_2H_5$, **c** $R_1 = C_6H_5$, $R_2 = C_2H_5$; **8**: **a** $R = CH_3$, **b** $R = C_2H_5$

In these RB sensitized photooxygenations, serious bleaching of the sensitizer was found and the total yields of products were not very high because a large amount of intractable polymerized-oxidized mixture was formed. In an attempt to improve the reaction conditions and raise the yield of products, we have found that use of TPP as sensitizer in a solvent mixture composed of benzene-pyridine (5:1 v/v) with pyridine as a base and hydrogen bond acceptor resulted in much cleaner reactions to give a high total yield of oxidation products.

As an example, irradiation of a solution of TPP (5×10^{-4} mol/L) and **1a** (5×10^{-2} mol/L) in benzene-pyridine (5:1 v/v) with light of wavelength longer than 400 nm under oxygen purging for 10 hrs led to the total consumption of **1a** and the formation of the triketone **2a** in 83 % yield. Photooxygenations of **1b-1e** under the same conditions gave two products, the corresponding triketones **2b-2e** and the 3-hydroxy-3-alkyl (aryl)aminocarbonylbenzoisofuran-1-ones **4b-4e** in high total yields as shown in Table 1.[6]

Scheme 1



The formation of products **4** is noteworthy since control experiments showed that **4** were not formed from the triketones **2** by hydrolysis in a secondary process under the action of a trace amount of water in the solvent. Treatment of **2b**, for example, in aqueous sodium hydroxide solution at room temperature indeed causes the hydrolysis of **2b**, but the product is **3f** (Scheme 1) which is formed by nucleophilic attack of the hydroxide ion on the 3-carbonyl group of the triketone. Products **4** are therefore formed directly in the photooxygenation reactions, presumably from the endoperoxide intermediates **V** which in turn were formed either *via* the rearrangement of the hydroperoxide intermediates **IV** or through a [4+2] cycloaddition of singlet oxygen with the enol forms **II** of **1** or with the corresponding enol anions, as shown in Scheme 1. We also found that warming of products **4** in acetic anhydride yielded the corresponding triketone products almost quantitatively. Therefore, the yields of triketones could be further significantly raised if necessary.

A few of the 1,3,4-isoquinolinetriones have previously been synthesized by ruthenium oxide[7a] or selenium oxide[7b] oxidation of the corresponding isoquinolinediones. The photooxygenations described here provide a

convenient alternative synthetic route for 1,3,4-isoquinolinetriones which are of current interest due to their biological activities.[8]

We have further investigated the dye sensitized photooxygenations of the 4-alkylated isoquinolinediones **5a-5c**. Photolyses of solutions of **5** in benzene-pyridine (5:1 v/v) with TPP as sensitizer yielded three products **6**, **7** and **8**. The alcohols **6** are derived from the hydroperoxides **7** [9] by thermal and photochemical decompositions during the photolyses. On the other hand, the benzoisofuranone products **8** are not secondary products formed by the decompositions of **7** since on prolonged standing in benzene-pyridine solutions, the only thermal decomposition products of **7** are the alcohols **6**. Products **8** are therefore produced directly in the photooxygenations through a mechanism as for the formation of **4** *via* endoperoxide intermediates like **V** in Scheme 1.

The mechanistic and synthetic aspects of these photooxygenations are being further investigated.

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6. Typical reaction conditions are examplified by the photooxygenation of **1e**: A solution of **1e** (510 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated with a 500 W medium pressure mercury lamp through an aqueous sodium nitrite solution filter (λ>400 nm) at room temperature under oxygen purging for 10 hrs. Solvents were removed *in vacuo* and the residue subjected to chromatographic separation on a silica gel column with petroleum ether (b.p. 60-90°C)-ethyl acetate as eluents to afford **2e** (338 mg, 63%) and **4e** (126 mg, 22%).
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9. All new compounds gave consistent microanalytical and spectral data. Spectral data of **7b**: IR(KBr) 3380, 1720, 1665, 1608, 1460, 1420, 1360, 1300, 1278, 1065, 768, 700 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) 0.661 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.831 (1H, sextet, J = 7.5, 13.5Hz, 1/2 CH_2), 2.097 (1H, sextet, J = 7.5, 13.5 Hz, 1/2 CH_2), 3.385 (3H, s, CH_3), 7.48-8.21 (4H, m, ArH) ppm. FAB-MS (m/z, %) 236 (M+1, base), 217 (M-H_2O, 19.9), 202 (M-OOH, 32.3), 190 (43.8).