Synthesis of the Bicyclo[4.3.1]decan-10-one System by Cycloalkylation of Specific Cyclohexanone Enolates with Reactive 1,4-Dichlorides

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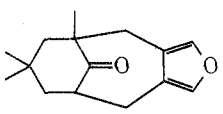
In an approach to the total synthesis of the hydroazulenic sesquiterpene velleral,[1] we set out to find a method of preparing compound **1**. Ketones with the bicyclo[4.3.1]decan-10-one skeleton have been synthesized from cycloheptanones[2] and by a cycloalkylation reaction of a propyl-2-tetralone with a 1,2-bis(chloromethyl)benzene using sodium hydride as base.[3] However, an attempt by us to prepare compound **4** by a similar base-induced cycloalkylation of 2-methylcyclohexanone yielded a complex mixture. In the present case the relative kinetic acidities of the α-methine and α-methylene protons can presumably account for the failure of the method, since spiro compounds could be formed if the first alkylation step does not take place at the methine carbon atom.



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We now wish to report a new method of reasonably general applicability which gives fair to excellent yields of the four bicyclic ketones shown in Scheme I. We considered the possibility of forming the specific enolate **2a** by the convenient procedure used by House, Gall, and Olmstead[4] for the preparation of 2,2-dialkylated ketones. These authors reported that the lithium *tert*-butoxide formed in the reaction caused some dialkylation. However, the lithium *tert*-butoxide can very suitably function as the base required in the second step of a cycloalkylation sequence using a reactive 1,4-dihalide as alkylating agent.

Reactions with **7** yielding **8** and **9** gave lower yields, partly owing to reaction of 2 mol of enolate with 1 mol of dichloride (by-product vpc–mass spectrum: M^+ 276, $C_{18}H_{22}O_2$). The preparation of **7** includes a hydrogenation of but-2-yne-1,4-diol to *cis*-but-2-ene-1,4-diol. It may be noted that this can be done excellently with a method (Pd on $BaSO_4$ in pyridine) indicated without experimental details by Fieser and Fieser[5] (though not mentioned in a recent review article[6]).

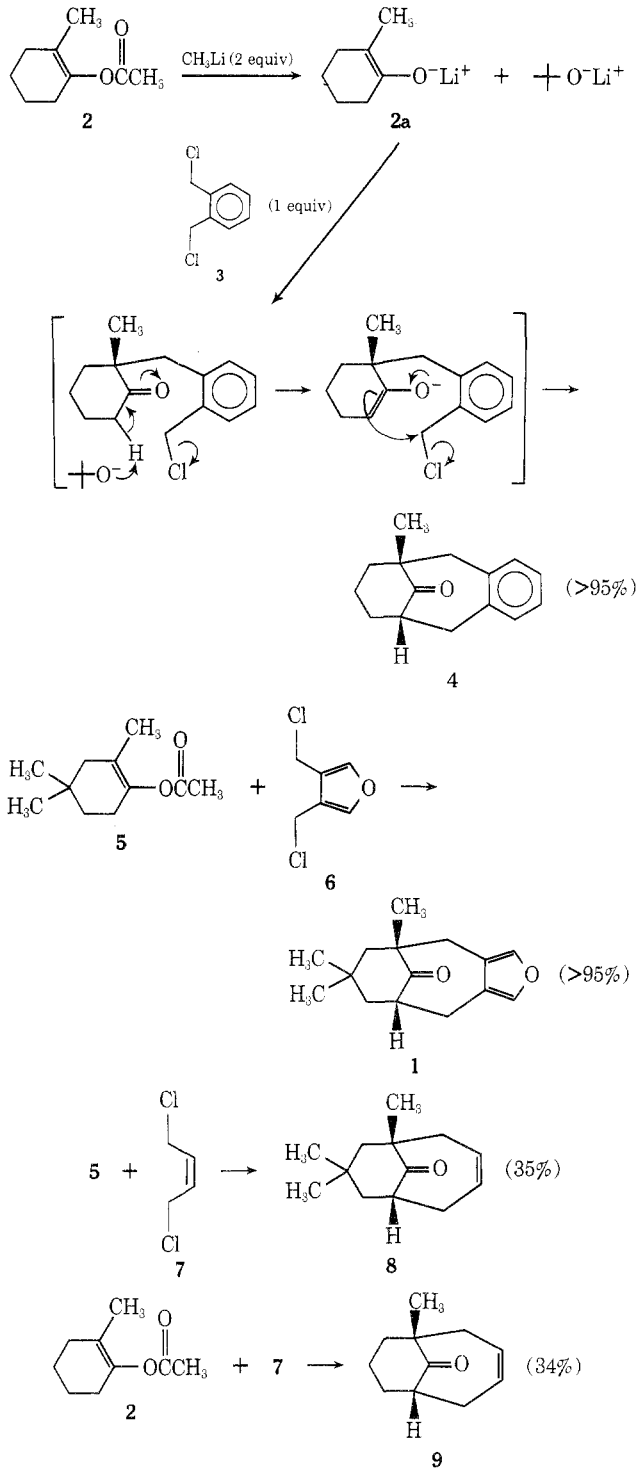
Ketones such as **8** and **9** can be suitable synthetic precursors for stereospecific preparations, for instance of *cis*-2,6-dialkylcyclohexanones, which are otherwise difficult to prepare free of the trans isomer and for syntheses of nine-membered ring compounds.[3] The present cycloalkylation method may be less suitable for some acyclic ketones because of the difficulty of obtaining the proper trisubstituted enol acetate.[4]

Experimental Section

Vpc was carried out on a 1.5 m × 3.1 mm XE-60 column (2% on Chromosorb G, 100–120 mesh) at 130–180°. Melting points are uncorrected. Nmr spectra were recorded on a Varian T-60 instrument and mass spectra on a LKB 1100 instrument (70 eV). Ir spectra refer to liquid films unless otherwise stated.

1-Acetoxy-2-methylcyclohexene (**2**) was prepared according to House, *et al.*,[4] 4,4-dimethylcyclohexanone according to Conia and Le Craz,[7] and 3,4-bis(chloromethyl)furan (**6**) and *cis*-1,4-dichlorobut-2-ene[8] (**7**) (from *cis*-but-2-ene-1,4-diol) according to Novitskii, *et al.*[9]

Scheme I



2-Methoxycarbonyl-4,4-dimethylcyclohexanone was prepared following a method of Corey, Mitra, and Uda:[10] yield 93%; bp 46.5–47° (0.2 mm); $n^{22}D$ 1.4819; ir 1752, 1720 (C=O of keto form), 1660, 1622 cm^{-1} (C=O and C=C of enol form); nmr ($CDCl_3$) δ 3.77 (s, 3), 2.26 (t, 2, J = 7 Hz), 2.02 (s, 2), 1.42 (t, 2, J = 7 Hz), 0.97 (s, 6).

Anal. Calcd for $C_{16}H_{20}N_4O_6$ (dinitrophenylhydrazone): C, 52.7; H, 5.5; N, 15.4. Found: C, 52.7; H, 5.5; N, 15.2.

The dinitrophenylhydrazone had mp 154–156° (EtOAc–EtOH–H_2O).

2-Methoxycarbonyl-2,4,4-trimethylcyclohexanone was prepared by the general procedure of Ritchie and Taylor:[11] yield 83%; bp 56–57° (0.3 mm); $n^{23}D$ 1.4585; ir 1730, 1745 (C=O), 1395, 1375 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 3.74 (s, 3), 1.27 (s, 3), 1.08 (s, 3), 1.00 (s, 3).

Anal. Calcd for $C_{17}H_{22}N_4O_6$ (dinitrophenylhydrazone): C, 54.0; H, 5.9; N, 14.8. Found: C, 53.9; H, 5.8; N, 14.7.

The dinitrophenylhydrazone had mp 152–154° (EtOAc–EtOH–H_2O).

2,4,4-Trimethylcyclohexanone[12] was prepared by the general procedure of Ritchie and Taylor:[11] yield 79%; bp 76–77° (15 mm); $n^{22}D$ 1.4481; ir 1718 (C=O), 1390, 1370 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 1.23 (s, 3), 1.01 (s, 6), 0.95 (d, 3, J = 7 Hz).

The dinitrophenylhydrazone had mp 150–151° (ethanol) (lit.[12] mp 149–150°).

1-Acetoxy-2,4,4-trimethylcyclohexene (5) was prepared following the general procedure of House, *et al.*:[4] yield 90%; bp 92.5–93.5° (15 mm); $n^{22}D$ 1.4514; ir 1760 (C=O), 1715 (C=C), 1390, 1370 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 2.12 (s, 3), 0.98 (s, 6).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0. Found: C, 72.4; H, 9.9.

1,2-Bis(chloromethyl)benzene[13] **(3).** Phthalyl alcohol (6.9 g, 0.05 mol) and triphenylphosphine (27.0 g, 0.103 mol) were refluxed in 200 ml of dry carbon tetrachloride for 22 hr.[14] The reaction mixture was cooled to 0° and poured into petroleum ether (400 ml, bp 40–60°) to complete the precipitation of triphenylphosphine oxide. Filtration, evaporation, and distillation gave pure 1,2-bis(chloromethyl)benzene: yield 5.2 g (61%); bp 55–56° (0.3 mm); mp 55–56° (lit.[11] mp 54–55°); nmr ($CDCl_3$) δ 7.34 (s, 4), 4.74 (s, 4).

cis-**But-2-ene-1,4-diol**[15] was prepared by hydrogenation of but-2-yne-1,4-diol (20.0 g) in 300 ml of pyridine (5% Pd on $BaSO_4$, 1.0 g)[5] in 88% yield.

General Cycloalkylation Procedure. Methyllithium in ether (21 mmol) was added to 50 ml of dimethoxyethane (DME) and the bulk of the ether was removed under reduced pressure. The enol acetate (10 mmol) in 5 ml of DME was added dropwise to the methyllithium solution containing a white precipitate (0°, slow N_2 stream, magnetic stirring). After 15 min the reaction mixture was heated to 60° to dissolve the lithium *tert*-butoxide. The dichloride (10 mmol) in 5 ml of DME was added in one lot. After *ca.* 5 min the reaction was complete (vpc and nmr; prolonged reaction time did not affect the yield significantly) and the reaction mixture was poured into an ice-cooled mixture of 5% sodium bicarbonate solution (100 ml) and pentane (50 ml). The water phase was extracted with pentane (2 × 50 ml), the combined pentane extracts were dried (Na_2SO_4), and the solvent was evaporated to yield the crude reaction product.

1,8,8-Trimethylfuro[3,4-*c*]bicyclo[4.3.1]decan-10-one (1) was prepared from **5** and **6**. The crude reaction product (yield >95%) was practically pure **1** (nmr, ir). Sublimation *in vacuo* gave an analytical sample: mp 108–110°; ir (KBr) 3125, 3100 (furan), 1697 (C=O), 1393, 1378 (*gem*-CH_3), 878 cm^{-1} (furan); nmr ($CDCl_3$) δ 7.30 (s, 2), 1.27 (s, 3), 0.98 (s, 3), 0.92 (s, 3); mass spectrum m/e 232 (M^+).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.6; H, 8.7. Found: C, 77.5; H, 8.7.

1-Methyl-3,4-benzobicyclo[4.3.1]decan-10-one (4) was prepared from **2** and **3**. The crude reaction product (yield >95%) was almost pure **4** (nmr). Distillation gave a colorless oil which crystallized on cooling: yield 65%; bp 110–112° (0.4 mm); mp 64–65.5°; $n^{21}D$ 1.5555; ir 3030 (aromatic CH), 1708 (C=O), 750 cm^{-1}; nmr ($CDCl_3$) δ 7.06 (s, 4), 1.08 (s, 3); mass spectrum m/e 214 (M^+).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.1; H, 8.5 Found: C, 84.1; H, 8.5.

1,8,8-Trimethylbicyclo[4.3.1]dec-3-en-10-one (8) was prepared from **5** and **7**. The crude reaction product was chromatographed on silica (50 g) with methylene chloride as eluent to give **8** in 35% yield: $n^{25}D$ 1.4913; ir 1706 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.93–5.70 (m, 2), 3.10–2.55 (m, 1, J = 4.4 Hz), 1.20 (s, 3), 0.93 (s, 3), 0.87 (s, 3); mass spectrum m/e 192 (M^+).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.2; H, 10.5. Found: C, 80.9; H, 10.3.

1-Methylbicyclo[4.3.1]dec-3-en-10-one (9) was prepared from **2** and **7**. The crude reaction product was chromatographed on silica (50 g) with methylene chloride as eluent to give **9** in 34% yeild: bp 59–60° (0.4 mm); $n^{26}D$ 1.4998; ir 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.92–5.67 (m, 2), 1.11 (s, 3); mass spectrum m/e 164 (M^+).

Anal. Calcd for $C_{17}H_{20}N_4O_4$ (dinitrophenylhydrazone): C, 59.3; H, 5.9; N, 16.3. Found: C, 59.6; H, 5.8; N, 16.2.

The dinitrophenylhydrazone had mp 177–179° (EtOAc–EtOH–H_2O).

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Registry No.—1, 50388-42-6; **2,** 1196-73-2; **3,** 612-12-4; **4,** 50388-44-8; **5,** 50388-45-9; **6,** 6372-18-5; **7,** 1476-11-5; **8,** 50388-48-2; **9,** 50388-49-3; **9** 2,4-dinitrophenylhydrazone, 50388-50-6; 2-methoxycarbonyl-4,4-dimethylcyclohexanone, 50388-51-7; 2-methoxycarbonyl-4,4-dimethylcyclohexanone 2,4-dinitrophenylhydrazone, 50388-52-8; 2-methoxycarbonyl-2,4,4-trimethylcyclohexanone, 50388-53-9; 2-methoxycarbonyl-2,4,4-trimethylcyclohexanone 2,4-dinitrophenylhydrazone, 50388-54-0; 2,4,4-trimethylcyclohexanone, 2230-70-8; phthalyl alcohol, 612-14-6; *cis*-but-2-ene-1,4-diol, 6117-80-2; but-2-yne-1,4-diol, 110-65-6.

References and Notes

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Addition of Chlorine to 1,3-Butadiene with Antimony Pentachloride

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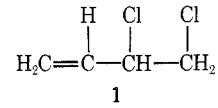
The reaction of $SbCl_5$ with simple olefins was reported recently.[1] The reaction yielded vicinal dichloroalkanes by a cis addition, as evidenced by the formation of *cis*-1,2-dichlorocyclohexane from cyclohexene, presumably by a concerted pathway.

We report here on the reaction of $SbCl_5$ and 1,3-butadiene (BDN) to produce dichlorobutene (DCB) isomers. This reaction is strongly stereoselective toward the formation of **2** when compared to the reaction of molecular



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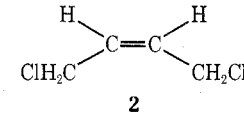

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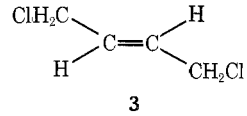

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chlorine and butadiene under similar conditions. The latter reaction has been studied previously,[2] and data indicate only trace quantities of **2**. These data have been confirmed by our work, using conditions and apparatus com-