



## The *O*-neophyl rearrangement of 1,1-diaryloxy radicals. Experimental evidence for the formation of an intermediate 1-oxaspiro[2,5]octadienyl radical

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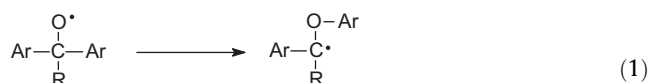
### ABSTRACT

A product study on the reactivity of a 1,1-diaryloxy radical bearing 2,2-diphenylcyclopropyl groups in the *para*-positions has been carried out. The exclusive formation of a product deriving from cyclopropyl ring-opening has been observed, indicating that 1,1-diaryloxy radicals exist in equilibrium with a bridged 1-oxaspiro[2,5]octadienyl radical. This represents the first experimental evidence in support of the stepwise nature of the *O*-neophyl rearrangement of 1,1-diaryloxy radicals.

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Alkoxy radicals represent an important class of highly reactive oxygen-centered radicals. These species play a key role in several chemical and biological processes, such as the photooxidation of hydrocarbons in the atmosphere,<sup>1</sup> lipid peroxidation,<sup>2</sup> and the anti-malarial action of natural endoperoxides,<sup>3</sup> and are involved moreover in a variety of synthetically useful procedures.<sup>4</sup> The uni- and bimolecular reactions of alkoxy radicals have been thoroughly investigated. Relevant examples of the former processes include intramolecular hydrogen atom transfer<sup>5</sup> and C–C bond fragmentation reactions ( $\beta$ -scission,<sup>6</sup> and *O*-neophyl rearrangement<sup>7</sup>). Typical bimolecular processes are represented by hydrogen atom abstraction reactions<sup>8</sup> and by addition reactions to C=C double bonds,<sup>9</sup> organophosphorus,<sup>10,11</sup> and organoboron compounds.<sup>11</sup>

The *O*-neophyl rearrangement of alkoxy radicals, first described by Wieland in 1911,<sup>12</sup> has received since then considerable attention. This process converts an oxygen-centered radical into a significantly more stable (benzylic) carbon-centered radical through a 1,2-aryl shift, and has been observed for radicals that bear at least two aryl groups in the  $\alpha$ -position (Eq. (1)).



R = H, Me, *cPr*, Ar

A strongly debated question has been whether this rearrangement is a concerted or a stepwise process,<sup>13–16</sup> with a bridged

1-oxaspiro[2,5]octadienyl radical structure representing, respectively, a transition state or a discrete intermediate along the reaction pathway. Only recently, however, computational studies have provided convincing support to the hypothesis that the *O*-neophyl rearrangement of 1,1-diaryloxy radicals proceeds through the reversible formation of an intermediate 1-oxaspiro[2,5]octadienyl radical as described in Scheme 1.<sup>17,18</sup>

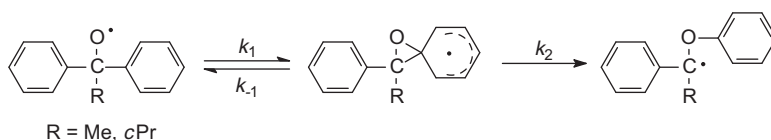
No conclusive experimental evidence in support of this hypothesis is instead available. In this context, it is, however, important to point out that a recent product and time-resolved kinetic study carried out by some of us has clearly shown that the *para*-(2,2-diphenylcyclopropyl)cumyloxy radical (**1**) exists in equilibrium with a 2,2-dimethyl-1-oxaspiro[2,5]octadienyl radical (**2**).<sup>19</sup>

Cumyloxy radicals are known to undergo C–CH<sub>3</sub>  $\beta$ -scission as the exclusive unimolecular reaction (Scheme 2, path **a**),<sup>6f,6g,20,21</sup> and the failure to observe the *O*-neophyl rearrangement (Scheme 2, path **b**) reasonably reflects the lower stability of the 2-phenoxy-2-propyl radical as compared to the 1-phenoxy-1-phenylalkyl one displayed in Scheme 1.

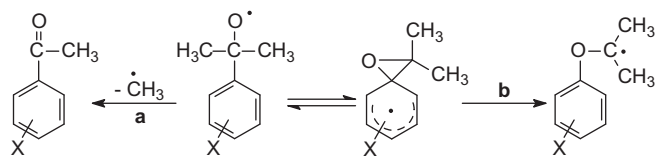
Along this line, by introducing a 2,2-diphenylcyclopropyl *reporter* group in the *para*-position, the exclusive formation of product **A** (Scheme 3) has been observed.<sup>19</sup>

A result that has been interpreted in terms of the existence of an equilibrium between **1** and **2** followed by a fast 2,2-diphenylcyclopropylcarbinyl  $\rightarrow$  1,1-diphenyl-3-butenyl radical rearrangement in the latter radical. The failure to observe *para*-(2,2-diphenylcyclopropyl) acetophenone (**B**) deriving from C–CH<sub>3</sub>  $\beta$ -scission in **1** clearly indicates that in the presence of two phenyl substituents on the cyclopropyl group, this process does not compete with cyclopropyl ring-opening in **2**.<sup>22</sup>

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Scheme 1.



Scheme 2.

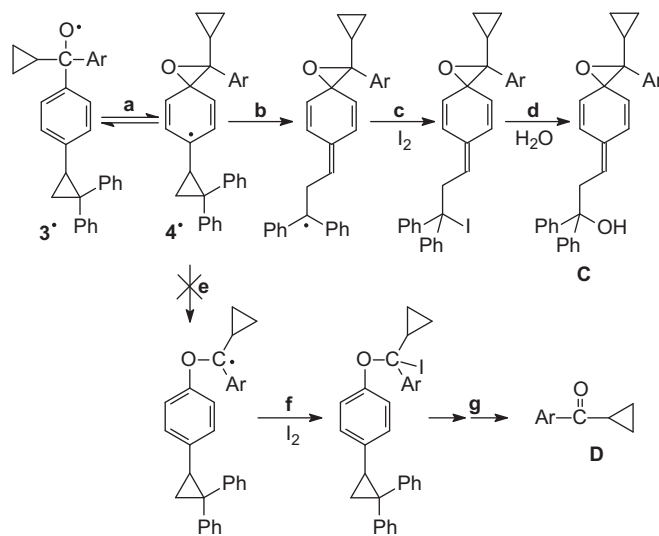
On the basis of these results, it seemed particularly interesting to extend the approach described above for the cumyloxy radical also to 1,1-diaryloxy radicals, in order to establish if a bridged 1-oxaspiro[2,5]octadienyl radical is actually an intermediate in the *O*-neophyl rearrangement, and moreover, if the existence of this equilibrium is a general feature of arylcarbinoyloxy radicals. For this purpose, we have synthesized cyclopropyl[bis(4-(2,2-diphenylcyclopropyl)phenyl)]methanol (**3**), precursor of the 1,1-diaryloxy radical **3<sup>•</sup>**, whose structure is displayed below.<sup>24</sup> **3<sup>•</sup>** has been generated photochemically by visible light irradiation of CH<sub>2</sub>Cl<sub>2</sub> solutions containing **3**, (diacetoxy)iodobenzene (DIB), and I<sub>2</sub>. It is well established that under these conditions the DIB/I<sub>2</sub> reagent converts alcohols (ROH) into hypiodites (ROI) that are then photolyzed to give alkoxy radicals (RO<sup>•</sup>), precursors of the observed reaction products.<sup>14b,25,26</sup>

Under these conditions the reaction of **3** led to the exclusive formation of 2-cyclopropyl-2-(4-(2,2-diphenylcyclopropyl)phenyl)-6-(3-hydroxy-3,3-diphenylpropyliden)-1-oxaspiro[2,5]octa-4,7-diene (**C**) (Scheme 4).

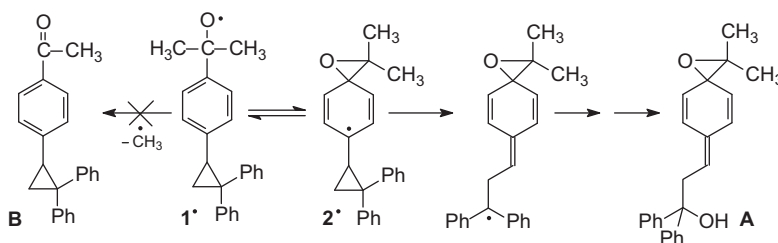
Product **C** has been isolated by preparative TLC and unambiguously characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and correlation NMR (see Supplementary data). In addition, the spectroscopic data are in excellent agreement with those obtained previously for the structurally related product 2,2-dimethyl-6-(3-hydroxy-3,3-diphenylpropyliden)-1-oxaspiro[2,5]octa-4,7-diene (**A**), obtained after visible light irradiation of 2-(4-(2,2-diphenylcyclopropyl)phenyl)-

2-propanol in the presence of DIB and I<sub>2</sub> as described above (Scheme 3).<sup>19</sup>

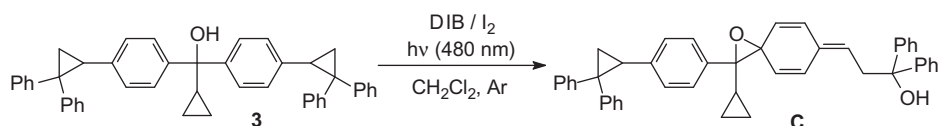
The formation of **C** can be rationalized in terms of cyclopropyl ring-opening in the intermediate-bridged radical **4<sup>•</sup>** (Scheme 5, pathways **b–d**, Ar = 4-(2,2-diphenylcyclopropyl)phenyl),<sup>27</sup> in line with the hypothesis of the existence of an equilibrium between this radical and **3<sup>•</sup>**. This finding clearly represents the first experimental evidence for the formation of an intermediate-bridged 1-oxaspiro[2,5]octadienyl radical in the reactions of 1,1-diaryloxy radicals, in full agreement with the computational results discussed above.<sup>17,18</sup>



Scheme 5.



Scheme 3.



Scheme 4.

The failure to observe the product deriving from *O*-neophyl shift in **3** (cyclopropyl 4-(2,2-diphenylcyclopropyl)phenyl ketone (**D**)) indicates that in the presence of two phenyl substituents on the cyclopropyl group, **4** undergoes cyclopropyl ring-opening (path **b**) significantly faster than the opening of the oxirane ring (path **e**). This is in line with the estimated rate constants for the two processes, as it can be reasonably assumed that cyclopropyl ring-opening occurs with the same rate in **4** and **2** (for which a value of  $k \approx 7.5 \times 10^8 \text{ s}^{-1}$  has been estimated),<sup>19</sup> whereas that rate constants for *O*-neophyl shift in 1,1-diaryllalkoxyl radicals bearing electron-releasing ring substituents have been shown to be  $\leq 2.4 \times 10^6 \text{ s}^{-1}$ ,<sup>14b</sup> and a similar (or lower) value can be reasonably predicted also for **3**.

In conclusion, by means of a detailed product study, convincing experimental evidence in support of an equilibrium between 1,1-diaryllalkoxyl radical **3** and an 1-oxaspiro[2,5]octadienyl radical has been obtained, in agreement with previous computational results. The existence of this equilibrium appears to be a general feature of arylcarbinyloxy radicals, strongly supporting the hypothesis that the *O*-neophyl rearrangement of 1,1-diaryllalkoxyl radicals proceeds through the formation of a bridged 1-oxaspiro[2,5]octadienyl radical intermediate.

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### Supplementary data

Supplementary data (details on product studies, synthesis of substrate **3** and characterization of product **C**) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.05.149](https://doi.org/10.1016/j.tetlet.2010.05.149).

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- When employing the DIB/I<sub>2</sub> system carbon radicals rapidly react with I<sub>2</sub> to give the corresponding alkyl iodides.<sup>14b,25</sup> As mentioned previously,<sup>19</sup> it is thus reasonable to propose that also in this case **C** is formed during workup following solvolysis of the tertiary iodide (Scheme 5, path **d**).