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A New Synthesis of 3-Alkyl-2-cyclopenten-2-ol-1-ones

CHARLES M. LEIR[1]

Chemical Research Laboratories, Chas. Pfizer & Co., Groton, Connecticut 06340

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A new synthesis of 3-methyl-2-cyclopenten-2-ol-1-one (**3**) and 3-ethyl-2-cyclopenten-2-ol-1-one (**4**) is described. Dieckmann cyclization of dimethyl adipate and alkylation in *N,N*-dimethylformamide gave keto esters **1a** and **1b**; chlorination in acetic acid produced dichloro keto esters **2a** and **2b** which were hydrolyzed and decarboxylated to afford **3** and **4** in 65–70% overall yields. This route has been demonstrated to be a convenient, general method for the preparation of other 3-alkyl-substituted 2-cyclopenten-2-ol-1-ones.

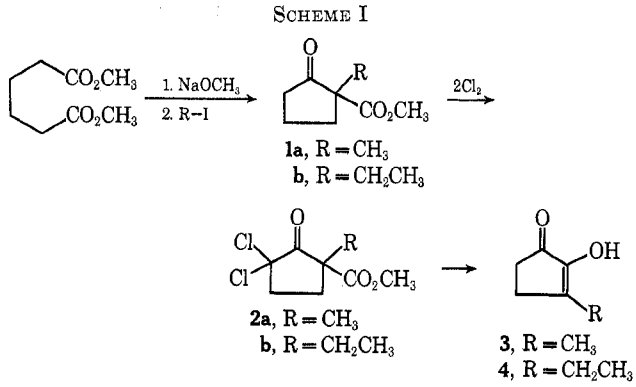
For some time 3-methyl-2-cyclopenten-2-ol-1-one (**3**) has been recognized, as a flavor constituent, for example, in coffee aroma[2] and maple flavor,[3] and the material has found commercial use when incorporated as a flavorant in various food items. It has been reported[2] as well that the homolog, 3-ethyl-2-cyclopenten-2-ol-1-one (**4**), is also a constituent of coffee aroma. In addition, it has been observed[4] that the ethyl compound **4** possesses organoleptic qualities superior to those of **3**.

Besides being available from natural sources, **3** has been synthesized by a variety of methods reported in the literature.[5] The preparation of **4** also has been reported.[5a,6] These methods have not been entirely satisfactory, particularly for larger scale preparations, owing to low overall yields and/or inaccessibility of starting materials.

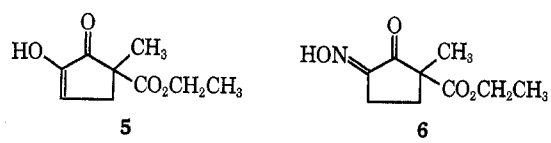
In this paper, we describe a convenient method for the preparation of 3-methyl-2-cyclopenten-2-ol-1-one and the more potent 3-ethyl-2-cyclopenten-2-ol-1-one, which is adaptable as a general method for the preparation of a variety of other alkyl-substituted 2-cyclopenten-2-ol-1-ones. Starting with dimethyl adipate, the route proceeds as outlined in Scheme I in excellent overall yield.

The Dieckmann cyclization of dimethyl adipate was conducted in *N,N*-dimethylformamide (DMF) solution and afforded the sodium enolate of 2-carbomethoxycyclopentanone which was alkylated with methyl or ethyl iodide giving **1a** and **1b** in high yield (85%).

SCHEME I



Sato, *et. al.*,[5b] have employed the corresponding ethyl ester of **1a**, 2-methyl-2-carbethoxycyclopentanone, as an intermediate in the synthesis of **3**. They were able to introduce the requisite α-carbonyl group with selenium dioxide to afford **5**, or with *n*-butyl nitrite to give oxime **6**. In both cases, the yields were low, as was the yield of **3** from the subsequent hydrolysis of **5** or **6**.



5 **6**

The possibility that a *gem*-dichloro group α to the carbonyl of **1a** and **1b** might serve as the necessary ketone precursor appeared attractive, especially from the standpoint of ease of preparation. Indeed, **2a** and **2b** were obtained in quantitative yield from the chlorination of **1a** and **1b** in acetic acid.

The hydrolysis of **2a** to **3** in 10% sulfuric acid was complete in 6 hr, but, under the same conditions, **2b** was

(1) Biochemical Research Laboratory, 3M Co., St. Paul, Minn.

(2) M. A. Gianturco, A. S. Giammarino, and R. G. Pitcher, *Tetrahedron*, **19**, 2051 (1963).

(3) V. J. Filipic, J. C. Underwood, and C. O. Willits, *J. Food Sci.*, **30**, 1008 (1965).

(4) (a) A. Torres and C. R. Stephens, unpublished results. (b) A. O. Pittet, P. Rittersbacher, and R. Muralidhara, presented to the Annual Meeting of the American Association of Cereal Chemists, Chicago, Ill., April 27–May 1, 1969.

(5) (a) K. Tonari, I. Ichimoto, H. Ueda, and C. Tatsumi, *J. Agr. Chem. Soc. Jap.*, **44**, 46 (1970). (b) K. Sato, S. Suzuki, and Y. Kojima, *J. Org. Chem.*, **32**, 339 (1967), and references therein. (c) K. Sato, Y. Kojima, and H. Sato, *ibid.*, **35**, 2374 (1970).

(6) M. A. Gianturco and P. Friedel, *Tetrahedron*, **19**, 2039 (1963).

unaffected. Extended periods of reflux served only to decompose this material to a black tar. After experimentation with various conditions, high yields (~80%) of **4** were obtained when **2b** was hydrolyzed in large volumes of 5% hydrochloric acid containing 15% acetic acid. Under these conditions, 12 hr were required for complete reaction. Although no attempt was made to optimize conditions for the hydrolysis of **2a** to **3**, good results were obtained with the use of 5% hydrochloric acid containing 5% acetic acid (~70% overall yield).

Surprisingly, 3-ethyl-2-cyclopenten-2-ol-1-one proved to be notably less stable on standing than the methyl homolog **3**. In *ca.* 6–8 hr after isolation, samples of the material (mp 42–44°) kept at room temperature had partially decomposed, forming viscous brown oils which contained a small amount of a new, more polar substance when examined by tlc. The nature of this decomposition reaction remains unexplained, but, fortunately, a facile method for preserving the product was found. In concentrated (80%) ethanol solution, **4** suffered no significant change over extended periods of time.[7]

Several other 3-alkyl-2-cyclopenten-2-ol-1-ones were prepared by this procedure as an indication of the generality of the method. These compounds, several of which were previously unreported, are listed in Table I with their physical constants and microanalyses. The yields reported are overall yields from dimethyl adipate to recrystallized products. In these experiments, the intermediates were not purified, and no attempts were made to optimize conditions in the final hydrolysis step.

TABLE I

3-Alkyl-2-cyclopenten-2-ol-1-one	Bp, °C (0.1 mm)	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % C	Yield, %
Propyl[a]	75–80	54–56	68.54	8.63	68.71	8.75	30
Isobutyl	92–93	90–92	70.10	9.15	69.85	9.24	30
Benzyl[b]		98–100	76.57	6.43	76.28	6.61	26

[a] Lit.[5a] bp 107–109 (8 mm), mp 56–58°. [b] Alkylation with benzyl chloride.

Experimental Section

Melting points and boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a Varian Aerograph 90P-3 instrument using a 5-ft SE-30 column. The following spectrometers were used: nmr, Varian A-60 (TMS as internal standard); ir, Perkin-Elmer Model 21; uv, Cary Model 14. Microanalyses were performed by the analytical services group of these laboratories.

2-Methyl-2-carbomethoxycyclopentanone (1a).—To a stirred mixture of 56.4 g (1.06 mol) of sodium methoxide in 250 ml of dry *N,N*-dimethylformamide was added rapidly 174.0 g (1.0 mol) of dimethyl adipate. The clear brown solution was stirred and heated under vacuum (165 mm) while methanol and dimethylformamide were allowed to distil from the reaction. In ~45 min, the head temperature was constant at 105–108°, and the solution was cooled to ~35–40° under nitrogen. A solution of methyl iodide (170.4 g, 1.2 mol) in 150 ml of dimethylformamide was added with stirring to the solution while the temperature was maintained at ~40–55° with external cooling. After addition was complete, a heavy precipitate of sodium iodide formed and the temperature rose to 60–65°. The pasty mass was stirred rapidly with cooling until the pH had dropped to neutral (~45 min). An equal volume of dry ether was added, the solid was filtered and washed well with ether, and the ether and dimethylformamide of the combined filtrate and washings were evaporated on a rotary evaporator giving a brown oil. This was taken up in ether, washed with water, dried, and evaporated to afford a light yellow oil (~150 g). Distillation gave pure **1a** as a colorless oil (132.2 g, 85% yield), bp 85–90° (5 mm) [lit.[8] bp 100–106° (13 mm)].

2-Ethyl-2-carbomethoxycyclopentanone (1b).—The procedure was identical with that for the preparation of **1a** above except that 187.0 g (1.2 mol) of ethyl iodide was used in place of methyl iodide. Work-up gave 155 g of crude product which was distilled to afford 144.6 g (85%) of **1b**: bp 114–117° (17 mm); ir ($CHCl_3$) 5.70, 5.75 μ; nmr ($CDCl_3$) δ 3.68 (s, 3, CO_2CH_3), 2.00 (m, 8), 0.88 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.39; H, 8.53.

Dichloro Keto Ester 2a.—Chlorine was bubbled rapidly into a stirred solution of 132.2 g (0.85 mol) of **1a** in 1 l. of glacial acetic acid. The temperature of the exothermic reaction was held at 45–50° by means of a water bath. After 130 g (1.8 mol) of chlorine had been added, the addition was stopped and the solution stirred until the vpc of an aliquot indicated complete conversion to the dichlorinated material (~1 hr). Evaporation of the acetic acid gave a colorless oil which was distilled to afford **2a** (186.7 g, 98%): bp 90–95° (0.3 mm); ir ($CHCl_3$) 5.60, 5.75 μ; nmr ($CDCl_3$) δ 3.73 (s, 3, CO_2CH_3), 2.75 (m, 2), 2.15 (m, 2), 1.51 (s, 3, CH_3).

Anal. Calcd $C_8H_{10}Cl_2O_3$: C, 42.69; H, 4.48. Found: C, 42.88; H, 4.50.

Dichloro Keto Ester 2b.—The procedure was identical with that for the preparation of **2a** above. From 144.6 g (0.85 mol) of **1b** there was obtained 196.0 g (97%) of pure **2b**: bp 100–106° (0.3 mm); ir ($CHCl_3$) 5.55, 5.70 μ; nmr ($CDCl_3$) δ 3.72 (s, 3, CO_2CH_3), 2.70 (m, 2), 2.00 (m, 4), 0.92 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{12}Cl_2O_3$: C, 45.21; H, 5.06. Found: C, 44.94; H, 5.05.

3-Methyl-2-cyclopenten-2-ol-1-one (3).—A mixture of 186.7 g (0.83 mol) of **2a**, 1800 ml of 5% HCl, and 100 ml of glacial acetic acid was stirred and heated under reflux until carbon dioxide evolution ceased (~6 hr). The yellow solution was cooled to ~15°, neutralized to pH ~5 with concentrated NaOH solution, and extracted with seven 500-ml portions of ethyl acetate. The combined extracts were washed with saturated sodium bicarbonate solution until basic and the organic layer was evaporated to dryness to afford a yellow solid. Recrystallization from ethyl acetate gave 63.8 g (58.4 g plus 5.4 g from a second crop) of pure **3** (68% yield, 57% overall yield from dimethyl adipate). The product had mp 104.5–106° and was identical in all respects with the authentic material: uv max (H_2O) 256 mμ (ε 12,400); nmr ($CDCl_3$) δ 6.98 (s, 1, **OH**), 2.39 (s, 4), 2.00 (s, 3, **CH_3**) [lit.[5b] mp 105–106°; uv max (EtOH) 257 mμ (ε 13,350); nmr δ 6.33 (s), 2.37 (s), 1.97 (s)].

In another preparation in which the intermediates were not purified by distillation, slightly higher overall yields were obtained. Thus 174.0 g (1.0 mol) of dimethyl adipate gave 71.0 g of **3** (63% yield) of mp 102–104°.

3-Ethyl-2-cyclopenten-2-ol-1-one (4).—A mixture of 196.0 g (0.83 mol) of **2b**, 3600 ml of 5% HCl, and 600 ml of glacial acetic acid was stirred and heated under reflux until the vpc of an aliquot showed the complete disappearance of **2b** (~12 hr). The clear brown solution was cooled to room temperature and extracted with five 700-ml portions of ethyl acetate. The combined extracts were evaporated to dryness to give a brown oil. Distillation afforded 81.9 g (79% yield, 65% overall yield from dimethyl adipate) of **4**: bp 73–75° (0.3 mm); uv max (CH_3OH) 258 mμ (ε 13,200); nmr ($CDCl_3$) δ 7.15 (s, 1, **OH**), 2.46 (m, 6), 1.17 (t, 3, J = 7 Hz, CH_2CH_3) [lit.[6] bp 65–68° (1 mm); uv max (EtOH) 259 mμ (ε 10,100)]. According to vpc, the product was >99% pure. Recrystallization from cold (−78°) hexane gave 70.0 g (2 crops) of white, crystalline **4** of mp 42–44°. This material was dissolved in 14 g of 95% ethanol immediately after drying to avoid decomposition.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.37; H, 8.06.

Slightly higher overall yields were realized in another preparation in which the intermediates were not purified by distillation.

(7) The author is indebted to Mr. Anibal Torres of these laboratories for making this observation.

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From 174.0 g (1.0 mol) of dimethyl adipate there was obtained 87.0 g (70% yield) of distilled 3-ethyl-2-cyclopenten-2-ol-1-one of >99% purity according to vpc.

Registry No.—**1b**, 25684-00-8; **2a**, 25684-01-9; **2b**, 25684-02-0; **3**, 80-71-7; **4**, 21835-01-8; Table I—propyl, 25684-04-2; isobutyl, 25684-05-3; benzyl, 25684-06-4.

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Diels–Alder Reaction of Acetoxy-1,3-dienes with Dimethyl Acetylenedicarboxylate and Chloromaleic Anhydride. A Synthesis of Benzene Derivatives

JOSEPH WOLINSKY* AND ROBERT B. LOGIN[1]

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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Acyclic acetoxy-1,3-dienes, generated *in situ* from α,β-unsaturated aldehydes and ketones, undergo the Diels–Alder reaction with dimethyl acetylenedicarboxylate or chloromaleic anhydride to yield phthalic acid derivatives. Cyclic acetoxy-1,3-dienes and dimethyl acetylenedicarboxylate give bicyclo[2.2.2]octadiene derivatives. Heating the bicyclo[2.2.2]octadiene derivatives above 200° yields dimethyl acetoxyphthalates.

Acetoxy-1,3-dienes, preformed[2,3] or generated *in situ*,[4,5] readily participate in the Diels–Alder reaction. This paper describes a convenient one-step synthesis of phthalate derivatives by the reaction of acetoxy-1,3-dienes with dimethyl acetylenedicarboxylate or chloromaleic anhydride. This procedure complements and extends the methods for direct construction of benzene rings developed by Blanc[6] and Hill.[7]

Heating an acyclic α,β-unsaturated aldehyde or ketone in isopropenyl acetate, containing a catalytic amount of *p*-toluenesulfonic acid, with 1.5 equiv of dimethyl acetylenedicarboxylate affords a dimethyl phthalate derivative in good yield. Scheme I shows a pathway for the production of phthalate derivatives and lists representative examples used to demonstrate the scope of this reaction.

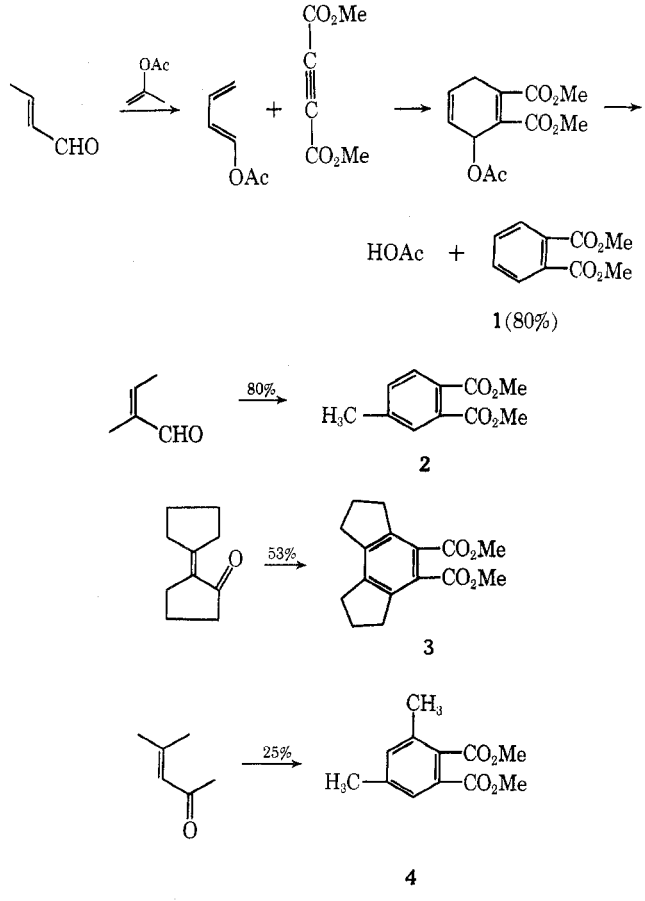
When chloromaleic anhydride is used as the dienophile the corresponding phthalic anhydride derivative is obtained (see Scheme II). The intermediate chloro acetate produced in this reaction must eliminate 1 equiv of acetic acid and hydrogen chloride to give the aromatic system.

Cyclic acetoxy-1,3-dienes were found to undergo the Diels–Alder reaction with dimethyl acetylenedicarboxylate, but not with chloromaleic anhydride. Dimedone gave a white, crystalline adduct **9** whose nmr spectrum exhibited singlets at 0.99, 1.11, 2.08, 2.11, and 3.78 ppm assigned to a *gem*-dimethyl group, two acetate groups, and two methoxy groups, respectively. The methylene group appeared as an AB-type quartet at 1.69 and 2.05 with a coupling constant of 12 Hz, while the bridgehead proton is observed at 3.48 and is coupled (J = 2 Hz) with the vinyl proton at 6.21 ppm.

Hydrolysis of adduct **9** gave keto acetate **10** and keto alcohol **11** which were readily separated by column chromatography. The C-7 methylene group of keto acetate **10** appeared as an AB pattern (J = 12 Hz) in which the upfield signal centered at 1.82 ppm was split into a doublet of doublets *via* long-range coupling (J = 2 Hz) through a "W" arrangement[8] with the endo proton at C-2, whose nmr signal was located at 2.72 ppm.

The structure of keto alcohol **11** was established by its conversion to keto acetate **10** by prolonged heating with acetic anhydride containing a catalytic amount of *p*-toluenesulfonic acid. The unique feature of the nmr

SCHEME I



* Author to whom correspondence should be addressed.

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