Tetrahedron Letters Vol. 21, pp 1043 - 1046
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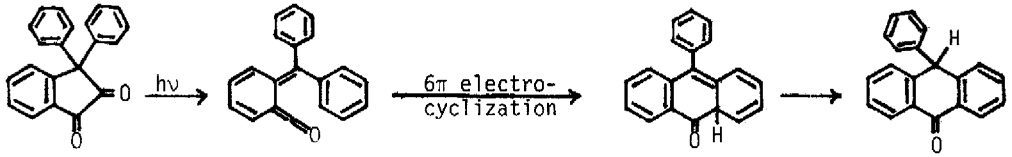
0040-4039/80/0308-1043$02.00/0

ANTARAFACIAL ROLE OF AN AROMATIC NUCLEUS; A NOVEL REGIOSPECIFIC [$_\pi 4_a + _\pi 2_a$] INTRAMOLECULAR CYCLOADDITION OF THE ENE-KETENE WITH AN AROMATIC RING

Masayuki Kuzuya*, Fumio Miyake and Takachiyo Okuda
Gifu College of Pharmacy, 5-6-1, Mitahora-Higashi, Gifu, 502, Japan

Summary: The thermally generated ene-ketene undergoes a facile and regiospecific intramolecular cycloaddition with N,N-dimethylaniline to result in the novel formation of the azulenone derivative via a norcaradiene intermediate.

It is well established that several linearly conjugated cyclohexadienones photoisomerize to the ene-ketenes, which undergo intramolecular cycloaddition with the ethylene double bond either to the starting dienones or to bicyclo[3.1.0] hexenones,[1] whereas little notice has been taken in such cycloadditions with an aromatic ring, although 3,3-diphenyl-1,2-indandione has been shown to undergo light-induced decarbonylation to result in the formation of 9-phenyl-10-anthrone via the ene-ketene intermediate.[2] In all cases the ene-ketenes were photochemically generated, which leads to uncertainties as to the electronic states involved in these reactions.[1g]

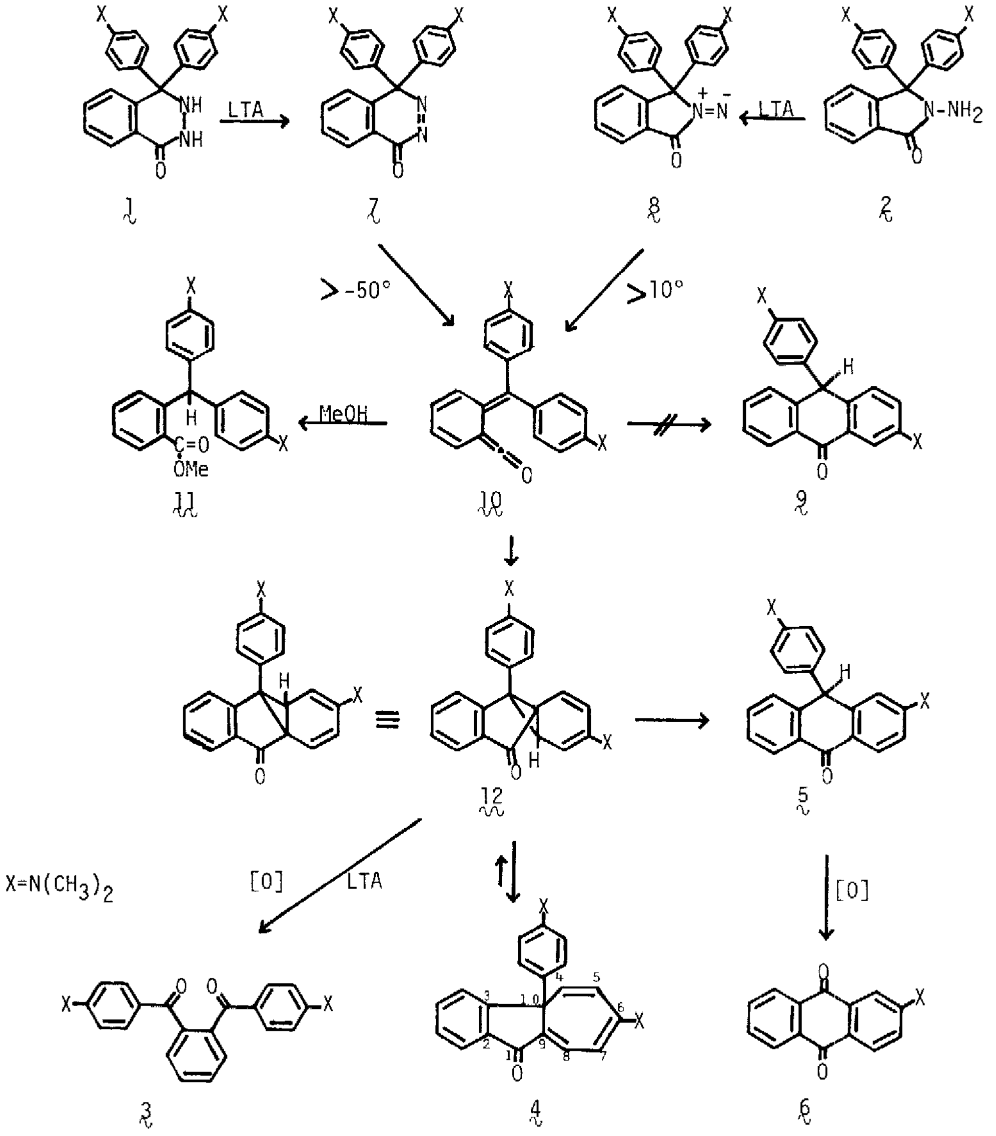


An intramolecular cycloaddition of an ene-ketene with an aromatic ring bearing an electron-donating substituent at the para position could be qualitatively predicted to afford a norcaradiene derivative, if the cyclization proceeds along the line derived from frontier orbital theory, the validity of which has been now proven for the problems in all types of cycloadditions as documented by K. N. Houk[3] and other theoretical chemists.[4] However, the experimentations for such a substituent effect on the aromatic ring to the regioselectivity have not been tested, previously.

We have studied the intramolecular cycloadditions of the ene-ketene with p-(N,N-dimethyl)-aniline ring, and we wish to present here what we believe is the first evidence of an antarafacial role of an aromatic ring by which the ene-ketene undergoes a facile and regiospecific intramolecular cycloaddition with N,N-dimethylaniline to result in the novel formation of a norcaradiene followed by the ring opening to an azulenone derivative.

When either 4,4-bis(p-dimethylaminophenyl)-3,4-dihydro-1(2H)-phthalazinone, **1**,[5] or 3,3-bis(p-dimethylaminophenyl)-N-aminophthalimine, **2**,[5] was oxidized with equimolar lead tetraacetate (LTA) in methylene chloride at ambient temperature, spontaneous nitrogen-elimination occurred as expected, and there were obtained four products on column chromatographic separation (300 mesh neutral alumina, chloroform eluent). These were identified as o-bis(benzoyl)benzene derivative **3**, the azulenone **4**, the anthrone **5** and the anthraquinone **6** in the ratio of ca. 9:3:1:1 in both cases.[6]

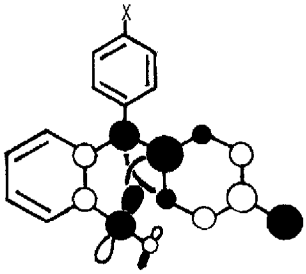
The similar oxidation at -78°, however, afforded emerald-green solution,[7] warming of the solution (above -50° in case of 1, and above 10° in case of 2) resulting in a slow nitrogen evolution and the formation of the azulenone 4 as a sole product in virtually quantitative yield. The structures of 3 and 6 were easily identified by comparison with authentic samples[8,9](mixed mp, mp, ir and nmr), respectively. The structures of 4 and 5 follow from their respective spectral properties.[10] Compelling evidence in favor of the structure 5 and against a possible alternate structure 9, which is a regioisomer of the cycloaddition, was furnished by a facile conversion of 4 to 5, when heated in chloroform for 15 minutes.[12] Separate experiment also showed that 5 is susceptible to air to be readily oxidized into the anthraquinone, 6.[13] On the basis of the above results, we deduced the following reaction sequences as shown, where all products are originated from the norcaradiene, 12.



The ene-ketene, 10, which might be in equilibrium with benzocyclobutenone, was confirmed by trapping with methanol to give methyl o-[bis(p-dimethylamino)-phenyl]-methyl benzoate 11[14] by adding methanol containing a small amount of sodium methoxide into the reaction mixture at low temperature. The formation of 3 can be interpreted by LTA oxidation of the norcaradiene, 12, since 12 would be already present before LTA has been consumed due to instability of 7 or 8 at high temperature oxidation.

The especially interesting features of these results are that the ene-ketene intermediate was thermally generated and underwent the regiospecific cycloaddition which can be viewed formally as a thermally allowed $[_{\pi}4_{a} + {}_{\pi}2_{a}]$ process. This occurs in the absence of compelling constraints, when 2_{π} component is part of an aromatic ring, and is presumably induced by the substituent effect of dimethylamino group. This spectacular substituent effect could be rationalized in terms of the greater HOMO-LUMO interaction, i.e. frontier orbital theory. Introduction of the electron-donating dimethylamino substituent splits the degeneracy of benzene HOMO and the resulting HOMO has the largest coefficient at the para-position. On the other hand, the propensity for an antarafacial character of the ketene has been analyzed as the result of the electrophilicity of the central carbon atom of the ketene due to the in-plane π*-orbital.[15]

In view of Houk's generalization[16] that the fastest reaction should be that with the smallest HOMO-LUMO separation, the dominant HOMO-LUMO interaction in the transition state should involve the HOMO of N,N-dimethylaniline (dienophile) and LUMO of the ene-ketene (diene), and the cyclization would be initiated by preferential bond formation between the central carbon of the ketene moiety and the para-carbon of N,N-dimethylaniline. These combined factors lead to formation of a norcaradiene, 12, exclusively. The relevant orbital interactions are shown.



Our results, the formation of azulenone, represent the first synthesis of norcaradiene from a benzene ring other than the route of carbene addition.

It is hoped that more insight into regioselectivity on this type of the cyclization will be gained in the course of attempts now in progress to define the scope and limitations.

Acknowledgement: We wish to thank Professor K. N. Houk for his kind comments.

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5. **1** and **2** were prepared from Malachite green lactone (MGL). All new compounds reported here gave satisfactory elemental analyses.
6. Nmr spectrum of the crude reaction mixture did not show the presence of **5** and **6**, which were presumably arised during the work-up. The products ratio, therefore, varied somewhat with the condition of work-up.
7. The primary product for the oxidation of **1** is likely to be the hitherto unknown six-membered mono-α-carbonyl azo compound (i.e. 4,4-disubstituted-1(4H)-phthalazinone), which was found to contain some interesting chemistries. A detailed account of the nature of this compound **7** will be provided in a forthcoming publication.
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9. Limpricht, Ann. Chem. 312 (1899)
10. **4** (reddish oragne needles) mp 170°(decompd), ir(KBr); ν 1650 cm^{-1}(C=O), uv(EtOH); λ max 263 nm (log ε=4.42), 461 nm (log ε=4.41), mass(70 eV) m/e; 356(M$^+$, base), nmr(δ ppm, $CDCl_3$)[11] 2.83 (6H, s, N-methyl at C-6), 2.88 (6H, s, N-methyl of aromatic), 5.43 (1H, d.d, J=2.3 and 8.2 Hz, H_7), 6.00 (1H, d, J=10.2 Hz, H_4), 6.26 (1H, d.d, J=2.3 and 10.2 Hz, H_5), 7.48 (1H, d, J=8.2 Hz, H_8), 6.47 (2H, d, J=8.5 Hz, aromatic at C-10), 6.95 (2H, d, J=8.5 Hz, aromatic at C-10. 7.26-7.95 (4H, m, aromatic). **5** (yellow needles) mp 160°(decompd), ir(KBr); ν 1640 cm^{-1}(C=O). uv(EtOH); λ max 250 nm (log ε=4.54), 367 nm (log ε=4.36), mass(70 eV) m/e; 356(M$^+$, base), nmr(δ ppm, $CDCl_3$)[11]; 2.86 (6H, s, N-methyl), 2.95 (6H, s, N-methyl), 5.18 (1H, s, H_9), 6.58 (2H, d, J=8.5 Hz, aromatic at C-9), 6.98 (2H, d, J=8.5 Hz, aromatic at C-9), 6.41 (1H, d, J=2.3 Hz, H_1), 6.71 (1H, d.d, J=2.3 and 10.2 Hz, H_3), 8.25 (1H, d, J=10.2 Hz, H_4), 7.23-7.50 and 8.28-8.42 (4H, m, aromatic).
11. Double resonance studies, taken together with Eu-shift data, allow the unambiguous assignments as above. In **4**, irradiation of the signal at 6.26 caused collapse into singlet of the doublet at 6.00 and change into doublet (8.2 Hz) of the doubly doublet at 5.43. In **5**, irradiation of the signal at 6.41 caused change into doublet (10.2 Hz) of the doubly doublet at 6.71 and irradiation of the signal at 6.71 caused collapse into singlet of the doublet at 8.25.
12. The alternate structure **9** for the anthrone **5** can be also ruled out by nmr coupling pattern, since the signal at 8.25 assigned to H_4 showed the splitting by 10.2 Hz, consistent with ortho-coupling constant, while the splitting of H_4 in **9** should be 2-3 Hz due to meta-coupling constant.
13. The precise mechanism for this oxidation is not elucidated yet, but this does not affect what we are communicating here.
14. 35 % yield. **11** was identified with an authentic sample independently prepared from MGL.
15. R.B.Woodward and R.Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, N.Y. 1970, p 163. See also R.Sustmann, A.Ansmann and F.Vahrenholt, J. Amer. Chem. Soc., **94**, 8099 (1972).
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(Received in Japan 26 November 1979)