A Facile Annulation Sequence

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Annulation of six-membered carbon rings normally involves the attachment of a 3-oxo-C_4 chain to a cyclic or open-chain ketone to construct a cyclohexenone ring. We report here a facile two-step annulation sequence which involves the attachment of a C_3 unit to a 2-formylcycloalkanone followed by intramolecular cyclocondensation. An annulation reaction of this type is the earlier reported[1] condensation of acetone with

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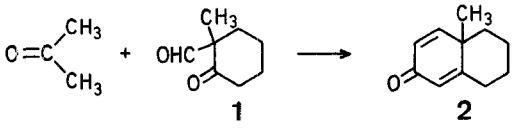
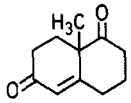
2-formyl-2-methylcyclohexanone (**1**) to give 10-methyl-2-oxo-2,4a,5,6,7,8-hexahydronaphthalene (**2**) in 62% yield (isolated as the 2,4-DNP derivative) without isolation of the intermediate. This approach to dienone **2** has not proved to be sufficiently attractive.



1 **2**

Using a related method, dione **3** has been prepared in relatively low yield by the condensation of acetonedicarboxylic acid with formaldehyde and 2-methyl-1,3-cyclohexanedione[2].



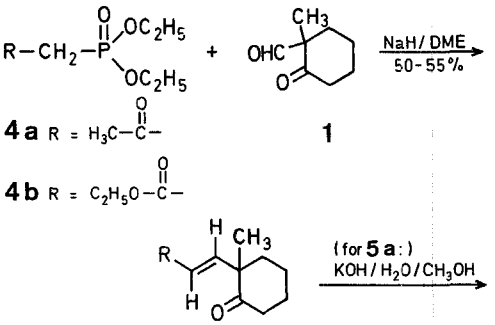
3

Cyclohexenones of the 3-oxo-Δ^4-steroid may be converted to the corresponding cyclohexadienones by dehydrogenation with iodylbenzene[3].

Our method for the preparation of cyclohexadienone derivative **2** is based on the regioselective Wittig-Horner reaction of 2-formyl-2-methylcyclohexanone (**1**) with diethyl 2-oxopropanephosphonate (**4a**). The carbonyl olefination product **5a** thus obtained in 50–55% yield is the *(E)*-isomer as evidenced by the coupling constant of the olefinic protons of *J*-18 Hz. It has been stated[4] that the *trans* geometry of compound **5a** might be unfavorable for cyclization to compound **2**. Nevertheless, we found that enedione **5a** undergoes cyclodehydration in the presence of strong base to give dienone **2** in 80% yield.

The Wittig-Horner reaction of oxoaldehydes **1** and **6** with triethyl phosphonoacetate (**4b**) were also found to be regioselective, the 3-(2-oxocycloalkyl)-propenoic esters **5b** and **7b**, respectively, being obtained in 50–55% yield.

In contrast to the facile cyclization of compound **5a**, all our attempts to cyclodehydrate the analogous cyclopentanone derivative **7a** [obtained from diethyl 2-oxopropanephosphonate (**4a**) and oxoaldehyde **6**] were unsuccessful.

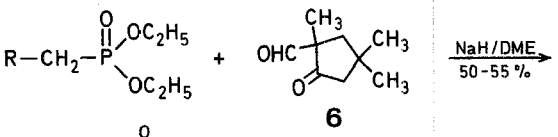


4a R = $H_3C-\overset{O}{\overset{\|}{C}}-$

4b R = $C_2H_5O-\overset{O}{\overset{\|}{C}}-$

1

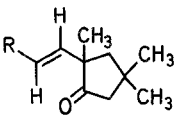
5a,b **2**



6

4a R = $H_3C-\overset{O}{\overset{\|}{C}}-$

4b R = $C_2H_5O-\overset{O}{\overset{\|}{C}}-$



7a,b

The use of 2-oxopropylidene- and ethoxycarbonylmethylene-triphenylphosphoranes (Wittig reagents) in place of phosphonic esters **4a, b** in the above reactions gave nearly identical results without any appreciable increase in yields. Other reported routes[5,6] to compounds of the types **5** and **7** give unsatisfactory yields. Cyclohexanone derivatives of the type **5** have recently been synthesized[7] using phenylselenoacetaldehyde.

***trans*-2-(3-Oxo-1-butenyl)-cycloalkanones (5a, 7a) and Ethyl 3-(2-Oxocycloalkyl)propenoates (5b, 7b); General Procedure:**

A solution of diethyl 2-oxopropanephosphonate (**4a**; 0.1 mol) or triethyl phosphonoacetate (**4b**; 0.1 mol) in 1,2-dimethoxyethane (20 ml) is added dropwise to a stirred suspension of sodium hydride (4.8 g of

Table. Cycloalkanone Derivatives **5** and **7** prepared

Product	Yield[a] [%]	b.p./torr [°C]	Molecular formula[b]	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]
5a	51	103–105°/ 0.5–0.8	$C_{11}H_{16}O_2$ (180.2)	2960 (s); 2930, 1710 (s); 1680 (s); 1620 (m); 1450, 1360, 1250, 980	1.3 (s, 3H); 1.6–2.1 (m, 8H); 2.3 (s, 3H); 6.0 (d, 1H, CO—CH=CH, J=18 Hz); 7.0 (d, 1H, CO—CH=CH, J=18 Hz)
5b	55	100–110°/ 0.5–1.0	$C_{12}H_{18}O_3$ (210.3)	2960 (s); 2930, 1710–1720 (b); 1640 (m); 1450, 1300, 1270, 1170 (s)	1.15 (s, 3H); 1.2 (t, 3H); 1.5–2.6 (m, 8H); 4.14 (q, 2H); 5.7 (s, 1H, CO—CH=CH, J=18 Hz); 7.0 (d, 1H, CO—CH=CH, J=18 Hz)
7a	55	—[c]	$C_{12}H_{18}O_3$ (210.3)	2960 (s); 2930, 1740 (s); 1680 (s); 1620 (m); 1460, 1410, 1390, 1370, 1360, 1260, 1210, 1180, 1150, 1060, 980	1.1 (s, 3H); 1.15 (s, 3H); 1.2 (s, 3H); 2.0 (q, 2H, J=11 Hz); 2.2 (s, 2H); 2.25 (s, 3H); 6.1 (d, 1H, CO—CH=CH, J=18 Hz); 6.8 (d, 1H, CO—CH=CH, J=18 Hz)
7b	53	105–110°/ 0.5–1.0	$C_{13}H_{20}O_3$ (224.3)	2960 (s); 2930, 1740 (s); 1720 (s); 1640 (m); 1460, 1440, 1360, 1310, 1100	1.13 (s, 3H); 1.2 (s, 3H); 1.27 (s, 3H); 1.3 (t, 3H); 2.0 (q, 2H, J=11 Hz); 2.2 (s, 2H); 4.15 (q, 2H); 5.8 (d, 1H, CO—CH=CH, J=18 Hz); 6.85 (d, 1H, CO—CH=CH, J=18 Hz)

[a] The products were >99% pure as determined by G.L.C. analysis (Instruments Company; 15% DEGS on chromosorb, 1/8″ × 6′, TCD, carrier gas N_2, 2.1 kg/cm², 185 °C).

[b] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.31; H, ±0.21.

[c] Not distilled; purified by column chromatography.

50% NaH, 0.1 mol) in 1,2-dimethoxyethane (100 ml). Stirring is continued until gas evolution ceases (~ 1 h) and then the oxoaldehyde **1** or **6** (0.1 mol) is added at such a rate as to keep the temperature below 35 °C. Stirring is continued for 3–4 h at room temperature. The formation of a thick gelatinous semisolid indicates completion of the reaction. The mixture is poured into water (200 ml) and extracted with chloroform (3 × 100 ml). The organic extract is dried with sodium sulfate and evaporated to give the crude product which is purified by passing through a column of silica gel (250 g) using benzene as solvent or by distillation under reduced pressure.

4a-Methyl-2-oxo-2,4a,5,6,7,8-hexahydronaphthalene (2):
Aqueous 50% potassium hydroxide (2 ml) is added to a solution of 2-methyl-2-(3-oxo-1-butenyl)-cyclohexanone (**5a**; 360 mg, 2 mmol) in methanol (10 ml) under nitrogen and the mixture is refluxed for 7 h. The solvent is then removed, the residue diluted with water (20 ml), and extracted with ether (5 × 10 ml). The extract is dried with sodium sulfate and evaporated to give the liquid product **2**; yield: 260 mg (80%).

I.R. (CCl_4): ν = 2960, 1660 (s), 1620 (m), 1440, 1390.

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.3 (s, 3H); 1.5–2.4 (m, 8H); 6.0 (m, 2H, J = 8 Hz); 6.7 ppm (d, 1H, J = 8 Hz).

Compound **2** is purified by column chromatography on silica gel and is characterised by its ^{1}H-N.M.R. and I.R. spectra. The structure is further confirmed by treatment with acetic anhydride/sulfuric acid according to Ref.[1] to give *5-acetoxy-8-methyltetralin;* m.p. 82 °C (Ref.[1], m.p. 82 °C); mixture m.p. with an authentic sample: 82 °C.

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