An Improved Preparation of $\Delta^{8,9}$-Octal-1-one

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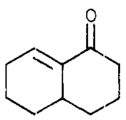
The known methods[1,2] for the preparation of $\Delta^{8,9}$-octal-1-one (**1**) are relatively laborious and inefficient. The procedure of House and Thompson,[2] for example, affords reasonably pure **1** only after separation from isomer **2**. Having need of substantial quantities of **1** as a starting material for synthesis of certain decalin derivatives to be used in studies of nucleophilic amine catalysis,[3] we sought an improved synthesis. This has been achieved through an extension of the cyclopentene annulation method developed by Marfat and Helquist,[4] which involves copper-catalyzed conjugate addition to enones of the Grignard reagent from 1,1-(ethylenedioxy)-3-bromopropane, followed by acetal hydrolysis and cyclization. In an analogous manner, reaction of the magnesium derivative (**3**) of 1,1-(ethylenedioxy)-4-chlorobutane (**4**) with cyclohexenone (**5**) leads to **1** in ca. 60% overall yield.

Chloro acetal **4** was prepared by the sequence used by Forbes,[5] rather than by that employed by Johnson.[6] Use of activated magnesium powder,[7] as in Marfat and Helquist's work,[4] facilitated preparation of Grignard reagent **3** from **4** under mild conditions and helped to avoid the difficulties in working with **3** noted by Forbes.[5]

Addition of an ethereal solution of **5** to 3 equiv of **3**[8] in THF containing a solution of cuprous bromide–dimethyl sulfide complex in dimethyl sulfide[9] at −78 °C led to formation of **6**, which could be isolated chromatographically in ca. 80% crude yield. Several sets of conditions for conversion of **6** to **1** by acid hydrolysis to **7**, followed by base- or acid-catalyzed ring closure, were examined, but the most efficient method found for formation of **1** consisted in direct treatment of the crude product from the conjugate Grignard addition with THF containing aqueous HCl at reflux for 12 h. Direct distillation of the resulting material afforded **1**, uncontaminated by **2**.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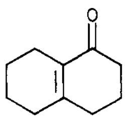
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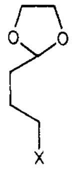
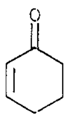


3, X = MgCl
4, X = Cl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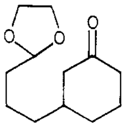

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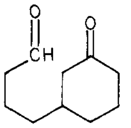

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Experimental Section

Melting points were determined in a Thomas-Hoover apparatus in unsealed capillaries and are uncorrected. Infrared (IR) spectra were recorded as neat liquids on NaCl plates, using a Perkin-Elmer Model 599 spectrophotometer. Ultraviolet (UV) spectra were recorded on a Cary 219 spectrophotometer using 1-cm quartz cuvettes. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Hitachi Perkin-Elmer R-24 instrument (60-MHz ^1H) or on a JEOL FX-60Q multinuclear Fourier-transform NMR spectrophotometer (60-MHz ^1H). Chemical shifts are reported in parts per million downfield from Me_4Si. Low-resolution mass spectra were determined on a Finnigan Model 4000 gas chromatograph/mass spectrometer. Brine refers to saturated aqueous sodium chloride solution.

$\Delta^{8,9}$-Octal-1-one (1). 1,1-(Ethylenedioxy)-4-chlorobutane (**4**) was prepared from tetrahydrofuran via conversion to 4-chlorobutan-1-ol,[10] followed by oxidation to 4-chlorobutanal and acetalization as was done by Forbes,[5] except that we found it necessary to purify the 4-chlorobutanal by distillation before use. Activated magnesium powder was prepared according to the method of Riecke.[7] A solution of 31.45 g (330 mmol) of anhydrous magnesium chloride (Aldrich) and 25.0 g (640 mmol) of potassium metal in 175 mL of THF, which had been freshly distilled from sodium and benzophenone, was refluxed under a nitrogen atmosphere which was maintained until workup. After 2.5 h the THF was allowed to boil away to a final volume of 80 mL over 30 min, and the magnesium slurry was allowed to cool to room temperature with stirring over 30 min. A mixture of 5 mL of ether and 47.01 g (312 mmol) of **4**, bp 51–53 °C (0.5 mm), was then added dropwise over 40 min while the temperature was kept below 25 °C by an ice bath. After addition was complete the mixture was cooled to −78 °C and 60 mL of dry THF was added. A solution of 5.42 g of cuprous bromide–dimethyl sulfide[9] in 10 mL of dimethyl sulfide was then added in one portion and the mixture was stirred for 1 additional h at −78 °C. A solution of 10.01 g (104 mmol) of 2-cyclohexen-1-one (**5**; 93+% pure by GLC analysis) in 50 mL of anhydrous ether was then added dropwise over 3 h. The resulting mixture was stirred at −78 °C for 10 h and then allowed to warm slowly to room temperature over 7.5 h. The mixture was then poured into 150 mL of saturated aqueous NH_4Cl solution, which had been adjusted to pH 8 with NH_4OH, with stirring in an ice bath. The aqueous layer was extracted with ether (4 × 50 mL), and the combined organic layers were washed with water (50 mL) and brine (2 × 40 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield 49.86 g of pale yellow liquid. In a different experiment, the product at this stage was chromatographed on a silica gel column, using ether–hexane as eluent, to afford fractions containing keto acetal **6** in 85% yield. Further purification by preparative TLC afforded 59% **6**: IR 1720 cm^{-1}; NMR δ 3.9 (br s, 4), 4.85 (t, 1).

The 49.86 g of product was refluxed in 100 mL of THF containing 10 mL of water and 12 mL of 1 M HCl for 12.5 h. The resulting mixture was diluted with 150 mL of brine and extracted with ether (2 × 40 mL). The organic layers were washed with saturated $NaHCO_3$ solution (2 × 25 mL) and brine (2 × 25 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield 34.15 g of reddish orange liquid which was distilled to afford 6.66 g of forerun, bp 40–65 °C (0.35–0.2 mm), followed by 9.29 g (60%) of **1**: bp 73–77 °C (0.2–0.15 mm) [lit.[2] bp 53–58 °C (0.08 mm)]; IR 1625, 1695 cm^{-1}, with no trace of the analogous absorptions for **2** (lit.[2] IR (CCl_4) for **1**, 1623, 1678 cm^{-1}; for **2**, 1634, 1664 cm^{-1}); NMR δ 6.63 (d, 1, J = 3 Hz) (lit.[2] NMR δ 6.57 (d)); UV λ_{max} (EtOH) 246 nm (ϵ 5400)[11] (lit.[2] UV λ_{max} (EtOH) 246 nm (ϵ 6170)[11]). GC/MS analysis showed this **1** to be 95% pure and to have m/e 150 (M^+) (calcd for $C_{10}H_{14}O$ m/e 150). A 2,4-dinitrophenylhydrazone derivative of this **1** had mp 225–226 °C dec after

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[8] One run was made using only 1.5 equiv of **3**, but the yield of **1** was only about 40%. However, use of less than 3 equiv of **3** probably deserves further exploration.

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[11] It should be noted that our sample of **1** contained ca. 5% nonchromophoric impurity, whereas House and Thompson's sample of **1** contained ca. 5% **2**, which has λ_{max} (EtOH) 246 nm (ϵ 12 300).[2] When these facts are taken into account, the observed extinction coefficients (5400 and 6170) are the same within experimental uncertainty but are both less than the ϵ of 7300 reported for **1** by Warnhoff.[1]

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recrystallization from ethyl acetate (lit. mp 226–226.5 °C dec,[2] 223.5–224 °C dec[1]).

The 8.56 g of undistilled residue was dissolved in 3:7 ether–hexane and filtered through a short column of silica gel. The eluent was evaporated and the residue was distilled (short path) to afford 0.85 g (5%) of slightly yellow 1, bp 75–85 °C (0.15 mm).

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Registry No. 1, 24037-79-4; 2, 18631-96-4; 4, 16686-11-6; 5, 930-68-7; 6, 75506-74-0; 7, 75506-75-1.

Acid-Catalyzed Annelation of α-Alkyl Aldehydes and α,β-Unsaturated Ketones. A One-Pot Synthesis of 4,4-Dimethyl-2-cyclohexen-1-one

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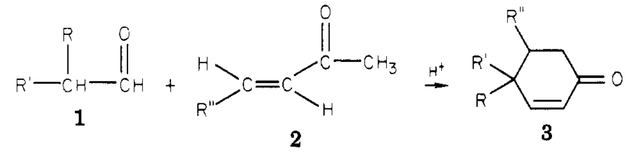
Annelations involving α-alkyl aldehydes, especially the condensation of methyl vinyl ketone and isobutyraldehyde, have been widely used. Base catalysis has customarily been utilized to effect this condensation. The yields under these conditions are not particularly good and byproducts are numerous. A thorough study of the base-catalyzed condensation of methyl vinyl ketone and isobutyraldehyde was recently reported by Krabbenhoft.[1] An alternative to base catalysis is to convert the aldehyde to an enamine, condense it with methyl vinyl ketone, hydrolyze the resulting Diels–Alder adduct, and finally cyclize under acidic conditions. This approach, which is described in *Organic Syntheses*,[2] is somewhat involved but gives a good overall yield. Spiroannelations have been accomplished by Martin and by Kane using the same principle.[3]

A publication by Heathcock et al. reporting the successful acid-catalyzed annelation of cyclic ketones[4] inspired us to consider applying similar conditions to the condensation of methyl vinyl ketone and isobutyraldehyde. Since isobutyraldehyde has only one α-hydrogen, an acid-promoted dimerization would produce an aldol that cannot dehydrate readily. Aldol formation should, therefore, be a particularly facile equilibrium wherein steric factors favor the monomeric aldehyde. As expected, addition of a small amount of acid to a mixture of methyl vinyl ketone and isobutyraldehyde caused a very smooth and moderately exothermic condensation to the desired 2,2-dimethyl-5-oxohexanal. This intermediate can be isolated in high yield, but it is more convenient to carry out the cyclization directly using an azeotropic distillation to remove the water.

The reluctance of isobutyraldehyde to participate in acid-catalyzed aldol condensations is further evidenced by the fact that a subsequent reaction of this aldehyde with the cyclized product (a major side reaction in the case of base catalysis[1]) does not appear to be significant in the presence of acid. For this reason it is possible to use excess isobutyraldehyde as the solvent for the azeotropic distillation. The net result is an extremely simple, one-pot synthesis of 4,4-dimethyl-2-cyclohexen-1-one in which the starting materials are mixed in a 2:3 (ketone–aldehyde) ratio, treated with acid, cooled initially, then refluxed through a Dean–Stark trap, and finally distilled.

Table I. Results of Several Annelations



R	R′	R″	solvent[a]	% yield[b]	bp, °C (mmHg)	lit. bp, °C (mmHg)
Me	Me	H	IBA	71	56-61 (5)	73-74 (14)[2]
Me	Me	H	Ben	70	73-76 (14)	
Me	Et	H	Ben	65	73-78 (7)	91 (14)[5]
Et	Et	H	Ben	75	92-96 (5)	80-90 (4)[6]
Me	Ph	H	Ben	74	127-130 (1)	93-94 (0.25)[7]
-(CH_2)$_5$-		H	Ben	56	122-126 (5)	83 (0.2)[8]
Me	Me	Me	IBA	36[c]	66-84 (5)	86-87 (14)[9]

[a] IBA = isobutyraldehyde, Ben = benzene. [b] Except for the last entry, yields given are for distilled, analytically and spectrally pure product. [c] NMR revealed minor impurities.

The acid-catalyzed annelation has been applied to other α-alkyl aldehydes and methyl vinyl ketone with comparable success. With other aldehydes a 1:1 ratio of substrates was used and cyclization was carried out by using a benzene/water azeotrope. Table I lists the results from a number of cases. Isobutyraldehyde and 3-penten-2-one have also been condensed to afford 4,4,5-trimethyl-2-cyclohexen-1-one. The yield in this case, although adequate, was substantially lower than that in the case of methyl vinyl ketone.

Experimental Section

General. Aldehydes used were reagent grade except for the 2-phenylbutanal, which was techical (90%). The unsaturated ketones were usually distilled before use, but yields were not noticeably changed with undistilled material. Boiling ranges are uncorrected. The NMR spectrum was determined by using a Varian Associates T-60 spectrometer with Me_4Si as an internal standard.

4,4-Dimethyl-2-cyclohexen-1-one. A mixture of 272 mL (3 mol) of isobutyraldehyde and 162 mL (2 mol) of methyl vinyl ketone was treated at room temperature with 2.0 mL of concentrated H_2SO_4. The solution was warmed cautiously to 45–50 °C and maintained at that temperature by means of occasional cooling with a cold-water bath. (**Caution**: A violent reaction may ensue if the temperature is allowed to exceed 65 °C.) The exothermic reaction subsided within about 1 h. The solution was then refluxed through a Dean–Stark trap until water removal ceased (ca. 3 h). Distillation of the mixture at 6 mm of pressure gave a forerun of isobutyraldehyde followed by the product. High temperatures were needed to drive the last of the product from the viscous residue in the pot. As a result, the boiling range was sometimes broadened due to superheating. The collected product was nonetheless quite pure. Redistillation produced a sharper boiling range with negligible loss.

General Procedure for Condensation in Benzene. A solution of 0.5 mol each of the aldehyde and methyl vinyl ketone

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