A Novel Ketal Fragmentation with Aluminium Iodide

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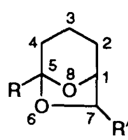
Aluminium iodide, prepared from dry aluminium foil and iodine, in acetonitrile is shown to convert bicyclic ketals in the 6,8-dioxabicyclo[3.2.1]octane series into a cyclohexenone and a substituted pyridine in one step. Details of the structural analysis are discussed. The role of the 1,5-diketone as intermediate for the formation of the cyclohexenone and the pyridine from the bicyclic ketal was secured by subjecting the isolated diketone to various reaction conditions.

As part of our continuing research into the rich chemistry associated with bicyclic ketals in the 6,8-dioxabicyclo[3.2.1]-octane series, **1**, we have carried out an investigation of reagent/reactions that would provide new chemistry. Reductive cleavage of **1** (R = R′ = Me) by aluminium iodide provided an intermediate having the correct stereochemical orientation needed for a stereoselective synthesis of compound **2**, a



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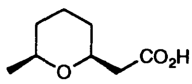

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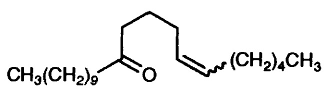

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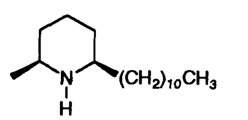

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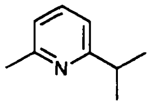

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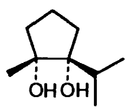

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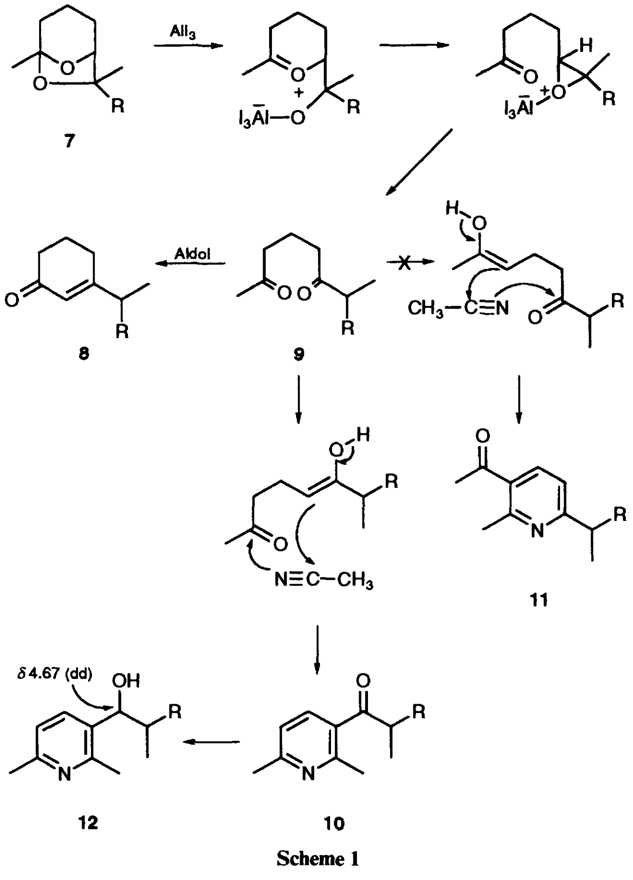
component of the glandular secretion of the Asian civet cat.[1] Fragmentation of **1** (R = $C_{10}H_{21}$, R′ = C_5H_{11}) with acetyl iodide directly provided **3**, a sex pheromone of the Douglas fir tussock moth.[2] A similar reaction resulted in the precursor needed for the preparation of solenopsin A, **4**, a constituent of the venom of the fire ant.[2] The reaction of a bicyclic ketal with aluminium trichloride, acetic acid and hydroxylamine affords 2,6-disubstituted pyridine, **5**.[3,4] Another reaction with aluminium trichloride, acetic acid and zinc affords *cis*-cyclopentane-1,2-diol, **6**.[5,6] Since our early work was reported, several other groups have enjoyed success in the use of ketals as versatile synthetic intermediates.[7–9]

The reaction of bicyclic ketal **7** (R = Pr^i) with aluminium iodide in acetonitrile provides the most recent example of a novel fragmentation process. Two products, in a ratio of about 5:1, were found from this reaction. The major product had higher mobility on TLC (silica gel, hexane–diethyl ether 7:3). The structure of the minor product (9% isolated yield) was readily apparent from an analysis of the spectral data. HRMS showed a formula of $C_{11}H_{18}O$ (Found: 166.1359, requires *M*, 166.1358). The IR (thin film) gave a strong signal at 1669 cm^{-1}, indicative of an enone. The expected ^1H and ^{13}C NMR data for structure **8** are seen. A mechanism to account for the formation of the cyclohexenone product is relatively straightforward (Scheme 1). Initial attack of the Lewis acid on O-6 has been suggested in previously reported fragmentation reactions.[10,11] The 1,5-diketone intermediate **9**, which should be cyclized to **8** *via* aldol condensation, is seen to be critical for the formation of both products.

The structure of the major product (46%) was more difficult to elucidate. ^1H NMR indicated the presence of five methyls; three doublets appear at δ 1.09, 0.92 and 0.85. There were two highly deshielded singlets at δ 2.63 and 2.54. Two complex methine signals were found at δ 2.01 and 3.04. These protons are coupled with one another. Irradiation of the δ 3.04 signal



Scheme 1

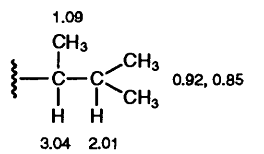


Fig. 1 ^{1}H NMR (δ)

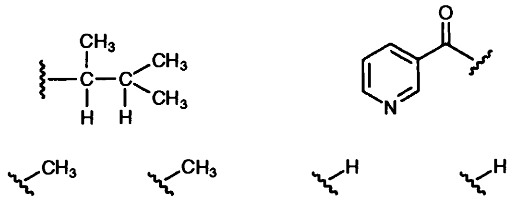
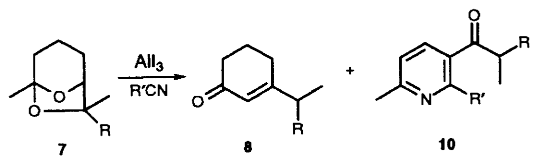


Fig. 2

Table 1 Preparation of cyclohexenone **8** and pyridine derivatives **10**



Entry	R	R′	% Yield (isolated) 8	10
a	Pr^i	Me	9	46
b	Me	Me	11	48
c	Ph	Me	12	37
d	Me	Pr	9	42

frequency collapsed the δ 1.09 doublet while irradiation of the δ 2.01 signal gave two singlets at δ 0.92 and 0.85. These data are in accord with the partial structure shown in Fig. 1.

The ^{1}H NMR spectrum also exhibited two highly deshielded protons at δ 7.71 and 7.04. These two protons are coupled, with *J* 8 Hz. The ^{13}C NMR spectrum revealed 13 signals. There were four highly deshielded singlets (δ 207.3, 159.9, 157.2 and 121.2), four doublets (δ 30.2, 50.0, 119.9 and 135.7) and five quartets (δ 12.5, 18.4, 21.4, 23.9 and 24.4). The UV spectrum (EtOH) contained maxima at 274 (ε 4140) and 239 nm (ε 6640 dm^3 mol^{-1} cm^{-1}). The partial fragments elucidated from this information are shown in Fig. 2. The two highly-deshielded adjacent protons (δ 7.71 and 7.04) are a useful clue to the final assembly of the pieces. This suggested the structures **10** or **11**.

The origin of the two new carbons and the nitrogen must be the acetonitrile. Based on our isolation of the diketone intermediate **9**,[12] we suggest that the formation of the pyridine compound arises from insertion of the acetonitrile *via* an enol intermediate. An alternative insertion mode can be imagined leading to compound **11**. Structure **11** was readily eliminated by reduction of the carbonyl group to an alcohol **12**. The carbinol proton at δ 4.67 was seen as a doublet of doublets confirming **10** as the structure.

The role of the diketone **9** as intermediate was confirmed by treating it with aluminium iodide in acetonitrile to give the expected products, **8** and **10**. This reaction has also been carried out on the ketal, 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane **7b** as shown in Table 1. Here the cyclohexenone product **8b** was obtained in 11% yield, and the pyridine **10b** in 48%. An aromatic substituent **7c** was also tolerated under these reaction conditions to give the expected products, **8c** and **10c**. Butyronitrile was used instead of acetonitrile to broaden the range of nitrogen source for the pyridine derivatives and resulted in the formation of pyridine **10d** in 42% yield.

Experimental

General Experimental Details.—The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer at 200 and 50 MHz, respectively, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (*J*) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Infrared spectra were recorded on a Shimadzu IR-435 spectrometer with absorption frequencies reported in cm^{-1}. Mass spectra were obtained using a VG MM16 mass spectrometer and accurate mass data were obtained using a VG 7070 high resolution mass spectrometer. GLC analyses were performed using a Varian Aerograph series 2700 gas chromatograph equipped with an 11 ft × $\frac{1}{4}$ in, 10% OV-17 column. The m.p. was determined using a Fisher-Johns melting point apparatus and is uncorrected. Most of the chemicals used were purchased from Aldrich and were used without further purification unless noted otherwise. Bicyclic ketals **7** were prepared from methyl vinyl ketone (MVK).[12] Flash chromatography was carried out using silica gel Merck 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with *p*-anisaldehyde.

General Procedure for the Preparation of Cyclohexenone **8** *and Pyridine* **10** *from Bicyclic Ketal* **1**.—Dry aluminium foil (1 equiv.) and iodine (1.6 equiv.) in acetonitrile (3 cm^3) were refluxed together in a two-necked flask (25 cm^3) for 3 h after which time the iodine colour had disappeared. Ketal **7a** (100 mg) was added to it and the reaction mixture was refluxed for 18 h, after which time it was cooled and poured into water (20 cm^3). The reaction mixture was extracted with diethyl ether and the extract was washed with 5% NaOH and then 10% sodium thiosulfate. The organic layer was dried ($MgSO_4$), filtered and evaporated to leave a liquid product which was then chromatographed (two products in a GLC ratio of 1:5; TLC and flash chromatography, hexane–diethyl ether 7:3) to give a less polar product **10a** (50 mg, 46%, R_f 0.35) and a more polar product **8a** (8 mg, 9%, R_f 0.25).

3-(1,2-*Dimethylpropyl*)*cyclohex*-2-*enone* **8a**. (9%) δ_H(200 MHz; $CDCl_3$) 5.84 (1 H, br s), 2.36 (1 H, m), 2.24 (2 H, t, *J* 6), 2.02–1.88 (4 H, m), 1.65 (1 H, m), 1.04 (3 H, d, *J* 7), 0.88 (3 H, d, *J* 7) and 0.83 (3 H, d, *J* 7); δ_C($CDCl_3$) 199.9 (s), 170.7 (s), 125.8 (d), 48.8 (d), 37.7 (t), 31.1 (d), 27.4 (t), 22.9 (t), 21.6 (q), 19.5 (q) and 15.8 (q); γ_{max}(neat)/cm^{-1} 2941, 1669, 1456, 1376, 1245, 890 and 731; *m/z* 166 (M$^+$), 151, 148, 124 (base), 109, 96, 81, 67, 55 and 41 (Found: 166.1359. $C_{11}H_{18}O$ requires *M*, 166.1358).

1-(2,6-*Dimethyl*-3-*pyridyl*)-2,3-*dimethylbutan*-1-*one* **10a**. (46%) δ_H(200 MHz; $CDCl_3$) 7.71 (1 H, d, *J* 8), 7.04 (1 H, d, *J* 8), 3.04 (1 H, m), 2.63 (3 H, s), 2.54 (3 H, s), 2.01 (1 H, m), 1.09 (3 H, d, *J* 7), 0.92 (3 H, d, *J* 7) and 0.85 (3 H, d, *J* 7); δ_C($CDCl_3$) 207.3 (s), 159.9 (s), 157.2 (s), 135.7(d), 121.2 (s), 119.9 (d), 50.0 (d), 30.2 (d), 24.4 (q), 23.9 (q), 21.4 (q), 18.4 (q) and 12.5 (q); γ_{max}(neat)/cm^{-1} 2941, 1681, 1587, 1447, 1370, 1250, 1222, 1190, 1136, 1021, 966, 919, 896, 833 and 732; λ_{max}(EtOH)/nm 274 (ε/dm^3 mol^{-1} cm^{-1} 4140) and 239 (ε 6640); *m/z* 205 (M$^+$), 190, 163, 134 (base), 106, 79, 63, 53 and 41 (Found: 205.1472. $C_{13}H_{19}NO$ requires *M*, 205.1466).

3-*Isopropylcyclohex*-2-*enone* **8b**. (11%) δ_H(200 MHz; $CDCl_3$) 5.83 (1 H, br s), 2.33 (5 H, m), 1.97 (2 H, m) and 1.05 (6 H, d, *J* 7); δ_C($CDCl_3$) 200.7 (s), 172.4 (s), 124.0 (d), 38.1 (t), 36.2 (d), 28.2 (t), 23.5 (t) and 21.1 (q, 2 × Me); γ_{max}(neat)/cm^{-1} 2960, 1662, 1619, 1284, 906 and 729; *m/z* 138 (M^+), 123 (base), 108, 95, 80, 71 and 41 (Found: 138.1046. $C_9H_{14}O$ requires *M*, 138.1045).

1-(2,6-*Dimethyl*-3-*pyridyl*)-2-*methylpropan*-1-*one* **10b**. (48%) δ_H(200 MHz; $CDCl_3$) 7.89 (1 H, d, *J* 8.1), 7.07 (1 H, d, *J* 8.1), 3.04 (1 H, septet, *J* 7), 2.72 (3 H, s) 2.55 (3 H, s) and 1.28 (6 H, d, *J* 7); δ_C($CDCl_3$) 200.7 (s), 170.3 (s), 158.2 (s), 138.1 (d), 130.7 (s), 117.7 (d), 37.0 (d), 29.8 (q), 25.5 (q) and 22.9 (q × 2); γ_{max}(neat)/cm^{-1} 2929, 1709, 1684, 1585, 1460, 1378, 1278, 1240, 1182, 1108, 1074, 958, 905 and 730; *m/z* 177 (M^+), 176, 162 (base), 149, 135, 119, 92, 74, 65 and 43 (Found: 177.1149. $C_{11}H_{15}NO$ requires *M*, 177.1154).

3-(1-*Phenylethyl*)*cyclohex*-2-*enone* **8c**. (12%) δ_H(200 MHz; $CDCl_3$) 7.36–7.15 (5 H, m), 6.06 (1 H, d, *J* 2), 3.56 (1 H, q, *J* 7), 2.36 (2 H, m), 2.16 (2 H, m), 1.92 (2 H, m) and 1.44 (3 H, d, *J* 7); δ_C($CDCl_3$) 220.8 (s), 169.2 (s), 143.3 (s), 129.2 (d × 2), 127.9 (d × 2), 127.4 (d), 125.4 (d), 47.4 (d), 38.1 (t), 29.0 (t), 23.4 (t) and 19.6 (q); γ_{max}(neat)/cm^{-1} 3028, 2861, 1669, 1620, 1581, 1492, 1451, 1113, 762 and 699; *m/z* 200 (M^+), 185, 123 (base), 108, 93, 78, 65 and 41 (Found: 200.1202. $C_{14}H_{16}O$ requires *M*, 200.1201).

1-(2,6-*Dimethyl*-3-*pyridyl*)-2-*phenylpropan*-1-*one* **10c**. (37%) δ_H(200 MHz; $CDCl_3$) 7.60 (1 H, d, *J* 8), 7.16 (5 H, m), 6.88 (1 H, d, *J* 8), 4.37 (1 H, q, *J* 7), 2.49 (3 H, s) 2.41 (3 H, s) and 1.20 (3 H, d, *J* 7); δ_C($CDCl_3$) 212.6 (s), 159.3 (s), 157.6 (s), 151.3 (s), 139.2 (d), 132.4 (s), 129.3 (d × 2), 128.4 (d × 2), 121.5 (d), 121.3 (d), 56.3 (d), 30.4 (q), 29.3 (q) and 24.3 (q); γ_{max}(neat)/cm^{-1} 2901, 1681, 1582, 1401, 1369 and 716; *m/z* 239 (M^+), 223, 208, 160, 145 and 134 (base) (Found: 239.1307. $C_{16}H_{17}NO$ requires *M*, 239.1310).

1-(6-*Methyl*-2-*propyl*-3-*pyridyl*)-2-*methylpropan*-1-*one* **10d**. (42%) δ_H(200 MHz; $CDCl_3$) 7.79 (1 H, d, *J* 8), 7.13 (1 H, d, *J* 8), 3.29 (1 H, m), 2.94 (2 H, t, *J* 7), 2.67 (3 H, s), 1.76 (2 H, m), 1.18 (6 H, d, *J* 7) and 1.04 (3 H, t, *J* 7); δ_C($CDCl_3$) 207.3 (s), 159.1 (s), 156.6 (s), 142.5 (d), 134.0 (s), 124.7 (d), 39.2 (d), 33.2 (t), 24.9 (q), 19.9 (t), 18.2 (q × 2) and 14.1 (q); γ_{max}(neat)/cm^{-1} 2954, 1682, 1605, 1370, 907 and 730; *m/z* 205 (M^+), 190, 177, 162, 86, 84 and 49 (base) (Found: 205.1465. $C_{13}H_{19}NO$ requires *M*, 205.1467).

Preparation of 1-(2,6-*Dimethyl*-3-*pyridyl*)-2,3-*dimethylbutan*-1-*ol* **12a** *from the Ketone* **10a**.—To a solution of sodium borohydride (0.5 equiv.) in isopropyl alcohol (10 cm^3) was added the ketone **10a** (15 mg) and then the reaction mixture was stirred for 1 h at ambient temperature. The isopropyl alcohol was evaporated and then water (10 cm^3) was added to hydrolyse the reaction. The reaction mixture was extracted with several portions of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and then evaporated to leave a slightly yellow solid product, which was recrystallized from pentane to give the alcohol **12a** as a white powder (9.6 mg, 64%); m.p. 159–162 °C; δ_H(200 MHz; $CDCl_3$) 7.60 (1 H, d, *J* 8), 7.08 (1 H, d, *J* 8), 4.67 (1 H, dd, *J* 3, 9) 2.54 (3 H, s), 2.49 (3 H, s), 2.29 (1 H, m), 1.78 (1 H, m), 1.67 (1 H, d, *J* 3), 0.95 (3 H, t, *J* 7), 0.89 (3 H, t, *J* 7) and 0.51 (3 H, t, *J* 7); *m/z* 207 (M^+), 174, 136 (base), 108, 92, 77, 65, 51 and 41 (Found: 207.1622. $C_{13}H_{21}NO$ requires *M*, 207.1623).

Acknowledgements

J.-G. Jun acknowledges the support of the Research Center for New Bio-Materials in Agriculture, Korea Science and Engineering Foundation. B. P. Mundy acknowledges the support of the Montana Agricultural Experiment Station.

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Paper 4/01619J
Received 18*th March* 1994
Accepted 25*th May* 1994