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On the Reactions of 1,3-Isoquinolinediones with Singlet Oxygen

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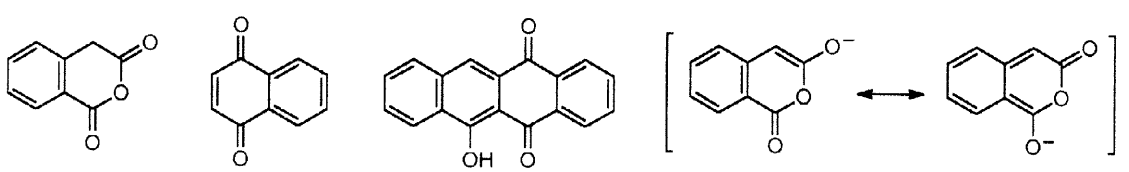
Abstract: Reactions of 1,3-isoquinolinediones **5** and 4-alkylated 1,3-isoquinolinediones **13** with singlet oxygen are entirely dominated by their enolization and proceed smoothly in benzene in the presence of pyridine as a base and a hydrogen bond acceptor. The products are triketones **6** and benzoisofuranones **7** for **5**, and hydroperoxides **14**, hydroxides **15** and benzoisofuranones **16** for **13**. It was found that hydrolysis of **6** afforded the isoindolones **8** and not products **7**, whereas alkaline cleavage of the hydroperoxide **14a** yielded not only **16a**, but also the isoindolone **19a**. In view of these observations, an unusual [4+2] cycloaddition of the electron-rich enol **21** with singlet oxygen is proposed to be responsible for the formation of products **7** and **16**, while products **6**, **14** and **15** arise from both the [4+2] cycloaddition and the usual Schenck ene reaction pathways. This special diene reactivity of the isoquinolinone system towards singlet oxygen is further interpreted by frontier molecular orbital (FMO) interaction considerations.

Keywords: 1,3-isoquinolinediones, photooxygenation, enolization, singlet oxygen, Schenck ene reaction, [4+2] cycloaddition.

INTRODUCTION

Homophthalic anhydride **1** is a useful building block for the construction of a variety of heterocyclic and polycyclic systems.[1] For example, **1** could react with dienophiles such as quinone **2** in alkaline media to afford the biologically important *peri*-hydroxyquinone **3**.[1a-1c] A key feature of the reactions of homophthalic anhydride **1** with dienophiles is its deprotonation by a strong base to the enolic anion **4** which serves as a highly electron-rich diene species to take part in the subsequent normal electron demand Diels-Alder reactions.[1c] Although great efforts have been made to explore the general scope of these novel reactions, there are still controversies concerning the reaction mechanisms.[1d]



1 **2** **3** **4**

On the other hand, as the *N*-analogues of homophthalic anhydride, 1,3-isoquinolinedione **5a** and its derivatives have a wide range of biological activities and their structural modifications with the aim of finding new drugs and medicine have drawn increasing research interest.[2] In a preliminary communication, we have

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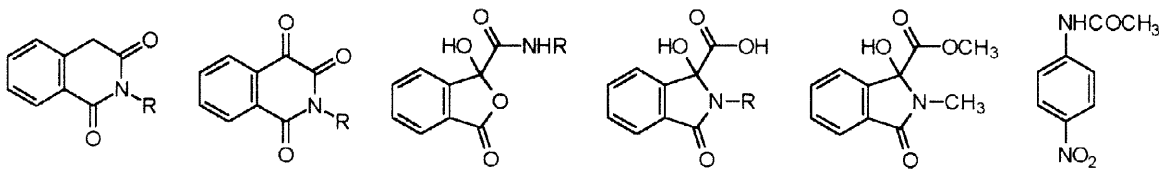
demonstrated that enolization of 1,3-isoquinolinediones may also play an important role in their reactions with the smallest dienophile, singlet oxygen ($^1O_2$), and a Diels-Alder type [4+2] cycloaddition reaction may be involved in these novel reactions as well.[3] In this paper, we wish to report our further studies on these singlet oxygen reactions[4] which not only disclose the characteristic reactivity of 1,3-isoquinolinediones as a diene *via* their enol form and therefore render mechanistic clues for the Diels-Alder reactions of homophthalic anhydride, but also provide convenient methods for practical syntheses of 1,3,4-isoquinolinetriones and other 4-oxyfunctionalized 1,3-isoquinolinediones.

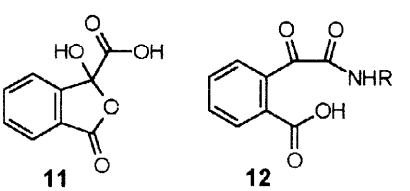
RESULTS AND DISCUSSION

Results

Tetraphenylporphin (TPP) sensitized photooxygenation of 1,3-isoquinolinedione **5a** in benzene-pyridine (5:1, v/v) with light of wavelength longer than 400 nm gave 1,3,4 (*2H*)-isoquinolinetrione (**6a**) as the sole product in 83 % yield. Under the same conditions, TPP-sensitized photooxygenations of **5b-5i** afforded, in addition to the triketones **6b-6i**, the *N*-alkyl (aryl)-3-hydroxybenzoisofuran-1-one-3-carbamides **7b-7i** in high total yields (Table 1).



5-8,12 **a**: R =H, **b**: R = CH_3, **c**: R = C_2H_5, **d**: R = $CH_2C_6H_5$, **e**: R = CH_2CH_2OH, **f**: R = C_6H_5, **g**: R = 4-$CH_3OC_6H_4$, **h**: R = 4-FC_6H_4, **i**: R = 1-Naphthyl, **j**: R = 4-$O_2NC_6H_4$



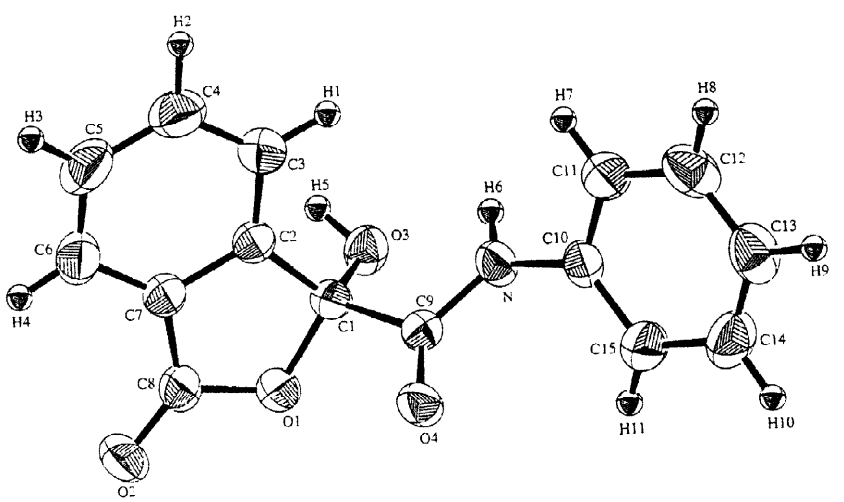


Fig. 1 ORTEP Drawing of Product **7f**

The structures of products **6** are readily assigned on the basis of their analytical and spectral data and by comparison of them with those reported in the literature,[5,6] whereas the structures of products 7 need to be carefully distinguished from the isomeric structures **8**. It was found that all the triketones reacted easily with nucleophiles such as water or an alcohol with the catalysis of a base.[5] For example, in the presence of sodium acetate, product **6b** smoothly underwent hydrolysis to give **8b**, which displays different physical and spectral properties from those of **7b**, or underwent methanolysis to give **9**. To further establish the isomeric structures of 7 and **8**, a crystallographic analysis for product **7f** was carried out which unambiguously determined the assigned structures of 7 (see Fig. 1) and **8**.

It is interesting to note that in the similar photooxygenation of **5j**, no corresponding product **7j** was found and the isolated products were the triketone **6j** and 4-nitroacetoanilide **10** (Table 1). Therefore, it is presumed that, during the separation of the reaction mixture on silica gel column with petroleum ether (b.p. 60-90 °C)-ethyl acetate as eluents, hydrolysis of the unstable primary product **7j** gave the carboxylic acid **11** and 4-nitroaniline, the latter subsequently reacting with ethyl acetate to yield **10** possibly on the catalysis of the released α-keto acid **11**.

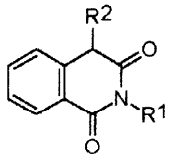
Table 1 Dye Sensitized Photooxygenations of 1,3-Isoquinolinediones **5** and 4-Alkyl-1,3-isoquinolinediones **13**[a]

Entry	Substrate[b]	Sensitizer[c]	Solvent	Irrad. time (h)	Products and yields (%)[d]
1	**5a**	TPP	PhH-Py (5:1, v/v)	10	**6a** (83)
2	**5b**	TPP	PhH-Py (5:1, v/v)	11	**6b** (76), **7b** (15)
3	**5c**	TPP	PhH-Py (5:1, v/v)	11	**6c** (75), **7c** (12)
4	**5d**	TPP	PhH-Py (5:1, v/v)	12	**6d** (78), **7d** (10)
5	**5e**	TPP	PhH-Py (5:1, v/v)	11	**6e** (74), **7e** (13)
6	**5f**	TPP	PhH-Py (5:1, v/v)	12	**6f** (65), **7f** (20)
7	**5g**	TPP	PhH-Py (5:1, v/v)	8	**6g** (76), **7g** (18)
8	**5h**	TPP	PhH-Py (5:1, v/v)	10	**6h** (63), **7h** (22)
9	**5i**	TPP	PhH-Py (5:1, v/v)	8	**6i** (75), **7i** (14)
10	**5j**	TPP	PhH-Py (5:1, v/v)	13	**6j** (42), **10** (49)
11	**13a**	TPP	PhH-Py (5:1, v/v)	15	**14a** (64), **15a** (10), **16a** (16)
12	**13b**	TPP	PhH-Py (5:1, v/v)	15	**14b** (50), **15b** (27), **16b** (13)
13	**13c**	TPP	PhH-Py (5:1, v/v)	15	**14c** (45), **15c** (30), **16c** (15)
14	**13d**	TPP	PhH-Py (5:1, v/v)	15	**14d** (47), **15d** (30), **16b** (16)
15	**13e**	TPP	PhH-Py (5:1, v/v)	15	**14e** (37), **15e** (39)
16	**13f**	TPP	PhH-Py (5:1, v/v)	15	**14f** (38), **15f** (34)
17[e]	**5a**	MB	MeOH	60	**6a** (80)
18[e]	**5a**	MB	MeCN	110	**6a** (81)
19[e]	**5b**	MB	MeOH	72	**6b** (67), **7a** (17)
20[e]	**5b**	MB	MeCN	132	**6b** (67), **7b** (18)

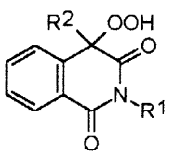
[a]Irradiation wavelength, λ> 400 nm (aqueous $NaNO_2$ solution filter) for TPP and λ> 500 nm (aqueous $K_2Cr_2O_7$ solution filter) for MB. [b]The concentration of the substrates was 5×10^{-2} mol dm^{-3}. [c]The concentration of sensitizer was 5×10^{-4} mol dm^{-3}. [d]Yields of isolated pure products. [e]A similar procedure of work up was employed as in TPP sensitized photooxygenation reactions except that the sensitizer need not to be removed prior to the chromatographic separation (see the experimental section).

As shown in Fig. 1, products 7 exist exclusively in the benzoisofuranone form in crystalline state. However, tautomerization may play some role in their behavior in solution. For example, while there are only two carbonyl stretching vibration bands at ~1760 and ~1660 cm^{-1} in the IR spectra of 7 (in KBr pellets), which are in accordance with the benzoisofuranone structures 7, ^1H NMR (500 MHz) spectrum of product **7b** in acetone-d_6 showed two singlets at δ 2.79 and 2.80 ppm in a nearly 1:1 ratio. This is obviously due to the absorption of the *N*-methyl groups of the two possible tautomers **7b** and **12b** (see the experimental section).

It was also found that products **7** could easily be cyclized to the corresponding triketones **6**. For example, warming of **7b** in acetic anhydride gave **6b** in almost quantitative yield. Therefore, a simple and efficient method for the preparation of 1,3,4-isoquinolinetriones from 1,3-isoquinolinediones[5,6] was developed by using a one pot procedure which has proven suitable for gram scale preparations in good yields as exemplified by the preparations of **6a**, **6b** and **6f** in the experimental section.

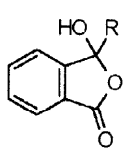


13a-13f

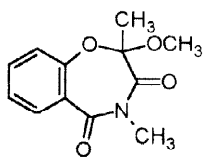


14a-14f

15a-15f



16a-16e



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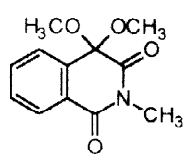
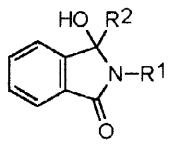


18

13-15, 19 **a**: $R^1 = R^2 = CH_3$, **b**: $R^1 = CH_3$, $R^2 = C_2H_5$; **c**: $R^1 = CH_3$, $R^2 = CH_2C_6H_5$; **d**: $R^1 = C_6H_5$, $R^2 = C_2H_5$; **e**: $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$; **f**: $R^1 = CH_3$, $R^2 = CH_2COC_6H_5$

16a: $R = CH_3$
16b: $R = C_2H_5$
16c: $R = CH_2C_6H_5$
16d: $R = CH_2CH{=}CH_2$
16e: $R = CH_2COC_6H_5$



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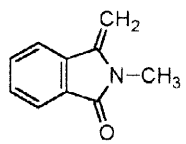


20

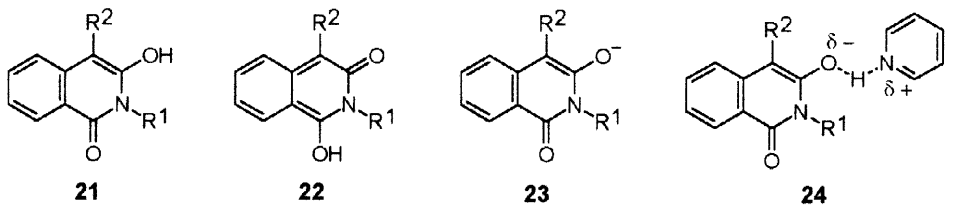
Under the above mentioned reaction conditions, TPP-sensitized photooxygenations of 4-alkylated 1,3-isoquinolinediones **13** afforded the hydroperoxides **14**, the hydroxides **15** and the benzoisofuranones **16** with the exception of reactions of **13e** and **13f** where the corresponding products **16d** and **16e** were not found, probably due to their further oxidation during the photooxygenation reactions (Table 1). The structures of products **14-16** are determined on the basis of their analytical and spectral data. The difference in chemical shift between the two diastereotopic protons of the methylene group in the hydroperoxides **14b-14f** is larger than that in the corresponding hydroxides **15b-15f** in the ^1H NMR spectra (500 MHz, see the experimental section). Attempts to obtain compounds **17** or **18** by a hydroperoxide rearrangement of **14a** in methanol in the presence of dry HCl failed. Reduction of **14a** by triphenylphosphine gave **15a** in a nearly quantitative yield. Treatment of **14a** in ^{t}BuOH in the presence of ^{t}BuOK resulted in the C-C bond cleavage to afford **16a** and **19a**, the latter was easily dehydrated to give **20** in the presence of an acid.

Mechanistic Discussion

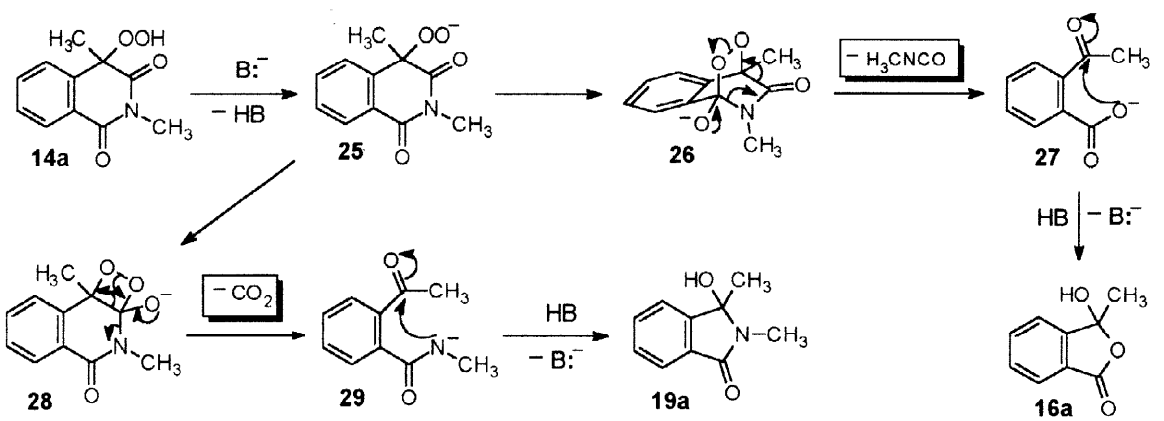
It was found that all the singlet oxygen reactions were quite sensitive to the polarity of solvents and even to the sensitizers used. For example, while methylene blue (MB) sensitized photooxygenation of **5b** in methanol needed 72 hours to lead to the total consumption of the starting material, similar reaction in acetonitrile was much slower (132 hours needed) although the yields and the ratio of the products are essentially the same (Table 1). In sharp contrast to these, TPP sensitized photooxygenation of **5b** in neat benzene did not proceed even on prolonged irradiation (100 hours). On the other hand, as we have demonstrated,[3] the same photooxygenation of **5b** proceeded rapidly (2 hours) in methanol in the presence of the anionic sensitizer Rose Bengal (RB), although this reaction suffered from the formation of a substantial amount of intractable polymerized-oxidized products and resulted in low yields of **6b** (26%) and its secondary methanolysis product **9** (28%). We eventually optimized the reaction conditions by using TPP as a sensitizer and a mixture of benzene and pyridine as solvent, when all the reactions proceeded smoothly and the total yield of products was high (Table 1). These observations suggested that the enolization of 1,3-isoquinolinediones may play a predominant role in these singlet oxygen reactions with the keto form being inert to singlet oxygen and the possible enol forms (**21** and **22**) were the active species toward singlet oxygen.

^1H NMR spectroscopic studies of 1,3-isoquinolinediones provided further evidence for this argument. For example, in common solvents such as benzene-d_6, acetonitrile-d_3 and methanol-d_4, compounds **5b** and **13a**

existed almost exclusively in the keto form and no enol tautomers could be detected. However, a significant hydrogen-deuterium exchange on the 4-C (α-C of 3-carbonyl) was observed in protic solvents such as methanol-d_4. These results indicated that the tautomeric equilibrium between the keto and enol forms of **5b** and **13a** may be easily established but lay heavily on the side of the keto form in these solvents.[7] At the same time, in the ^{1}H NMR spectrum of **13a** in pyridine-d_5, besides the absorption of the major keto component **13a** (with the *N*-methyl appearing at 3.36 ppm as a singlet and 4-methyl at 1.58 ppm as a doublet), two weak singlets emerged at 3.38 and 1.81 ppm. It is interesting that, on shaking with solid sodium hydroxide, the intensity of these two peaks gradually increased while the signals of the keto form decreased (see the experimental section). The ^{1}H NMR spectrum thus obtained is obviously an undissociated sodium salt of the enolic anion **23**, while in neat pyridine, the same signals probably result from a strongly polar complex of the enol **21** with pyridine which is formed through hydrogen bonding and has a structure between the enol **21** and the enolic anion **23** such as **24**. The ratio of the keto **13a** and **24** is about 98:2 and no other signals corresponding to the enol **22** could be detected.

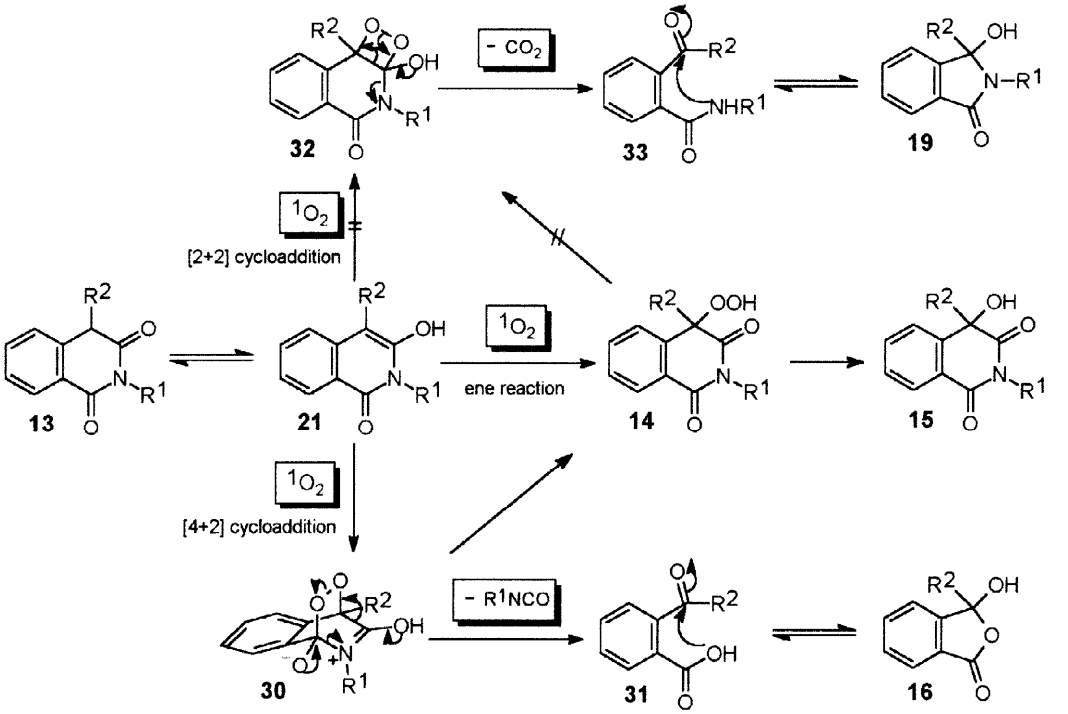


Within the constraint that the keto and the enol tautomers are all in planar configurations, *ab initio* calculations of the three tautomers of **5b** showed that the total electronic energies of the keto form **5b**, and the enol forms **21**, **22** ($R^1 = CH_3$, $R^2 = H$) are -588.1515213; -588.1155278 and -588.0933303 hartree, respectively. Considering the fact that the keto form **5b** should actually have a more stable twisted structure, this result indicated that the enol **21** is more stable than **22**, while the keto form **5b** is much more stable than the two enol forms **21** and **22**. Therefore, we may conclude that in the singlet oxygen reaction of 1,3-isoquinolinediones **5** and **13** in methanol, acetonitrile and benzene-pyridine, the main reactive substrates are the enol **21** and/or the enol complex **24**, although the involvement of enol form **22** and the enolic anion **23** cannot be completely excluded. On the other hand, *ab initio* calculations also showed that the total atomic charges on C^4 in the enols **21**, **22** and the enolic anion **23** ($R^1 = H$, $R^2 = CH_3$) are -0.349, -0.449 and -0.509, respectively and all C^4 are the most heavily negative charged carbon atoms in the molecules. This result reveals that the enol **21** is a highly electron-rich alkene, while the enol complex **24** is yet more electron-rich than **21** due to the hydrogen bond formation. Therefore, the initial attack of singlet oxygen will occur exclusively on the C^4 atoms in **21** and/or **24**.



Scheme 1 Mechanism for Alkaline Cleavage of **14a**

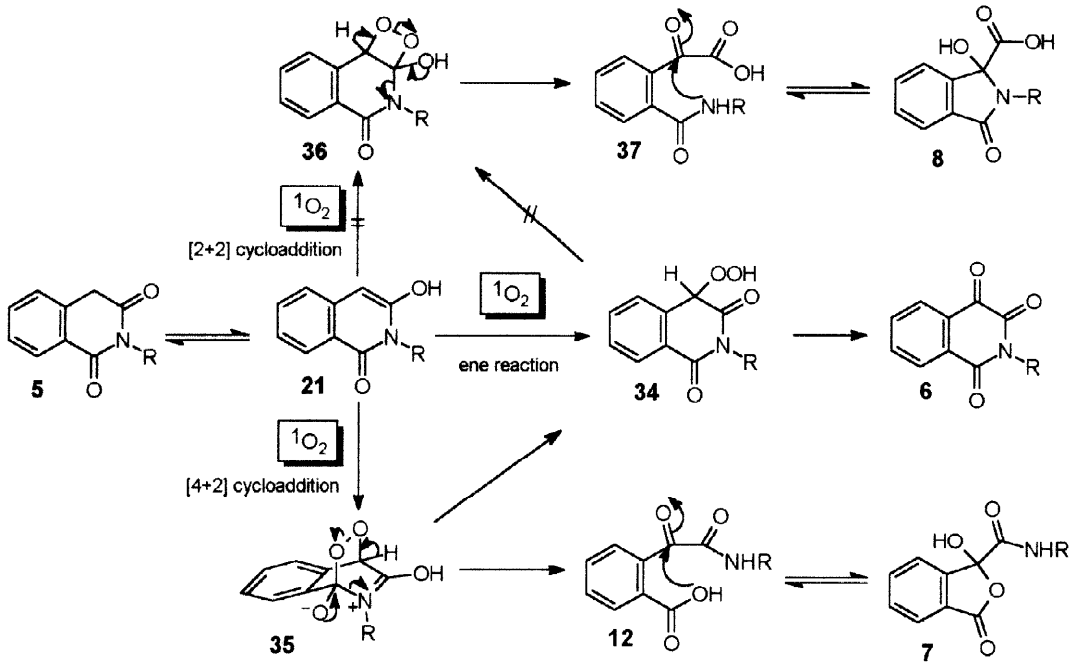
A good understanding of the behavior of hydroperoxides **14** will help to elucidate the mechanism of these novel singlet oxygen reactions. It was found that all the pure crystalline hydroperoxides **14** were stable even at 120 °C. Standing at room temperature or warming at 50 °C of a solution of **14a** in benzene-pyridine (5:1, v/v) caused no reaction, whereas prolonged irradiation of this solution under the above mentioned photooxygenation conditions afforded only **15a** without formation of product **16a**. These observations strongly suggested that products **15** were actually derived from the photoinduced O-O homolysis of the primary products **14** during the photooxygenation reaction of **13**, whereas products **16** did not result from further decomposition of **14**, but were directly formed from the singlet oxygen reactions. It is interesting to note that under alkaline conditions (^{t}BuOK/^{t}BuOH), **14a** underwent a facile C^3–C^4 cleavage to afford products **16a** and **19a**.[8] The lack of any ^{t}BuOH ester products and the ease of this alkaline cleavage under anhydrous conditions exclude the possibility of a nucleophilic attack of ^{t}BuO$^-$ or OH$^-$ on the carbonyl groups in **14a**. A possible mechanism for this alkaline cleavage is illustrated in Scheme 1. Deprotonation of **14a** gave the hydroperoxidic anion **25**. Transannular nucleophilic attack of the peroxy anion in **25** on the 1-carbonyl group afforded the endoperoxide intermediate **26**, which subsequently lost a methyl isocyanate (H_3C–N=C=O) molecule leading to the formation of **16a** *via* **27**. On the other hand, the peroxy anion in **25** could also attack the 3-carbonyl group to give the 1,2-dioxetane intermediate **28**, decarboxylation of which yielded product **19a** *via* **29**. The product distribution (38:55, **16a**:**19a**) reflected the higher electrophilicity of the 3-carbonyl group over that of the 1-carbonyl group.



Scheme 2 Mechanism for Singlet Oxygen Reactions of 4-Alkyl-1,3-isoquinolinediones **13**

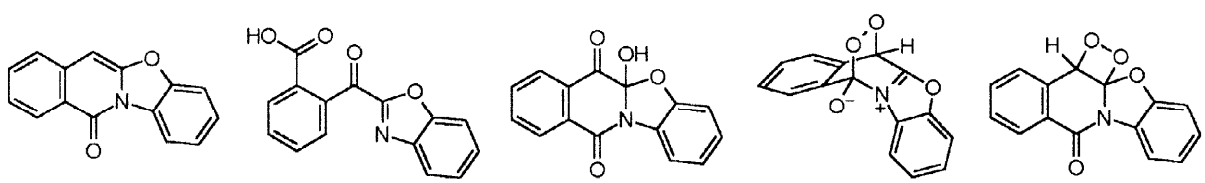
Based on the above observations, a possible mechanism for singlet oxygen reactions of 4-alkylated 1,3-isoquinolinediones **13** was proposed as shown in Scheme 2, in which, besides the two usual reaction pathways of singlet oxygen with the enols **21**, namely Schenck ene reaction and [2+2] cycloaddition, an unusual [4+2] cycloaddition pathway is also illustrated. However, the absence of even a trace amount of products **19** (which were the major products in the alkaline cleavage of **14**) in the singlet oxygen reactions of **13** readily ruled out the 1,2-dioxetane intermediates **32** and in turn excluded the [2+2] cycloaddition pathway. In contrast, the stability of products **14** toward C^3–C^4 cleavage under photooxygenation conditions and the formation of products **16** (which were the minor products in the alkaline cleavage of **14**) in singlet oxygen reactions of **13** clearly indicated

the involvement of the endoperoxide intermediates **30**, which were not derived from the hydroperoxides **14**, but directly formed *via* the [4+2] cycloaddition pathway. On the other hand, the hydroperoxides **14** may be formed both from the ring opening of **30** and *via* the Schenck ene reaction pathway (Scheme 2). It should be noted that, besides the above mentioned photoinduced O-O homolysis pathway, products **15** can also be formed from the reduction of **14** by amines arising from the hydrolysis of the isocyanates (R^1NCO) released during the photooxygenation reactions of **13** under the action of a trace amount of water in the solvent.[9]



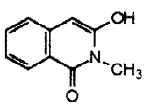
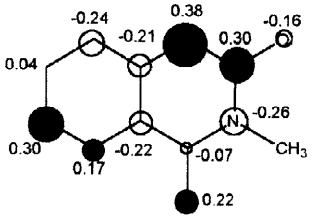
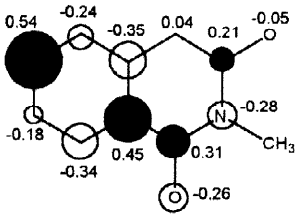
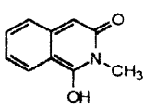
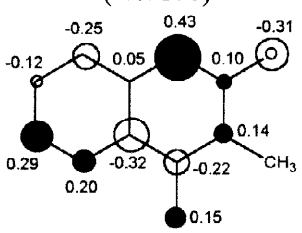
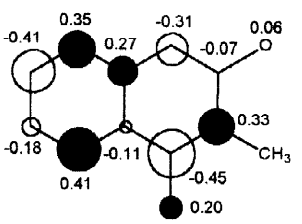
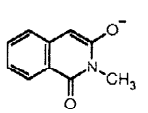
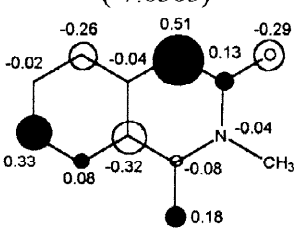
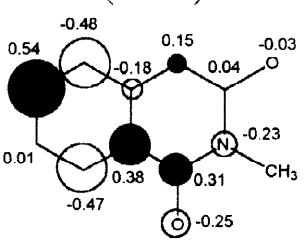
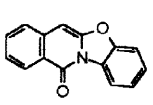
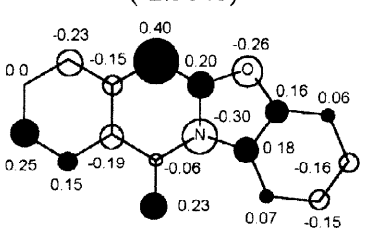
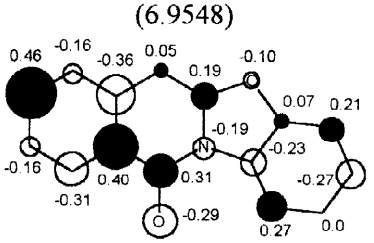
Scheme 3 Mechanism for Singlet Oxygen Reactions of 1,3-Isoquinolinediones **5**

A similar mechanism for singlet oxygen reactions of 1,3-isoquinolinediones **5** is presented in Scheme 3 with hydroperoxides **34** and endoperoxides **35** as intermediates. The only difference between the hydroperoxides **34** and **14** is the presence of an acidic C^4–H bond in **34**, which is susceptible to attack by nucleophiles such as pyridine and methanol.[9] This will subsequently cause a facile dehydration reaction leading to the formation of products **6**. A similar β–elimination reaction may also play a predominant role in the decomposition of the possible reaction intermediates such as **35** and **36**, so that no C^3–C^4 cleavage product was observed in these singlet oxygen reactions. As mentioned above, hydrolysis of the triketones **6** gave no products **7**, but only products **8** which were formed by the attack of OH^- on the more electrophilic 3–carbonyl group in **6**. Again, the absence of even a trace amount of products **8** in these singlet oxygen reactions excluded a [2+2] cycloaddition pathway, whereas the formation of products **7** in these reactions indicated a [4+2] cycloaddition pathway, and the hydroperoxides **34** may come from both the Schenck ene reaction pathway and the ring opening of **35** (Scheme 3).



From the above discussion, we may reach the conclusion that, in addition to the usual Schenck ene reaction pathway, an unusual [4+2] cycloaddition was indeed involved in the reactions of singlet oxygen with the enol **21** and/or the enol complex **24**. Similar results were also observed in our previous study on the singlet oxygen reactions of some benzannelated isoquinolinones such as the enol ether **38**, where only product **39** was obtained in aprotic solvents which may be well explained by an endoperoxidic intermediate **41**, and not even a trace amount of product **40** arising from a 1,2-dioxetane intermediate **42** was found.[10]

Table 2 FMO Coefficients and Energy Levels (E) of Ground States (S_0) of **21**[a], **22**[a], **23**[a] ($R^1 = CH_3$, $R^2 = H$) and **38**[b], and the Energy Gaps (ΔE) between FMOs of These Substrates and Singlet Oxygen[c]

Substrates	HOMO (E_{HOMO}, ev)	LUMO (E_{LUMO}, ev)	ΔE_1 (ev)[d]	ΔE_2 (ev)[e]
 **21**	 (-7.7176)	 (2.8600)	9.0842	15.1024
 **22**	 (-7.0305)	 (2.0502)	8.3971	14.2926
 **23**	 (-2.3846)	 (6.9548)	3.7512	19.1972
 **38**	 (-7.2876)	 (2.3531)	8.6542	14.5955

[a]This work by using HF/6-31G*. [b]Previous work.[1e] [c]The FMO energy levels of singlet oxygen ($^1\Delta_g$) are E_{HOMO} = -12.2424 ev and E_{LUMO} = 1.3666 ev, respectively; the FMO coefficients are 0.67, -0.67 for HOMO, and 0.70, -0.70 for LUMO respectively as calculated in this work by using HF/6-31G*.[11] [d]Energy gaps between HOMOs of the substrates and the LUMO of singlet oxygen. [e]Energy gaps between LUMOs of the substrates and the HOMO of singlet oxygen.

This special diene reactivity of the isoquinolinone system towards singlet oxygen was further examined by frontier molecular orbital (FMO) interaction considerations.[12] *Ab initio* was employed to calculate the FMO

coefficients and the FMO energy levels of ground states of **38** and the two enol forms (**21** and **22**) and the enolic anion **23** of compound **5b** by using the restricted Hartree-Fock method with 6-31G* basis set. The results are listed in Table 2, together with the energy gaps between the FMOs of these substrates and singlet oxygen (HOMO-LUMO and LUMO-HOMO). Naturally, the energy gaps between the HOMOs of all the substrates and the LUMO of singlet oxygen as an electrophile (ΔE_1 4~9 ev) are much smaller than the corresponding energy gaps between the LUMOs of these substrates and the HOMO of singlet oxygen (ΔE_2 14~19 ev). Therefore, as is always the case in singlet oxygen reactions with alkenes, the interactions between the HOMOs of the substrates and the LUMO of singlet oxygen play a predominant role in deciding the reaction pathway.[11] It is also noted from Table 2 that the HOMO coefficients on C^1 and C^4 are always negative and positive respectively in all the substrates with differences only in the magnitude. As mentioned above, the enol form **22** is the least stable tautomer and should have little contribution to the singlet oxygen reactions despite the fact that it has a typical diene structure and may readily undergo a [4+2] cycloaddition with singlet oxygen, while the enolic anion **23**, though also having very little contribution to the singlet oxygen reactions, may partially reflect the properties of the enol complex **24**. Therefore, our discussion will mainly focus on the enol **21**, the enolic anion **23** and the enol ether **38**. Fig 2 shows the FMO interactions between **21**, **23**, **38** and singlet oxygen in three possible reaction modes; *i. e.*, (a) an *anti* attack of singlet oxygen toward **21** leading to the formation of a perepoxide intermediate which subsequently results in the usual Schenck ene reaction;[4e] (b) an *anti* attack of singlet oxygen toward **21**, **23** and **38** leading to the formation of a perepoxide intermediate and then resulting in a [2+2] cycloaddition;[4] and (c) a *syn* attack of singlet oxygen toward **21**, **23** and **38** also leading to the formation of a perepoxide but finally resulting in a [4+2] cycloaddition. Apparently, in the case of **21**, FMO interactions in (a) and (c) are more favorable than in (b), while in the case of **23** and **38**, FMO interactions in (c) are also more favorable than in (b) both due to the more efficient positive orbital overlaps. This means that in the reaction of **38** with singlet oxygen, the [4+2] cycloaddition is more favorable than the [2+2] cycloaddition pathway, whereas in the reactions of 1,3-isoquinolinediones **5** and **13** with singlet oxygen, the Schenck ene reaction and the [4+2] cycloaddition are also more favorable than the [2+2] cycloaddition. This conclusion is in good agreement with the experimental observations in this work and in our previous report.[10] Although it is difficult to evaluate the appropriate contributions of the Schenck ene reaction and the [4+2] cycloaddition pathways in the singlet oxygen reactions of 1,3-isoquinolinediones at this stage, the exceptionally low yield of the triketone **6j** (arising from the hydroperoxide **34**) as well as the high yield of **10** (corresponding to **7j** and in turn derived from the endoperoxide **35**) in singlet oxygen reaction of **5j** (Table 1), which reflected the high nucleofugality of the *N*-(4-nitrophenyl)imino group compared with that of other imino leaving groups in **35**, did reveal the endoperoxidic origin (at least partial) of the hydroperoxides **34** in these singlet oxygen reactions (Scheme 3).

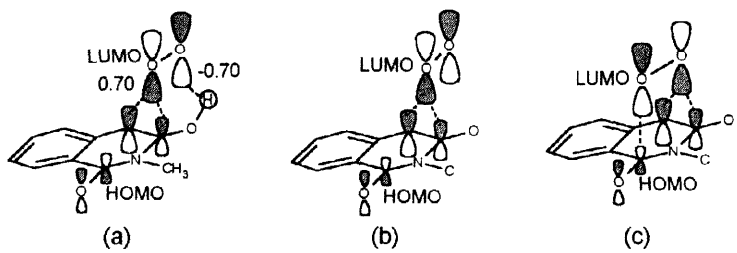


Fig. 2 Three FMO Interaction Modes between HOMOs of the Substrates and the LUMO of $^1O_2$

In summary, reactions of 1,3-isoquinolinediones **5** and **13** with singlet oxygen were entirely dominated by their enolization and could proceed smoothly in benzene in the presence of pyridine as a base and a hydrogen bond acceptor. The products were triketones **6** and benzoisofuranones **7** for **5**, and hydroperoxides **14**, hydroxides **15** and benzoisofuranones **16** for **13**. A [4+2] cycloaddition of the electron-rich enol **21** with singlet oxygen was proposed to be responsible for the products **7** and **16**, while products **6**, **14** and **15** are formed from both the [4+2] cycloaddition and the usual Schenck ene reaction pathways. These results are parallel to our

previous study on the singlet oxygen reaction of the enol ether derivative **38**, where only the [4+2] cycloaddition reaction is observed.[10] This unusual diene character of the isoquinolinone system **21** and **38** towards singlet oxygen was further interpreted by FMO interaction considerations. In addition, these reactions of 1,3-isoquinoline-diones and 4-alkylated 1,3-isoquinolinediones with singlet oxygen also provided facile access to 1,3,4-isoquinolinetriones and other 4-oxyfunctionalized 1,3-isoquinolinediones which are of current interest due to their biological activities.[13]

EXPERIMENTAL SECTION

Melting points were measured on a YANACO microscopic melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL PMX-60 SI spectrometer at 60 MHz or on a Bruker AC-500 spectrometer at 500 MHz with $SiMe_4$ as internal standard and $CDCl_3$ as solvent unless otherwise stated. *J* Values are given in Hz. IR spectra were taken with a Shimadzu IR 408 or a Nicolet 5DX FT-IR spectrometer in KBr pellets. Mass spectra were recorded with a VG ZAB-HS spectrometer. Elemental analyses were obtained using a Perken-Elmer-240 C analyzer.

2-Alkyl-1,3-isoquinolinediones **5a-5e** were prepared in 70-80% yields by mixing homophthalic anhydride **1** with an excess amount of alkylamines, then distilling and fusing the residues at 180 °C.[14] 2-Aryl-1,3-isoquinoline-diones **5f-5j** were obtained in 80-90% yields by refluxing homophthalic anhydride **1** with aromatic amines in acetic acid.[15] 4-Alkyl-1,3-isoquinolinediones **13** were prepared in 60-80% yields by refluxing an alkyl halide with a solution of 1,3-isoquinolinedione (large excess) and sodium methoxide (10:1 ratio) in methanol or THF-methanol, the excess 1,3-isoquinolinediones were removed by crystallization and the pure products were obtained by flash chromatographic separation of the residues. Acetonitrile (CP grade) was first refluxed with phosphorus pentoxide and distilled, then refluxed with anhydrous potassium carbonate and redistilled. Benzene (AR grade) was dried with sodium and distilled before use. Pyridine (AR grade) was dried with potassium hydroxide and distilled before use. ^{t}BuOH was first dried with sodium and distilled, then further dried with potassium and redistilled immediately before use. Other reagents were CP or AR grade and were used as received without further purification.

TPP Sensitized Photooxygenation Reactions of 1,3-Isoquinolinediones 5 and 13

General procedure: The light source was a 500 W medium pressure mercury lamp in a water cooling jacket which was further surrounded by a layer of solution filter (aqueous sodium nitrite) to cut off light of wavelength shorter than 400 nm. The solution of 1,3-isoquinolinediones **5** or **13** and TPP was placed in several glass tubes (20 ml each) and irradiated around the light source under constant dry oxygen bubbling. The reaction course was monitored by TLC. For the reactions of **5a-5j**, the following procedure of work up was employed which could efficiently avoid the hydrolysis of the triketones **6b-6j** on silica gel during the chromatographic separation: At the end of reaction, the solvents were removed *in vacuo* and the residue was dissolved in acetonitrile. The precipitated TPP was removed by filtration and washed with acetonitrile. The combined filtrate and washings were concentrated to ca. 10 ml and diluted with benzene (10 ml) and then further diluted with petroleum ether (b.p. 60-90 °C, 60 ml). The resultant solution was immediately poured onto the top of a silica gel column and eluted with an excess of petroleum ether (b.p. 60-90 °C) to remove the benzene and acetonitrile. Subsequent elution of the column with petroleum ether (b.p. 60-90 °C)-ethyl acetate afforded the photooxygenation products. For reactions of **13**, in order to avoid the possible thermal decomposition of the hydroperoxides **14**, a similar procedure of work up was used except that all the concentration of solutions containing the hydroperoxides was performed *in vacuo* at temperatures below 50 °C.

Reaction of ***5a***: A solution of **5a** (161 mg, 1 mmol) and TPP (5 mg, 0.01 mmol) in benzene-pyridine (5:1 v/v, 20 ml) was irradiated for 10 h to afford **6a** (145 mg, 83 %). No corresponding product **7a** was found.

1,3,4(*2H*)-Isoquinolinetrione 6a. Yellow prisms from acetonitrile, m.p. 229-230 °C (sublimes, decomp.) (lit. 229-229.5 °C).[6a] IR: 3200, 3150, 3070, 2900, 1740, 1706, 1675, 1588, 1364, 1340, 1295, 1258, 1220, 971, 857, 748 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 7.8-8.3 (4H, m, ArH), 11.80 (1H, br, s, NH) ppm. MS (m/z, %): 175 (M^+, 8.0), 147 (M–CO, 67.4), 132 (19.0), 104 (100).

Reaction of ***5b***: A solution of **5b** (700 mg, 4 mmol) and TPP (20 mg, 0.04 mmol) in benzene-pyridine (5:1 v/v, 80 ml) was irradiated for 11 h to afford **6b** (576 mg, 76 %) and **7b** (124 mg, 15 %).

2-Methyl-1,3,4(*2H*)-isoquinolinetrione 6b. Pale yellow prisms from ethyl acetate-acetone, m.p. 190-191 °C (sublimes) (lit. 190-191 °C).[6a] IR: 3050, 2910, 1725, 1700, 1662, 1582, 1415, 1358, 1329, 1283, 1238, 1078, 752 cm^{-1}. ^1H NMR (60 MHz): 3.60 (3H, s, CH_3), 7.9-8.7 (4H, m, ArH) ppm. MS (m/z, %): 189 (M^+, 2.6), 161 (M–CO, 55.8), 132 (8.3), 104 (100).

***N*-Methyl-3-hydroxybenzoisofuran-1-one-3-carbamide 7b**. Colorless needles from petroleum ether (b.p. 60-90 °C)-acetone, m.p. 170-172 °C (decomp.). IR: 3320, 3100, 2900, 2880, 1755, 1670, 1548, 1403, 1272, 1113, 930, 690 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6, in equilibrium with **12b**): 2.79 (3H, s, CH_3), 2.80 (3H, s, CH_3), 7.65 (2H, d, *J* 7.5, ArH), 7.68 (2H, t, *J* 7.5, ArH), 7.78 (2H, t, *J* 7.5, ArH), 7.86 (2H, d, *J* 7.5, ArH), 7.93 (2H, br, 2 × NH) ppm. FAB-MS (m/z, %): 208 (M+1, 11.0), 207 (M^+, 54.8), 206 (100), 190 (M+1–H_2O, 0.8), 162 (M+1–H_2O–CO, 16.5). Anal. $C_{10}H_9NO_4$. Calcd: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.00; H, 4.33; N, 6.74.

Reaction of ***5c***: A solution of **5c** (378 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 11 h to afford **6c** (305 mg, 75 %) and **7c** (53 mg, 12 %).

2-Ethyl-1,3,4(*2H*)-isoquinolinetrione 6c. Yellow plates from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 106-107.5 °C (lit. 107-107.5 °C).[6a] IR: 3080, 2980, 1721, 1698, 1669, 1583, 1360, 1338, 1281, 1249, 1103, 755 cm^{-1}. ^1H NMR (60 MHz): 1.25 (3H, t, *J* 7.5, CH_3), 4.10 (2H, q, *J* 7.5, CH_2), 7.7-8.1 (4H, m, ArH) ppm. MS (m/z, %): 203 (M^+, 36.1), 175 (M–CO, 21.7), 132 (18.4), 104 (100).

***N*-Ethyl-3-hydroxybenzoisofuran-1-one-3-carbamide 7c**. Colorless prisms from acetone, m.p. 194-196 °C (decomp.). IR: 3330, 3100, 2880, 2620, 1755, 1665, 1530, 1461, 1268, 1095, 915, 708, 690 cm^{-1}. ^1H NMR (60 MHz, acetone-d_6, in equilibrium with **12c**): 1.05 (6H, t, *J* 7.5, 2 × CH_3), 3.12 (2H, q, *J* 7.5, CH_2), 3.13 (2H, q, *J* 7.5, CH_2), 7.2-7.9 (8H, m, ArH), 8.4 (2H, br, 2 × NH) ppm. FAB-MS (m/z, %): 222 (M+1, 1.0), 204 (M+1–H_2O, 0.4), 91 (100). Anal. $C_{11}H_{11}NO_4$. Calcd: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.75; H, 4.85; N, 6.34.

Reaction of ***5d***: A solution of **5d** (502 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 12 h. The mixture was concentrated and the precipitated **6d** was filtered out and washed with benzene. The combined filtrate and washings were removed of TPP and separated to afford **6d** (totally 415 mg, 78 %) and **7d** (57 mg, 10 %).

2-Benzyl-1,3,4(*2H*)-isoquinolinetrione 6d. Bright yellow prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate-acetonitrile, m.p. 190-191 °C (sublimes) (lit. 185-186 °C).[6a] IR: 3050, 3020, 2980, 1719, 1702, 1674, 1595, 1430, 1357, 1280, 1242, 755, 700 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 5.66 (2H, s, CH_2), 7.1-7.5 (5H, m, ArH), 7.7-8.1 (4H, m, ArH) ppm. MS (m/z, %): 265 (M^+, 38.7), 237 (M–CO, 6.4), 219 (7.8), 174 (7.1), 132 (9.0), 118 (10.4), 104 (100).

***N*-Benzyl-3-hydroxybenzoisofuran-1-one-3-carbamide 7d**. Colorless needles from petroleum ether (b.p. 60-90 °C)-acetone, m.p. 196-198 °C (decomp.). IR: 3270, 3050, 2800, 1750, 1655, 1540, 1269, 930, 695 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6, in equilibrium with **12d**): 4.31 (2H, s, CH_2), 4.32 (2H, s, CH_2), 7.22-7.26 (6H, m, ArH), 7.29-7.32 (4H, m, ArH), 7.62 (2H, br, ArH), 7.68 (2H, t, *J* 7.5, ArH), 7.79 (2H, br, ArH), 7.88 (2H, d, *J* 7.5, ArH), 9.17 (2H, br, 2 × NH) ppm. FAB-MS (m/z, %): 284 (M+1, 1.9), 266 (M+1–H_2O, 0.3), 91 (100). Anal. $C_{16}H_{13}NO_4$. Calcd: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.62; H, 4.75; N, 5.03.

Reaction of ***5e***: A solution of **5e** (410 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 11 h to afford **6e** (322 mg, 74 %) and **7e** (62 mg, 13 %).

2-(2-Hydroxyethyl)-1,3,4(*2H*)-isoquinolinetrione 6e. Pale yellow prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 119-121 °C (lit. 121-123 °C).[5] IR: 3330 (broad), 3080, 2950, 2900, 2880, 1723, 1700, 1670, 1585, 1378, 1350, 1280, 1258, 1240, 1082, 750 cm^{-1}. ^1H NMR (60 MHz): 3.77 (2H, t, *J* 7.5, CH_2), 4.18 (2H, t, *J* 7.5, CH_2), 7.7-8.1 (4H, m, ArH) ppm. MS (m/z, %): 219 (M^+, 36.0), 191 (M–CO, 3.8), 176 (82.1), 160 (74.1). 132 (37.6), 104 (100). Anal. $C_{11}H_9NO_4$. Calcd: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.23; H, 4.32; N, 6.31.

***N*-(2-Hydroxyethyl)-3-hydroxybenzoisofuran-1-one-3-carbamide 7e**. Colorless needles from benzene-acetone-ethyl acetate, m.p. 138-139.5 °C. IR: 3320, 3230, 3020, 2800, 2640, 1775, 1672, 1540, 1460, 1250, 1089, 930, 680 cm^{-1}. ^1H NMR (60 MHz, acetone-d_6, in equilibrium with **12e**): 3.1-3.8 (8H, m, 4 × CH_2), 7.4-8.0 (8H, m, ArH) ppm. FAB-MS (m/z, %): 238 (M+1, 26.3), 220 (M+1–H_2O, 7.8), 91 (100). Anal. $C_{11}H_{11}NO_5$. Calcd: C, 55.70; H, 4.67; N, 5.91. Found: C, 55.83; H, 4.82; N, 5.90.

Reaction of ***5f***: A solution of **5f** (474 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 12 h to afford **6f** (324 mg, 65 %) and **7f** (108 mg, 20 %).

2-Phenyl-1,3,4(*2H*)-isoquinolinetrione 6f. Pale yellow prisms from petroleum ether (b.p. 60-90 °C)-benzene-acetonitrile, m.p. 228-229 °C (sublimes) (lit. 203-205 °C).[16] IR: 3080, 1738, 1710, 1685, 1595, 1362, 1290, 1263, 1000, 750 cm^{-1}. ^1H NMR (60 MHz): 7.4-7.7 (5H, m, ArH), 8.5-8.8 (4H, m, ArH) ppm. MS (m/z, %): 251 (M^+, 35.5), 223 (M–CO, 41.9), 179 (40.8), 132 (15.1), 104 (100).

***N*-Phenyl-3-hydroxybenzoisofuran-1-one-3-carbamide 7f**. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 181-183 °C (decomp.). IR: 3285, 3050, 2810, 1760, 1663, 1598, 1527, 1430, 1256, 1131, 1110, 942, 695 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, in equilibrium with **12f**): 7.17 (2H, t, *J* 7.5, ArH), 7.35-7.38 (4H, m, ArH), 7.64-7.70 (8H, m, ArH), 7.78 (2H, t, *J* 7.5, ArH), 7.92 (2H, d, *J* 7.5, ArH), 9.37 (2H, br, 2 × NH) ppm. FAB-MS (m/z, %): 270 (M+1, 5.5), 269 (M^+, 32.2), 268 (100), 224 (M+1–H_2O–CO, 22.0). Anal. $C_{15}H_{11}NO_4$. Calcd: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.97; H, 4.15; N, 5.13.

Reaction of ***5g***: A solution of **5g** (534 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 8 h. The mixture was concentrated and the precipitated **6g** was filtered out and washed with benzene. The combined filtrate and washings were removed of TPP and separated to afford **6g** (totally 425 mg, 76 %) and **7g** (108 mg, 18 %).

2-(4-Methoxyphenyl)-1,3,4(*2H*)-isoquinolinetrione 6g. Yellow prisms from acetonitrile, m.p. 287-288 °C (sublimes, decomp.). IR: 3080, 2950, 2850, 2760, 1731, 1723, 1684, 1588, 1506, 1361, 1290, 1259, 745 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 3.83 (3H, s, CH_3), 7.00 (2H, d, *J* 8.0, ArH), 7.22 (2H, d, *J* 8.0, ArH), 7.8-8.3 (4H, m, ArH) ppm. MS (m/z, %): 281 (M^+, 76.6), 253 (M–CO, 100), 238 (72.0), 104 (85.1). Anal. $C_{16}H_{11}NO_4$. Calcd: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.44; H, 3.89; N, 4.80.

***N*-(4-Methoxyphenyl)-3-hydroxybenzoisofuran-1-one-3-carbamide 7g**. Colorless needles from benzene-acetone, m.p. 153-155 °C. IR: 3310, 3030, 2800, 1760, 1660, 1533, 1502, 1247, 1100, 935, 691 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, in equilibrium with **12g**): 3.73 (6H, s, 2 × OCH_3), 6.90 (4H, d, *J* 8.0, ArH), 7.67-7.72 (8H, m, ArH), 7.80 (2H, br, ArH), 7.91 (2H, d, *J* 7.5, ArH), 9.25 (1H, br, OH), 10.32 (1H, br, NH), 10.61 (1H, br, NH), 13.58 (1H, br, OH) ppm. FAB-MS (m/z, %): 300 (M+1, 4.0), 299 (M^+, 32.3), 298 (100), 254 (M+1–H_2O–CO, 24.0). Anal. $C_{16}H_{13}NO_5$. Calcd: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.13; H, 4.13; N, 4.68.

*Reaction of **5h***: A solution of **5h** (510 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 10 h to afford **6h** (338 mg, 63 %) and **7h** (126 mg, 22 %).

2-(4-Fluorophenyl)-1,3,4(*2H*)-isoquinolinetrione 6h. Yellow prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate-acetonitrile, m.p. 242-243 °C (sublimes). IR: 3100, 3080, 3050, 1734, 1700, 1683, 1590, 1499, 1361, 1290, 1263, 1222, 841, 743 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 7.0-7.4 (4H, m, ArH), 7.8-8.3 (4H, m, ArH) ppm. MS (m/z, %): 269 (M^+, 32.2), 241 (M–CO, 62.0), 197 (55.7), 104 (100). Anal. $C_{15}H_8FNO_3$. Calcd: C, 66.92; H, 3.00; N, 5.20. Found: C, 66.76; H, 3.24; N, 5.17.

***N*-(4-Fluorophenyl)-3-hydroxybenzoisofuran-1-one-3-carbamide 7h**. Colorless needles from benzene-acetone, m.p. 164-166 °C. IR: 3280, 3240, 3100, 2550, 1760, 1663, 1535, 1500, 1258, 1217, 940, 835, 690 cm^{-1}. ^1H NMR (60 MHz, acetone-d_6, in equilibrium with **12h**): 7.16 (4H, dd, *J* 8.0, 9.0, ArH), 7.6-8.1 (12H, m, ArH) ppm. FAB-MS (m/z, %): 288 (M+1, 27.1), 270 (M+1–H_2O, 10.8), 254 (M+1–H_2O–CO, 24.0), 91 (100). Anal. $C_{15}H_{10}FNO_4$. Calcd: C, 62.72; H, 3.51; N, 4.88. Found: C, 62.55; H, 3.54; N, 4.78.

*Reaction of **5i***: A solution of **5i** (574 mg, 2 mmol) and TPP (10 mg, 0.02 mmol) in benzene-pyridine (5:1 v/v, 40 ml) was irradiated for 8 h. The mixture was concentrated and the precipitated **6i** was filtered out and washed with benzene. The combined filtrate and washings were removed of TPP and separated to afford **6i** (totally 453 mg, 75 %) and **7i** (89 mg, 14 %).

2-(1-Naphthyl)-1,3,4(*2H*)-isoquinolinetrione 6i. Bright yellow prisms from benzene-petroleum ether (b.p. 60-90 °C)-acetonitrile, m.p. 278-279 °C (sublimes). IR: 3050, 1729, 1680, 1582, 1390, 1357, 1283, 1269, 805, 778, 742 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 7.3-7.8 (4H, m, ArH), 7.8-8.3 (7H, m, ArH) ppm. MS (m/z, %): 301 (M^+, 100), 273 (M–CO, 87.0), 229 (37.4), 104 (68.0). Anal. $C_{19}H_{11}NO_3$. Calcd: C, 75.74; H, 3.68; N, 4.65. Found: C, 75.33; H, 3.97; N, 4.67.

***N*-(1-Naphthyl)-3-hydroxybenzoisofuran-1-one-3-carbamide 7i**. Colorless needles from benzene-acetone, m.p. 187-189 °C (decomp.). IR: 3230, 3040, 2780, 1758, 1669, 1518, 1500, 1265, 1258, 936, 792, 681 cm^{-1}. ^1H NMR (60 MHz, acetone-d_6, in equilibrium with **12i**): 7.3-8.1 (22H, m, ArH), 9.7 (2H, br, 2 × NH) ppm. FAB-MS (m/z, %): 320 (M+1, 3.4), 302 (M+1–H_2O, 1.1), 91 (100). Anal. $C_{19}H_{13}NO_4$. Calcd: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.35; H, 3.91; N, 4.28.

*Reaction of **5j***: A solution of **5j** (790 mg, 2.80 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 13 h. The mixture was concentrated and the precipitated **6j** was filtered out and washed with benzene. The combined filtrate and washings were removed of TPP and separated to afford **6j** (totally 350 mg, 42 %) and **10** (245 mg, 49 %).

2-(4-Nitrophenyl)-1,3,4(*2H*)-isoquinolinetrione 6j. Pale yellow prisms from acetonitrile, m.p. 269-270 °C (sublimes, decomp.). IR: 3090, 3060, 1730, 1700, 1681, 1590, 1510, 1357, 1339, 1279, 1255, 998, 853, 825, 740 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 7.57 (2H, d, *J* 8.0, ArH), 7.8-8.3 (4H, m, ArH), 8.33 (2H, d, *J* 8.0, ArH) ppm. MS (m/z, %): 296 (M^+, 10.3), 268 (M–CO, 61.0), 238 (15.5), 104 (100). Anal. $C_{15}H_8N_2O_5$. Calcd: C, 60.81; H, 2.72; N, 9.46. Found: C, 60.74; H, 2.78; N, 9.47.

4-Nitroacetanilide 10. Pale yellow needles from benzene-acetone, m.p. 217-219 °C (lit. 215-216 °C).[17] IR: 3280, 3170, 3130, 3060, 2780, 1675, 1610, 1590, 1558, 1494, 1339, 1323, 1295, 1260, 1106, 1000, 845, 750 cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): 2.06 (3H, s, CH_3), 7.80 (2H, d, *J* 9.0, ArH), 8.16 (2H, d, *J* 9.0, ArH), 10.5 (1H, br, NH) ppm. MS (m/z, %): 180 (M^+, 25.6), 138 (100), 108 (32.7).

Reaction of ***13a***: A solution of **13a** (567 mg, 3 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 15 h to afford **15a** (64 mg, 10 %), **14a** (427 mg, 64 %) and **16a** (80 mg, 16 %) respectively.

2,3-Dimethyl-3-hydroperoxy-1,3(*2H*)-isoquinolinedione 14a. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 150-151.5 °C. IR: 3310, 3000, 2940, 1722, 1668, 1610, 1465, 1420, 1373, 1302, 1283, 1088, 772, 700 cm^{-1}. ^1H NMR (60 MHz): 1.58 (3H, s, CH_3), 3.34 (3H, s, CH_3), 7.3-7.8 (3H, m, ArH), 8.21 (1H, d, *J* 8.0, ArH), 9.33 (1H, s, OH) ppm. FAB-MS (m/z, %): 222 (M+1, 7.7), 204 (M+1–O, 100), 187 (M+1–OOH, 23.1), 186 (M–OOH, 19.4). Anal. $C_{11}H_{11}NO_4$. Calcd: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.55; H, 4.97; N, 6.32.

2,3-Dimethyl-3-hydroxy-1,3(*2H*)-isoquinolinedione 15a. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 119-121 °C. IR: 3490, 3080, 3000, 2940, 1718, 1664, 1603, 1468, 1422, 1375, 1340, 1298, 1275, 1250, 1080, 1040, 778, 702 cm^{-1}. ^1H NMR (60 MHz): 1.61 (3H, s, CH_3), 3.33 (3H, s, CH_3), 3.72 (1H, s, OH), 7.3-7.8 (3H, m, ArH), 8.11 (1H, d, *J* 8.0, ArH) ppm. MS (m/z, %): 205 (M^+, 14.4), 187 (M–H_2O, 0.4), 190 (M–CH_3, 53.2), 162 (M–CH_3–CO, 24.4), 148 (42.2), 105 (100). Anal. $C_{11}H_{11}NO_3$. Calcd: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.53; N, 6.79.

3-Hydroxy-3-methylbenzoisofuran-1-one 16a. Colorless prisms from petroleum ether (b.p. 60-90 °C)-acetone, m.p. 119-120 °C. IR: 3260, 2998, 1722, 1465, 1295, 1252, 1215, 1035, 880, 770, 715 cm^{-1}. ^1H NMR (500 MHz): 1.63 (3H, s, CH_3), 4.25 (1H, br, OH), 7.31-7.33 (2H, m, ArH), 7.46 (1H, t, *J* 7.5, ArH), 7.53 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 164 (M^+, 0.8), 149 (M–CH_3, 100), 146 (M–H_2O, 50.9), 104 (39.9). Anal. $C_9H_8O_3$. Calcd: C, 65.85; H, 4.91. Found: C, 65.67; H, 4.88.

Reaction of ***13b***: A solution of **13b** (609 mg, 3 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 15 h to afford **15b** (177 mg, 27 %), **14b** (353 mg, 50 %) and **16b** (69 mg, 13 %) respectively.

3-Ethyl-3-hydroperoxy-2-methyl-1,3(*2H*)-isoquinolinedione 14b. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 120-122 °C. IR: 3370, 2980, 2950, 1720, 1665, 1608, 1460, 1422, 1360, 1298, 1276, 1069, 770, 700 cm^{-1}. ^1H NMR (500 MHz): 0.62 (3H, t, *J* 7.5, CH_3), 1.84 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 2.09 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 3.38 (3H, s, CH_3), 7.53 (1H, t, *J* 8.0, ArH), 7.70-7.73 (2H, m, ArH), 8.20 (1H, d, *J* 8.0, ArH), 10.21 (1H, br, OH) ppm. FAB-MS (m/z, %): 236 (M+1, 100), 220 (M+1–O, 19.4), 203 (M+1–OOH, 30.8), 202 (M–OOH, 32.3). Anal. $C_{12}H_{13}NO_4$. Calcd: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.21; H, 5.62; N, 5.82.

3-Ethyl-3-hydroxy-2-methyl-1,3(*2H*)-isoquinolinedione 15b. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 107-108 °C. IR: 3480, 3070, 2980, 2950, 2880, 1713, 1660, 1603, 1464, 1420, 1376, 1300, 1202, 1081, 1055, 1000, 925, 760, 697 cm^{-1}. ^1H NMR (500 MHz): 0.76 (3H, t, *J* 7.5, CH_3), 1.88 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 1.94 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 3.38 (3H, s, CH_3), 3.66 (1H, br, OH), 7.49 (1H, t, *J* 7.5, ArH), 7.66-7.71 (2H, m, ArH), 8.16 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 219 (M^+, 0.6), 201 (M–H_2O, 0.3), 190 (M–C_2H_5, 100), 162 (M–C_2H_5–CO, 18.9), 149 (53.3), 105 (22.3). Anal. $C_{12}H_{13}NO_3$. Calcd: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.80; H, 6.04; N, 6.37.

3-Ethyl-3-hydroxybenzoisofuran-1-one 16b. Colorless needles from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 88-89 °C. IR: 3270, 2940, 2900, 1730, 1460, 1345, 1288, 1130, 900, 767, 700 cm^{-1}. ^1H NMR (60 MHz): 0.92 (3H, t, *J* 7.5, CH_3), 2.27 (2H, q, *J* 7.5, CH_2), 4.45 (1H, br, OH), 7.4-8.0 (4H, m, ArH) ppm. MS (m/z, %): 178 (M^+, 0.1), 160 (M–H_2O, 86.7), 149 (M–C_2H_5, 33.8), 104 (100). Anal. $C_{10}H_{10}O_3$. Calcd: C, 67.41; H, 5.66. Found: C, 67.18; H, 5.62.

Reaction of ***13c***: A solution of **13c** (795 mg, 3 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 15 h to afford **15c** (255 mg, 30 %), **14c** (405 mg, 45 %) and **16c** (108 mg, 15 %) respectively.

3-Benzyl-3-hydroperoxy-2-methyl-1,3(*2H*)-isoquinolinedione 14c. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 136-138 °C. IR: 3375, 3050, 3020, 2960, 2930, 1717, 1663, 1602, 1455, 1419, 1362, 1303, 1280, 1055, 1028, 700 cm^{-1}. ^1H NMR (500 MHz): 3.07 (1H, d, *J* 12.5, 1/2 CH_2), 3.11 (3H, s, CH_3), 3.35 (1H, d, *J* 12.5, 1/2 CH_2), 6.48-6.49 (2H, m, ArH), 7.02-7.05 (2H, m, ArH), 7.13 (1H, t, *J* 7.5, ArH), 7.52 (1H, t, *J* 7.5, ArH), 7.76 (1H, t, *J* 7.5, ArH), 7.82 (1H, d, *J* 7.5, ArH), 8.00 (1H, d, *J* 7.5, ArH), 10.42 (1H, s, OH) ppm. FAB-MS (m/z, %): 298 (M+1, 33.3), 282 (M+1–O, 14.4), 265 (M+1–OOH, 6.7), 264 (M–OOH, 8.8), 91 (100). Anal. $C_{17}H_{15}NO_4$. Calcd: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.69; H, 5.09; N, 4.85.

3-Benzyl-3-hydroxy-2-methyl-1,3(*2H*)-isoquinolinedione 15c. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 130-131.5 °C. IR: 3450, 3080, 3020, 2940, 2900, 1710, 1660, 1605, 1420, 1362, 1305, 1285, 1213, 1055, 789, 700 cm^{-1}. ^1H NMR (500 MHz): 3.13 (1H, d, *J* 12.5, 1/2 CH_2), 3.17 (3H, s, CH_3), 3.22 (1H, d, *J* 12.5, 1/2 CH_2), 3.71 (1H, br, OH), 6.57 (2H, d, *J* 7.5, ArH), 7.11 (2H, t, *J* 7.5, ArH), 7.18 (1H, t, *J* 7.5, ArH), 7.48 (1H, t, *J* 7.5, ArH), 7.67-7.72 (2H, m, ArH), 7.99 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 281 (M^+, 0.2), 263 (M–H_2O, 0.4), 190 (M–CH_2Ph, 100), 162 (M–CH_2Ph–CO, 8.2), 149 (41.7), 91 (62.8). Anal. $C_{17}H_{15}NO_3$. Calcd: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.33; H, 5.34; N, 4.91.

3-Benzyl-3-hydroxybenzoisofuran-1-one 16c. Light brown viscous oil. IR: 3350, 2920, 1740, 1600, 1463, 1287, 1110, 950, 895, 772, 700 cm^{-1}. ^1H NMR (60 MHz): 3.42 (2H, s, CH_2), 4.24 (1H, br, OH), 7.1-7.8 (9H, m, ArH) ppm. MS (m/z, %): 222 (M–H_2O, 100), 194 (14.1), 165 (59.2), 149 (M–$PhCH_2$, 20.0), 104 (22.9). Anal. $C_{15}H_{12}O_3$. Calcd: C, 74.99; H, 5.03. Found: C, 74.87; H, 5.12.

Reaction of ***13d***: A solution of **13d** (795 mg, 3 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 15 h to afford **15d** (255 mg, 30 %), **14d** (420 mg, 47 %) and **16b** (85 mg, 16 %) respectively.

3-Ethyl-3-hydroperoxy-2-phenyl-1,3(*2H*)-isoquinolinedione 14d. Pale yellow prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 161-162.5 °C. IR: 3420, 3070, 2980, 2940, 2870, 1723, 1680, 1600, 1488, 1452, 1365, 1300, 1267, 1242, 1196, 1158, 945, 760, 709, 700 cm^{-1}. ^1H NMR (500 MHz): 0.83 (3H, t, *J* 7.5, CH_3), 1.95 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 2.20 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 7.15-7.17 (2H, m, ArH), 7.38-7.50 (3H, m, ArH), 7.54 (1H, t, *J* 8.0, ArH), 7.71-7.78 (2H, m, ArH), 8.22 (1H, d, *J* 8.0, ArH), 9.87 (1H, br, OH) ppm. FAB-MS (m/z, %): 298 (M+1, 48.9), 282 (M+1–O, 16.5), 265 (M+1–OOH, 13.0), 264 (M–OOH, 9.8), 91 (100). Anal. $C_{17}H_{15}NO_4$. Calcd: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.56; H, 4.96; N, 4.73.

3-Ethyl-3-hydroxy-2-phenyl-1,3(*2H*)-isoquinolinedione 15d. Pale yellow prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 154-155.5 °C. IR: 3480, 3362, 3050, 2970, 1723, 1674, 1645, 1593, 1550, 1490, 1358, 1315, 1238, 1217, 1190, 1164, 756, 700 cm^{-1}. ^1H NMR (500 MHz): 0.92 (3H, t, *J* 7.5, CH_3), 2.03 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 2.08 (1H, dq, *J* 13.5, 7.5, 1/2 CH_2), 3.71 (1H, br, OH), 7.21 (2H, d, *J* 8.0, ArH), 7.47 (1H, t, *J* 8.0, ArH), 7.51-7.57 (3H, m, ArH), 7.74 (1H, t, *J* 8.0, ArH), 7.79 (1H, d, *J* 8.0, ArH), 8.20 (1H, d, *J* 8.0, ArH) ppm. MS (m/z, %): 281 (M^+, 7.1), 263 (M–H_2O, 0.8), 252 (M–C_2H_5, 100), 224 (M–C_2H_5–CO,

78.7), 162 (53.6), 133 (46.1), 105 (61.2). Anal. $C_{17}H_{15}NO_3$. Calcd: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.61; H, 5.37; N, 4.77.

Reaction of 13e: A solution of **13e** (645 mg, 3 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 15 h to afford **15e** (270 mg, 39 %) and **14e** (275 mg, 37 %) respectively. The corresponding product **16d** was not found.

3-Allyl-3-hydroperoxy-2-methyl-1,3(*2H*)-isoquinolinedione 14e. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 75-77 °C. IR: 3300, 3060, 3000, 2950, 2840, 1717, 1665, 1600, 1455, 1417, 1360, 1300, 1075, 1023, 750, 700 cm^{-1}. ^1H NMR (500 MHz): 2.57 (1H, dd, *J* 6.5, 12.5, 1/2CH_2), 2.79 (1H, dd, *J* 8.5, 12.5, 1/2CH_2), 3.35 (3H, s, CH_3), 4.91 (1H, d, *J* 17.0, 1/2 =CH_2), 4.99 (1H, d, *J* 10.0, 1/2 =CH_2), 5.21 (1H, dddd, *J* 6.5, 8.5, 10.0, 17.0, =CH–C), 7.55 (1H, t, *J* 7.5, ArH), 7.74 (1H, d, *J* 7.5, ArH), 7.77 (1H, d, *J* 7.5, ArH), 8.20 (1H, d, *J* 7.5, ArH), 10.07 (1H, s, OH) ppm. FAB-MS (m/z, %): 248 (M+1, 100), 232 (M+1–O, 43.3), 215 (M+1–OOH, 48.6), 214 (M–OOH, 51.1). Anal. $C_{13}H_{13}NO_4$. Calcd: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.15; H, 5.49; N, 5.67.

3-Allyl-3-hydroxy-2-methyl-1,3(*2H*)-isoquinolinedione 15e. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 84-84.5 °C. IR: 3480, 3090, 2990, 2950, 1710, 1658, 1602, 1462, 1418, 1360, 1300, 1200, 1160, 920, 758, 695 cm^{-1}. ^1H NMR (500 MHz): 2.57 (1H, dd, *J* 7.0, 13.0, 1/2CH_2), 2.63 (1H, dd, *J* 8.0, 13.0, 1/2CH_2), 3.34 (3H, s, CH_3), 3.76 (1H, br, OH), 4.93 (1H, d, *J* 17.0, 1/2 =CH_2), 5.05 (1H, d, *J* 10.0, 1/2 =CH_2), 5.42 (1H, dddd, *J* 7.0, 8.0, 10.0, 17.0, =CH–C), 7.48 (1H, t, *J* 7.5, ArH), 7.67 (1H, t, *J* 7.5, ArH), 7.71 (1H, d, *J* 7.5, ArH), 8.14 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 232 (M+1, 0.9), 213 (M–H_2O, 0.2), 190 (M–$CH_2CH{=}CH_2$, 100), 162 (M–$CH_2CH{=}CH_2$–CO, 13.7), 149 (63.0), 104 (12.0). Anal. $C_{13}H_{13}NO_3$. Calcd: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.58; H, 5.65; N, 6.08.

Reaction of 13f: A solution of **13f** (879 mg, 3 mmol) and TPP (15 mg, 0.03 mmol) in benzene-pyridine (5:1 v/v, 60 ml) was irradiated for 15 h to afford the unreacted **13f** (45 mg, a conversion of 95 %), **14f** (315 mg, 34 %) and **15f** (335 mg, 38 %) respectively. The corresponding product **16e** was not found.

3-Benzoylmethyl-3-hydroperoxy-2-methyl-1,3(*2H*)-isoquinolinedione 14f. Colorless crystals from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 136-138 °C. IR: 3450, 3380, 3060, 2950, 1715, 1660, 1600, 1460, 1420, 1372, 1311, 1295, 1233, 1024, 762, 700 cm^{-1}. ^1H NMR (500 MHz): 3.31 (1H, d, *J* 13.5, 1/2 CH_2), 3.43-3.50 (4H, m, 1/2 CH_2 and CH_3), 7.36-8.23 (9H, m, ArH), 9.23 (1H, br, OH) ppm. FAB-MS (m/z, %): 326 (M+1, 1.3), 325 (M^+, 1.7), 310 (M+1–O, 3.8), 219 (M+1–OOH, 3.8), 218 (M–OOH, 3.0), 91 (100). Anal. $C_{18}H_{15}NO_5$. Calcd: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.46; H, 4.59; N, 4.45.

3-Benzoylmethyl-3-hydroxy-2-methyl-1,3(*2H*)-isoquinolinedione 15f. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 157-158 °C. IR: 3370, 3050, 2930, 1708, 1658, 1600, 1460, 1415, 1355, 1296, 1220, 1205, 1060, 1037, 765, 695 cm^{-1}. ^1H NMR (500 MHz): 3.35 (3H, s, CH_3), 3.80 (1H, d, *J* 16.0, 1/2 CH_2), 3.82 (1H, d, *J* 16.0, 1/2 CH_2), 4.00 (1H, br, OH), 7.40 (2H, t, *J* 7.5, ArH), 7.48 (1H, t, *J* 7.5, ArH), 7.54 (1H, t, *J* 7.5, ArH), 7.64 (1H, t, *J* 7.5, ArH), 7.72 (1H, d, *J* 7.5, ArH), 7.78 (2H, d, *J* 7.5, ArH), 8.20 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 309 (M^+, 0.5), 291 (M–H_2O, 3.5), 190 (M–CH_2COPh, 8.0), 161 (42.9), 120 (32.1), 105 (100). Anal. $C_{18}H_{15}NO_4$. Calcd: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.71; H, 4.88; N, 4.54.

Cyclization of 7b in the Presence of Acetic Anhydride

A mixture of **7b** (62 mg, 0.3 mmol) and acetic anhydride (1 ml) was heated at 100 °C until the white solid completely disappeared. The resulted yellow solution was evaporated *in vacuo* to give 56 mg of **6b**, yield 99 %. Pale yellow prisms from ethyl acetate-acetone, m.p. 190-192 °C (sublimes). The IR and ^1H NMR spectra were the same as those of an authentic sample.

Hydrolysis of ***6b***

To a solution of **6b** (189 mg, 1 mmol) in THF (50 ml) was added 800 mg of anhydrous sodium acetate and 20 ml of water, the solution was continuously stirred until **6b** completely disappeared. The THF was removed *in vacuo* and the aqueous residue was acidified with concentrated HCl to *pH* = 3, then saturated with NaCl and extracted with ether. The ether layer was collected and dried over anhydrous Na_2SO_4. Evaporation of the solution to dryness yielded **8b** (200 mg, 97 %).

1-Hydroxy-2-methyl-2,3-dihydro-3-oxo-*1H*-isoindole-1-carboxylic acid 8b. Colorless needles from benzene-methanol, m.p. 150-152 °C (decomp.). IR: 3380, 3150, 2950, 2780, 2590, 2500, 2470, 1724, 1690, 1642, 1600, 1480, 1431, 1390, 1270, 1255, 1220, 1120, 1078, 1045, 1000, 945, 780, 740, 700 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): 2.98 (3H, s, CH_3), 7.60 (1H, t, *J* 8.0, ArH), 7.65-7.68 (2H, m, ArH), 7.74 (1H, d, *J* 8.0, ArH) ppm. MS (m/z, %): 207 (M^+, 0.1), 190 (M–OH, 1.3), 163 (M–CO_2, 19.2), 162 (M–OH–CO, 51.3), 161 (M–H_2O–CO, 68.4), 147 (38.3), 146 (M–CO_2–OH, 100). Anal. $C_{10}H_9NO_4$. Calcd: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.77; H, 4.46; N, 6.72.

Methanolysis of ***6b***

To a solution of **6b** (189 mg, 1 mmol) in methanol (50 ml) was added 800 mg of anhydrous sodium acetate, the solution was continuously stirred until **6b** completely disappeared. The solvent was removed *in vacuo* and the residue was separated by flash chromatography to yield **9** (218 mg, 99 %).

Methyl 1-hydroxy-2-methyl-2,3-dihydro-3-oxo-*1H*-isoindole-1-carboxylate 9. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 131-133 °C. IR: 3500, 3380, 3050, 2900, 2600, 1741, 1682, 1435, 1385, 1261, 1126, 1082, 1002, 775, 700 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): 2.96 (3H, s, CH_3), 3.73 (3H, s, CH_3), 7.60 (1H, t, *J* 7.5, ArH), 7.64-7.66 (2H, m, ArH), 7.74 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 221 (M^+, 0.03), 189 (M–MeOH, 0.9), 162 (100), 161 (47.1), 104 (69.0). Anal. $C_{11}H_{11}NO_4$. Calcd: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.53; H, 4.92; N, 6.32.

Gram Scale Preparation of 1,3,4(2H)-Isoquinolinetriones by Using the Photooxygenation Procedure.

Preparation of ***6a***: A suspension of **5a** (10.0 g, 0.062 mol) in 340 ml benzene-pyridine (5:1, v/v) containing 200 mg of TPP was placed in 12 glass tubes and irradiated under oxygen bubbling for 36 h. The solvents were removed *in vacuo* and the residue was dissolved in 300 ml of acetonitrile. The solution was passed through a short activated charcoal column and the column was washed by a further 200 ml of acetonitrile. Subsequent concentration and crystallization gave 8.50 g of pure **6a**, yield 78 %.

Preparation of ***6b***: A solution of **5b** (10.0 g, 0.057 mol) in 340 ml benzene-pyridine (5:1, v/v) containing 200 mg of TPP was placed in 12 glass tubes and irradiated under oxygen bubbling for 36 h. The solvents were removed *in vacuo* and to the residue were added 50 ml of benzene and 15 ml of acetic anhydride. The mixture was refluxed for 10 min and the solvents were again removed *in vacuo*. The residue was dissolved in 300 ml of acetonitrile and the solution was passed through a short activated charcoal column. The column was washed by a further 200 ml of acetonitrile. Concentration and crystallization gave 9.20 g of pure **6b**, yield 85 %.

Preparation of ***6f***: By using a procedure similar to that for the preparation of **6b**, from 10.0 g of **5f** and with 36 h of irradiation, we obtained 8.50 g of pure **6f**, yield 81 %.

Reduction of ***14a*** *with Triphenylphosphine*

To a solution of **14a** (155 mg, 0.7 mmol) in acetone (10 ml) was added 262 mg (1 mmol) of triphenyl phosphine, the exothermal reaction effected swiftly. The solvent was removed *in vacuo* and flash chromato-

graphic separation of the residue gave 137 mg of **15a** (96 % yield). Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 119-120 °C. The IR and ^{1}H NMR spectra were identical with those of an authentic sample.

*Alkaline Cleavage of **14a***

To a solution of ^{t}BuOK prepared by dissolving potassium (160 mg, 4 mmol) in absolute ^{t}BuOH (20 ml) was added, under stirring at room temperature, 160 mg of **14a** (0.72 mmol). The mixture was further stirred until **14a** completely disappeared and then was allowed to stand overnight. The resultant light yellow solution was poured into aqueous NH_4Cl (250 mg in 100 ml water) and extracted with ether. The ether layer was collected, dried over anhydrous Na_2SO_4, concentrated and crystallized to give **19a** (70 mg, 55 %). The aqueous layer was further carefully neutralized with concentrated hydrochloric acid to *pH* = 4 and extracted with ether. The ether layer was again collected and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* and subsequent flash chromatographic separation of the residue afforded **16a** (45 mg, 38 %).

1-Hydroxy-1,2-dimethyl-2,3-dihydro-3-oxo-*1H*-isoindole 19a. Colorless prisms from petroleum ether (b.p. 60-90 °C)-ethyl acetate, m.p. 134-136 °C (decomp.). IR: 3240, 2980, 2930, 1675, 1615, 1470, 1430, 1396, 1138, 1100, 1080, 950, 762, 700 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 1.56 (3H, s, CH_3), 2.87 (3H, s, CH_3), 7.50 (1H, t, *J* 7.5, ArH), 7.61-7.65 (3H, m, ArH) ppm. MS (m/z, %): 177 (M^+, 2.7), 162 (M–CH_3, 68.7), 160 (M–OH, 22.4), 159 (M–H_2O, 100), 130 (92.0). Anal. $C_{10}H_{11}NO_2$. Calcd: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.63; H, 6.38; N, 8.01.

*Dehydration of **19a***

To a solution of **19a** (40 mg, 0.23 mmol) in chloroform (1 ml) was added one drop of dry Et_2O/HCl and the mixture was allowed to stand overnight. Evaporation of the solvents afforded **20** (35 mg, yield 97 %).

1-Methylene-2-methyl-2,3-dihydro-3-oxo-*1H*-isoindole 20. Colorless oil. IR: 2970, 2900, 1702, 1643, 1470, 1422, 1380, 1135, 1055, 1024, 772, 700 cm^{-1}. ^{1}H NMR (500 MHz): 3.27 (3H, s, CH_3), 4.85 (1H, d, *J* 1.7, 1/2 =CH_2), 5.34 (1H, d, *J* 1.7, 1/2 =CH_2), 7.48 (1H, t, *J* 7.5, ArH), 7.56 (1H, t, *J* 7.5, ArH), 7.68 (1H, d, *J* 7.5, ArH), 7.81 (1H, d, *J* 7.5, ArH) ppm. MS (m/z, %): 160 (M+1, 100), 159 (M^+, 53.0), 130 (43.8), 104 (37.9). Anal. $C_{10}H_9NO$. Calcd: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.53; H, 5.64; N, 8.87.

*Crystal Structure of **7f***

$C_{15}H_{11}NO_4$, *M* = 269.26. Monoclinic, space group $P2_1/n$(#14) with *a* = 10.001(1), *b* = 9.791(2), *c* = 13.345(3) Å, α = 90°, β = 101.32(2)°, γ = 90°, *V* = 1281.2(4) Å^3, *Z* = 4, *Dc* = 1.396 g cm^{-3}. Absorption coefficient 1.025 mm^{-1}, *F*(000) = 560.00. A colorless prismatic crystal of 0.20 × 0.20 × 0.30 mm was used. Data were collected on a Rigaku AFC7R diffractometer equipped with graphite-monochromated Mo-Kα radiation using the ω-2θ scan technique to a maximum 2θ value of 50.0°. The structure was solved by direct method (MITHRIL84) and refined by full-matrix least-squares method. A total of 2411 independent reflections [*R* (int) = 0.044] were used in the refinement which converged with *R* = 0.038 and *Rw* = 0.039.

*^{1}H NMR Studies on the Enolization of Compounds **5b** and **13a** in Solution*

*Compound **5b** in methanol-d_4.* The ^{1}H NMR (500 MHz) spectrum of a solution of **5b** in CD_3OD (ca. 0.1 mol dm^{-3}) immediately recorded after preparation showed normal absorption of a single keto tautomer: 3.31 (3H, s, CH_3), 4.06 (2H, s, CH_2), 7.34 (1H, d, *J* 7.5, 5-H), 7.42 (1H, t, *J* 7.5, 7-H), 7.60 (1H, t, *J* 7.5, 6-H), 8.09 (1H, d, *J* 7.5, 8-H) ppm. On standing at 30 °C for 30 min, the intensity of the peak at 4.06 ppm decreased and a new

triplet appeared at 4.04 ppm ($J_{H\text{-}D}$ = 3.3 Hz) which indicated that a H-D exchange on C_4 of the keto form **5b** occurred. On prolonged standing, both the singlet at 4.06 ppm and the triplet at 4.04 ppm disappeared. In all cases, no other absorption except that of the keto form could be detected.

Compound 13a in pyridine-d_5. The ^{1}H NMR (500 MHz) spectrum of **13a** in pyridine-d_5 (ca. 0.1 mol dm^{-3}) revealed that it existed predominantly as a single keto tautomer: 1.58 (3H, d, *J* 7.5, 4-CH_3), 3.36 (3H, s, NCH_3), 3.95 (1H, q, *J* 7.5, 4-H), 7.31 (1H, d, *J* 7.5, 5-H), 7.38 (1H, t, *J* 7.5, 7-H), 7.54 (1H, t, *J* 7.5, 6-H), 8.32 (1H, d, *J* 7.5, 8-H) ppm. However, there were also two weak singlets appearing at 1.81 and 3.38 ppm which were assigned to the signals of the two methyl groups in the enol complex **24** ($R^1 = R^2 = CH_3$, see below), the portion of which, determined by integration, was about 2 %. No other signals were detected.

On vigorously shaking with solid NaOH, the above solution turned from nearly colorless to yellow with the absorption of the keto form gradually decreased and eventually signals of a sodium salt of the enolic anion **23** ($R^1 = R^2 = CH_3$) were obtained which was identical to those of **24**: 1.81 (3H, s, 4-CH_3), 3.38 (3H, s, NCH_3), 7.43 (1H, t, *J* 7.5, 7-H), 7.67 (1H, t, *J* 7.5, 6-H), 8.07 (1H, d, *J* 7.5, 5-H), 8.29 (1H, d, *J* 7.5, 8-H) ppm.

Ab Initio Calculations

The geometric optimizations were carried out at HF/6-31G* level and by using Schlegel's algorithm[18], with the planar constraint of all the skeleton ring, and the Mulliken population analyses were performed at HF/6-31G* optimized structure. All the calculations were performed by using the Gaussian-94 program package[19] at an SGI station.

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