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Photochemical formation and decomposition of 8-[β-arylethenyl]-2,2,6-trimethyl-7,9,10-trioxa-tricyclo[6.2.2.0^{1,6}]dodec-11-ene to novel 6-hydroxy-1,7,7-trimethyl-2-oxa-bicyclo[4.4.0]dec-4-en-3-one in the presence of oxygen

Vishal Sharma [a], Vivek Gupta [b], Sumati Anthal [b], Ajit K. Saxena [c], Mohan Paul S. Ishar [a,*]

[a] Bio-Organic and Photochemistry Laboratory, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, Punjab, India
[b] Post-Graduate Department of Physics, University of Jammu, Jammu Tawi 180 006, India
[c] Indian Institute of Integrative Medicine, Jammu Tawi 180 006, India

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ABSTRACT

Irradiation of (*E,E*)-arylidene-β-ionones in the presence of oxygen leads to the formation of 8-[β-arylethenyl]-2,2,6-trimethyl-7,9,10-trioxa-tricyclo[6.2.2.0^{1,6}]dodec-11-enes (**3**). However, prolonged irradiation in the presence of oxygen leads to their conversion to 6-hydroxy-1,7,7-trimethyl-2-oxa-bicyclo [4.4.0]dec-4-en-3-one (**4**), apparently proceeding through addition of oxygen to the side chain π-bond in 3.

Endoperoxides include 1,2-dioxanes, 1,2,4-trioxanes, and 1,2,4,5-tetraoxanes, all of which possess the critical peroxide linkage. These are of significant interest on account of their synthetic applications as well as their valuable biological activities.[1] Among them, the 1,2,4-trioxane moiety constitutes the pharmacophore responsible for cytotoxic and antimalarial activity.[2] The molecules possessing the 1,2,4-trioxane moiety have attracted increasing attention after a naturally occurring endoperoxide, artemisinin and its synthetic derivatives, emerged as the first line drug for the treatment of uncomplicated *Plasmodium falciparum* malaria.[3] It has also been discovered that Fe^{2+}-triggered activation of endoperoxide moiety leads to the formation of radical species, which are implicated in cytotoxicity, DNA damage, oxidative stress, and damage to the electron transport chain with possible anticancer applications.[4]

Advancements have been made in the preparation of both semi-synthetic and synthetic endoperoxides, however, in general, endoperoxides are still considered as unstable entities and are difficult to isolate, particularly, in many photooxidation reactions.[5] Various methods reported to synthesize stable endoperoxides include cyclization of vicinal hydroxyl-hydroperoxide with ketones,[6] cyclization of hydroperoxyacetals with olefins or epoxides,[7] trapping of β-peroxycarbocations with aldehydes or ketones,[8] and autooxidation of imines in the presence of aldehydes.[9]

Attention has also been focused on the preparation of stable endoperoxides photochemically. Earlier we had reported that on irradiation of (*E,E*)-arylidine-β-ionones in the presence of oxygen, the in situ generated diene (tetrahydrobenzopyran, **2**) undergoes regioselective photocycloaddition with molecular oxygen to generate endoperoxide (**3**) possessing a stable trioxane moiety (Scheme 1).[10] These molecules are thermally stable and can be stored even at ambient temperature for long durations.

Herein, we report the formation of endoperoxides **3a–c** through direct irradiation of (*E,E*)-arylidine-β-ionones (**1a–c**) in thiophene-free dry benzene under constant bubbling of oxygen, using immersion well type Pyrex glass, water-cooled photoreactor with UV light from a 125-Watt medium pressure Hg arc placed coaxially inside the reactor. However, when **1d** and **1e** were directly irradiated under UV light in the presence of oxygen there is no formation of endoperoxides **3d** and **3e**. Therefore, **1d** and **1e** were irradiated under nitrogen atmosphere to obtain pyrans **2d** and **2e**, which upon further irradiation in the presence of oxygen afforded endoperoxides **3d** and **3e**. Endoperoxides **3a–e** were characterized by rigorous spectroscopic techniques such as IR, ^{1}H & ^{13}C NMR, and mass. It was observed that another compound (**4**) was also formed in traces along with endoperoxides (Scheme 2 and Table 1). Finally, the structure of **3a** was confirmed by X-ray crystallography (Fig. 1).[11]

To investigate the formation of compound **4**, endoperoxides **3a–e** were further irradiated in the presence of oxygen when they were completely transformed into **4** and their respective aldehydes (**5**, Scheme 3). Compound **4** and aldehydes were characterized

* Corresponding author. Tel.: +91 183 2258802x3321; fax: +91 183 2258820.
E-mail address: mpsishar@yahoo.com (M.P.S. Ishar).

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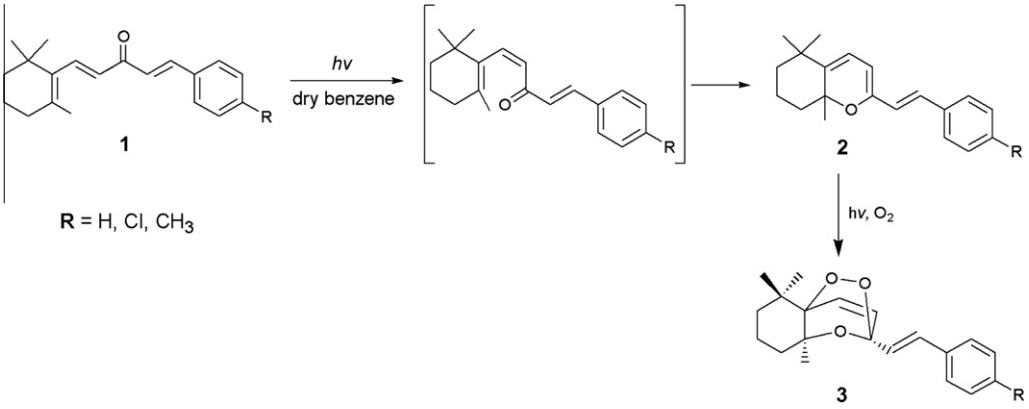
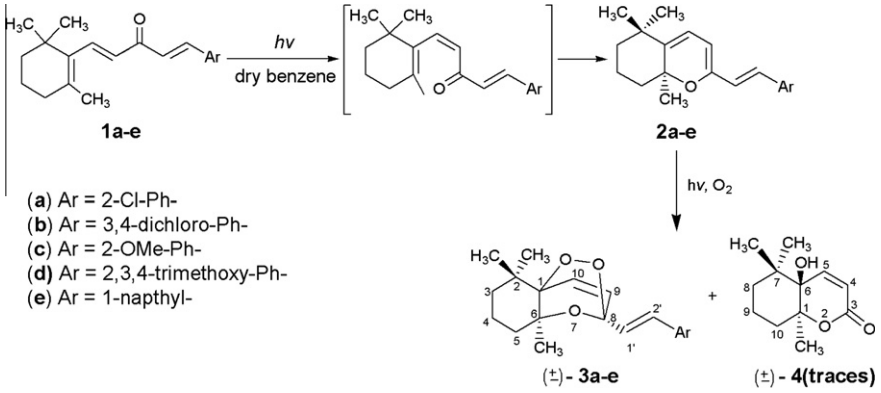


Scheme 1. Formation of stable endoperoxides.



Scheme 2. Synthesis of endoperoxides **3a–e** and compound **4**.

Table 1
Reaction time (min) and yield (%) of products (**3a–e**)

Compound no.	Reaction time (min)	Yield (%) of **3**
3a	40	65
3b	40	60
3c	35	65
3d	30	60
3e	30	60

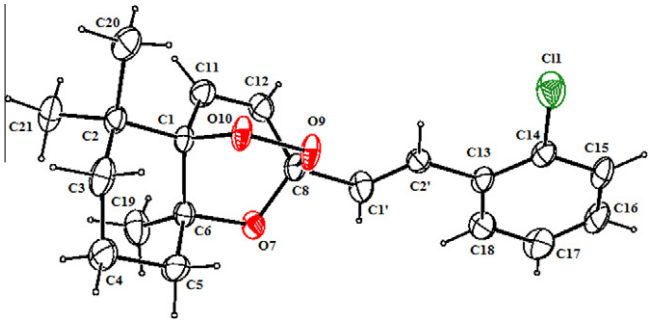
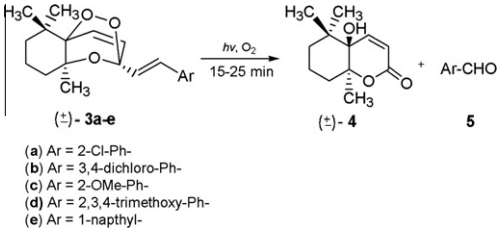


Figure 1. X-ray structure of **3a**.

spectroscopically (IR, ^{1}H & ^{13}C NMR, mass) and finally, the structure of **4** was confirmed by X-ray crystallography (Fig. 2).[12]

As such endoperoxides **3a–e** do not decompose when irradiated in UV light under inert atmosphere (nitrogen atmosphere). The probable mechanism for the formation of compound **4** may involve the decomposition of 1,2-dioxetane which are formed in situ by 1,2-cycloaddtion of singlet $^{1}O_2$ at the C_1'-$C_2'\pi$ bond of the



Scheme 3. Photodecomposition of **3a–e** in the presence of O_2.

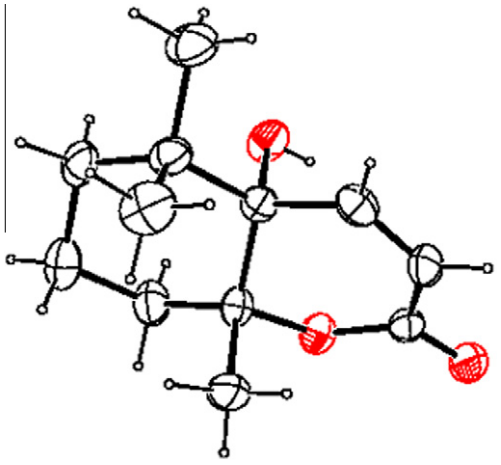


Figure 2. X-ray structure of **4**.

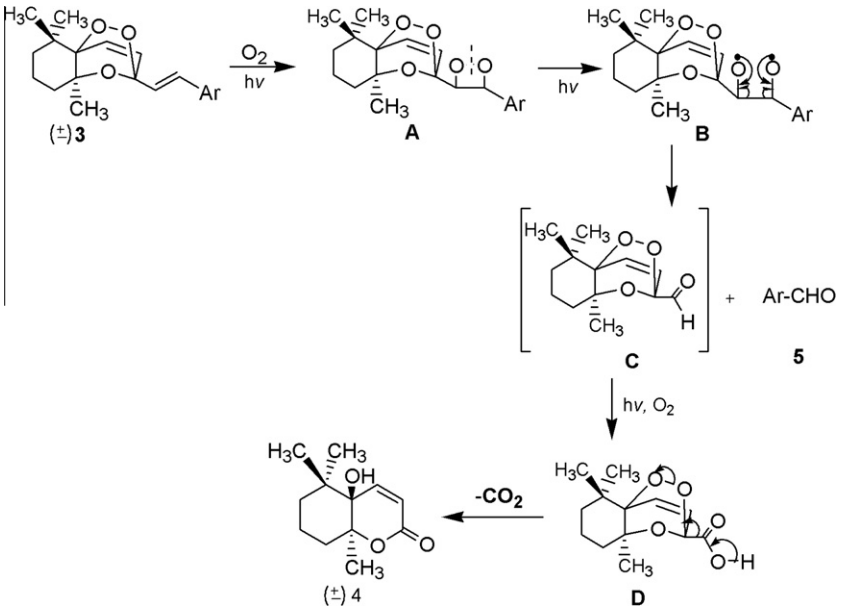


Figure 3. Mechanism for the formation of **4**.

Table 2
Reaction time (min) and yield (%) of **4**

Decomposition of compounds	Reaction time (min)	Yield (%) of **4**
3a	25	40
3b	25	40
3c	20	40
3d	15	45
3e	15	45

endoperoxides (Fig. 3). Formation and decomposition of 1,2-dioxetanes into carbonyl compounds has precedents in the literature.[13]

It was also observed that compounds **1d–e** possessing electron rich aryl moieties readily undergo photocycloaddition with molecular oxygen to generate endoperoxides (**3d–e**) in 30 min without using any sensitizer and take less time (15 min) for decomposition to **4** whereas compounds **1a–c** take longer time for formation (40 min) and decomposition (Table 2) of endoperoxides (**3a–c**).

Thus, the present investigations have revealed that although the endoperoxides **3a**–**e** are stable under nitrogen atmosphere, these are decomposed when irradiated by UV light in the presence of oxygen. Apparently, the aryl moiety acts as sensitizer for the formation of endoperoxides **3a**–**e** and also for 1,2-dioxetanes. There are reports available for the addition of molecular oxygen to electron rich molecules under photochemical conditions in the absence of sensitizer wherein several mechanisms for $^1O_2$ generation have been described.[14]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.028.

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