Mechanistic Observations on the Unusual Reactivity of Dioxenone Photosubstrates in the Synthesis of Ingenol

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Dedicated to our friend and colleague Professor Dieter Seebach.

Abstract: The irradiation of allylically substituted dioxenone photosubstrates 6 and 21 lead to unexpected products, the formation of which can be explained by a series of transannular hydrogen atom abstractions.

Key Words: photochemistry, natural products, rearrangements, radicals, cycloadditions

We have recently described the first total synthesis of the protein kinase C activator, ingenol (1) based on the retrosynthetic analysis presented in Scheme 1. The key step is the photocycloaddition of allylically substituted dioxenone 5. This reaction leads to the establishment of both the critical ‘inside-outside’ C-8/C-10 trans intra-bridgehead stereochemical relationship and the incorporation of the C-14 ‘X’ substituent which is used to generate the C13,14-alkene from which the dimethylcyclopropane is derived. We describe herein the results of our studies on the role of X in the photocycloaddition reaction and a mechanistic proposal for the unusual products that result.

Irradiation of 6 led to the formation of a mixture of three products 7 (16%), 8 (15%), and 9 (5%) in 36% combined yield based on recovered starting material (Scheme 2). These results are notable for several reasons. First, only
toadduct 7 was observed. None of the C-14α alcohol corresponding to 7 was seen, a result that is consistent with photosubstrate conformation A, which was originally proposed to account for the formation of the C-8/C-10 trans intrabridgehead stereochemistry via biradical 10. It appears that only the C-14β epimer of 6 can undergo the desired cycloaddition via initial β-bond formation (relative to the dioxenone), leading to selective formation of the observed photoadduct 7.

We propose that the unfavorable interaction shown in B for the C-14α epimer of 6 leads to a different reaction course. Initial bond formation at the α-carbon of the triplet excited state dioxenone could proceed to give 11. Previous work from our laboratory suggests that ring closure of 11 would produce cyclobutane photoadduct 13 with C-8 stereochemistry epimeric with that shown in 7. Conformational relaxation of biradical intermediate 11, which is faster than the intersystem crossing to the singlet biradical, leads to the formation of the less strained photoadduct 13. However, cyclobutane photoadduct formation from intermediate 11 is not observed. Instead, intramolecular hydrogen atom abstraction of the carbinol methine in 11 leads to the formation of enol 12, which can then tautomerize to the observed ketone 8. We note that while the results obtained with the allylic chloride photosubstrate (see Scheme 5, vide supra) substantiate this mechanistic rationale, the low yield (36% combined) of photoproducts obtained on irradiation of 6 does not allow us to preclude the possibility that photoproducts 7–9 are obtained from a single diastereomer (i.e., C-14β) of 6.

Support for this mechanistic pathway comes from two independent results. First, irradiation of deuterated photosubstrate 14 leads to the formation of the deuterated ketone 15 (Scheme 3), a result that is consistent with the intramolecular H atom abstraction shown for the formation of 12 from 11 in Scheme 2.

Previous results from our laboratory had established that selective formation of the triplet biradical resulting from initial bond formation from the β-carbon of the dioxenone chromophore is observed. It is therefore striking that the formation of 8 and 9 is now explained via initial bond formation from the α-carbon of the dioxenone as shown in 11. The regiochemical difference between initial α or β bond formation from the ‘nonadiene’ dioxenone chromophore 6 would appear to be attenuated relative to that for octadiene dioxenone photosubstrates.

Evidence for the attenuation of the difference in energy between these two isomeric bond-forming pathways from the dioxenone triplet is provided by irradiation of the enone photosubstrate 16, which leads to the formation of a ca. 2:1 mixture of diastereomeric photoadducts 17 and 18 in 39% yield. NOESY correlation of the C-8 proton to the dioxanone methyl in 18 and not in 17 supports the stereochemical assignments shown (Scheme 4). Careful analysis of the 1H NMR of the crude reaction mixture obtained on irradiation of 16 suggests that the formation of both photoadducts is a kinetic result, and not due to epimerization of a unique photoadduct subsequent to the irradiation.

The formation of the more stable photoadduct 18, containing a cis-fused bicyclo[5.2.0]nonane moiety, albeit as a minor product in the photoreaction, can be attributed to the stabilization of initial α bond formation in the photo-reaction by stabilization of the incipient biradical by the carbonyl group as shown in 19. Conformational relaxation of 19 to 20 prior to intersystem crossing then leads to the formation of 18.

The formation of the minor enone product 9 on irradiation of 6 can be attributed to sensitizer-induced oxidation of 8 (Scheme 2). We have established that cyclobutane photoadduct 7 is inert to the photochemical reaction conditions, as irradiation of 7 leads to the recovery of unchanged 7 without the formation of either 8 or 9. However, irradiation of 8 in the presence of acetophenone leads to the slow formation of 9. The formation of 9 from 8 was not observed in the absence of acetophenone. This result suggests that the formation of 9 is due to hydrogen atom abstraction of 8 from the sensitizer and not transannular Norrish type II abstraction and is consistent with the observed formation of acetophenone photodimer in the irradiation.

The low yield observed in the formation of 7 prompted us to examine alternative allylic substituents in the photo-
The selective formation of the C-14β chloro photoadduct 22 is reminiscent of the selective formation of 7 from 6. The remarkable formation of the C-13β chloro product 23 can be attributed to the pathway shown in Scheme 6. We propose that only the C-14β chloro isomer of 21 can lead to a cyclobutane photoadduct, i.e., 22. The selective formation of the C-13β chloro photoadduct from the C-14α chloro photosubstrate can be attributed to intramolecular hydrogen atom abstraction from the dioxenone triplet (re-drawn as 21') to give 24, which can then give the bridged chloronium species 25, in which the two substituents are oriented trans on the chloronium ring. Chlorine-bridged radical intermediates have recently been invoked by Tan and coworkers to explain stereoselective 1,2-chlorine atom migrations in acyclic systems.6 Rearrangement of 25 to allylic radical 26, followed by a second intramolecular hydrogen atom abstraction, would then regenerate the dioxenone triplet to give 27, which has been re-drawn as 27'. Intramolecular [2+2] photocycloaddition of 27' would then give the observed C-13β photoadduct 23. Careful analysis of the unreacted dioxenone photosubstrate 21 during the course of the irradiation revealed the formation of 27 as a single diastereomer, a result that is consistent with this mechanistic scheme.

The differences observed with the allylic alcohol and allylic chloride photosubstrates are striking and underscore the diverse reactivities that can be observed on the triplet surface. Further experiments to examine the scope of the observed migration are underway in our laboratory and our results will be reported in due course.

**Irradiation of 6**

A solution of dioxenone 6 (380 mg, 1.19 mmol) and acetophenone (0.4 mL) in MeCN (350 mL) was degassed under vigorous argon bubbling for 1 h at 0 °C in a water-chilled pyrex immersion well. The mixture was subsequently irradiated for 3 h with a Hanovia medium pressure mercury lamp. The reaction mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography to afford recovered starting material (92 mg, 0.287 mmol), photoadduct 7 (47 mg, 16%), rearranged product 8 (42 mg, 15%), and olefin 9 (14 mg, 5%).

**Scheme 6**
1H NMR (CDCl 3, 500 MHz): δ = 3.35 (dd, J = 6.0, 11.0 Hz, 1 H), 2.84 (dd, J = 3.7, 11.3, 14.1 Hz, 1 H), 2.57 (dd, J = 6.0, 13.9 Hz, 1 H), 2.47 (dd, J = 2.4, 5.8, 11.0 Hz, 1 H), 2.41 (dd, J = 12.6, 12.6 Hz, 1 H), 2.15–2.11 (m, 1 H), 2.04 (dd, J = 8.0, 13.8 Hz, 1 H), 1.80 (s, 3 H), 1.75–1.50 (m, 12 H), 1.29–1.22 (m, 1 H), 1.18 (d, J = 7.1 Hz, 3 H).

1C NMR (CDCl 3, 125 MHz): δ = 207.83, 173.38, 107.29, 88.38, 65.51, 55.43, 42.27, 41.85, 40.94, 39.09, 32.84, 32.21, 30.81, 28.35, 28.10, 27.11, 26.92, 19.44, 15.37.

HRMS: m/z calcd for C 19 H 28 NaO 4 (M + Na) + : 341.1729, found: 341.1740.

**Figure 1**

**Allylic Chloride 21**

To a solution of allylic alcohol 6 (2.76 g, 8.6 mmol) in CH 2 Cl 2 –Et 2 O (1: 1, 90 mL) at 0 °C was added Ph 3 P (3.01 g, 11.5 mmol) and hexachloroacetone (2.84 mL, 11.5 mmol) and the mixture was stirred for 1 h. The reaction was quenched with sat. aq NaHCO 3 solution and the aqueous phase extracted twice with CH 2 Cl 2. The combined organic phases were dried (MgSO 4) and concentrated in vacuo. Flash chromatography (silica gel, hexane–EtOAc, 95:5) afforded allylic chloride 21 (2.43 g, 83%) as a colorless oil.

**Photodadducts 22 and 23**

A deoxygenated solution of dioxeneone 21 (2.48 g, 7.3 mmol) in MeCN–acetone (9: 1, 1 L) at 0 °C was irradiated with a 450 W Hanovia medium pressure mercury lamp for 16 h. Concentration in vacuo followed by flash chromatography (silica gel, hexane–EtOAc, 93: 7) afforded a mixture of photodadducts 22 and 23 (1.50 g, 60%; 3:4 = 5:2) as a white solid. Further chromatography of the mixture afforded analytical samples.

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1.59–1.46 (m, 4 H), 1.33–1.28 (m, 1 H), 1.24–1.18 (m, 1 H), 0.87 (d, J = 7.2 Hz, 3 H).

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta = 170.74, 108.28, 94.21, 63.16, 57.64, 52.98, 45.33, 42.54, 41.91, 41.05, 40.83, 34.98, 34.04, 31.20, 31.03, 30.81, 28.65, 26.07, 19.94.

HRMS (ES): $m/z$ calcd for C$_{19}$H$_{29}$ClO$_3$: 339.172698, found: 339.170356.

White solid; mp 136 °C (THF–pentane).

IR (film): 2954, 2874, 1743, 1457, 1384, 1337, 1317, 1282, 1239, 1199, 1129, 1082, 1050, 952 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 4.52$ (t, J = 4.8 Hz, 1 H), 3.16 (dddd, J = 2.2, 8.7, 10.9, 12.9 Hz, 1 H), 2.58–2.53 (m, 1 H), 2.43–2.35 (m, 5 H), 2.14 (dd, J = 8.9, 11.3 Hz, 1 H), 2.04 (ddd, J = 1.7, 8.3, 15.0 Hz, 1 H), 1.91–1.82 (m, 2 H), 1.79 (s, 3 H), 1.69 (s, 3 H), 1.67–1.62 (m, 1 H), 1.56–1.50 (m, 4 H), 1.36–1.31 (m, 1 H), 0.91 (d, J = 7.2 Hz, 3 H).

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta = 170.97, 108.24, 94.52, 63.22, 62.49, 52.89, 44.22, 41.32, 40.44, 35.66, 35.08, 34.89, 34.52, 34.19, 31.27, 30.86, 28.95, 26.41, 20.20.

Anal. Calcd for C$_{19}$H$_{29}$ClO$_3$: C, 67.34; H, 8.03. Found: C, 67.38; H, 8.38.

Irradiation of 21 (Isolation of 27)

The allylic chloride $^{21}$ (650 mg, 1.92 mmol) in MeCN–acetone (384 mL, 9:1, 5 mL) was degassed in a 500 mL photoreactor (Pyrex) at 25 °C by bubbling Ar through the solution for 0.5 h. The solution was then cooled to 0 °C by submerging the reactor in an ice-H$_2$O bath and irradiated using a medium pressure Hg lamp for 3 h. The crude reaction mixture was concentrated and purified by separation of the UV active material (30.0 mg) from the photoadduct mixture $^{22}$ and $^{23}$ (321 mg, 49%) by column chromatography (silica gel, 10% EtOAc in hexanes). The UV active material contained a mixture of several compounds which were separated using column chromatography (silica gel, 10% EtOAc in hexanes). The UV active material was separated using AgNO$_3$ impregnated silica gel (40% hexanes in CH$_2$Cl$_2$) affording the homoallylic chloride $^{27}$ (1.6 mg) and an unidentified mixture of compounds (6.4 mg).

Photosubstrate 27

IR (film): 2945, 2863, 1735, 1648, 1411 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 5.80–5.89$ (m, 1 H), 5.11–5.15 (m, 2 H), 3.94–3.99 (m, 1 H), 2.73–2.79 (m, 1 H), 2.47–2.56 (m, 2 H), 2.41–2.44 (m, 1 H), 2.13–2.17 (m, 1 H), 2.00–2.04 (m, 1 H), 1.72–1.84 (m, 3 H), 1.71 (s, 3 H), 1.66 (s, 3 H), 1.57–1.63 (m, 2 H), 1.39–1.51 (m, 3 H), 0.95 (d, J = 6.8 Hz, 3 H).

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta = 173.16, 160.43, 134.17, 118.41, 108.25, 103.61, 63.64, 61.21, 44.02, 41.99, 40.99, 36.99, 36.38, 34.61, 33.49, 26.44, 25.97, 24.65, 15.45.

HRMS: $m/z$ calcd for C$_{19}$H$_{28}$ClO$_3$ (M + H)$^+$: 339.172698, found: 339.170356.

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