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Formation of 1,2,4-trioxolanes via 9,10-dicyanoanthracene(DCA)-sensitized photo-oxygenation of 2,2-diaryl-3-(2,2-diarylvinyl)oxiranes

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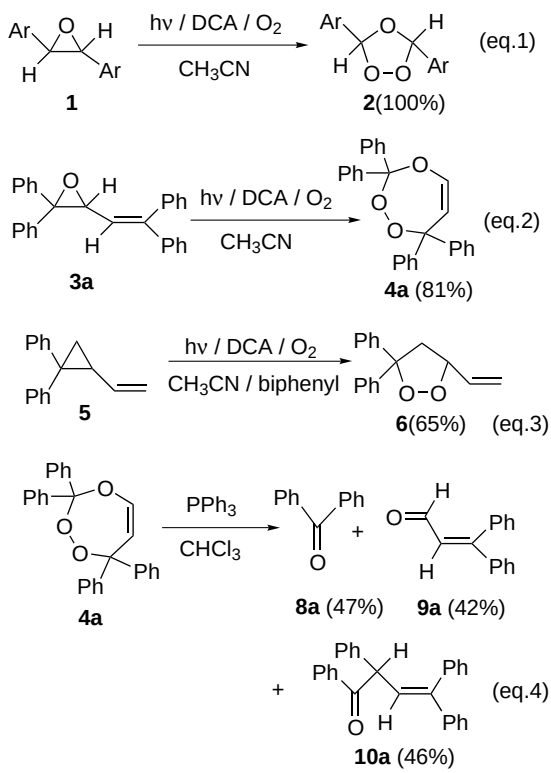
Abstract—9,10-Dicyanoanthracene-sensitized photo-oxygenation of 2,2-diaryl-3-(2,2-diarylvinyl)oxiranes **3** in acetonitrile did not afford the corresponding 1,2,4-trioxepines **4**, but 1,2,4-trioxolanes **7**. The structural assignment of **7** was reported, and the mechanism of the formation of **7** was proposed. © 2001 Elsevier Science Ltd. All rights reserved.

Extensive efforts have been devoted on the synthesis of cyclic peroxides since the discovery of artemisinin and related antimalarial 1,2,4-trioxanes.[1–8] Photoinduced electron transfer (PET)[9–11] oxygenation is an unique method in preparing cyclic peroxides because peroxide structure is easily constructed for arylated cyclopropanes,[12] oxiranes,[13,14] aziridines,[15] and olefins.[16–22,†] Futamura et al. reported that 9,10-dicyanoanthracene(DCA)-sensitized photo-oxygenation of 1,2-diaryloxiranes **1** afforded the corresponding five-membered compounds, 1,2,4-trioxolanes **2** (eq. 1 in Scheme 1).[23,24] However, same authors reported that DCA-sensitized photo-oxygenation of 2,2-diphenyl-3-(2,2-diphenylvinyl)oxirane **3a** afforded the corresponding seven-membered ring compound, 1,2,4-trioxepine **4a** (eq. 2 in Scheme 1).[25] On the contrary, it was also reported that DCA-sensitized photo-oxygenation of 1,1-diphenyl-2-vinylcyclopropane **5** afforded a five-membered ring compound, 1,2-dioxolane **6** (eq. 3 in Scheme 1).[26] These contrastive results and our own experiences in preparing various arylated cyclic peroxides[27–32] let us question the formation of **4a** from **3a** and prompted us to study PET oxygenation of the aryl substituted vinyloxiranes **3**. Herein, we wish to report that DCA-sensitized photo-oxygenation of 2,2-diaryl-3-(2,2-diarylvinyl)oxiranes **3** did not afford the trioxepines **4**, but 1,2,4-trioxolanes **7**.



Scheme 1.

Keywords: 1,2,4-trioxolane; vinyl oxirane; 9,10-dicyanoanthracene; photo-oxygenation; electron transfer; reaction mechanism.

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† 9,10-Dicyanoanthracene(DCA)-sensitized PET oxygenation reaction is utilized for the synthesis of antimalarial cyclic peroxides such as 1,5-diaryl-6,7- dioxabicyclo[3.2.2]nonanes[17–19] and 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes.[20–22]

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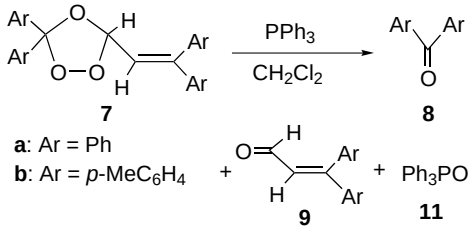
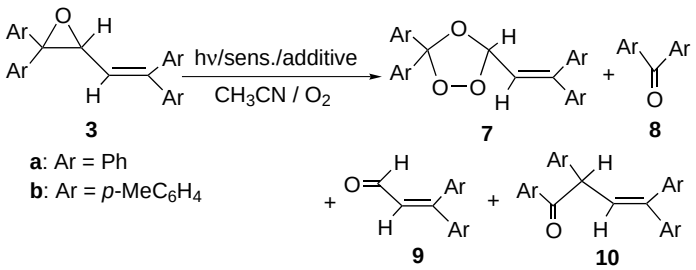
When an oxygen purged acetonitrile (50 ml) solution of **3a** (0.50 mmol) and DCA (0.01 mmol) was selectively irradiated (λ>360 nm) with a 2 kW Xe lamp for 7 h, 3,3-diphenyl-5-(2,2-diphenylvinyl)-1,2,4-trioxolane **7a** (37%) was obtained along with benzophenone **8a** (18%) and 3,3-diphenyl-2-propenal **9a** (6%) at 59% conversion (Scheme 2, run 1 in Table 1).‡ However, the trioxepine **4a** was not produced at all. The structure of **7a** was determined by its spectral data. The absorption at 258.5 nm (ε=18400 in acetonitrile) in the UV spectrum could be due to the 2,2-diphenylvinyl moiety which is inconsistent with the structure of trioxepine **4a**. The structure of **7a** was also confirmed by comparisons of the NMR data of *cis*- and *trans*-3-phenyl-5-(2-phenylvinyl)-1,2,4-trioxolanes.[33,34] Further structural confirmation was achieved by the reduction of **7** by triphenylphosphine. Futamura et al. reported that **8a** (47%), **9a** (42%) and 1,2,4,4-tetraphenyl-3-butenone **10a** (46%) were produced in the deoxygenation of **4a** by triphenylphosphine (eq. 4 in Scheme 1). It is considerably difficult to rationalize the formation of **10a** from **4a**. However, when **7ab** were treated with triphenylphosphine in dichloromethane at 20–25°C, diarylketones **8ab**, 3,3-diaryl-2-propenals **9ab**, and triphenylphosphine oxide **11** were isolated in excellent yields (Scheme 3, run 1–2 in Table 2).

In order to get insight into the reaction, we carried out the following experiments. When **3a** was subjected to the photo-oxygenation in the presence of biphenyl (3 equiv. to **3a**) under otherwise the same conditions, significant increase in the yield of **7a** (80%) was observed with concomitant decrease in the reaction time from 420 to 7 min (run 2 in Table 1).[13,14] This observation is consistent with a mechanism in which biphenyl radical cation catalyzes the formation of **7**. The electron transfer mechanism was further supported by the observation that **7a** was still formed in the 2,4,7-trinitrofluorenone(TNF)-sensitized oxygenation of **3** (runs 3 and 6 in Table 1). No oxygenation of **3a** to **7a** occurred in the absence of DCA, oxygen, and/or visible light. Similar photo-oxygenation was also observed for



Scheme 3.



Scheme 2.

Table 1. Photo-sensitized oxygenation of 3-vinyloxiranes **3** by using various sensitizers[a]

Run	Substrate	Sensitizer	Irrad. time (min)	Conv. (%)	Yields of products/%[b]			
					7	**8**	**9**	**10**
1	**3a**	DCA[c]	420	59	37	18	6	0
2	**3a**	DCA-BiP[d]	7	100	80	15	5	0
3	**3a**	TNF[e]	40	100	5	5	0	49
4	**3b**	DCA[c]	30	100	47	36	5	0
5	**3b**	DCA-BiP[d]	5	100	52	24	6	0
6	**3b**	TNF[e]	50	100	17	25	0	9

[a] **3**=0.5 mmol, CH_3CN=50 ml; irradiated by a 2 kW Xe lamp, λ>360 nm.
[b] Isolated yield.
[c] DCA=0.01 mmol
[d] DCA=0.01 mmol, BiP(biphenyl)=1.5 mmol.
[e] **3**=0.2 mmol, TNF (2,4,7-trinitrofluorenone)=0.1 mmol, CH_3CN=20 ml.

‡ All products were isolated by silica gel TLC and characterized by their spectral data. Selected data for **7a**: mp 120–120.5°C (*n*-hexane); IR (KBr, cm^{-1}) 3060, 3045, 2940, 1635,1600, 1578, 1492, 1080, 1058, 1030, 990; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85 (d, 1H, J=8.1 Hz), 5.93 (d, 1H, J=8.1 Hz), 7.18–7.50 (m, 18H), 7.53–7.66 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 102.97 (d, 1C), 110.42 (s, 1C), 119.49 (d, 1C) 126.69 (d, 2C), 127.15 (d, 2C), 128.07 (d, 2C), 128.16 (d, 3C), 128.22 (d, 5C), 128.39 (d, 1C), 128.60 (d, 2C), 129.14 (d, 1C), 130.04 (d, 2C), 137.69 (s, 1C), 137.90 (s, 1C), 140.37 (s, 1C), 140.84 (s, 1C), 151.93 (s, 1C); Anal. C, 82.70; H, 5.70, requires C, 82.74; H, 5.46; MS (EI) 374 (M^+–32, 100); UV λ_{max} (CH_3CN) 258.5 (ε 18400) nm.

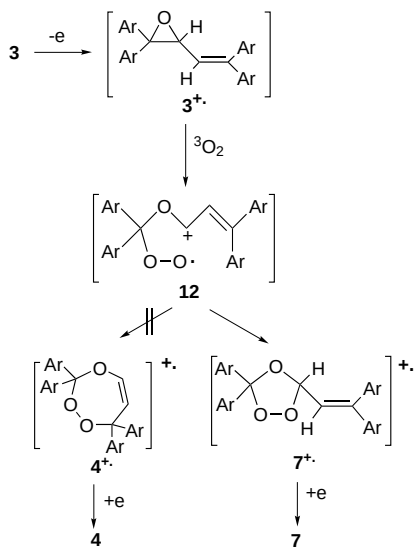
Table 2. Deoxygenation of trioxolanes **7** by triphenylphosphine.[a]

Run	Substrate	Time (min)	Conv. (%)	Yields of products (%)[b]		
				8	**9**	**11**
1	**7a**	90	98	96	94	94
2	**7b**	90	100	81	93	99

[a] **7** = 0.2 mmol, PPh_3 = 0.2 mmol, CH_2Cl_2 = 10 ml, 20–25°C.
[b] Isolated yield.

3b. Thus, trioxolane **7b** was also obtained in moderate yield along with 4,4′-dimethylbenzophenone **8b** and 3,3-di(*p*-methylphenyl)-2-propenal **9b** (runs 4–5 in Table 1), which may extend the generality of the DCA-sensitized conversion of the vinyl oxiranes **3** to trioxolanes **7**.[§]

On the basis of the above results, we propose a plausible mechanism involving a peroxy cation radical **12** for the formation of trioxolane **7** (Scheme 4). Thus, single electron oxidation of **3** produces the radical cation of **3** ($\mathbf{3}^{+\bullet}$) which reacts with molecular oxygen to generate **12**. The resulting peroxy radical cation **12** undergoes cyclization to give a trioxolane cation radical ($\mathbf{7}^{+\bullet}$), which would be reduced to afford **7**. Molecular orbital calculations (PM3) strongly support the preferential formation of $\mathbf{7}^{+\bullet}$ rather than $\mathbf{4}^{+\bullet}$. Thus, the heats of formation of **12**, $\mathbf{7}^{+\bullet}$, and $\mathbf{4}^{+\bullet}$ were calculated to be 275.6, 261.2, and 294.4 kcal/mol, respectively, which indicates that conversion of **12** to $\mathbf{4}^{+\bullet}$ is endothermic but that of **12** to $\mathbf{7}^{+\bullet}$ is highly exothermic.[¶]



Scheme 4.

In summary, we have discovered that the DCA-sensitized PET oxygenation of arylvinyl oxiranes **3** afforded 1,2,4-trioxolanes **7**. We are now conducting the studies on the relationship between the Fe(II)-mediated fragmentation, the antimalarial intermediates, and the antimalarial activities for **7** and other cyclic peroxides.

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[§] *cis*-3-Phenyl-5-(2-phenylvinyl)-1,2,4-trioxolane was also obtained in 47% yield by the DCA-sensitized photo-oxygenation of *trans*-2-phenyl-3-(2-phenylvinyl)-1,2,4-trioxolane in the presence of biphenyl. The structure was determined by its authentic spectral data.[33]

[¶] The geometries of **12**, $\mathbf{4}^{+\bullet}$, and $\mathbf{7}^{+\bullet}$ were fully optimized and the details will be reported elsewhere.

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