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The Order of First Bond Formation in the Intramolecular Photocycloaddition of 2-(4'-pentenyl)-cyclohex-2-enones

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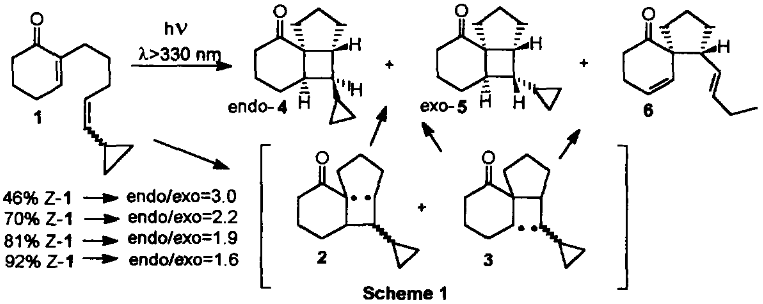
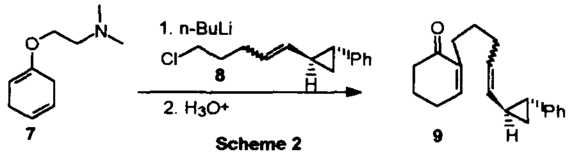
Abstract: Complete trapping of 1,4-diradical intermediates, formed in the photocycloaddition of **9**, provide direct evidence that first bond formation takes place at either C(α) or C(β) positions of the cyclic enone. No cleavage of the 1,4-diradical **10** or *endo*-diradical intermediates **11** and **12** could be detected. However, partial cleavage of the *exo*-diradical intermediates **13** and **14** was measured. Unusual long-range aromatic radical substitution was obtained in a competing rate with the cyclopropyl carbinyl radical rearrangement.

The intramolecular photocycloaddition of alkenes to cyclic enones of type **1**, has been investigated by Becker and co-workers.[1] The regioselectivity of this reaction, which is related to the preferred position of the first bond formation and the validity of the "rule of five"[2] is still under active investigation in several research groups.[3] Becker has shown that irradiation[1b] of compounds **1** (*Z*/*E*=1.5) at 36°C afforded two isomers of [2+2]-photoproducts **4** and **5** (56%) and a trapping product **6** (37%). The *endo*/*exo* ratio of the [2+2]-photoproducts was strongly affected by the ratio of the *Z*/*E* isomers at the alkenyl side chain in the starting material **1**. Based on this, it was concluded that [2+2]-photoproducts are formed *via* both diradical intermediates **2** and **3**.



Scheme 1

Recently we have demonstrated[4] that the fast rearrangement (3x10^{11} sec^{-1})[5] of 2'-phenylcyclopropyl carbinyl radical to homoallyl radical afforded complete trapping of 1,4-diradical intermediates. Applying this method in the photocycloaddition of **1** was expected to afford complete trapping of the 1,4-diradical intermediates of type **3**. We report here trapping experiments which revealed direct evidence that first bond formation in the photocycloaddition of **9** takes place mainly at the C(α) position of the cyclic enone and a smaller percentage (11%-22%) at the C(β) position.



Scheme 2

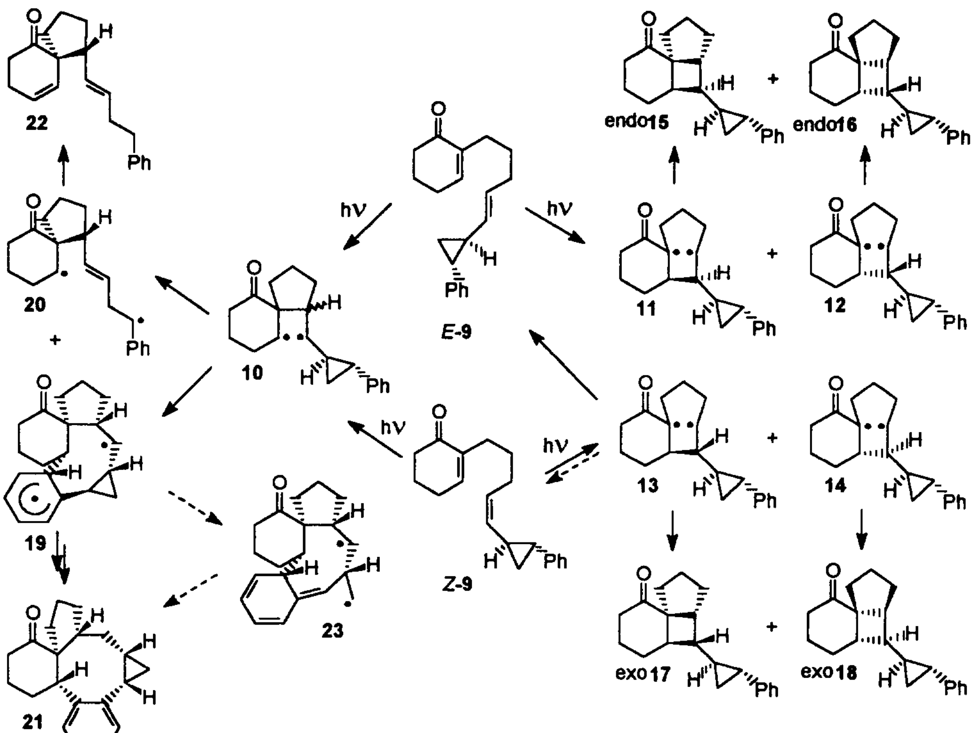
Compounds **9** were prepared by coupling of Z/E isomeric mixture of chiral cyclopropanes[4] **8** with **7**, following previously reported procedure.[1a] The *Z*-**9** and *E*-**9** isomers were separated by column chromatography. Irradiation studies were carried out under the usual conditions[6] in the temperature range of -55°C to +40°C. The results are summarized in table 1. Based on previous studies,[1] only five diradical intermediates **10-14** should be considered after first bond formation of **9** under these irradiation conditions (scheme 3). Mixture of *endo*-**15+16** and *exo*-**17+18**, are expected *via* diradical **10**, whereas complete trapping of diradical **10** and selective formation of the [2+2] photoproducts *via* intermediates **11-14** (obtained by first bond formation at the C(β) position of the enone) and no cleavage of the diradical intermediates during the irradiation are essential features for obtaining *selective formation* of *endo*-**15+16** or *exo*-**17+18** photoproducts upon irradiation of *E*-**9** or *Z*-**9** respectively.

Table 1: Irradiation of *E*-**9** and *Z*-**9**.

Entry	Comp.	Temp.	25	22	26	21	27	*endo*-15+16	*exo*-17+18
1	*E*-9	- 55 °C	4.6	54.5	1.7	17.1	4.8	19.3	--
2	*E*-9	0 °C	4.3	53.4	2.6	12.6	7.0	20.1	--
3	*E*-9	+ 25 °C	3.8	49.4	4.3	9.7	11.5	21.2	--
4	*E*-9	+ 40 °C	3.9	47.8	4.2	10.3	11.8	21.9	--
5	*Z*-9	- 55 °C	1.8	64.9	--	19.7	2.5	--	11.0
6	*Z*-9	0 °C	2.3	62.6	1.5	15.1	3.5	2.5	12.5
7	*Z*-9	+ 25 °C	2.7	61.1	2.2	12.5	5.1	3.1	13.4
8	*Z*-9	+ 40 °C	2.5	57.1	2.6	12.6	7.2	4.8	13.1

Irradiation of *E*-**9** at -55°C resulted in selective formation of the *endo*-[2+2] photoproducts **15+16** (19.3% total) with no detectable amount (GC) of the corresponding *exo*-**17+18** isomers. However, irradiation of *Z*-**9** at -55°C afforded *exo*-**17+18** (11%) with no detectable amount of *endo*-**15+16**, along with the same trapping products **21** (19.7%) and **22** (64.9%). Compounds **15-18**, **21** and **22** were separated and their structures determined by NMR.[7] The structures of the isomeric products (GC-MS) **25-27** (ca. 4 - 13%) were not determined. The fact that undefined products **25-27** obtained in the irradiation of both photosubstrates suggests their formation *via* diradical **10**. The obtained regioselectivity is strongly in the favor of first bond formation at the C(α) position of the cyclic enone, following the "role of five"[2].

Interestingly, Irradiation of *E*-**9** at different temperatures afforded the *endo*-[2+2] photoproducts (**15+16**) with no detectable amount of the corresponding *exo*-**17+18** or *E*→*Z* geometrical isomerization of the alkene in the starting material during the irradiation. However, *Z*→*E* geometrical isomerization was obtained upon irradiation of *Z*-**9** at higher temperatures along with formation of *endo*-[2+2] photoproducts (**15+16**) which is attributed to this isomerization. The observed *endo*/*exo* selectivity in the irradiation of *E*-**9** at the temperature range of -55°C - +40°C and *Z*-**9** at -55°C, clearly indicate that [2+2] photoadducts were exclusively formed *via* diradical intermediates **11-14**, with complete trapping of the diradical intermediate **10**. Similar selectivity found in the irradiation of *Z*-**9** at higher temperatures (entries 6-8). The obtained *endo*-[2+2] photoproducts (**15+16**) is attributed to the ca. 5% detected geometrical isomerization of the alkenyl side chain in the starting material, obtained *via* fragmentation of the *exo*-diradicals **13** and **14** during the irradiation.



Scheme 3

The structure of the unexpected trapping product **21** was determined by NMR.[7] The NOE enhancements obtained between the methyne protons, summarized in figure 1, allowed determination of the relative configuration at the stereogenic centers, further support of the structure was obtained by its X-ray structure analysis[8]. The formation of this product is proposed *via* diradical **19**, obtained by unusual long-range intramolecular radical aromatic substitution at the *ortho*-position of the phenyl substituent,[3b,9] followed, presumably, by 1,6-hydrogen abstraction then photochemical isomerization of the cyclopropyl unit.[10] However, selective *exo*-ring opening of the cyclopropyl carbinyl radical[11] in **19**, to its corresponding homoallyl radical **23** then recyclization to the *cis*-cyclopropyl diradical intermediate followed by 1,6-hydrogen abstraction to afford **21** could also be proposed.

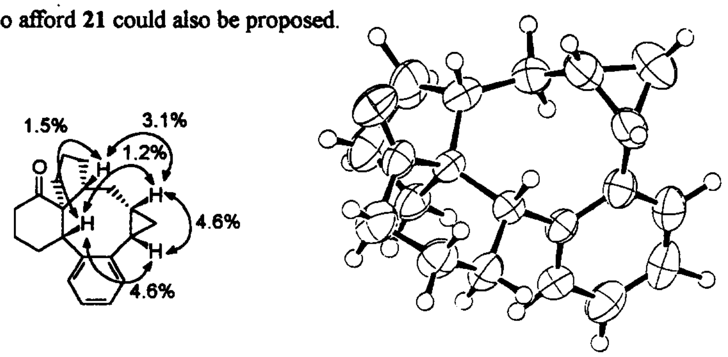


Figure 1: X-ray structure and selected NOE enhancements of compound **21**

In summary, We present for the first time, direct evidence for the formation of diradical **10** and seven-member ring diradical intermediates (**11-14**) in the intramolecular photocycloaddition of alkenes to cyclohexenones of type **9**. The regioselectivity was accurately and unambiguously determined *via* complete trapping of diradical **10**. The geometrical isomerization in photosubstrate *Z*-**9** is attributed to the fragmentation of the *exo*-diradical intermediates **13** and **14** which is consistent with the low percentage (<10%) isomerization previously reported on the irradiation of related systems.[1a]

Acknowledgment

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6. 80-W Hanau mercury vapor lamp (Q-81) was used for irradiations *via* a Uranium glass filter ($\lambda > 330$). All irradiations were carried out in 18 mL of hexane as solvent under nitrogen atmosphere. The concentrations always kept below 0.05 M and the reactions followed by TLC or GC.
7. All new compounds were characterized by full spectroscopic data, yields refer to chromatographed materials with purity of >95%. The relative stereochemical relationship of the stereogenic centers was determined by NOE-difference. The location of these protons determined by COSY-45, XH-CORR, JMOD-XH methods and was supported by NOE experiments. For determination of similar structures by NMR see ref. 1a and: Becker, D.; Haddad, N. *Isr. J. Chem.* **1989**, *29*, 303.
8. X-ray analysis of **21**: Empirical formula $C_{20}H_{24}O$, F.W. 280.4, T = 293K, lattice monoclinic, space group $P2_{1/n}$, a = 13.632(6), b = 9.088(5), c = 25.465(12) Å, $\beta = 97.37(5)°$, V = 3129.6 $Å^3$, Z = 8, F(000) = 1216, Dx = 1.191 $g.cm^{-3}$, radiation Mo Kα, $\lambda = 0.7107$ Å, $\mu = 0.071$ mm^{-1}, θ range for data collection 2-25°, index ranges $-16 \leq h \leq 16$, $0 \leq k \leq 0$, $0 \leq 1 \leq 30$, No. of unique reflections 5564, structure solved by SHELXS86(a), and refined by SHELXL76(b) programs, refinement method full matrix least squares on F^2, 2092 reflections for which $Fo \geq 3\sigma(Fo)$, No. of parameters 571, R = 0.077, wR2 = 0.118, largest diff. peak 0.183 $eÅ^{-3}$. (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467; (b) Sheldrick, G. M. (1976) SHELX76, program for crystal structure determination. University of Cambridge, England.
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