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(25) Dimethyl (2-oxoheptyl)phosphonate is now available from Aldrich Chemical Co.
(26) Available from the Aldrich Chemical Co.

Intramolecular Friedel–Crafts Reaction of 3-Cyclohexen-1-acetyl Chloride and Its 4-Methyl Analog[1]

Stephen A. Monti* and Gary L. White

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

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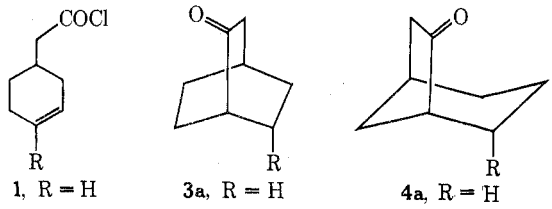
Stannic chloride catalyzed cyclization of 3-cyclohexen-1-acetyl chloride (**1**) yielded a mixture of 6-chlorobicyclo[2.2.2]octan-2-one (**3b**) and 2-chlorobicyclo[3.2.1]octan-7-one (**4b**). Reductive fragmentation of **3b** and **4b** with lithum aluminum hydride gave 2-(3-cyclohexenyl)ethanol. Treatment of the keto chloride mixture with DBN–HMPA gave bicyclo[3.2.1]oct-3-en-6-one (**9**) as the only elimination product. Cyclization of 4-methyl-3-cyclohexen-1-acetyl chloride (**2**) followed by DBN–HMPA elimination furnished 4-methylbicyclo[3.2.1]oct-3-en-6-one (**15**) in good yield. These intramolecular Friedel–Crafts acylations provide a regioselective synthetic route to bicyclo[3.2.1]octane systems containing differentiated functionality in two bridges.

The intramolecular Friedel–Crafts acylation of aliphatic substrates to give fused-ring products is well documented.[2,3] This method also provides an attractive synthetic route to bicyclic derivatives characterized by differentiated functionality in two bridges.[4] An investigation of the Lewis acid catalyzed cyclization of 3-cyclohexen-1-acetyl chloride (**1**) and its 4-methyl analog **2** was undertaken to evaluate further this approach to functionalized bicyclooctane skeletons.

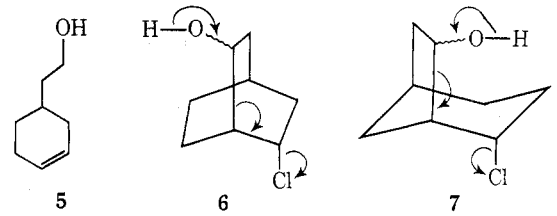
Treatment of acid chloride **1** with stannic chloride in carbon disulfide (−15°, 1 hr) yielded a mixture of three bicyclic keto chlorides (ratio 11:6:6) in 90% yield. Reduction of this mixture with tri-*n*-butyltin hydride gave two ketones which were identified as bicyclo[2.2.2]octan-2-one (**3a**) and bicyclo[3.2.1]octan-6-one (**4a**) by comparison with authentic materials. Separation of the keto chloride mixture and reduction of the individual components revealed that the major isomer furnished **3a**, one minor isomer gave **4a**, and the other minor isomer was not reduced under these conditions. Assignment of structure **3b** to the major keto chloride component and structure **4b** to one of the minor isomers was based on the observation that treatment of the keto chloride mixture with lithium aluminum hydride gave alcohol **5** in 75% yield. A reductive fragmentation[4a] of **3b** and **4b** (see arrows in **6** and **7**) readily accounts for the formation of **5** and suggests the anti disposition of the carbonyl group and the chlorine atom shown in **3b** and **4b**.



1, R = H
2, R = Me

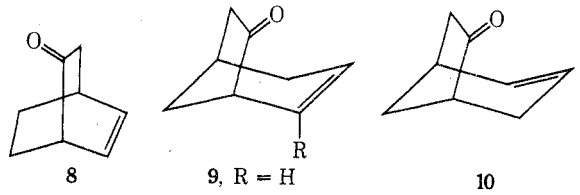
3a, R = H
b, R = Cl

4a, R = H
b, R = Cl



5 6 7

When the initial keto chloride mixture was heated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in hexamethylphosphortriamide (HMPA) solution (115°, 5 hr) a *single* bicyclic keto olefin was isolated together with recovered keto chloride(s). Vpc comparison of this new material with known samples of the possible elimination products, 8[5] and a mixture[6] of **9** and **10**, indicated that it was one of the bicyclo[3.2.1]octenes **9** or **10**. Initial structural assignment as

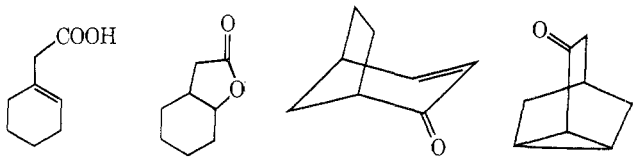


8 9, R = H
15, R = CH_3 10

9 was made on the basis of the lanthanide shift nmr analysis method of Willcott and Davis[7] (see Experimental Section for details) and was confirmed by comparion with authentic **9**.[8] The reluctance of keto chloride **3a** to undergo

dehydrochlorination under these conditions to give the bicyclo[2.2.2]octene **8** certainly reflects the steric strain associated with elimination in this system.[9] The favored trans, antiparallel elimination geometry is easily achieved in the chlorobicyclo[3.2.1]octane skeleton **4b.**

In two recent related studies, cyclohexene acid **11**[10] and and lactone **12**[11] were treated with polyphosphoric acid to give α,β-unsaturated ketone **13** and cyclopropyl ketone **14**



11 **12** **13** **14**

as major products. Closure of the monocyclic precursor 3-cyclohexene-1-acetic acid (**1**, Cl = OH) to either a bicyclo[2.2.2]- or a bicyclo[3.2.1]octyl cation, followed by subsequent rearrangement to **13** and **14**, was proposed in both cases. The same bicyclic cations may be generated when acid chloride **1** is treated with $SnCl_4$ but, in contrast to the PPA solutions, a good nucleophile is present to trap these cations before rearrangement occurs.

Cyclization of acid chloride **2** was examined next with the expectation that the vinyl methyl substituent would direct ring closure to give regioselective formation of the bicyclo[3.2.1]octane skeleton (*e.g.*, **15**). Treatment of **2** with $SnCl_4$ gave a mixture of two bicyclic keto chlorides which underwent smooth elimination (DBN–HMPA) to give 4-methylbicyclo[3.2.1]oct-3-en-6-one (**15**) in 51% overall yield from the starting acid **2**, Cl = OH. The nmr spectrum of **15** showed a vinyl methyl signal at δ 1.73 and a one-proton vinyl absorption at δ 5.4 ppm which confirm initial ring closure to give the bicyclo[3.2.1]octane skeleton.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer. Nmr spectra were measured on a Varian Associates A-60 or a Perkin-Elmer R-12 spectrometer and chemical shifts are reported in ppm downfield (δ) from internal TMS. Gas chromatographic analysis were performed on a Varian Aerograph 1200 instrument. Combustion analyses were done by Chemalytics, Inc., Tempe, Ariz.

6-Chlorobicyclo[2.2.2]octan-2-one (3b) and 2-Chlorobicyclo[3.2.1]octan-7-one (4b). A solution of acid chloride[12] **1** (1.00 g, 6.3 mmol), prepared from the corresponding acid[13] ($SOCl_2$ in benzene), in carbon disulfide (5 ml) was added to a mixture of $SnCl_4$ (1.64 g, 6.3 mmol) in carbon disulfide (5 ml) at −15° under a nitrogen atmosphere. This mixture was stirred for 1 hr, water (15 ml) was added, the organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give 0.90 g (90%) of products which could be purified by chromatography in silica gel or by sublimation: mp 120–128°; ir ($CHCl_3$) 1740 cm^{-1}; nmr ($CDCl_3$) δ 4.3 (m, 1) and 2.8–1.5 ppm (m, 10); vpc analysis (15% QF-1 on Chrom W, 180°) revealed three components in the ratio of 11:6:6 in order of increasing retention times.

Anal. Calcd for $C_8H_{11}ClO$: C, 60.57; H, 6.99. Found: C, 60.16; H, 6.63.

Tri-*n*-Butyltin Hydride Reduction of 3b and 4b. A. The above keto chloride mixture (0.30 g, 1.9 mmol) and tri-*n*-butyltin hydride[14] (0.55 g, 1.9 mmol) were mixed under a nitrogen atmosphere. After the initial exotherm, this mixture was heated at 50° for a total of 16 hr at which time vpc analysis showed complete disappearance of the two keto chlorides with the shortest retention times and the appearance of **3a**[15] and **4a**[16] (ratio of *ca.* 8:5) as judged by comparison to authentic samples.

B. Preparative vpc separation of the above keto chloride mixture and reduction of the individual components as described in A indicated that the shortest retention time keto chloride **3b** yielded **3a**, the second, **4b**, gave **4a** and the longest retention time keto chloride was recovered unchanged. The structure of the latter remains unknown.

Lithium Aluminum Hydride Reduction of 3b and 4b. The above keto chloride mixture (0.80 g, 5.0 mmol) and $LiAlH_4$ (0.26 g, 7.0 mmol) in THF (10 ml) were heated at reflux under a nitrogen atmosphere for 6 hr. The mixture was cooled, dilute HCl was added dropwise, the layers were separated after removal of solid precipitate by filtration, and the aqueous phase was extracted twice with ether. The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give 490 mg of residue (75%). Distillation gave pure **5:** bp 107–112° (23 mm) [lit.[12] bp 110–112° (23 mm)]. The ir and nmr spectra and vpc retention time of **5** were identical with authentic material prepared by hydroboration–oxidation of 4-vinylcyclohexene with diisoamylborane.[17]

Bicyclo[3.2.1]oct-3-en-6-one (9). The above keto chloride mixture (1.0 g, 6.3 mmol) and DBN (2.4 g, 6.3 mmol) in HMPA (10 ml) were heated at 115° for 5 hr under a nitrogen atmosphere. Water (10 ml) was added, and the mixture was extracted with ether. After drying ($MgSO_4$) the organic phase was evaporated to give 325 mg of crude product (42%). Vpc analysis indicated the presence of **9** (68%) and recovered keto chlorides (32%). A pure sample of **9** was obtained by evaporative distillation: bp 110° (bath temperature) (1.7 mm); ir ($CHCl_3$) 1740 cm^{-1}; nmr ($CDCl_3$) δ 5.7 (broad d, 2), and 3.0–1.5 ppm (m, 8). Vpc analysis (15% QF-1, 140°) showed a single peak with retention time of 3.0 min; authentic[5] **8** showed retention time of 2.6 min and a mixture[6] of **9** and **10** showed retention times of 2.4 and 3.0 min; authentic[8] **9** showed retention time of 3.0 min.

Lanthanide Shift Nmr Analysis of 9. Nmr spectra of **9** were obtained with 12 increasing concentrations of $Yb(fod)_3$[7b] using an internal TMS standard. Using a set of relative shifts for eight distinguishable proton groups, minimum values of R[7a] of 6.90% for **9** and 11.96% for **10** were obtained. The calculated ratio for the two vinyl proton relative shifts of 2.23 for **9** agrees quite well with the experimentally observed value of 2.04; the calculated ratio for **10** is 1.21. These data establish structure **9.**[18]

4-Methyl-3-cyclohexen-1-ylmethanol. Ethyl 4-methyl-3-cyclohexene-1-carboxylate[19] (74.0 g, 0.48 mol) and $LiAlH_4$ (19.0 g, 0.50 mol) in ether (150 ml) were stirred for 1 hr at room temperature under a nitrogen atmosphere. Dilute HCl was added carefully, the layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was distilled to give 50.0 g (84%) of product: bp 108–109° (20 mm); nmr (CCl_4) δ 5.31 (broad s, 1), 3.88 (s, 1), 3.40 (d, 2, J = 6 Hz), 1.62 (s, 3), and 2.2–1.1 ppm (m, 7).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.52; H, 11.54.

4-Methyl-3-cyclohexene-1-acetonitrile. The above alcohol (16.0 g, 0.13 mol) and *p*-toluenesulfonyl chloride (28.6 g, 0.15 mol) in pyridine (120 ml) were stirred at 0° for 3 hr. Ice was added, the layers were separated, and the organic phase was extracted with ether. The combined organic phases were washed with 6 *N* HCl and then water and finally were dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude tosylate was used in the next step.

Crude tosylate (from 0.4 mol of alcohol) in DMSO (150 ml) was added dropwise to a stirred slurry of NaCN (56.1 g, 1.14 mol) in DMSO (600 ml) at 90°. The resulting solution was stirred for 2 hr, cooled to room temperature, diluted with water (450 ml), and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a residue which was distilled to yield 41.2 g (85%) of product: bp 117–118° (17 mm); nmr ($CDCl_3$) δ 5.35 (broad s, 1), 2.32 (d, 2, J = 7 Hz), 1.68 (s, 3), 2.3–1.6 ppm (m, 7).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.96; H, 9.89; N, 10.47.

4-Methyl-3-cyclohexene-1-acetic Acid. The above nitrile (12.2 g, 0.09 mol) and NaOH (14.4 g, 0.36 mol) in water (150 ml) were heated at reflux for 24 hr. After cooling to 0° the solution was neutralized with 6 *N* HCl and then extracted with a mixture of ether–benzene. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give 13.0 g (94%) of product: mp 58–60°; nmr ($CDCl_3$) δ 11.8 (s, 1), 1.64 (s, 3), and 2.5–1.5 ppm (m, 10).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.14; H, 9.42.

4-Methylbicyclo[3.2.1]oct-3-en-6-one (15). A solution of thionyl chloride (5.0 g, 0.04 mol) in benzene (60 ml) was added to a suspension of the sodium salt of 4-methyl-3-cyclohexene-1-acetic acid (5.4 g, 0.03 mol) in benzene (60 ml). After stirring for 17 hr at room temperature the solution was evaporated *in vacuo* and the

crude acid chloride was dissolved in carbon disulfide (30 ml). To this solution was added stannic chloride (7.9 g, 0.03 mol) in carbon disulfide (30 ml) at 0°. This mixture was stirred for 0.5 hr at 0°, and then 4 hr at room temperature. After cooling to 0°, water (20 ml) was added, the layers were separated, and the aqueous phase was washed with ether. The combined organic phases were washed with 10% Na_2CO_3 solution, dried ($MgSO_4$), and evaporated to give 3.2 g (61%) of crude keto chlorides. Vpc analysis showed two components. Using the procedure described for **9**, the crude keto chlorides (1.7 g, 9.5 mmol) and DBN (3.7 g, 30 mmol) yielded 1.1 g (82%) of **15** which was purified by chromatography on silica gel or by evaporative distillation: bp 160° (bath temp) (19 mm); ir ($CHCl_3$) 1740 cm^{-1}; nmr ($CDCl_3$) δ 5.4 (broad s, 1), 1.73 (broadened s, 3), and 2.8–1.6 ppm (m, 8).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.24; H, 8.96.

Registry No.—**1**, 7086-71-7; **3a**, 2716-23-6; **3b**, 53216-65-2; **4a**, 6553-12-4; **4b**, 53216-66-3; **5**, 18240-10-3; **9**, 31444-32-3; **15**, 53216-75-4; DBN, 3001-72-7; 4-methyl-3-cyclohexen-1-ylmethanol, 39155-38-9; ethyl 4-methyl-3-cyclohexene-1-carboxylate, 20292-15-3; 4-methyl-3-cyclohexene-1-acetonitrile, 53216-76-5; 4-methyl-3-cyclohexene-1-acetic acid, 7086-66-0; 4-methyl-3-cyclohexene-1-acetic acid sodium salt, 53216-77-6.

References and Notes

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Stereochemistry of the Thermal Addition of β-Pinene to Methyl Pyruvate[1]

H. Kenneth Spencer and Richard K. Hill*

Department of Chemistry, University of Georgia, Athens, Georgia 30602

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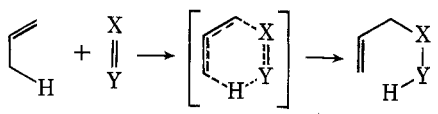
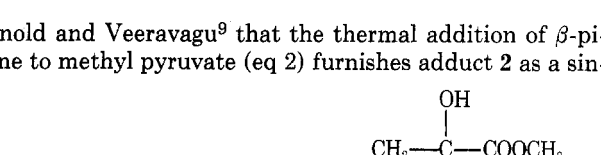
An nmr investigation of the adduct **2** formed in the ene reaction between β-pinene and methyl pyruvate has shown it to be a 1:1 mixture of diastereomers, not a single stereoisomer as originally believed. The pure adducts have been separated and their absolute configurations determined by degradation to citramalic acid. It is concluded that steric and stereoelectronic factors play little part in creating the new asymmetric center.

Many olefins react thermally with compounds containing reactive double bonds (C=C, C=O, N=N, etc.) to form 1:1 adducts in a process believed usually to involve a cyclic transition state[2] and broadly classified as the "ene" reaction[3] (eq 1). Consistent with its description as a concerted


(1)

1,5-sigmatropic hydrogen transfer, the ene reaction exhibits several facets of stereospecificity. (1) The new C–C and C–H bonds are generated cis to each other.[4] (2) Asymmetric induction may be observed when the α carbon of the olefin is chiral, transferring chirality to the new asymmetric center in the enophile.[5] (3) In an olefin with multiple asymmetric centers, one of the diastereotopic allylic hydrogens is selectively transferred; in β-pinene (**1**), *e.g.*, only the endo hydrogen is involved in ene reactions.[6,7] It is not yet clear whether this is due to simple steric factors or to a stereoelectronic preference for breaking that C–H bond parallel to the π orbitals of the double bond. (4) In the cases so far investigated, endo orientation of the addends predominates over exo.[7,8]

During the course of our studies[5,7] on the stereospecificity of the ene reaction, we were attracted by the report of Arnold and Veeravagu[9] that the thermal addition of β-pinene to methyl pyruvate (eq 2) furnishes adduct **2** as a single stereoisomer. Most ene adducts of β-pinene, such as those with maleic anhydride, methyl maleate, and methyl fumarate,[10] as well as the maleic anhydride adducts of cyclopentene and *cis*- and *trans*-2-butene,[8] are mixtures of stereoisomers resulting from competing endo and exo addition, and it is surprising that this simple keto ester should exhibit such pronounced stereospecificity.[11] Arnold and Veeravagu suggested that the favored transition state should be that with minimum nonbonded repulsions, in which the pyruvate approaches the olefin from the methylene bridge side with the carbomethoxyl group oriented away from the hydrocarbon moiety.[9] As depicted in Chart IA, this would result in an *R* configuration at the new asymmetric center. On the other hand, were stereoelectronic considerations to favor endo orientation (Chart IB) as is the case with other ene additions of β-pinene,[7] then the


(2)

1 **2**