Synthesis of Spiro[4.6]undecane-1,6-dione

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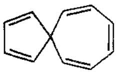
Received October 2, 1973

As a part of our long-range objective of exploring the chemistry of spirarenes,[2,3] we have undertaken the synthesis of spiro[4.6]undeca-1,3,6,8,10-pentaene (**1**). An attractive precursor in the synthesis of **1** is the previously unknown spiro[4.6]undecane-1,6-dione (**4**). We now wish to report the synthesis of **4**, prepared as shown, *via* an acid-catalyzed intramolecular Claisen condensation of 4-(2′-oxocycloheptyl)butyric acid (**3**).



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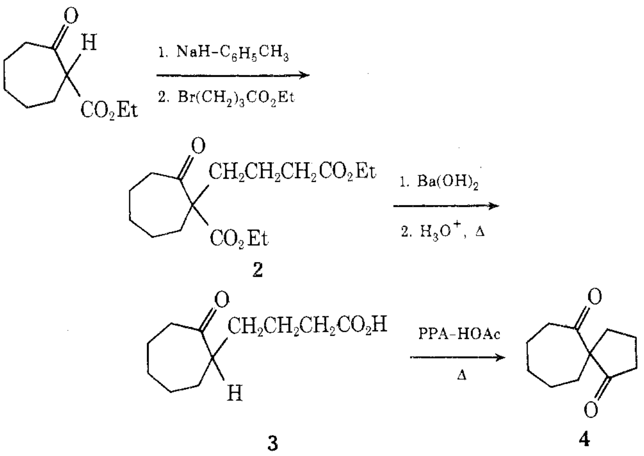

The acid-catalyzed intramolecular Claisen condensation represents a reaction type which only recently has been exploited as a means of synthesizing in moderate to high yields nonenolizable β-diketones.[4] Our procedure is an extension of the work of Gerlach and Müller, who have reported[5,6] that 4-(2′-oxocyclopentyl)butyric acid undergoes cyclization with polyphosphoric acid–acetic acid solution to give an 85% yield of spiro[4.4]nonane-1,6-dione. The lower yield in the synthesis of **4** (52%) as compared to that of spiro[4.4]nonane-1,6-dione is presumably due to the higher strain energy of the former.

The structure of the spiro ketone **4** was confirmed by physical methods. The infrared spectrum of **4** showed $\bar{\nu}_{max}$ at 1735 and 1695 cm^{-1} due to the carbonyl stretching frequency of cyclopentanone and cycloheptanone rings, respectively. The nmr, uv, mass spectrum, and composition analysis are all consistent with the structure proposed for **4**.

The acid-catalyzed intramolecular Claisen condensation described here offers a facile method for the synthesis of spirocyclic 1,3-diketones. Furthermore, this method should be general and provide an alternate synthetic route to spiro molecules in which at least one of the rings is a five- or six-membered ring.

Experimental Section[7]

Preparation of Diethyl 4-(1′-Carbethoxy-2′-oxocycloheptyl)-butyrate (2).[8] The keto diester **2** was prepared by the general procedure of Huisgen and Pawallek.[8] A 56% yield of **2** was obtained as a clear oil: bp 133–137° (0.10 mm) [lit.[8] bp 110–115° (0.01 mm)]; ir (CCl_4) 1730 (ester C=O), 1700 (cycloheptanone C=O), 1175 cm^{-1}; nmr (CCl_4) δ 1.40 (6 H, six lines), 1.40–2.20 (m, 12 H), 2.20–2.90 (m, 4 H), 4.30 (m, 4 H).

Preparation of 4-(2′-Oxocycloheptyl)butyric Acid (3).[9] The keto acid **3** was obtained by the procedure of Kimeki and Bien.[9] An 84% yield of **3** was obtained as a clear oil: bp 142–145° (0.15 mm) [lit.[9] bp 138–140° (0.01 mm)]; ir (CCl_4) 3400–3000 and 2700–2400 (OH), 1700 (C=O), 935 cm^{-1}; nmr ($CDCL_3$) δ 2.1–1.0 (m, 12 H), 2.9–2.1 (m, 3 H), 11.26 (s, 1 H).

Preparation of Spiro[4.6]undecane-1,6-dione (4). To a stirred solution of 34.1 g (0.10 mol) of polyphosphoric acid[10] and 65.0 g (1.08 mol) of purified glacial acetic acid[11] under N_2 was added (dropwise) 10.0 g (0.051 mol) of **3.** The reaction mixture was heated for 6 hr at 100° in an oil bath, cooled, poured onto ice, and extracted with benzene (3 × 100 ml). The combined benzene extracts were washed with saturated $NaHCO_3$ (3 × 100 ml) and dried ($MgSO_4$), and the benzene was removed. Vacuum distillation of the residue gave 4.75 g (52%) of **4** as a clear, colorless oil: bp 101–103° (1.25 mm); ir (CCl_4) 1735 (cyclopentanone C=O), 1695 (cycloheptanone C=O), 1145 cm^{-1}; uv (95% ethanol) λ_{max} 303 nm (ε 127); nmr (CCl_4) δ 2.90–1.0 (m); mass spectrum (70 eV) *m/e* (rel intensity) 180 (23, M^+), 152 (16), 135 (16), 125 (25), 124 (17), 123 (25), 110 (17), 97 (24), 96 (31), 95 (22), 81 (38), 79 (18), 69 (15), 68 (15), 67 (37), 57 (28), 55 (88), 54 (17), 53 (17), 43 (100), 39 (39).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.45; H, 8.75.

Acknowledgment. We gratefully acknowledge the support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and thank Dr. George Hertel of Florida Technological University for providing the mass spectra.

Registry No.—**2,** 50987-56-9; **3,** 33366-38-0; **4,** 50987-57-0.

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(7) Ir spectra were recorded with a Perkin-Elmer Model 457 spectrometer. Ultraviolet spectra were determined in 95% ethanol with a Beckman DK-2A spectrometer. Nmr spectra were obtained with a Varian T-60 spectrometer using TMS as an internal standard. The mass spectra were obtained at an ionizing energy of 70 eV on a magnetic sector mass spectrometer with a modified Nier-type source. This mass spectrometer was constructed by Dr. George Hertel of Florida Technological University. Microanalyses were performed by Robertson Laboratory, Florham Park, N. J.
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(10) Matheson Coleman and Bell polyphosphoric acid, practical, was used without further purification.
(11) Commercial glacial acetic acid was treated with 5% (by weight) $KMnO_4$ and distilled. This material was redistilled from P_2O_5.

Utilization of the 1,4-Conjugated Wittig Reaction for the Synthesis of Substituted 1,3-Cyclohexadienes

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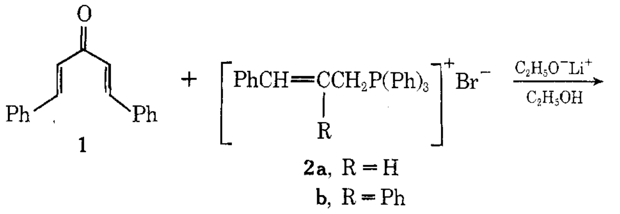
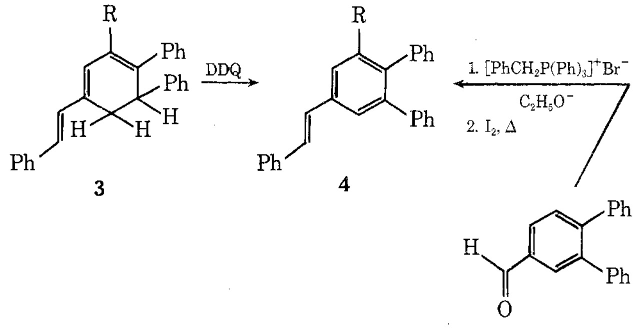
Received November 7, 1973

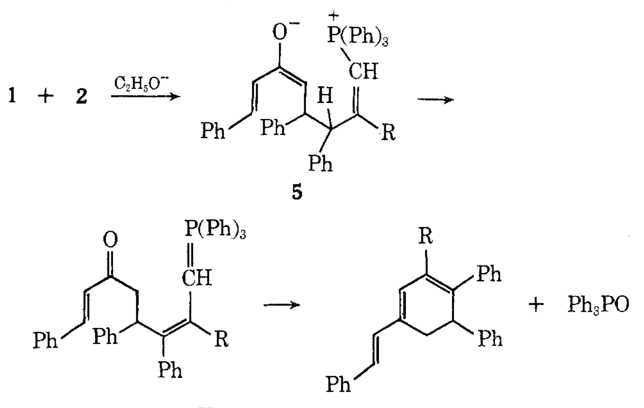
Despite the enormous success of the Wittig reaction for the preparation of olefins,[1-4] this method does have certain limitations. One complication is that the alkylidenephosphorane can function as a proton acceptor and promote enolate condensation reactions.[1] Another side reaction that occasionally occurs in the 1,4 addition of the alkylidenephosphorane to the β-carbon atom of a conjugate ketone.[5] We now report a study which shows that the Michael addition of certain alkylidenephosphoranes with α,β-unsaturated ketones can be advantageously utilized for the synthesis of substituted 1,3-cyclohexadienes.

Treatment of an ethanolic solution of *trans,trans*-1,5-diphenylpentadien-3-one (1) and *trans*-cinnamylphosphonium bromide (**2a**) with lithium ethoxide for 12 hr at room temperature afforded (*E*)-1-(4,5-diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3a**), mp 161–163°, in good yield. The structure assigned to cyclohexadiene **3a** rests on its spectral data and chemical behavior. Oxidation of **3a** with dichlorodicyanoquinone (DDQ) afforded (*E*)-1-(4,5-diphenylbenzen-1-yl)-2-phenylethylene (**4a**). The structure of compound **4a** was unambiguously established by an independent synthesis which utilized the Wittig reaction of 3,4-diphenylbenzaldehyde and triphenylbenzylphosphonium bromide. A similar set of products were obtained when 1 was treated with triphenyl-*trans*-2,3-diphenylallylphosphonium bromide (**2b**) in the presence of lithium ethoxide.





The above reactions can best be described as involving a Michael addition of the organophosphorane derived from 2 with *trans,trans*-1,5-diphenylpentadien-3-one to give intermediate **5**. A subsequent proton transfer, ketonization, and intramolecular Wittig cyclization nicely rationalize the observed products. After the completion of this work, several reports appeared describing a related set of 1,4-conjugated Wittig reactions.[6-9]



Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany. The infrared absorption spectra were determined on a Perkin-Elmer infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra at 60 MHz were determined with the Varian Associates high-resolution spectrometer and at 100 MHz using a Jeolco MH-100 spectrometer.

(*E*)-1-(4,5-Diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (3a). A solution of lithium ethoxide (prepared by dissolving 0.4 g of lithium wire in 25 ml of absolute ethanol) was added to a stirred slurry of *trans,trans*-1,5-diphenylpentadien-3-one (5 g) and *trans*-cinnamylphosphonium bromide (9.8 g). The resulting mixture was allowed to stir at room temperature overnight. The precipitate that formed was collected by filtration and recrystallized from ethanol to give 3.6 g (45%) of (*E*)-1-(4,5-diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3a**): mp 161–163°; ir (KBr) 6.23, 6.7, 6.9, 9.28, 9.70, 10.48, 11.68, 12.18, 12.95, 13.3, 13.9, 14.25, and 14.5 μ; uv (cyclohexane) 372 nm (ϵ 34,280), 266 (4850), and 233 (9860); nmr ($CDCl_3$) τ 7.01 (m, 2 H), 5.85 (dd, 1 H, J = 8.0 and 4.0 Hz), 3.6 (broad d, 1 H, J = 7.0 Hz), 3.28 (d, 1 H, J = 16.0 Hz), 3.02 (d, 1 H, J = 6 Hz), 2.98 (d, 1 H, J = 16.0 Hz), and 2.2–2.8 (m, 15 H); *m/e* 334 (M^+).

Anal. Calcd for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 93.02; H, 6.59.

The structure of the above product was verified by oxidation to (*E*)-1-(4,5-diphenylbenzen-1-yl)-2-phenylethylene (**4a**).

Oxidation of (*E*)-1-(4,5-Diphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene. A solution containing 300 mg of cyclohexadiene **3a** and 250 mg of dichlorodicyanoquinone in 50 ml of toluene was heated at reflux for 30 hr. The solution was evaporated to dryness and the brown residue was chromatographed through a Florisil column using benzene as the eluent. The benzene fractions were concentrated under reduced pressure to afford (*E*)-1-(4,5-diphenylbenzen-1-yl)-2-phenylethylene (**4a**, 203 mg, 66%): mp 121–123°; ir (KBr) 6.2, 6.75, 6.9, 9.25, 10.25, 10.95, 12.05, 12.8, 13.0, 13.2, 13.55, and 14.45 μ; nmr ($CDCl_3$) τ 2.0–3.0 (m, aromatic and vinyl); uv (cyclohexane) 315 and 230 nm (ϵ 38,980 and 21,930); *m/e* (parent) 332.

Anal. Calcd for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 93.82; H, 6.09.

(*E*)-1-(4,5-Diphenylbenzen-1-yl)-2-phenylethylene was also independently synthesized by treating 3,4-diphenylbenzaldhyde with triphenylbenzylphosphonium bromide. The desired 3,4-diphenylbenzaldehyde was prepared from 1-carbomethoxy-4,5-diphenylcyclohexa-1,4-diene.[10]

(*E*)-1-(3,4,5-Triphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (3b). A solution of lithium ethoxide (prepared by dissolving 0.4 g of lithium wire in 25 ml of absolute ethanol) was added to a stirred slurry of benzalacetone (4.4 g) and triphenyl-*cis*-2,3-diphenylallylphosphonium bromide (10.1 g). The resulting mixture was allowed to stir at room temperature for 12 hr. The precipitate that formed was collected by filtration and recrystallized from ethanol to give 3.7 g (51%) of (*E*)-1-(3,4,5-triphenyl-1,3-cyclohexadien-1-yl)-2-phenylethylene (**3b**): mp 151–153°; ir (KBr) 6.23, 6.7, 6.92, 9.33, 9.68, 10.41, 11.36, 11.92, 12.25, 13.0, 13.3, 13.9, 14.3, and 14.5 μ; nmr ($CDCl_3$) τ 6.8–7.1 (ddd, 2 H, J = 4.0, 8.0, and 18.0 Hz), 5.9 (dd, 1 H, J = 4.0 and 8.0 Hz), 3.1–3.6 (m, 3 H, vinyl), and 2.4–3.0 (m, 20 H, aromatic); uv (cyclohexane) 371, 283 and 238 nm (ϵ 36,850, 18,200, and 19,860); *m/e* (parent) 4.10.

Anal. Calcd for $C_{32}H_{26}$: C, 93.62; H, 6.58. Found: C, 93.21; H, 6.51.

A mixture containing 300 mg of compound **3b** and 300 mg of dichlorodicyanoquinone was heated in 50 ml of toluene for 29 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed through a Florisil column using benzene as the eluent. The combined benzene fractions were evaporated under reduced pressure and the residue was taken up in hot ethanol. Upon standing at room temperature, 170 mg (60%) of (*E*)-1-(3,4,5-triphenylbenzen-1-yl)-2-phenylethylene (**4b**) precipitated: mp 201–203°; ir (KBr) 6.2, 6.68, 6.9, 7.08, 9.25, 10.37, 11.17, 12,88, 13.05, 13.25, and 13.4 μ; nmr ($CDCl_3$) τ 2.3–3.1 (m, vinyl and aromatic); uv (cyclohexane) 316 and 258 nm (ϵ 39,450 and 29,900); *m/e* (parent) 408.

Anal. Calcd for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 93.99; H, 6.08.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. The National Science Foundation provided financial assistance in the purchase of the nmr spectrometer used in this research.

Registry No.—**1**, 35225-79-7; **2a**, 38633-40-8; **2b**, 51003-89-5; **3a**, 51003-12-4; **3b**, 51003-13-5; **4a**, 51003-14-6; **4b**, 51002-94-9; benzalacetone, 122-57-6.

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Reductions of Benzyl and Cyclohexyl Chloroformates with Tri-*n*-butyltin Hydride

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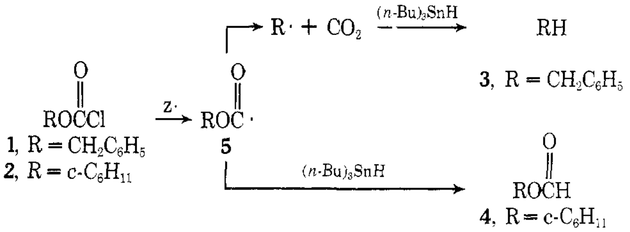
Received September 27, 1973

The lowering of transition-state energy provided by the generation of carbon dioxide in conjunction with the formation of carbonium ions and silver chloride in the reactions of chloroformates with silver ion[1] suggests that the same driving force might be available to promote the conversion of chloroformates to a formal chlorine atom, carbon dioxide, and a carbon radical. If the carbon radical could be reduced by a hydrogen-atom donor, such a process would be of synthetic value as part of a route for the deoxidation of alcohols alternative to other procedures.[2] In fact, Kuivila and Walsh have reported that benzyl chloroformate is reduced by tri-*n*-butyltin hydride to a 4:6 ratio of toluene and benzyl formate and that ethyl chloroformate gives solely ethyl formate under similar conditions.[3] It has been noted by a number of workers that the alkoxycarbonyl radical, an intermediate in the tri-*n*-butyltin hydride reduction,[4] while thermodynamically disposed to fragment to carbon dioxide and a carbon radical,[5] does have an appreciable activation energy toward such decomposition.

When the reaction of benzyl chloroformate (**1**) with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) as initiator is carried out for 22 hr in hexane at 36° at concentrations of less than 0.3 *M* in each reactant, the sole product is toleune (**3**) in 22% yield and less than 1% benzyl formate. Increase in the concentration of the hydride, however, leads to increasing amounts of benzyl formate at the expense of toluene. Reduction of benzyl chloride to toluene under the same conditions is *ca.* 1.6 times faster than the reduction of **1**. However, no significant conversion of benzyl chloroformate to benzyl chloride occurs in the absence of the other reactants, and a methanol quench of a partial reaction showed an upper limit of 4% benzyl chloride present after a reaction of 13 hr.

Reaction of cyclohexyl chloroformate (**2**) under conditions similar to those which gave toluene from benzyl chloroformate produced only cyclohexyl formate (**4**) and less than 1% cyclohexane. Greater dilutions did not produce cyclohexane.

Rationalization of these results in terms of the alkoxycarbonyl radical **5** is consistent with previous studies which suggest that the rate of fragmentation of **5** is dependent on the stability of the radical formed.[3-6] The reciprocal relationship of toluene and benzyl formate as a function of hydride concentration suggests that fragmentation and reduction of the benzyloxycarbonyl radical can be competitive under these conditions. Apparently the stability of the benzyl radical is sufficiently influential to foster fragmentation, whereas a stabilized radical would not be produced by loss of carbon dioxide from cyclohexyloxycarbonyl radical, and it survives to be reduced. A related result and similar rationale have been reported for the conversions of benzyl and *n*-octyl formate to toluene and *n*-octyl alcohol, respectively, with palladium.[7] Conversion of the chloroformate function to a hydrocarbon may be of some specialized synthetic value for cases in which the intermediate radical is stabilized, although the present procedure would involve product isolation by gas chromatography. The formation of cyclohexyl formate from cyclohexyl chloroformate does suggest, however, that unless a stabilized radical is possible the present procedure does not offer an attractive general route for the deoxidation of alcohols by the reduction of chloroformates.



Numerous attempts were made to convert cyclohexyl chloroformate to cyclohexane by reduction with lithium aluminum hydride–aluminum chloride or triethylsilane and by photolysis with tri-*n*-butyltin hydride, triphenylsilane, and triethylsilane. In no case was a glpc peak corresponding to more than 5% cyclohexane observed. Attempted reductions of cyclohexyl chlorosulfite and cyclohexyl chloroglyoxylate with tri-*n*-butyltin hydride were also unsuccessful and gave destruction of starting material in exothermic reactions, but cyclohexane could not be detected.

Experimental Section

All reactions were run in a dry nitrogen atmosphere. Gas chromatography was performed on an Aerograph A90-P3, with a 3- or 10-ft column packed with 20% XF 1150 on 60/80 acid-washed, DMCS-treated Chromosorb P. Benzyl[8] and cyclohexyl[9] chloroformates and cyclohexyl chloroglyoxalate[10] were prepared by reaction of the purified alcohols with phosgene or oxalyl chloride and gave satisfactory C, H, and Cl microanalyses. Cyclohexyl chlorosulfinate[11] was prepared by reaction of cyclohexanol with thionyl chloride and by reaction of dicyclohexyl sulfite with thionyl chloride[12] and was characterized by ir and nmr spectroscopy. Tri-*n*-butyltin hydride was prepared by lithium aluminum hydride reduction of the chloride[13] and its purity was determined as >96% by refractive index, reduction of benzyl chloride, and titration.[14]

Reaction of Benzyl Chloroformate with Tri-*n*-butyltin Hydride. Reaction of benzyl chloroformate (52.6 mg, 0.308 mmol), tri-*n*-butyltin hydride (83.9 mg, 0.88 mmol), and azobisisobutyronitrile (AIBN, 1.5 mg, 0.01 mmol) in hexane (1.00 ml) with stirring for 22 hr at 36° showed 22% yield of toluene and less than 1% benzyl formate. AIBN initiator increased the rate of reaction. Increase in metal hydride or decrease in solvent quantity increased the percentage of benzyl formate formed at the expense of toluene; a reaction twice as concentrated as that described above gave a toluene:benzyl formate ratio of 24:1, while a reaction six times as concentrated produced the same products in a ratio of 2.3:1. Benzene or ether solvent did not appreciably change the rate of reaction but gave somewhat lower toluene yields. In no instance was a significant amount of benzyl alcohol formed. Toluene and benzyl formate were identified by collection from the gas chromatograph and comparison of infrared spectra with those of authentic samples.

Since benzyl chloride was found to reduce to toluene under conditions similar to those under which benzyl chloroformate is reduced, a control experiment was carried out by quenching the reaction with methanol after 13 hr. Benzyl chloroformate reacts