Synthesis of Two 2-(Oxoalkyl)-3-methyl-2-cyclopentenones

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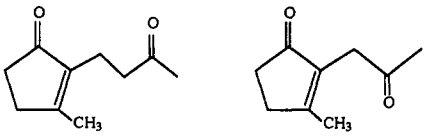
Reported here are the preparations of 2-(2-oxopropyl)-3-methyl-2-cyclopentenone and the 2,2-dimethyl-1,3-propanediol ketal of 2-(3-oxobutyl)-3-methyl-2-cyclopentenone. A reagent for the convenient preparation of such cyclic ketals is described.

Introduction

In connection with a more complex synthesis yet to be accomplished, we required a supply of 2-(3-oxobutyl)-3-methyl-2-cyclopentenone (1) with the side chain carbonyl



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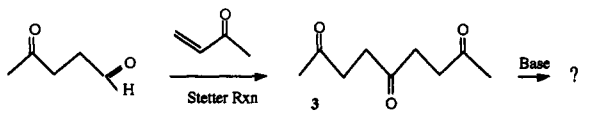
protected. The structural similarity of this molecule with dihydrojasmone[1] suggested a model pathway for the synthesis of 1. In their work, Stetter, Kuhlmann, and Haeses[1] first prepared a substituted 2,5-hexanedione by a Stetter reaction.[2] The latter was then cyclized via a base-catalyzed aldol reaction giving a 2-alkyl-3-methyl-2-cyclopentenone.

As a trial of the above procedure, it was decided that diketone 2 would first be attempted as a simpler example. Since these compounds might be of use to others as synthetic intermediates, we report the results of the study here.

Results and Discussion

Levulinic aldehyde was extended by the Stetter reaction forming the previously unknown 2,5,8-nonanetrione (3) in 90% yield. In contrast to the cyclization forming



3

dihydrojasmone,[1] the cyclization of 3 offers several additional possibilities which are detailed in Figure 1. Baldwin's rules are not very helpful in this regard as all processes are *exo-trig* where both five- and six-membered rings are favored. The formation of the eight-membered ring compound 7 is disfavored.

Base-catalyzed aldol cyclizations may be presumed to follow the usual reversible aldol mechanism including the dehydration step.[3] When five and six-membered rings are formed, dehydration seems to be the preferred terminus of the reaction. Possible ketols and their dehydration products from 3 are shown in Figure 1 along with their heats of formation. These were calculated by the semiempirical program MOPAC using the PM3 Hamiltonian.[4] Given thermodynamically driven equilibria, it is seen that at the ketol stage compounds 5 and 6 are favored. The eight-membered ring 7 is the less favored, and when combined with entropic considerations of the ring-closure process no further consideration was given to this possibility. As can be seen, the desired dehydration product 2 is the lowest energy dehydration product.

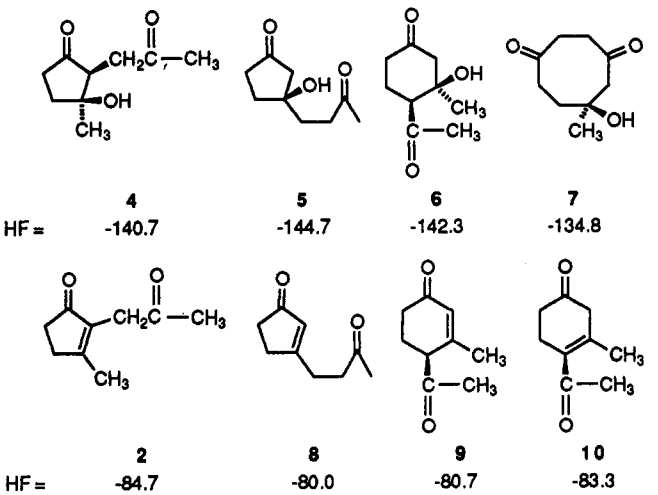


Figure 1. Possible base-catalyzed cyclization products from compound 3 with PM3 heats of formation (kcal/mol). Where pertinent only the lower energy epimer is shown.

The cyclization of 3 led to a single product (83.5% yield, crude product) which showed two methyl groups in the proton and ^{13}C NMR spectra. This ruled out compound 8 and any product derived from 7. Irradiation of the downfield side-chain methylene signals in an NOE difference experiment produced a strong positive enhancement of both methyl signals. This result is consistent only with structure 2 as the cyclization product.

It was decided that the side chain keto group in 1 could be most conveniently protected as the cyclic ketal of 2,2-dimethyl-1,3-propanediol as such ketals are generally considered to be somewhat more stable than those formed by ethylene glycol. In preparing cyclic ketals it is not uncommon to include triethyl orthoformate in the procedure. It is implied in the older literature that the purpose of the latter is to scavenge water as it is formed. When 2,2-dimethyl-1,3-propanediol is mixed with triethyl orthoformate in the presence of a small amount of *p*-toluenesulfonic acid, there is a rapid and quantitative conversion

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(1) Stetter, H.; Kuhlmann, H.; Haeses, W. *Organic Synthesis*; **1987**, *65*, 26.

(2) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.

(3) Jensen, J. L.; Hashtroudi, H. *J. Org. Chem.* **1976**, *41*, 3299.

(4) MOPAC, version 6, Quantum Chemistry Program Exchange no. 504, University of Indiana, Bloomington, IN 47405. The PM3 modification has been described by Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1. MOPAC is available in a Macintosh II version from Serena Software, Bloomington, IN.

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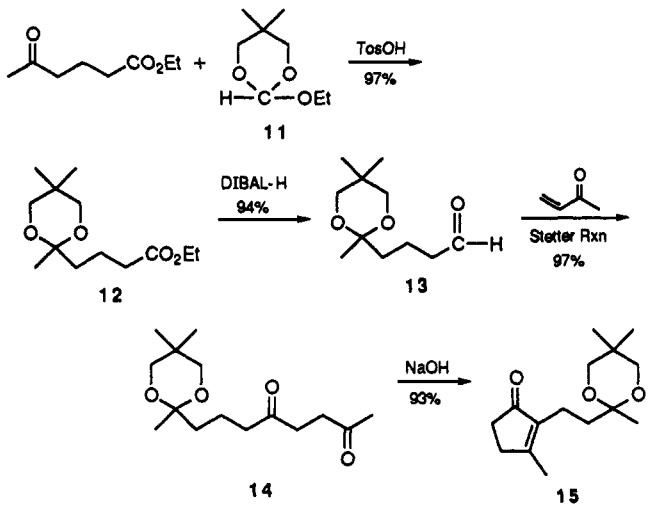
Scheme I



to 2-ethoxy-5,5-dimethyl-1,3-dioxane (11). The latter compound has been prepared and subjected to many studies (unrelated to the present work) reported in the Russian literature.[5] We have found that 11 offers a rapid, room-temperature method of preparing cyclic ketals requiring only a trace of acid. Such reactions are mildly exothermic producing ethyl formate, a small stable entity. As there appears to be no description of the preparation of 11 in the English literature, a preparation is included in the Experimental Section. Protected ketones derived from 11 are conveniently referred to as DPD ketals.

The path used in the synthesis of the DPD ketal of 1 is summarized in Scheme I. The decarboxylation of commercially available diethyl 2-acetylglutarate gave 5-ketohexanoic acid, which was esterified, and the keto group protected by the reagent 11. DIBALH reduction gave the aldehyde 13. The Stetter reaction of 13 with methyl vinyl ketone produced 2,5,9-decanetrione protected as the DPD ketal at C-9. Steps paralleling the earlier cyclization then gave 15, the DPD-protected form of compound 1.

Experimental Section

Unless otherwise specified all starting materials were from Aldrich Chemical Co. and used as received. High-resolution mass spectra were performed by the Midwest Center for Mass Spectrometry, Lincoln, NE. Ketones protected as the ketals of 2,2-dimethyl-1,3-propanediol will be referred to as DPD ketals. Standard workup consisted of extraction, drying over anhyd $MgSO_4$, and removal of the volatile solvent by rotary evaporation.

2,5,8-Nonanetrione (3). Levulinic aldehyde was prepared by the oxidation of 3-acetyl-1-propanol with PCC in CH_2Cl_2.[6] The ^{13}C NMR spectrum is given here for reference purposes. δ: 206.4 (CO), 200.4 (CHO), 37.5 (CH_2), 35.6 (CH_2), 29.7 (CH_3).

A mixture of 8.6 g (0.086 mol) of levulinic aldehyde, 7.22 g (0.103 mol) of methyl vinyl ketone, 2.32 g (0.0086 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, 5.22 g (0.0516 mol) of triethylamine, and 100 mL of absolute EtOH was refluxed for 17 h under an atmosphere of N_2. The mixture was concentrated by rotary evaporation, and 100 mL of $CHCl_3$ was added. The mixture was washed with 100 mL of 10% $(NH_4)_2SO_4$ solution and two 50-mL portions of H_2O. Standard workup gave crude 3 (13.2 g, 90%) distilled as a viscous oil, bp 120–130 °C (1.3 mm). ^1H NMR δ: 2.7 (s, 8H), 2.2 (s, 6H). ^{13}C NMR δ: 207.87 (CO), 207.1 (CO), 37.0 (CH_2), 36.1 (CH_2), 29.8 (CH_3). HRMS: calcd for $C_9H_{14}O_3$ ($M^{\cdot+}$) 170.0943, found 170.0951.

2-(2-Oxopropyl)-3-methyl-2-cyclopentenone (2). A solution of triketone 3 (3 g, 0.0176 mol) and 0.56 g (0.014 mol) of NaOH in 28 mL of H_2O and 7 mL of EtOH was refluxed for 6 h, cooled to room temperature, and extracted with ether. Standard workup gave crude 2 (2.3 g, 83.5%) identified by NMR. ^1H NMR δ: 3.3 (s, 2H), 2.6 (t, 2H), 2.44 (t, 2H, J = 4.4 Hz), 2.19 (s, 3H), 2.05 (s, 3H). ^{13}C NMR δ: 208.3 (CO), 204.5 (CO), 173.7 (C), 134.0 (C), 37.8 (CH_2), 34.1 (CH_2), 31.95 (CH_2), 29.8 (CH_3), 17.58 (CH_3). The methylene protons at 3.3 ppm were irradiated in a standard NOE difference determination. Strong positive enhancements were found for the methyl resonances at 2.05 and 2.19 ppm. HRMS: calcd for $C_9H_{12}O_2$ ($M^{\cdot+}$) 152.0837, found 152.0841.

2-Ethoxy-5,5-dimethyl-1,3-dioxane (11). A mixture of 20.8 g (0.2 mol) of 2,2-dimethyl-1,3-propanediol, 40 g (0.2 mol) of triethyl orthoformate, and 200 mg of *p*-toluenesulfonic acid was stirred for 30 min. EtOH (18.4 g) was removed under vacuum at room temperature. If heating was used to facilitate the process, only high molecular weight polyesters were formed. The crude product (NMR pure) was allowed to stand overnight over Na_2CO_3, filtered, and distilled, bp 78–84 °C (44 mm),[5] 26.1 g, 82% yield. For most purposes the reagent could be prepared in an NMR pure state by running the reaction as above and then tumbling the mixture on a rotary evaporator over Na_2CO_3 while pumping off the ethyl formate. ^1H NMR δ: 5.26 (s, 1H), 3.72 (dd, 2H, J = 11 Hz), 3.68 (q, 2H, J = 7 Hz), 3.36 (dd, 2H, J = 11 Hz), 1.10 (t, 3H, J = 7 Hz), 0.98 (s, 3H), 0.97 (s, 3H). ^{13}C NMR δ: 109.4 (CH), 72.0 (2 CH_2), 60.7 (CH_2), 29.7 (C), 22.6 (CH_3), 22.0 (CH_3), 15.0 (CH_3).

The DPD Ketal of Ethyl 5-Oxohexanoate (12). Ethyl 5-oxohexanoate was prepared by the hydrolysis, decarboxylation, and reesterification of diethyl 2-acetylglutarate.[7] The keto ester (10.0 g, 0.063 mol), 10.1 g (0.063 mol) of ketalization reagent 11, and 200 mg of *p*-toluenesulfonic acid were stirred overnight at room temperature. Initially, the reaction became perceptibly warm. NMR examination suggested the reaction was complete within 1 h. The mixture was diluted with 25 mL of methylene chloride, and 4 g of anhydrous sodium carbonate was added. Stirring was continued for 30 min. The mixture was filtered. Volatile components were removed by rotary evaporation. The yield of the NMR pure ester 12 was 14.8 g (96%). ^1H NMR δ: 4.13 (q, 2H, J = 7.1 Hz), 3.5 (dd, 2H, J = 11.4 Hz), 3.48 (dd, 2H, J = 11.4 Hz), 2.34 (t, 2H), 1.73 (m, 4H), 1.37 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.01 (s, 3H), 0.89 (s, 3H). ^{13}C NMR δ: 173.56 (CO_2-Et), 98.7 (C), 70.3 (2 CH_2), 60.17 (CH_2), 37.24 (CH_2), 34.35 (CH_2), 29.9 (C), 22.74 (CH_3), 22.5 (CH_3), 20.36 (CH_3), 19.09 (CH_2), 14.28 (CH_3). Anal. Calcd for $C_{13}H_{24}O_4$ (244): C, 63.94; H, 9.90. Found: C, 63.94; H, 9.58.

DPD Ketal of 5-Oxohexanal (13). Ketal ester 12 (20 g, 0.082 mol) in 100 mL of anhyd toluene was cooled to −78 °C, and 66 mL of 1.5 M diisobutylaluminum hydride (DIBALH) (0.099 mol) was added slowly over a period of 10 min. After the reaction mixture was stirred for 2 h at −78 °C, a slurry of potassium fluoride (5.72 g in 25 mL ether) was slowly added. The mixture was filtered and the residue washed several times with ether. The combined organic extracts were dried over anhyd magnesium sulfate. After filtration, volatile solvents were removed by rotary evaporation. This material (15.3 g, 94%) was used in the next step without further purification. ^1H NMR δ: 9.77 (s, 1H), 3.64 (dd, 2H, J = 11.4 Hz), 3.34 (dd, 2H, J = 11.4 Hz), 2.47 (t, 2H), 1.72 (m, 4H), 1.37 (s, 3H), 1.04 (s, 3H), 0.87 (s, 3H). ^{13}C NMR δ: 202.38 (CHO), 98.6 (C), 70.34 (2 CH_2), 43.9 (CH_2), 37.97 (CH_2), 29.9 (C), 22.84 (CH_3), 22.4 (CH_3), 19.89 (CH_3), 16.13 (CH_2).

Ketone 15. A mixture of 15 g (0.075 mol) of ketal aldehyde (13), 6.45 g (0.092 mol) of methyl vinyl ketone, 2.02 g (0.0075 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, 4.6 g (0.045 mol) of triethylamine, and 100 mL of absolute ethanol was refluxed for 17 h. When cool, the mixture was concentrated by rotary evaporation. Chloroform (100 mL) was added to the residue which was washed with 100 mL of 10% ammonium sulfate and water (2 × 50 mL). After drying over

(5) Karakhanova, N. K.; Kalashnikov, S. M.; Gordeeva, G. N.; Yashina, N. S.; Zlotskii, S. S.; Imashev and U. B.; Rakhmankulov, D. L., Vestn. *Mosk. Univ., Ser. 2: Khim.* **1985**, *26*(2), 196–201.

(6) Piancatelli, G.; Scetti, A.; D'Auria, M. *Synthesis* **1982**, 245.

(7) Beilstein H *3*, 686.

anhyd magnesium sulfate and filtering, the volatile components were removed by rotary evaporation. The yield of the crude diketone 14 was 19.8 g (97.7%). ^{1}H NMR δ: 3.49 (dd, 2H, J = 11.4 Hz), 3.47 (dd, 2H, J = 11.4 Hz), 2.69 (m), 2.49 (t, 2H), 2.18 (s, 3H), 1.68 (m), 1.36 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H). ^{13}C NMR δ: 209.22 (CO), 207.09 (CO), 98.8 (C), 70.37 (2 CH_2), 42.76 (CH_2), 37.39 (CH_2), 36.92 (CH_2), 36.06 (CH_2), 29.94 (C), 29.89 (CH_3), 22.8 (CH_3), 22.54 (CH_3), 20.27 (CH_3), 17.9 (CH_2).

Diketone 14 (19.6 g, 0.073 mol) was added to a solution of 2.33 g (0.06 mol) of sodium hydroxide, 117 mL of water, and 30 mL of ethanol. The mixture was refluxed for 6 h, cooled to room temperature, and extracted with ether. The combined ether extracts were dried (anhyd magnesium sulfate), filtered, and concentrated by rotary evaporation. The yield of the crude 15 was 17.1 g (93.4%). ^{1}H NMR δ: 3.5 (s, 4H), methyl singlets at 2.07, 1.40, 0.97, 0.96. ^{13}C NMR δ: 209.4 (CO), 169.9 (C), 140.3 (C), 98.6 (C), 70.4 (2 CH_2), 34.2 (CH_2), 33.7 (CH_2), 31.5 (CH_2), 29.9 (C), 22.6 (2CH_3), 21.4 (CH_3), 17.27 (CH_2), 17.14 (CH_3). HRMS: calcd for $C_{15}H_{24}O_3$ ($M^{\cdot+}$) 252.1725, found 252.1716.

Acknowledgment. A portion of the research was funded by the Texas Christian University Research Fund to whom grateful appreciation is expressed.

Supplementary Material Available: Proton (300 MHz) and carbon (75 MHz) spectra for compounds 2, 3, and 11–15 (8 pages). This material is contained in libraries on microfiche, immediately follows this article on the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.