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Remarkable aromatic substitution by a 1,5-diradical

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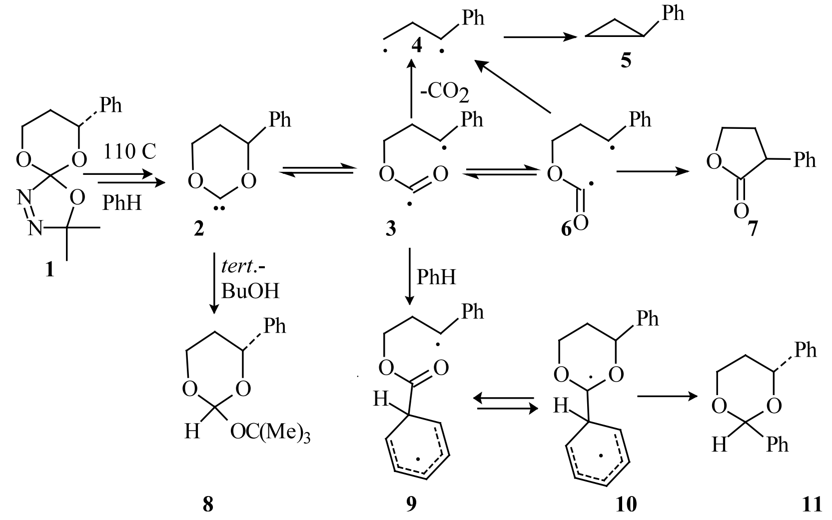
Abstract—Generation of 2,6-dioxa-3-phenylcyclohexylidene in benzene leads to 2,4-diphenyl-1,3-dioxane, the product of apparent insertion into a CH bond of benzene. However, that product arises from attack of a diradical intermediate on benzene. © 2002 Elsevier Science Ltd. All rights reserved.

Thermolysis of oxadiazoline **1**[1] in benzene at 110°C afforded 2,4-diphenyl-1,3-dioxane (**11**), the product of apparent insertion of carbene **2** into a CH bond of benzene, in about 12% yield.[2] The sequence of Scheme 1 was indicated by the fact that carbene **2** could be trapped in high yield with *tert*-butyl alcohol present in the solvent.[3] Compound **11** was not detectable when *tert*-butyl alcohol was present but it was obtained, together with phenylcyclopropane (**5**, ca. 20%) and α-phenyl-γ-butyrolactone (**7**, ca. 20%), in the absence of *tert*-butyl alcohol. Compound **5** is derived from the diradical intermediates **3** and **6**, through a decarboxylation/coupling sequence, while **7** is a product of intramolecular coupling of **6**, Scheme 1. A control experiment with a similar carbene (**13**) that cannot fragment readily was used to distinguish between a carbenic and a radical reaction with benzene. 4,4-Dimethyl-2,6-dioxacyclohexylidene (**13**), generated at 110°C in benzene by thermolysis of oxadiazoline **12**,[1] did not lead to **14** but formed dimer **15**,[4] Scheme 2. Analysis by GC, with authentic **14**[5] for comparison, revealed not a trace of **14**. That result appears to rule out insertion of carbene **2** into a CH bond of benzene as the source of **11**, because **13** should mimic the insertion tendencies of **2**. Insertion of a dialkoxycarbene into a CH bond of benzene is unprecedented, in any case.[6]



Scheme 1.

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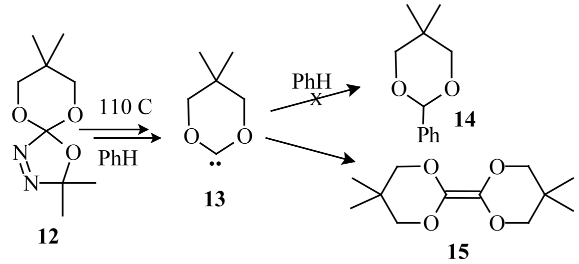

Scheme 2.

Homolytic fragmentation of cyclic oxycarbenes to diradicals[7] and of acyclic oxycarbenes[8–19] to an alkoxycarbonyl radical and another radical, both in the gas phase and in solution, is known experimentally and it has been studied by computation for model systems.[20–25] Aromatic substitution by alkoxycarbonyl radicals is also known.[26] Thus, methoxycarbonyl radicals, generated in benzene by thermolysis of methyl azodicarboxylate at 130°C, gave methyl benzoate in 13% yield.[27] That reaction might be considered to be a poor model for the reaction of **3** with benzene, because diradicals **3** and **6** have not only the additional option of decarboxylation but also that of cyclization to lactone **7**. Could attack on benzene be fast enough to compete?

The mechanism postulated in Scheme 1 was supported by means of computation. Conformer **3** cannot cyclize to the lactone **7** except by converting first to conformer **6**. That process is known to have a significant barrier, as shown by previous workers who modeled a similar isomerization of the hydroxycarbonyl radical.[28] With a combination of SCF results for the rotational barrier and CI calculations for the stable conformations and the in-plane inversions, the authors[28] estimated that the transition state for rotation lay ~6.7 kcal mol^{-1} above the *cis*-HOCO radical and ~23.9 kcal mol^{-1} below the energy of the most facile in-plane inversion pathway. In order to obtain a better estimate for the O–C=O rotational barrier in **3**, the methoxycarbonyl radical was used to model the rotational TS with the Gaussian 98, Revision A.7, system of programs.[29] Electron correlation was included with the B3LYP density functional hybrid method and the Møller–Plesset method with correlation energy truncated at the second order (MP2). Zero point energies were corrected using a scaling factor of 0.98 and 0.97 for the B3LYP and MP2 results respectively.[30] Rotation is predicted to involve a barrier of 8.0 and 8.9 kcal mol^{-1} from the *cis*-MeOCO radical, at the B3LYP/6-31+G* and MP2(FC)/6-31+G* levels, respectively, while the *trans*-MeOCO radical lies 0.5 and 0.1 kcal mol^{-1} higher in energy than the *cis* conformer. Thus, isomerization of conformer **3** to conformer **6**, a necessary first step for cyclization, must be relatively slow.

Rotations about the other single bonds[31] of **3** have barriers smaller than 4 kcal mol^{-1} and therefore **3** cannot retain its sickle shape long enough for rotation of the CO group. When that group eventually does rotate, those same single bonds must rotate in order to return to a sickle-shaped **6** that, if in the singlet state,[32] can cyclize to lactone **7**. The net effect of those entropic features is that cyclization to **7** can be expected to be slower than coupling of the 1,5-diyl would be, if it were born in the conformation **6**.[33] Thus, the diradical is probably long-lived enough to attack benzene in competition with decarboxylation to **4** and cyclization to **7**.

We were unable to find a rate constant for addition of an alkoxycarbonyl radical to benzene, but our product distribution enabled us to estimate that value as follows. From that distribution, one can conclude that decarboxylation and coupling are about twice as fast as attack on benzene. The rate constant for H-abstraction (k_H) from $HSnBu_3$ by alkoxycarbonyl radicals at 110°C was estimated to be 1.8×10^6 M^{-1} s^{-1} from the Arrhenius equation of Newcomb et al.[34] That number, together with the product ratio (RH:ROCHO = 38:25) from reaction of ROCO with $HSnBu_3$,[35] was then used to estimate the rate constant for decarboxylation of primary alkoxycarbonyls at 110°C, $k(CO_2) = 6.8\times10^4$ s^{-1}. Decarboxylation (of **3** and **6**) and coupling of **6** are about twice as fast as attack on benzene, permitting the conclusion that the calculated $k_{(CO2)} \sim 2\ k_{benzene}$ [benzene]. The concentration of benzene is about 10 M, and thus the rate constant for attack of **3** on benzene should have a value of roughly 3.4×10^3 or $<10^4$ M^{-1} s^{-1} at 110°C.

The literature is sparse with respect to substitution on benzene[26] by alkoxycarbonyl radicals, implying that the substitution is too slow to be generally useful. Possibly the reaction is slow overall because addition is reversible[36] and reversal competes effectively with the bimolecular H-transfer step leading to substitution product. In the case of **3** and benzene, the initial adduct (**9**) has an intramolecular follow-up step to compete with intramolecular reversal of addition and that feature could make the difference that effectively enhances the rate of aromatic substitution by **3**. We suggest that non-sickle conformations of diradicals **3** and **6** are largely responsible for **11** and for some of the **5**, because cyclization of the singlet via conformation **6** is expected to occur with only a small barrier.[33]

The final steps of Scheme 1, from **9** to **11**, are reasonable. 6-*Endo* cyclization to oxygen of a carbonyl group is known[37] as are other 6-*endo* cyclizations of radicals.[38] Neither the 6-*endo* nor the corresponding 5-*exo* cyclizations require rotation about the O–CO bond. Moreover, 5-*exo* cyclization of **9**, even if it were faster, is expected to be reversible.

6-*Endo* cyclization of **9** would generate diyl **10**, analogues of which were shown by Baldwin and Shukla to undergo the type of H-transfer that would convert **10** to **11**.[39] Thus, we conclude that the reaction that generates **11** from thermolysis of **1** in benzene is a diradical process rather than insertion of a carbene.

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