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Singlet oxygenation of 4-(4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran-5-yl)-2-pyridone: non-stereospecific 1,4-addition of singlet oxygen to a 1,3-diene system and thermal rearrangement of the resulting 1,4-endoperoxides to stable 1,2-dioxetanes

Masakatsu Matsumoto,* Shigeru Nasu, Manabu Takeda, Hiroyuki Murakami and Nobuko Watanabe

Department of Materials Science, Kanagawa University, Tsuchiya, Hiratsuka, Kanagawa 259-1205, Japan. E-mail: matsumo@info.kanagawa-u.ac.jp

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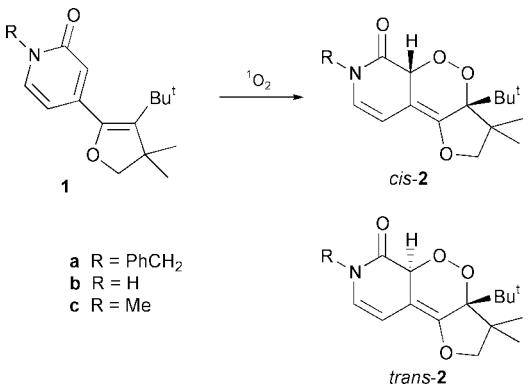
Singlet oxygen adds easily to a 1,3-diene 1, whose *E–Z* double bond isomerization can not take place, to give a mixture of stereoisomeric 1,4-endoperoxides 2 which rearranges into a thermally stable 1,2-dioxetane 5 selectively on heating in benzene.

Diels–Alder addition of singlet oxygen to certain 1,3-dienes has been reported to give 1,4-endoperoxides with lack of stereospecificity, for which two mechanisms have been proposed. The first is a mechanism where *E–Z* double bond isomerization of 1,3-diene proceeds under the reaction conditions and is followed by a concerted Diels–Alder addition of singlet oxygen.[1] The second is a stepwise addition of singlet oxygen, including participation of zwitterions, which causes isomerization of the initial 1,3-diene unit prior to the intramolecular cyclization.[2] Although these two are crucially different from each other (concerted or stepwise process), both mechanisms include, in common, isomerization of the initial double bond in the substrate followed by cyclization giving the endoperoxide. However, there formally remain other pathway(s) for Diels–Alder addition of singlet oxygen leading to a mixture of stereoisomeric endoperoxides without any isomerization of the initial double bond in a substrate; especially for the stepwise mechanism, if the intramolecular attack of a peroxidic intermediate such as peroxirane and zwitterion occurs onto both π-faces of the remaining double bond, the Diels–Alder addition would give a mixture of stereoisomeric endoperoxides (the third mechanism). We report here an example of non-stereospecific 1,4-addition of singlet oxygen for which the third mechanism would be the most advantageous. In addition, we report a unique rearrangement of the resulting 1,4-endoperoxides which occurs simply on heating without any catalyst to yield thermally stable 1,2-dioxetanes exclusively.

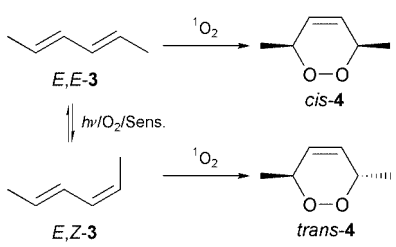
In the course of our investigation on the design of highly efficient chemiluminescent substrates, we attempted to examine the singlet oxygenation of *N*-benzyl-4-(4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran-5-yl)-2-pyridone **1a**. When a pyridone **1a** (100 mg) was irradiated together with a catalytic amount of tetraphenylporphin (TPP) in dichloromethane (5 mL) with a 940 W Na-lamp at −78 °C, singlet oxygenation proceeded smoothly (1 h) to give a 65 : 35 mixture of stereoisomeric 1,4-endoperoxides **2a** exclusively (Scheme 1).† The mixture was separated into *cis*-**2a** (major isomer, colorless granules, mp 127.0–128.0 °C) and *trans*-**2a** (minor isomer, colorless oil) by silica gel chromatography. These two endoperoxides were characterized by ^{1}H and ^{13}C NMR, ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, NOE, IR and mass spectral analysis.‡ It should be noted that little isomerization between *cis*- and *trans*-**2a** was observed under the reaction conditions and even at higher temperature. The parent pyridone **1b** and *N*-methyl analog **1c** were similarly oxygenated to give the corresponding mixture of isomeric endoperoxides **2b** and **2c**, respectively, though these mixtures could not be separated into pure isomers. These results provide the first example wherein singlet oxygenation of a 1,3-diene gives a mixture of stereoisomeric 1,4-endoperoxides though neither of the carbon–carbon double bonds of the diene system can undergo *E–Z* isomerization.

The rather simple 1,3-diene, (*E,E*)-hexa-2,4-diene (*E,E*-**3**) undergoes stereospecific 1,4-addition of singlet oxygen to give a *cis*-endoperoxide (*cis*-**4**), whereas singlet oxygenation of (*E,Z*)-hexa-2,4-diene (*E,Z*-**3**) affords a mixture of *cis*-**4** (main product) and its *trans*-isomer (*trans*-**4**).[1,2] Gollnick has suggested that the (*E,Z*)-diene isomerizes to the (*E,E*)-isomer prior to the concerted 1,4-addition of singlet oxygen as shown in Scheme 2,[1] and his suggestion has very recently been supported by Motoyoshiya *et al.* who have observed a similar phenomenon for the sensitized photooxygenation of 1-arylpenta-1,3-dienes.[3] On the other hand, O'Shea and Foote have suggested that the non-stereospecific endoperoxide formation from *E,Z*-**3** is most likely rationalized by the formation of a zwitterion which causes the isomerization leading to the *cis*-endoperoxide (*cis*-**4**) as shown in Scheme 3.[2] However, neither mechanism would apply to the present oxygenation of **1** giving **2** without any revision, since no *E-Z* double bond isomerization and only s-*cis*–s-*trans* isomerization can occur for the furanylpyridones **1**.

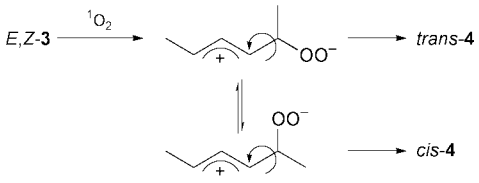
The concerted Diels–Alder reaction of singlet oxygen with **1** would give only *cis*-**2** so that this mechanism should be ruled out for the reaction giving *trans*-**2**, though *trans*-**2** could be formally produced by an antarafacial attack of singlet oxygen. Thus, a stepwise mechanism should be considered to rationalize



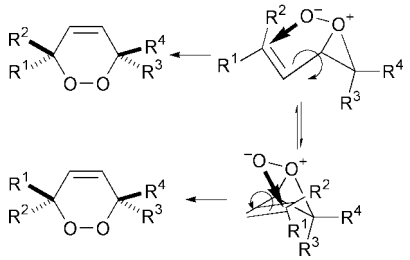
Scheme 1



Scheme 2



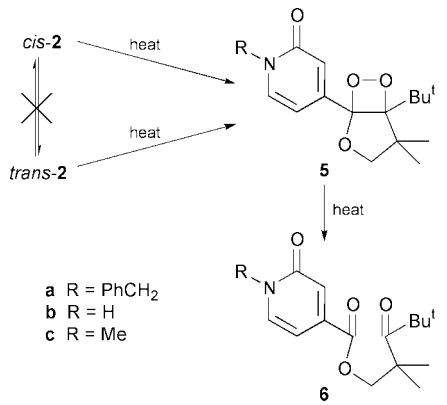
Scheme 3



Scheme 4

the present non-stereospecific 1,4-addition of singlet oxygen. Since no *E*–*Z* isomerization of the double bond in pyridone and dihydrofuran rings can occur for **1**, the isomerization of an intermediary zwitterion as in Scheme 3 can not proceed. The most likely explanation is that the initially formed peroxirane or zwitterion attacks the remaining double bond of the starting 1,3-diene from both π-faces. This process should be operable when two ethylene units of the 1,3-diene lie far from apart in the same plane as illustrated in Scheme 4 in which a peroxirane intermediate is adopted for convenience. Such structure of a 1,3-diene system is most likely feasible for **1** because of steric repulsion between the pyridone ring and a *tert*-butyl group in the dihydrofuran ring.§ Although singlet oxygen attacks possibly in the first step to a double bond of the pyridone and/or the double bond of dihydrofuran for **1**, the initial addition of singlet oxygen to the former may be more likely since the addition to the latter may lead more or less to a dioxetane as in the case of 4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofurans bearing an aryl[4] or a styryl group[5] at the 5-position.

Although endoperoxides *cis* and *trans*-**2a** were not isomerized to each other, both endoperoxides changed gradually into a dioxetane **5a** even at room temperature. On heating in hot benzene, **2a** was transformed selectively into **5a** (colorless needles, mp 114.0–115.0 °C)¶ which was stable enough for handling at room temperature though it decomposed into a ketoester **6a** in hot toluene (Scheme 5). It should be noted that the thermolysis of **5a** (90 °C, toluene) gave light (λ_{max} = 411 nm) whose spectrum was in good agreement with the fluorescence spectrum of **6a**. Both reaction rates for isomerization of endoperoxide **2a** to 1,2-dioxetane **5a** and for decomposition of dioxetane **5a** to ketoester **6a** followed first-order kinetics. Thus, these reaction rates were measured in toluene-d_8 at various temperatures by ^{1}H NMR spectroscopy, and their activation



Scheme 5

Table 1 Thermal rearrangement of 1,4-endoperoxides **2a** to 1,2-dioxetanes **5a** and thermal decomposition of **5a** to ketoesters **6a**[ab]

Peroxide	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}	$t_{1/2}$ (25 °C)/yr
cis-**2a**	29.8	13.9	25.7	0.07
trans-**2a**	29.1	11.9	25.5	0.05
5a	26.2	−9.5	29.1	19.6

[a] Rearrangement of **2a** to **5a** was carried out in toluene-d_8 at 40–60 °C, whereas decomposition of **5a** to **6a** was performed in toluene-d_8 at 90–110 °C. [b] For all the Arrhenius plots, $r > 0.999$.

parameters were estimated from Arrhenius plots as summarized in Table 1, which shows that dioxetanes **5a** are far more stable than endoperoxides **2a**. The other endoperoxides **2b** and **2c** rearranged thermally also into the corresponding dioxetanes **5b** and **5c**, whose thermolysis gave ketoesters **6b** and **6c**, respectively. Free energies of activation ($\Delta G^{\ddagger}$/kcal mol^{-1}) for these peroxides were also estimated as follows; **2b**: 24.3–24.4, **2c**: 24.4–24.7, **5b**: 27.1 and **5c**: 28.4.

Various 1,4-endoperoxides have been known to undergo acid-catalyzed decomposition to carbonyl fragments, presumably through 1,2-dioxetanes, whose spectroscopic identification and/or isolation has not been achieved in most cases. Schaap *et al*. have reported a successful spectroscopic identification of a dioxetane formed by the rearrangement of endoperoxide, and suggested that the relatively unstable dioxetane as a chemiluminescent substrate can be 'stored' as a precursor endoperoxide and generated when needed.[6] In contrast, the present dioxetanes **5** are far more stable than endoperoxides **2** so that they can be stored as such rather than be regarded as precursors.

Notes and references

† Similar singlet oxygenation of **1a** at 0 °C gave a 57 : 43 mixture of *cis* and *trans* isomers of **2a**.

‡ *Selected data*: for *cis*-**2a**: δ_H(500 MHz, $CDCl_3$) 1.11 (s, 3H), 1.15 (s, 9H), 1.25 (s, 3H), 3.81 (d, *J* 8.2 Hz, 1H), 4.41 (d, *J* 15.1 Hz, 1H), 4.45 (d, *J* 8.2 Hz, 1H), 4.82 (d, *J* 15.1 Hz, 1H), 5.13 (d, *J* 2.3 Hz, 1H), 5.59 (d, *J* 5.7 Hz, 1H), 6.95 (dd, *J* 5.7 and 2.3 Hz, 1H), 7.16–7.20 (m, 2H), 7.28–7.38 (m, 3H); δ_C(125 Hz, $CDCl_3$) 18.1, 24.9, 26.4, 36.5, 45.3, 47.0, 78.1, 80.6, 82.6, 106.0, 113.1, 128.1, 128.2, 129.0, 134.9, 135.1, 138.3, 167.4; MS (*m*/*z*, %) 369 (M^+, 46), 325 (4), 313 (9), 285 (12), 284 (16), 230 (33), 212 (60), 91 (100).

For *trans*-**2a**: δ_H(500 MHz, $CDCl_3$) 1.11 (s, 3H), 1.12 (s, 9H), 1.28 (s, 3H), 3.79 (d, *J* 8.2 Hz, 1H), 4.31 (d, *J* 15.4 Hz, 1H), 4.49 (d, *J* 8.2 Hz, 1H), 5.06 (d, *J* 15.4 Hz, 1H), 5.23 (d, *J* 2.3 Hz, 1H), 5.61 (d, *J* 5.5 Hz, 1H), 6.93 (dd, *J* 5.5, 2.3 Hz, 1H), 7.19–7.23 (m, 2H), 7.30–7.39 (m, 3H); δ_C(125 Hz, $CDCl_3$) 18.0, 24.8, 26.7, 36.3, 45.3, 46.9, 78.8, 80.7, 83.2, 105.7, 113.4, 128.0, 128.3, 129.1, 134.5, 135.2, 138.2, 167.0; MS (*m*/*z*, %) 369 (M^+, 47), 313 (10), 285 (13), 284 (17), 230 (35), 212 (63), 91 (100).

§ An MM2 calculation suggested that the torsion angle between the pyridone ring and the dihydrofuran ring in **1a** was 73.4° at the most stable conformation.

¶ *Selected data* for **5a**: δ_H(500 MHz, $CDCl_3$) 1.08 (s, 9H), 1.13 and 1.31 (2 s, 6H), 3.80 (d, *J* 8.3 Hz, 1H), 4.54 (d, *J* 8.3 Hz, 1H), 5.09 (d, *J* 14.4 Hz, 1H), 5.20 (d, *J* 14.4 Hz, 1H), 6.32 (dd, *J* 7.4, 1.8 Hz, 1H), 6.94 (d, *J* 1.8 Hz, 1H), 7.23–7.38 (m, 6H); δ_C(125 Hz, $CDCl_3$) 18.2, 24.9, 27.0, 36.7, 45.5, 51.8, 80.7, 105.3, 105.7, 114.7, 121.4, 128.1, 128.1, 129.0, 135.9, 136.7, 147.8, 161.9; MS (*m*/*z*, %) 369 (M^+, 51), 337 ($M^+ - O_2$, 2), 313 (11), 230 (39), 212 (71), 185 (15), 91 (100).

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