Timed Diels-Alder reactions

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Abstract
In this paper a unique approach to the synthesis of polycyclic ring systems is disclosed. The approach features an intermolecular Diels-Alder reaction followed by an intramolecular Diels-Alder reaction where the regiochemistry of addition is controlled by substituents on the bisdiene and bisdienophile. This methodology has been applied to the synthesis of the fluorenone ring system.

Disciplines
Chemistry | Inorganic Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments
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Timed Diels–Alder Reactions

George A. Kraus* and Michael J. Taschner

Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa 50011. Received June 25, 1979

Abstract: In this paper a unique approach to the synthesis of polycyclic ring systems is disclosed. The approach features an intermolecular Diels–Alder reaction followed by an intramolecular Diels–Alder reaction where the regiochemistry of addition is controlled by substituents on the bisdiene and bisdienophile. This methodology has been applied to the synthesis of the fluorenone ring system.

An efficient convergent strategy is vital for the practical synthesis of polycyclic systems. This postulate has motivated the creation of ingenious routes to steroids, vitamins, and alkaloids. We have recently discovered a novel method, the general features of which are depicted below. In this polycyclic system is formed regiospecifically in a single reaction. In principle, a number of compounds might be formed. However, one of the diene units in the bisdiene is more reactive than the other unit. The same feature is true for the bisdienophile. Thus, the initial ring is created by cycloaddition of the more reactive diene and dienophile. The second and third rings are formed by the intramolecular cycloaddition of the less reactive diene and dienophile. At present, we have confined our study to the formation of the fluorenone ring system.

Results and Discussion

Synthesis of Reactants. The bisdienes used in this investigation were compounds 1 and 2. The preparation of 1 was readily accomplished by the use of a Wittig reaction on 4-(2-furyl)-3-buten-2-one. It could be purified by bulb to bulb distillation or by filtration through silica gel. Bisdiene 2 could be synthesized by trapping the kinetic anion of 3,5,7-octa-

condensation (termed a “timed Diels–Alder”) a tricyclic ring system is formed regiospecifically in a single reaction. In principle, a number of compounds might be formed. However, one of the diene units in the bisdiene is more reactive than the other unit. The same feature is true for the bisdienophile. Thus, the initial ring is created by cycloaddition of the more reactive diene and dienophile. The second and third rings are formed by the intramolecular cycloaddition of the less reactive diene and dienophile. At present, we have confined our study to the formation of the fluorenone ring system.

8. The enynones 3 and 4 were made by the coupling of cuprous phenylacetylide with the requisite acid chloride according to the method of Normant. Enynone 5 was similarly prepared.

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Dienones 6 and 7 were efficiently synthesized from ketone 9 by aldol condensation, dehydration, and a retrograde Diels-Alder reaction. Dehydration could be most effectively accomplished by mesylation followed by reaction with triethylamine to form 10a or 10b. Compounds 10a and 10b were exclusively trans enones. These compounds were then subjected to flow pyrolysis conditions (600 °C, 20 mm) to afford dienones 6 and 7. Diynone 8 had been previously prepared.

**Diels-Alder Reactions.** The optimal conditions for the polycycloaddition reaction were found to be the reaction in refluxing CCl₄ to form the first cyclohexene ring followed by a sealed tube reaction at elevated temperatures to effect closure to the tricyclic system. No tricyclic product was obtained after reaction at ambient temperature for 1 week. If the reactants were simply heated at 240 °C, the yield of the desired tricyclic structure was greatly reduced owing to polymer formation. The results with dienones 6 and 7 and bisdiene 2 are illustrated below. The proposed structure of 11a is supported by infrared absorptions at 1720 and 1740 cm⁻¹. Similar information (absorption at 1735 cm⁻¹) can be obtained from the spectra for 11b. Both compounds are homogeneous by thin layer chromatography.

Enynones 3, 4, and 5 undergo Diels-Alder reaction with 2 as illustrated below. Cyclohexenes 12a,b show absorptions corresponding to enynes (2200, 1620 cm⁻¹). The NMR spectra indicate the absence of enone hydrogens. After thermal cyclization, compounds 13a or 13b are obtained. The infrared spectra of both 13a and 13b lack the intense acetylenic absorption characteristic of 12a and 12b. In contrast to the behavior of enynones 3 and 4, the Diels-Alder reaction of 5 with bisdiene 2 afforded only monoaddition to yield 14. In this case the orientation was governed by the directing effects of the carbomethoxy group. The Diels-Alder reaction of diynone 8 with 2 presented unexpected difficulty because of the instability of the monocyclic adduct at elevated temperatures. The optimal conditions for cyclization involved heating the reactants in warm carbon tetrachloride overnight. Adduct 15 could be smoothly dehydrogenated to the fluorenone with DDQ. Compound 16 exhibited the ultraviolet and infrared spectra characteristic of a 3-alkoxyfluorenone. Both high-resolution and low-resolution mass spectroscopy also support the assigned structure.

The Diels-Alder reactions of bisdiene 1 with enynones 4 and 5 proceed only to the monocyclic compound. No conditions
could be found for the cyclization of mono adduct 17a or 17b. While this work was in progress, Parker and co-workers published results on simpler systems which support our observations.

From the results presented above, it is clear that a delicate balance between relative reactivity and the directing effects of substituents on the bisdiene is involved for the successful cycloaddition. If one of the diene units in the bisdiene is unreactive or if an unfavorable equilibrium exists between adduct and un cyclized compound, this polycycloaddition concept cannot be used successfully. Another interesting facet of this reaction is the control of stereochemistry. In the cycloaddition between 2 and a diene none of the chiral centers are created, whereas between 2 and an enyne only four chiral centers are developed. The assumptions of a concerted cycloaddition and the well-documented preference for endo addition limited the number of stereochemistry must begin with a study of the initially formed stereoisomers had been formed. This mixture could not be separated by column or gas chromatography. Analysis of the mixture could not be separated by column or gas chromatography. Analysis of the trum of 0.56 g (4.18 mmol, 84%) of 12a showed that only one isomer had been formed. In the case of adduct 12b, the NMR spectrum indicated only one singlet corresponding to the quaternary methyl group. After thermal cycloaddition to the adduct 13a or 13b, however, the NMR spectrum indicated only one adduct, since the stereochemistry created in the acetylene...
General Procedure for Second Cycloaddition. The appropriate monocy cloaddition product was dissolved in enough toluene to make the solution ~0.10 M. The solution was degassed by bubbling argon through for ~5 min. The solution was heated in a sealed tube at 240 °C for 3.5 h. The solution was concentrated and the residue chromatographed on silica gel using ether–hexane as the solvent.

1,2,4a,7,8,8a,9a-Octahydro-7,8-dimethyl-3,9-H-fluoren-9-one (11b): yield 0.02 g (32% overall); NMR (CCL 4 ) δ 0.20 (s, 6 H), 0.70 (d, J = 7 Hz), 1.0 (s, 9 H), 5.05 (m, 1 H), 6.20 (m, 2 H), 7.5 (m, 5 H); IR (film) cm⁻¹ 1735, 1648, 1250, 1190, 835, 780; high-resolution mass spectrum C₂₆H₃₄O₂Si requires 408.248 47, measured 408.248 56.

1,2,4a,7,8,8a,9a-Octahydro-7-methyl-8-phenyl-1,2,4a,4b,7,9a-Hexahydro-7-methyl-8-phenyl-3,9H-fluoren-9-one (13a): yield 0.24 g (30% overall); NMR (CCL 4 ) δ 0.2 (s, 6 H), 1.0 (s, 9 H), 5.1 (m, 1 H), 5.85 (m, 1 H), 6.0 (m, 1 H), 7.4 (m, 5 H); IR (film) cm⁻¹ 1720, 1660, 1250, 1190, 832; high-resolution mass spectrum C₂₇H₃₆O₂Si requires 406.232 70, measured 406.232 81.

Production of a Fluorescent Conjugate Acid of 8-Methoxypsoralen and an Unusual Mechanism for Its Nonradiative Decay

Himangshu R. Bhattacharjee, Eva L. Menger,* and George S. Hammond*

Contribution from the Corporate Research Center, Allied Chemical Corporation, Morristown, New Jersey 07960, and Division of Natural Sciences, University of California, Santa Cruz, California 95060. Received May 10, 1979

Abstract: The protonation constant (pKₐH⁺) of 8-methoxypsoralen was determined from measurements of its absorption in various concentrations of sulfuric and perchloric acids using Hammett acidity functions. Proton nuclear magnetic resonance spectra of highly acidic solutions indicated protonation of the exocyclic oxygen atom. With D₂SO₄, proton exchange with the solvent was rapid. The conjugate acid (C₂₆H₃₄O₂Si) requires 420.248 46, measured 420.248 38.

7-Methyl-1,2,4a,4b,7,9a-Hexahydro-7-methyl-8-phenyl-1,2,4a,4b,7,9a-Hexahydro-7-methyl-8-phenyl-3,9H-fluoren-9-one (16). To a stirred solution of 22 mg of 15 in 2 mL of toluene was added 30 mg of DDO. The reaction mixture was refluxed for 24 h. The solution was diluted with ether, filtered, and concentrated: yield 0.21 g (100%); NMR (CDCI 3 ) δ 0.28 (s, 6 H), 1.02 (s, 9 H), 2.36 (s, 3 H), 7.45 (m, 6 H); IR (CHCl 3 ) cm⁻¹ 1700, 1600, 1255, 1215, 833, 791; high-resolution mass spectrum C₂₇H₃₆O₂Si requires 324.154 56, measured 324.151 14; UV (MeOH) 256, 278 nm.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

(4) L. Ciitisen, Ber., 44, 2489 (1911).
(9) Anhydrous benzene could also be used with comparable yields.
(13) The compound appeared homogenous on several TLC conditions.

Production of a Fluorescent Conjugate Acid of 8-Methoxypsoralen and an Unusual Mechanism for Its Nonradiative Decay

Himangshu R. Bhattacharjee, Eva L. Menger,* and George S. Hammond*

Introduction

Initially, our interest in 8-methoxypsoralen (8-MOP) was sparked by the use of that compound in a novel and experimental treatment of psoriasis. In the treatment, the compound is ingested or applied topically, and after a suitable time interval the patient is irradiated with ultraviolet radiation of wavelengths longer than 300 nm. While the mechanism by which the photochemotherapy alleviates the symptoms is not fully understood, it is believed to involve the photoaddition of 8-MOP to epidermal DNA.

We were examining the fluorescence quenching of 8-MOP with various quenchers with the intent of using this data to help elucidate the distribution of the compound in tissue samples. One of the first quenchers we studied was H⁺, provided by different strong acids. The quenching followed Stern–Volmer kinetics but, much to our surprise, we observed no new fluorescence, attributable to the conjugate acid of 8-MOP. We had reasoned by analogy to the related compounds, the 7-amino-