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A Novel Photochemical Vinylcyclopropane Rearrangement Yielding 6,7-Dihydro-5*H*-benzocycloheptene Derivatives

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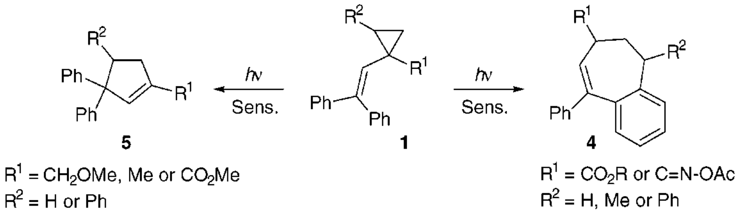
ABSTRACT



1-Substituted 1-(2,2-diphenylvinyl)cyclopropanes with electron-accepting groups at C1 undergo a novel rearrangement to benzocycloheptenes on triplet-sensitized irradiation. In some instances competition between rearrangement to cyclopentenes and formation of cycloheptenes takes place. When electron-acceptor groups are not present at C1, conventional ring opening to cyclopentenes occurs exclusively. A mechanism involving intramolecular SET from the diphenylvinyl unit to the electron-acceptor group is proposed for this novel photoreaction.

The photochemistry of vinylcyclopropanes has received considerable attention in the past.[1] Studies carried out in this area have shown that vinylcyclopropanes undergo basically three types of photoreactions including (1) *E*/*Z* isomerization of the cyclopropane ring and the vinyl unit, (2) ring opening to conjugated dienes, and (3) rearrangement to cyclopentenes.[1] Most of the past efforts have concentrated on all-carbon systems. However, when functional groups are incorporated to the cyclopropane ring, alternative reaction modes have been observed. Thus, in a recent study of the photoreactivity of 1-substituted 3-(2,2-diphenylvinyl)-2,2-dimethylcyclopropanes, with different functional groups at C1 of the cyclopropane ring, we have observed novel photorearrangements to different heterocycles such as 1,2-oxazines and furan derivatives.[2]

We report here a novel photochemical rearrangement of 1-substituted 1-(2,2-diphenylvinyl)cyclopropanes that yields cycloheptene derivatives. The ring expansion of vinylcyclopropanes to seven-membered ring derivatives has been described in the thermal and photochemical rearrangement of 1,2-divinylcyclopropanes that yields 1,4-cycloheptadienes.[3] However, as far as we are aware, this reaction has never been observed before in monovinylcyclopropanes.

As part of our studies on the 1-aza-di-π-methane (1-ADPM) rearrangement[4] we were interested at one point in

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[1] For reviews see: (a) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 899. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (c) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (d) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247.

[2] Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R. *J. Org. Chem.* **1999**, *64*, 1056.

[3] For a review on the divinylcyclopropane−cycloheptadiene rearrangement, see: Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1.

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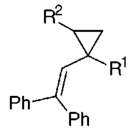
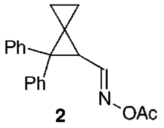
exploring the possibility of extending the reaction to cyclopropane derivatives such as **1a**. 1-ADPM rearrangement of **1a** would bring about the formation of the spirocyclopentane **2**. Spirocyclopentanes units are present in active pirethroids.[5] Thus, the 1-ADPM reaction might serve as a possible method for synthesis of these substances.

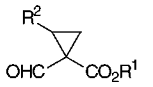
To test this proposal **1a** was synthesized by a route starting with methyl 1-formylcyclopropanecarboxylate **3a**,[6] which is transformed to **1b** by Horner−Emmons olefination with diethyl diphenylmethylphosphonate.[7] Reduction of **1b** by using LAH (→ **1c**), followed by PCC oxidation, yielded the corresponding aldehyde that was transformed into **1a** by sequential reaction with hydroxylamine hydrochloride and acetyl chloride.[8]



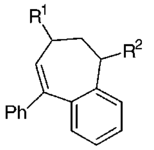
1a: R^1 = CH=N-OAc; R^2 = H
1b: R^1 = CO$_2$Me; R^2 = H
1c: R^1 = CH$_2$OH; R^2 = H
1d: R^1 = CN; R^2 = H
1e: R^1 = CH$_2$OMe; R^2 = H
1f: R^1 = Me; R^2 = H
1g: R^1 = CH=N-OAc; R^2 = Me
1h: R^1 = CH=N-OAc; R^2 = Ph
1i: R^1 = CN; R^2 = Me
1j: R^1 = CN; R^2 = Ph



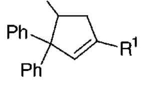
2



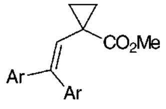
3a: R^1 = Me; R^2 = H
3b: R^1 = Et; R^2 = Me
3c: R^1 = Et; R^2 = Ph



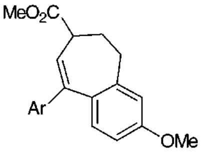
4a: R^1 = CH=N-OAc; R^2 = H
4b: R^1 = CN; R^2 = H
4c: R^1 = CO$_2$Me; R^2 = H
4d: R^1 = CN; R^2 = Me
4e: R^1 = CN; R^2 = Ph



5a: R^1 = CO$_2$Me; R^2 = H
5b: R^1 = CH$_2$OH; R^2 = H
5c: R^1 = CH$_2$OMe; R^2 = H
5d: R^1 = Me; R^2 = H
5e: R^1 = CN; R^2 = Ph



14: Ar = *p*-MeOC$_6$H$_4$



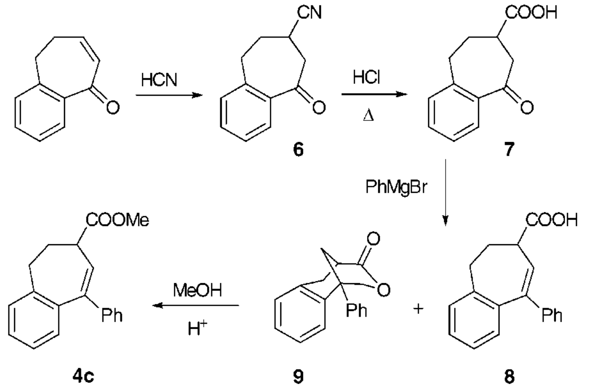
15: Ar = *p*-MeOC$_6$H$_4$

A solution of cyclopropane **1a** (224 mg, 0.8 mmol) in CH$_2$Cl$_2$ was irradiated for 80 min, with acetophenone (7 g, 58 mmol) used as a sensitizer.[9] Under these conditions a complex mixture of oxime acetate and nitrile products (as judged by inspection of the ^{1}H NMR spectrum of the crude photolyzate) was obtained. To facilitate product isolation, the reaction mixture was refluxed in toluene for 10 h to promote the quantitative conversion of oxime acetates into the corresponding nitriles. Column chromatography of the mixture on silica gel (hexane/Et$_2$O 95:5) yielded the nitrile **1d** (76%), which arises by elimination of acetic acid in **1a**, and a new product (12%) whose mass spectral data suggest that it is an isomer of nitrile **1d**. The ^{1}H NMR spectrum showed a doublet at δ 6.25 corresponding to a vinyl hydrogen and three multiplets at 2.48, 2.63, and 3.03 corresponding to aliphatic hydrogens. These resonances are not compatible with those expected for the ADPM-derived spirocyclopentane **2**. The ^{13}C NMR spectrum is particularly helpful in the assignment of structure since it shows three high-field saturated carbon atoms at δ 27.9, 30.8, and 40.0 corresponding to a methyne and two methylenes respectively, as well as signals for two alkene carbons, one cyano group, and two phenyl rings. The combined spectroscopic data are compatible with a structure of benzocycloheptene **4b**, which would arise by thermal AcOH elimination from photoproduct **4a**.

To determine the scope of this new reaction, the study was extended to compounds **1b** and **1e**. Irradiation of **1b** for 2 h, with *m*-metoxyacetophenone used as a sensitizer, followed by column chromatography on silica gel, yielded the benzocycloheptene **4c**[10] (16%) and an inseparable mixture (56%) of cyclopentene **5a** and recovered starting material (by ^{1}H NMR). To achieve separation, the mixture was reacted with LAH to form the corresponding alcohols **1c** and **5b**. These were separated by column chromatography on silica gel, yielding 22% of **5b**[11] and 65% of **1c**.[12]

The identity of **4c** was demonstrated by independent synthesis,[13] which was begun by Michael's addition of HCN 2,3-benzocyclohepta-2,6-dienone[14] to form **6**. Hydrolysis of **6** yields the ketoacid **7**. Reaction of **7** with phenylmagnesium bromide affords a mixture of the acid **8** and the lactone **9**. Finally, the ester **4c** is obtained from both the acid **8** and the lactone **9**, by treatment with acidic methanol (Scheme 1). The comparison of the spectral data for **4c** with those obtained for **4b** confirmed its assigned structure.

Scheme 1



In the case of **1b**, the novel rearrangement to form cycloheptene **4c** competes with the conventional vinylcyclopropane ring expansion to generate **5a**. However, irradia-

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(4) For reviews see: (a) Zimmerman, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065. (b) Armesto, D. *CRC Handbook of Organic Photochemistry and Photobiology*; CRC Press: New York, 1995; p 915.

(5) Naumann, K. *Chemistry of Plant Protection, Synthetic Pyrethroid Insecticides: Structure and Properties*; Springer-Verlag: Berlin, 1990; Vol. 4, p 192.

(6) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5400.

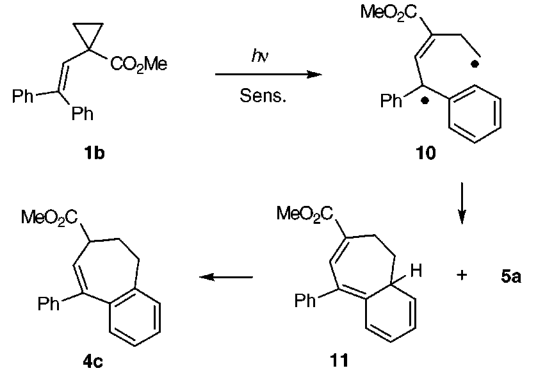
(7) Zimmerman, H. E.; Klun, R. T. *Tetrahedron* **1978**, *34*, 1775.

(8) For experimental conditions on the transformation of esters into oxime acetates, see: Armesto, D.; Ortiz, M. J.; Ramos, A.; Horspool, W. M.; Mayoral, E. P. *J. Org. Chem.* **1994**, *59*, 8115.

(9) The photolyses were carried out in a quartz immersion well apparatus with a Pyrex filter and a 400-W medium-pressure Hg arc lamp. Solutions of the compounds and the sensitizer in dry CH$_2$Cl$_2$ (420 mL) were purged for 1 h with argon and irradiated under a positive pressure of argon. After completion of the irradiation, the solvent and the sensitizer were removed under reduced pressure, and the products were separated by flash column chromatography on silica gel.

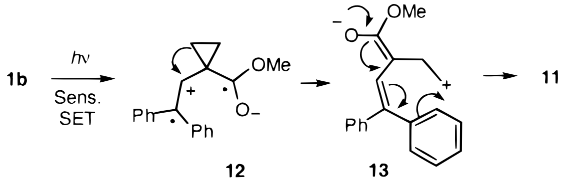
tion of **1e**, obtained from **1c** by standard methods, for 2 h, under the same conditions used for **1b**, yielded **5c** (6%) and recovered starting material **1e** (76%), exclusively. The corresponding benzocycloheptene derivative was not detected in the product mixture. Cyclopentenes **5a** and **5c** are the products expected to result from conventional vinylcyclopropane rearrangement.[1] However, the formation of **4a** and **4c** is surprising since, as far as we are aware, the photochemical ring expansion of vinylcyclopropanes to benzocycloheptenes has not been previously observed. The formation of **4a**, **4c**, **5a**, and **5c** can be interpreted by the operation of a conventional biradical mechanism (Scheme 2 for **1b**). Thus, excitation of **1b** to its triplet excited state is followed by homolytic rupture of the C1−C2 cyclopropane bond to produce biradical **10**. Radical recombination of **10** provides **11**. Compound **4c** results from the alternative cyclization mode involving addition of the primary radical to one of the phenyl rings affording the seven-membered-ring intermediate **11**. Hydrogen migration within **11** yields benzocycloheptene **4c**. Although this mechanism reasonably explains the products formed in these reactions, it leaves in question why the biradical intermediate **10** undergoes cyclization to cycloheptenes in the reactions of **1a** and **1b** while this path is not followed in reaction of **1e**.

Scheme 2



At this point, a possible alternative mechanism for the ring expansion to benzocycloheptenes was considered. The acetoxyimino and methoxycarbonyl groups present in **1a** and **1b**, respectively, could act as good electron acceptors for single-electron transfer (SET) from the triplet excited state of the diphenylvinyl chromophore (Scheme 3 for **1b**). Previous studies carried out by us support the feasibility of this process.[15] This SET process forms zwitterionic biradical **12** that then undergoes ring opening to produce dipolar intermediate **13**. Electrophilic addition to the aromatic ring in **13** is quite plausible; this yields intermediate **11**, the precursor of **4c**. In accord with this mechanistic proposal, the formation of the five-membered compound **5a** and the seven-membered derivative **4c** in the irradiation of **1b** could be due to a competition between the biradical path, yielding **5a** and the SET route that affords **4c**.

Scheme 3



To test this mechanistic hypothesis, the ester **14** was synthesized[16] and irradiated under the same conditions used for **1a**. The presence of *p*-methoxy groups in the phenyl rings should decrease the ionization potential of the alkene unit and favor intervention of the intramolecular SET route. Triplet-sensitized irradiation of **14** for 90 min yielded the benzocycloheptene **15** (19%) and recovered starting material (56%). The isomeric cyclopentene was not detected as a product of the photoreaction of **14**, a fact which can be explained by the increased efficiency of the SET path leading to the cycloheptene.

At this point it was considered necessary to obtain additional evidence that would demonstrate that in the absence of electron-acceptor groups at C1, the ring expansion to cycloheptenes would not take place. Thus, cyclopropane **1f**[17] was irradiated under the same conditions used for **1b**, for 5 h. In this instance, the only photoproduct obtained is the cyclopentene **5d** (10%).

The study was extended to cyclopropanes **1g** and **1h**. The presence of a methyl in **1g** and a phenyl in **1h** at C2 of the cyclopropane ring should facilitate the ring opening of the cyclopropane. These two compounds were synthesized by a route analogous to that used to prepare **1a**, starting from **3b** and **3c**, respectively.[18] Irradiation of **1g**, as a 7:3 mixture of (*Z*:*E*) diastereoisomers,[19] for 50 min, under the same conditions used for **1a**, followed by thermal elimination of AcOH, yielded cycloheptene **4d** (17%) and the nitrile **1i** (53%) as a 3:1 mixture of (*Z*:*E*) diastereoisomers. This result shows that

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(10) **Spectral Data for 4c**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.42 (m, 1H), 2.61 (m, 3H), 2.99 (m, 1H), 3.69 (s, 3H), 6.61 (d, $J = 6.6$ Hz, 1H), 6.98−7.82 (m, 9H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 31.5, 39.7, 42.8, 59.7, 125.5−142.6, 175.3.

(11) **Spectral Data for 5b:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.63 (s, 1 H), 2.48 (m, 2 H), 2.62 (m, 2 H), 4.26 (s, 2 H), 6.08 (s, 1 H), 7.17−7.29 (m, 10 H); ^{13}C NMR (63 MHz, CDCl$_3$) δ 32.2, 40.0, 61.3, 62.3, 126.0−148.8.

(12) These yields are calculated from the mixture of **5a** and **1b**.

(13) For experimental details on the synthesis of **4c** see the Supporting Information.

(14) Hart, H.; Dunkenblum, E. *J. Am. Chem. Soc.* **1978**, *100*, 5141.

(15) (a) Armesto, D.; Ramos, A.; Ortiz, M. J.; Mancheño, M. J.; Mayoral, E. P. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 514. (b) Armesto, D.; Austin, M. A.; Griffiths, O. J.; Horspool, W. M.; Carpintero, M. *Chem. Commun.* **1996**, 2715.

(16) The synthesis is analogous to that used for **1b** with the only difference that diethyl bis(*p*-methoxyphenyl)methylphosphonate is used in the Horner−Emmons step.

(17) Zimmerman, H. E.; Samuel, C. J. *J. Am. Chem. Soc.* **1975**, *97*, 4025.

(18) (a) Compounds **3b** and **3c** were obtained by DIBALH reduction (ref 18b) of the previously reported diethyl 2-methylcyclopropane-1,1-dicarboxylate and diethyl 2-phenylcyclopropane-1,1-dicarboxylate, respectively (ref 18c). (b) Davis, C. R.; Swenson, D. C.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 6843. (c) Landor, S. R.; Punja, N. *J. Chem. Soc. (C)* **1967**, 2495.

(19) The configurations of compounds **1g** and **1h** were established by means of NOE difference measurements.

the new rearrangement to benzocycloheptenes can be extended to vinylcyclopropanes substituted at C2.

The absence of the corresponding cyclopentene product in this process is reasonable, since the methyl at C2 should have a greater stabilizing effect on the dipolar intermediate **13** than the biradical **10**. Therefore, ring opening via the dipolar intermediate is favored over the biradical alternative in this process.

Irradiation of (*Z*)-**1h**, for 90 min, using *m*-methoxyacetophenone as a sensitizer, followed by acetic acid elimination, gives benzocycloheptene **4e** (20%), cyclopentene **5e** (25%), and the nitrile **1j** (22%) as a 3:2 mixture of (*E*:*Z*) diastereoisomers. The formation of cyclopentene **5e** in this reaction is surprising since **1g** yields the corresponding benzocycloheptene **4d** exclusively. A possible explanation for this result is that the incorporation of a phenyl group at C2 promotes the thermal cyclopropane rearrangement of **1h** to the cyclopentene **5e**. To test the validity of this postulate compound **1h** was heated in refluxing toluene for 5 h. Under these conditions **1h** yielded the cyclopentene **5e** in 89% yield.[20]

The results obtained in the irradiation of compounds **1g** and **1h** demonstrate that in addition to rearrangements to cyclopentenes and benzocycloheptenes, isomerization of the cyclopropane ring also occurs in the triplet excited states of these compounds.

In summary, 1-substituted 1-(2,2-diphenylvinyl)cyclopropanes, containing electron-accepting groups (such as acetoxyimino and methoxycarbonyl) at C1, undergo a novel photorearrangement to form benzocycloheptene derivatives on triplet-sensitized irradiation. The normal vinylcyclopropane rearrangement to cyclopentenes competes with this process in some cases. In the absence of electron-accepting groups, rearrangement to cyclopentenes is the only reaction pathway observed. The replacement of the 2,2-diphenylvinyl unit for a 2,2-bis(*p*-methoxyphenyl)vinyl moiety increases the efficiency of the cycloheptene formation and suppresses formation of the corresponding cyclopentene. A mechanism involving intramolecular SET from the vinyl unit to the electron-acceptor group is proposed to account for this novel rearrangement reaction. As far as we are aware, these are the first examples of photochemical vinylcyclopropane rearrangements that yield benzocycloheptene derivatives. Further studies are in progress to determine the scope and synthetic applications of this novel reaction.

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Supporting Information Available: Experimental procedures for preparation of compound **1b** and for the independent synthesis of **4c**, and analytical and spectral data for compounds **4b**, **4d**, **4e**, **5c**, **5d**, **5e**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] None of the other vinylcyclopropanes **1** rearrange to cyclopentenes under these reaction conditions.