New photochemistry of 2,5-cyclohexadien-1-ones and related compounds

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Abstract - New procedures for photorearrangement of 2,5-cyclohexadien-1-ones to bicyclo[3.1.0]hexenones and substituted phenols have been developed. The intermediate oxyallyl zwitterions undergo intramolecular cycloaddition to furan, the alkyl azide group, and a variety of olefins. Intramolecular 2+2 photocycloadditions of 4-(3'-alkenyl)-2,5-cyclohexadien-1-ones also are described.

INTRODUCTION

The photorearrangements of 2,4- and 2,5-cyclohexadien-1-ones have been of interest to organic chemists for many years. Cyclohexadienone photochemistry has been used in multistep organic synthesis, but the full synthetic potential remains to be exploited. A recent development of methods for the conversion of 1,4-cyclohexadienes 1 into 2,4-cyclohexadien-1-ones 2 (ref. 1) and 2,5-cyclohexadien-1-ones 3 (ref. 2) represents an important step towards this goal. Cyclohexadienes 1 are prepared by the alkali metal in ammonia-promoted reductive alkylation of benzoic acid derivatives. This methodology provides 2,4- and 2,5-cyclohexadien-1-ones with a wide range of substituents in both racemic and enantiomerically pure form.

This account will focus on the photochemistry of 2,5-cyclohexadien-1-ones 3 and related compounds. Particular emphasis will be directed at: 1) the intramolecular reactivity of oxyallyl zwitterions generated from photorearrangements of 2,5-cyclohexadien-1-ones and 2) the intramolecular 2+2 photocycloaddition of 2,5-cyclohexadien-1-ones.

![Chemical structures](image)

Although many research groups have contributed to the continually expanding body of dienone photochemistry, much of the current understanding of type A photoreactivity of 2,5-cyclohexadien-1-ones 4 is due to Zimmerman and Schuster (ref. 3). Convincing evidence has been gathered to support the existence of oxyallyl zwitterions 5 in the type A photorearrangement to bicyclo[3.1.0]hexenones 6.

![Chemical structures](image)

Chapman and co-workers have demonstrated the viability of intramolecular cycloaddition of furan and addition of methanol to oxyallyl zwitterions 7 generated from photorearrangement of bicyclo[3.1.0]hexenones (ref. 4). Subsequently, Williams and co-workers reported the first examples of intramolecular reactions of photochemically generated steroidal oxyallyl zwitterions related to 7 with proximate alcohol and ketone carbonyl groups (ref. 5).
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It has been shown that irradiations of 4-alkyl-4-carbomethoxy-2,5-cyclohexadien-1-ones 8 at 366 nm give phenols 9 and 10, presumably via photorearrangement of intermediate bicyclo-[3.1.0]hexenones; e.g., 6 (Ref. 2b). The exclusive migration of the carbomethoxy rather than the primary alkyl group in the intermediate zwitterion 7 is noteworthy. An analogous migration tendency has been determined for the carbethoxy group in the acid-catalyzed dienone-phenol rearrangement (Ref. 6).

\[ \text{8} \xrightarrow{hv, 366 \text{ nm}} \text{9} + \text{10} \]

The corresponding photorearrangements of 4-alkyl-4-cyano-2,5-cyclohexadien-1-ones 11 provide ~9:1 diastereoisomeric mixtures of bicyclo[3.1.0]hexenones 12 with no traces of phenolic products; e.g., 13 (Ref. 2b). In principle, the enhanced photostability of cyano-substituted bicyclohexenones, 12, might be a result of a retardation in the rate of photo-isomerization to the type 7 zwitterion. Alternatively, zwitterion 7 might be generated, but the failure to observe cyano group migration could be a result of a low "migration tendency" relative to the carbomethoxy group. Control experiments indicate that the first explanation probably is not correct. The photoisomerization of cyclohexadienones of type 11 may provide a unique opportunity to study the migration tendency of a cyano group to an electron deficient center in the absence of acidic catalysts.

In contrast to the photorearrangement of 8 to phenols 9 and 10, 366 nm irradiation of a series of 3-methoxy-2,5-cyclohexadien-1-ones 14 gave bicyclo[3.1.0]hexenones 15 and 16 with complete regioselectivity in good to excellent yields (Ref. 2b). Continued irradiation of

\[ \text{14} \xrightarrow{hv, 366 \text{ nm}} \text{15} + \text{16} \]

15 and 16 resulted in photoisomerization to predominately the diastereoisomeric series 15 with the carbomethoxy group endo to the 3-methoxyenone chromophore.

The stabilizing effect of the α-methoxy group in bicyclohexenones 15 and 16 is at least partially a result of the wavelength of light used in the photorearrangement of 14 to 15 and 16 (366 nm). Irradiation of 14 (or 15 and 16) with light > 300 nm provided the anticipated phenols. It is suspected that the reluctance of 15 and 16 to undergo photorearrangement to phenols (but, interestingly, not photointerconversion) may be related to the anticipated (Ref. 7) lowering of the σ + σ\(^*\) triplet state of the enone group by the 3-methoxy substituent. Indeed, the normal n + σ\(^*\) initiated photorearrangement to a bicyclohexenone is completely suppressed in the case of the 3,5-dimethoxy-2,5-cyclohexadien-1-one 12. This and other synthetically useful substituent effects are topics of current studies directed at an exploration of the excited state kinetics of 14, 17, and related substances.
Reductive alkylation of the chiral benzamide 18 provided 19a with a diastereoisomeric excess of 260:1 (ref. 8). Irradiation of the enantiomerically pure 2,5-cyclohexadien-1-one 20 derived from 19a demonstrated that photoisomerization of 16 to 15 (R=Me) occurs by external cyclopropane bond "b" cleavage rather than the internal bond "a" cleavage (ref. 2b). This chemoselectivity correlates with the reluctance of the 4-methoxybicyclohexenones 15 and 16 to undergo photoisomerization to phenols, a process that must occur by bond "a" cleavage to give zwitterion 7. It is tempting to relate bond "a" cleavage of the hypothetical bicyclohexenones that photorearrange to phenols 9 and 10 to \( n^+ + \pi^0 \) character and bond "b" cleavage in the 4-methoxybicyclohexenones to \( \pi^0 + \pi \) character.

It also was discovered that 20 undergoes photoracemization to 21, indicating that there is a pathway for return of the excited state of 20 and/or primary photoproduct to the 2,5-cyclohexadienone. Mechanistic speculation has been offered to account for this observation (ref. 2b) but, again, a detailed analysis of the excited state kinetics would be helpful in further elucidating the substituent effects.

![Chemical structures](image)

**INTRAMOLECULAR CYCLOADDITIONS TO OXYALLYL ZWITTERIONS GENERATED FROM PHOTOREARRANGEMENTS OF 2,5-CYCLOHEXADIEN-1-ONES**

Oxyallyl zwitterions 5 and 7 are produced by photorearrangements of 2,5-cyclohexadien-1-ones 4 and bicyclo[3.1.0]hexene 6. Although it should be possible to perform intramolecular cycloadditions with suitably substituted zwitterions of type 5 (ref. 9), this account is concerned only with intramolecular cycloadditions of the type 7 zwitterion.

We have found that it is possible to carry out intramolecular zwitterion cycloadditions to furan, the alkyl azide group, and various olefins. In all cases, it is necessary to consider alternative reaction pathways involving migrations within the zwitterion. For example, irradiation of 22a provides the expected bicyclohexenone 23a, which slowly photorearranges to phenol 24, indicating that intramolecular capture of the zwitterion by the furanyl substituent is not competitive with carbomethoxy group migration. However, 22b, modified to slow the migration process, photorearranges to furan adduct 25 (via the isolable intermediate bicyclohexenone 23b) in excellent yield (ref. 10a).

The photorearrangement of 23b to 25 provides strong additional evidence to support the contention that oxyallyl zwitterions are involved in the conversions of bicyclohexenones to phenols; e.g., 23a to 24. These photorearrangements occur with relatively poor quantum efficiency because of the C(4) methoxy group. By contrast, 2,5-cyclohexadien-1-ones 26a and 26b undergo \( \sim \) quantitative photorearrangement to 27 and 28 in 1.5 to 3 h. In both cases, the intermediate bicyclohexenones are too photoreactive to be detected by conventional \( ^1H \) NMR analyses (ref. 10a).

The cycloaddition of oxyallyl zwitterions to alkyl azides represents a new 3+3 annelation process; e.g., 26b + 26. It should be noted that the sequential photorearrangements of 26b and related 2,5-cyclohexadien-1-ones occur efficiently in the presence of the potentially photoreactive azide group. This chemoselectivity is a result of selective irradiation of the long wavelength UV absorption band of the dienone chromophore in a spectral region (~366 nm) for which the azide group is nonabsorbent.
Triazenes such as 28 appear to be useful synthetic intermediates, but only limited chemical reactivity data are available at present. It is noteworthy that reaction of 28 with atmospheric moisture results in loss of molecular nitrogen and incorporation of one equivalent of H₂O to give 1,2,3,4,4a,7,8,8a-octahydro-4a-(acetoxymethyl)-7-hydroxy-7,8a-dimethyl-8-oxoquinoline in high yield (ref. 10a).

Symmetrically substituted phenols are also convenient sources of photoreactive 2,5-cyclohexadien-1-ones. For example, 2,4,6-trimethyl phenol provides 4-furfuryloxy-2,4,6-trimethyl-2,5-cyclohexadien-1-one (29), albeit in low overall yield. Brief irradiation of 29 in benzene solution at 366 nm gave the bridged furan adduct 30 in excellent yield (ref. 10b). The molecular structure of 30 was determined by X-ray crystallographic analysis, confirming that this and other adducts obtained by intramolecular oxallyl zwitterion additions to the furan ring have the C(8)-C(9) double bond endo to the carbonyl group. Endo-Orientation also has been reported for the intermolecular process (ref. 4).

While the available data do not elucidate the timing of adduct bond formations (stepwise or concerted), it is apparent that orientational preference in the intramolecular process
correlates with product stability. Molecular models show that endo-30 is considerably more stable than the exo-isomer. Molecular mechanics calculations support this hypothesis and suggest that the major source of instability is ring strain in the connecting tetrahydrofuranyl unit. This reasoning can be extended to an analogous consideration of 25 and 27.

The vinyl substituted oxyallyl zwitterion behaves as a two-electron component in cycloadditions to furan and the azide group to give adducts 29, 27, and 28. This zwitterion in 32 reacts as a four electron component with olefins to give bridged carbocycles 33 and 34; heterocycle 35 also has been obtained. Preliminary data indicate that the distribution of products strongly depends on the nature of the substituents attached to the olefin (ref. 11).

INTRAMOLECULAR 2+2 PHOTOCYCLOADDITIONS OF 4-(3'-ALKENYL)-2,5-CYCLOHEXADIEN-1-ONES

In the course of an investigation of the photoreactivity of 4-(3'-butenyl)-2,5-cyclohexadien-1-ones, we discovered an intramolecular 2+2 photocycloaddition (ref. 12). Thus, irradiation of 36a gave an approximately equivalent distribution of phenol 37, the product of carbomethoxy group rearrangement in zwitterion 32, and 1-carbomethoxy[4.3.1.0]

tricyclodec-2-en-4-one (38). The nitrile derivative 36b was prepared to suppress the migration tendency of the C(4) substituent (vide supra). Irradiation of 36b produced bicyclohexenone 39, 1-cyanotricyclodecenone 40 (derived from photorearrangement of 39; cf., photostability of 12) and the tricyclodecenone 41.
The inter- and intramolecular 2+2 photocycloaddition of an α,β-unsaturated carbonyl system to an alkene is an important process for the construction of acyl substituted cyclobutanes (ref. 13). However, photocycloadditions of olefins or acetylenes to 2,5-cyclohexadien-1-ones are unprecedented. This chemistry is of mechanistic significance because the 2+2 cycloaddition must be in competition with the normally efficient type A photorearrangement of 2,5-cyclohexadien-1-ones.

The potential synthetic value of the formation of tricyclo-decenones of type 38 follows from: 1) the now general availability of 4,4-disubstituted-2,5-cyclohexadien-1-ones in racemic or enantiomerically pure form, 2) the diverse functionality in 38 and analogues that would be available for subsequent synthetic manipulation, and 3) the wide range of synthetic conversions of acyl substituted cyclobutanes already available (ref. 13).

This chemistry is of mechanistic significance because the 2+2 cycloaddition to 8-methyl and 8-methy substituted enone units.

Additional studies (ref. 12) with a wide range of substituted 4-(3'-butenyl)-2,5-cyclohexadien-1-ones have demonstrated that: 1) Biradicals appear to be involved in the intramolecular 2+2 photocycloaddition. 2) Quaternary centers may be generated at each carbon atom of the cyclobutane ring. 3) The partitioning of pathways for type A photoreactivity vs 2+2 cycloaddition in 36a and other substrates lacking 3-methoxy substitution is sensitive to changes in solvent composition and temperature; cyclobutane formation is favored in hydrocarbon solvents at low temperature. 4) The 4-allyl- and 4-(4'-pentenyl)-2,5-cyclohexadien-1-ones do not undergo 2+2 photocycloadditions under conditions utilized for 42 and related derivatives. 5) 4-Carbomethoxy-3-methoxy-4-(3'-pentynyl)-2,5-cyclohexadien-1-one and related acetylenic substrates undergo efficient 2+2 cycloaddition to give the corresponding cyclobutene in excellent yields. Preliminary characterization of the excited-state.
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responsible for 2+2 cycloaddition suggests that significant mixing of the $\pi + \pi^*$ triplet-state with the $n + \pi$ triplet-state normally associated with type A photoreactivity is required for diversion of the photochemistry of 2,5-cyclohexadien-l-ones from the type A process to intramolecular 2+2 cycloaddition.

The diastereoselective Birch reductive alkylation of chiral benzamides provides enantiomerically pure 2,5-cyclohexadien-l-ones with a wide range of substitution. In certain cases, it would be desirable to prepare symmetrical 2,5-cyclohexadien-l-ones and induce asymmetry during subsequent cyclizations. This principle is illustrated for the intramolecular 2+2 photocycloaddition of 44 to give 45 or the enantiomer 46.

We have examined the concept of remote stereocontrol (ref. 14) via placement of a chiral center on the butenyl side chain; e.g. 47. Racemic 47 was prepared to serve both as a potential synthetic intermediate in the preparation of racemic 9-isocyanopupukeane, a natural marine isocyanide (ref. 15) and as a probe of the mechanism of the intramolecular 2+2 photocycloaddition. If the transition state for formation of the cyclobutane ring resembles the starting 2,5-cyclohexadien-l-one, 47, then 48, in which the bulky carbomethoxy and isopropyl groups are anti disposed, ought to be the major product. If product development control operates, then 49 would be the expected product because the isopropyl group is away from the cup-shaped cavity defined by the tricyclo[4.3.l.0]decenone ring system. In fact, 47 gives only 49 as determined by X-ray crystallographic analysis of the derived 2,4-dinitrophenylhydrazone of 49 (ref. 16). This result and the discovery that 2+2 photocycloaddition probably involves reversible formation of 1,4-biradicals suggests that product development control may be a useful predictive model for photocyclization of 4-(3'-butenyl)-2,5-cyclohexadien-l-ones.

An alternative procedure for remote stereocontrol incorporates a chiral auxiliary at C(4) in 44. A small selectivity of 70:30 has been observed for the (2'S)-4-[(2'-methoxymethyl)pyrrolidinyl]carbonyl derivative. Separation of diastereoisomers and hydrolytic removal of the chiral auxiliary provides enantiomerically pure tricyclodecenone. Other potentially useful chiral auxiliaries are being examined (ref. 16).

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REFERENCES


