Preparation of 2-Oxabicyclo[2.2.2]oct-5-ene, 1,4-Dimethyl-2-oxabicyclo-[2.2.2]oct-5-ene, and 6-Oxabicyclo[3.2.1]oct-3-ene

Yoshinobu INOUYE, Kenji TOKUHISA, Morihiro MITSUYA, and Hiroshi KAKISAWA*
Department of Chemistry, University of Tsukuba, Tennodai, Tsukuba, Ibaraki 305
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Synopsis. Three bicyclic olefins having an allylic oxygen atom (see title) were prepared. Of those, 2-oxabicyclo[2.2.2]oct-5-ene could not be isolated in its pure state due to the volatility of the compound. The other two, however, could be isolated.

In the course of our research on the effect of allylic heteroatoms in cycloaddition reactions, we needed to prepare 2-oxabicyclo[2.2.2]oct-5-ene(**1**), the preparation of which has not yet been established in spite of its simple structure. Although 1,3,3-trimethyl-2-oxabicyclo[2.2.2]oct-5-ene(**2**) has been found in nature as dehydrocineole,[1] the basic compound **1** has been reported only in a patent;[2] the electrolysis of 2-cyclohexenemethanol was shown to afford **1** in 12% yield, though no detail properties were given. We wish to report on another approach to **1** and the preparation of the related hitherto unknown 1,4-dimethyl-2-oxabicyclo[2.2.2]oct-5-ene (**3**) and 6-oxabicyclo[3.2.1]oct-3-ene(**4**).

The strategy to produce **1** is not so difficult, since several functionalized 2-oxabicyclo[2.2.2]octane derivatives are known. Among them, we selected 6-*exo*-acetoxy-2-oxabicyclo[2.2.2]octane(**5**)[3] as the starting material. An acetate **5** was converted into dithiocarbonate **7** via an alcohol **6**. Pyrolysis of **7** at 165 °C however, afforded a mixture of the desired olefin **1** and the rearranged 6-oxabicyclo[3.2.1]oct-3-ene(**4**) in the ratio of 1 : 1, as shown by the ^{1}H NMR spectrum. The facile neighboring oxygen participation during pyrolysis was recognized, as revealed by the presence of two dithiocarbonates **8** and **9**, in the reaction mixture (see Experimental). Even though both isomers **1** and **4** were separable by a chromatographic technique, the desired isomer **1** was unfortunately quite sublimable and it was very difficult to separate **1** in its pure state from a volatile solvent, such as pentane or ether. The ratio of **1** to **4** could be increased to 4 : 1 when pyrolysis was conducted at 160 °C, though conversion was low. In order to prevent any rearrangement, we also tried the modified Bamford-Stevens reaction[4] on tosylhydrazone **11**, prepared from the corresponding ketone **10** which, in turn, was derived from alcohol **6**. In this case, only **1** was recognized in the product, as revealed by TLC and ^{1}H NMR spectrum.

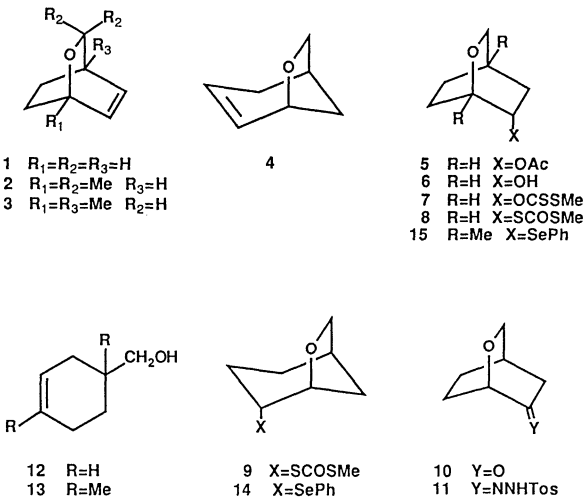

Fig. 1.

Another strategy for producing oxabicyclic compounds is based on the benzeneselenylation of monocyclic 3-cyclohexenemethanol derivatives followed by an oxidative removal of the selenium function.[5]

When 3-cyclohexenemethanol(**12**) was treated with benzeneselenenyl chloride at −78 °C, only 4-*exo*-phenylseleno-6-oxabicyclo[3.2.1]octane(**14**) was isolated in 74% yield. An oxidative removal of the selenium function afforded 6-oxabicyclo[3.2.1]oct-3-ene(**4**) in 66% yield after purification by column chromatography. On the other hand, the regioselectivity may be changed to give 2-oxabicyclo[2.2.2]octane derivatives if one methyl substituent is present on the double bond.[1,6] Thus, 1,4-dimethyl-3-cyclohexenemethanol(**13**) could be converted into 1,4-dimethyl-6-phenylseleno-2-oxabicyclo[2.2.2]octane(**15**) in 68% yield when **13** was treated with benzeneselenenyl chloride in the presence of *s*-collidine. In the absence of the base, significant amounts of the by-products formed by the action of hydrogen chloride on **13** were observed. An aliphatic amine base, such as triethylamine or diisopropylethylamine, lowered the yield of **15** due to a side-reaction[7] between the base and benzeneselenenyl chloride. The base could be excluded when the trimethylsilyl ether of **13** was subjected to a reaction (see Experimental).

An oxidative removal of the selenium function in **15** afforded 1,4-dimethyl-2-oxabicyclo[2.2.2]oct-5-ene(**3**) in 70% yield. **3** was also volatile but could be purified by short path distillation under moderate reduced pressure.

Experimental

The melting points are uncorrected. The IR spectra were taken on a Hitachi 215 grating spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ either on a JEOL FX90Q (90 MHz) or a Bruker AM500 (500 MHz) spectrometer and the chemical shifts were recorded relative to TMS as an internal standard. Flash-chromatography was performed using Wakogel C-300 with the stated solvent. Micro analyses were performed at the Analytical Center, University of Tsukuba.

6-*exo*-Acetoxy-2-oxabicyclo[2.2.2]octane(5). According

to a method described in the literature,[3] **5** was prepared from 3-cyclohexenecarboxylic acid.

5: Bp 80—90 °C/0.3 mmHg (1 mmHg=133.3 Pa) (lit, bp 80 °C/0.01 mmHg); ^{1}H NMR δ=1.3—2.5 (m, 7H), 2.04 (s, 3H), 3.6—4.0 (m, 3H), and 5.05 (dt, 1H, J=10.0 and 4.5 Hz).

2-Oxabicyclo[2.2.2]octan-6-*exo*-ol(6). To a solution of 14.32 g of **5** in 150 ml of methanol, 17.55 g of potassium carbonate was added under an argon atmosphere; the mixture was then stirred at room temperature for 1 h. After filtration through a silica-gel layer, the solvent was removed by evaporation and the residue was flash-chromatographed with ethyl acetate to give 9.08 g (84%) of alcohol **6**.

6: Mp 181—183 °C in a sealed tube (from benzene-hexane); IR ($CHCl_3$) 3550, 3420 br, 1110, and 1045 cm^{-1}; ^{1}H NMR δ= 1.2—2.4 (m, 7H), 3.5—3.9 (m, 3H), and 4.19 (dt, 1H, J=10.0 and 4.0 Hz). Found: C, 65.41; H, 9.52%. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.43%.

Methyl *O*-2-Oxabicyclo[2.2.2]oct-6-*exo*-yl Dithiocarbonate(7). To a solution of 10.02 g of **6** in 350 ml of dry THF at 0 °C under an argon atmosphere, 57 ml of a 1.52 M (1 M=1 mol dm^{-3}) BuLi/hexane solution was added; the mixture was then stirred at room temperature for 1 h. After being completely cooled to 0 °C, 5.2 ml of carbon disulfide was added. The mixture was stirred at room temperature for 1 h. After the addition of 90 ml of iodomethane to the cooled solution, the mixture was stirred at room temperature overnight. The organic layer was separated and the aqueous layer was extracted with ether. After drying and evaporating, the residue was flash-chromatographed with ethyl acetate-hexane (1 : 10) to give **7** (11.62 g, 68%) as a viscous oil.

7: Kugelrohr dist. 110—125 °C/0.2 mmHg; IR ($CHCl_3$) 1130, 1080, and 1045 cm^{-1};^{1}H NMR δ=1.5—2.4 (m, 7H), 2.55 (s, 3H), 3.3—4.0 (m, 3H), and 5.75 (m, 1H). Found: C, 49.52; H, 6.60%. Calcd for $C_9H_{14}O_2S_2$: C, 49.51; H, 6.46%.

Pyrolysis of the Dithiocarbonate 7. 1) The dithiocarbonate **7** (1.433 g) was heated in a round-bottom flask at 165 °C, while the products were condensed in a dry-ice trap by evaporation under reduced pressure (ca. 15 mmHg) through calcium chloride and potassium hydroxide tubes. After 24 h, 440 mg (52%) of a mixture of **1** and **4** (**1** : **4**=1 : 1) was obtained. Though both were separated by flash-chromatography with pentane-ether (8 : 1), the solvents could not be removed due to the volatility of **1**.

During pyrolysis, there appeared a new spot on TLC (CH_2Cl_2) after one hour. Separation of the spot by flash-chromatography gave a mixture of dithiocarbonates **8** and **9** [IR ($CHCl_3$) 1640 and 865 cm^{-1}; ^{1}H NMR (500 MHz) 4.16 (dddd, 0.57×1H, J=13.3, 5.8, 3.8, and 2.1 Hz) and 3.74 (td, 0.57×1H, J=3.8 and 1.9 Hz) for **8** and 4.29 (dd, 0.43×1H, J=5.3 and 5.0 Hz) and 3.93 (dd, 0.43×1H, J=5.8 and 5.0 Hz) for **9**].

2) When the dithiocarbonate **7** (1.58 g) was heated at 160 °C under similar conditions for 21 h, 142 mg (18%) of a crystalline mixture of **1** and **4** (**1** : **4**=4 : 1) was obtained.

1; ^{1}H NMR (500 MHz) δ=1.27—1.37 (m, 2H), 1.63—1.69 (m, 1H), 2.04—2.11 (m, 1H), 2.59 (m, 1H), 3.23 (ddd, 1H, J=7.2, 2.6, and 2.4 Hz) , 3.77 (dd, 1H, J=7.2 and 1.7 Hz),4.35 (m, 1H), and 6.44 (m, 2H); ^{13}C NMR (125 MHz) δ=21.2 (t), 27.0 (t), 30.7 (d), 65.5 (d), 66.8 (t), 133.3 (d), and 133.6 (d). Elementary analysis for the mixture of **1** : **4**(=4 : 1). Found: C, 76.37; H, 9.30%. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15%.

2-Oxabicyclo[2.2.2]octan-6-one *p*-Toluenesulfonylhydrazone(11). To a mixture of dried dichloromethane (24 ml) and pyridine (1.6 ml) was added 981 mg of chromium trioxide; this mixture was stirred at room temperature for 30 min. Alcohol **6** (209 mg) was added, and the mixture stirred for 4 h. After filtering the solution through a silica-gel column, 370 mg of *p*-toluenesulfonylhydrazine was added; then, 1% hydrochloric acid/ethanol solution was added until the initially turbided solution became clear. The mixture was stirred for 22 h at room temperature. After concentrating in vacuo, the residue was treated with dichloromethane and the organic layer washed with 1 M hydrochloric acid. Evaporating the solvent gave 510 mg (100%) of **11**.

11: Mp 203—205 °C (from EtOH). Found: C, 56.90; H, 6.21; N, 9.45%. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52%.

Decomposition[4] of the *p*-Toluenesulfonylhydrazone 11. To a stirred solution of **11** (100 mg) in dry THF (3 ml) there was added 0.9 ml of 0.76 M BuLi/hexane solution; the mixture was stirred overnight. After the mixture had been poured into hexane (150 ml), adsorption took place on silicic acid and the product was eluted with dichloromethane. ^{1}H NMR spectrum of the solution revealed the presence of **1**.

4-*exo*-Phenylseleno-6-oxabicyclo[3.2.1]octane(14). A solution of 10.78 g of benzeneselenenyl chloride in 60 ml of dry dichloromethane was drop-by-drop added to a solution of 5.79 g of 3-cyclohexenemethanol(**12**) in 700 ml of dichloromethane at −78 °C. This mixture was warmed to room temperature and stirred for an additional 3 h at that temperature. Evaporating the solvent and column-chromatography of the residue on silica gel gave 10.26 g (74%) of **14** as an oil.

14; Kugelrohr dist. 140—150 °C/0.3 mmHg; ^{1}H NMR δ=1.4—2.5 (m, 7H), 3.50 (br. t, 1H), 3.70—3.95 (m, 2H), 4.40 (t, 1H, J=5.5 Hz), and 7.20—7.70 (m, 5H). Found: C, 58.21; H, 6.10%. Calcd for $C_{13}H_{16}OSe$: C, 58.43; H, 6.04%.

6-Oxabicyclo[3.2.1]oct-3-ene(4). An aqueous solution of hydrogen peroxide (22%, 10 ml) was drop-by-drop added to a mixture of 2.00 g of **14**, 1.25 ml of pyridine, and 25 ml of dichloromethane at 0 °C. After stirring at room temperature for 4 h, 15 ml each of dichloromethane and saturated sodium hydrogencarbonate were added and an organic layer was separated. The organic layer was washed with 3 M HCl (18 ml) and saline (18 ml). After evaporating the solvent, the residue was purified by column chromatography to give 542 mg (66%) of **4**.

4: ^{1}H NMR (500 MHz) δ=1.82 (m, 2H), 2.07 (dddd, 1H, J=18.2, 4.2, 2.2, and 2.0 Hz), 2.45 (dddd, 1H, J=18.2, 6.3, 2.6, and 2.2 Hz), 2.53 (m, 1H), 3.69 (d, 1H, J=8.2 Hz), 3.95 (ddd, 1H, J=8.2, 5.6, and 2.6 Hz), 4.30 (dt, 1H, J=5.4 and 2.8 Hz), 5.66 (m, 1H, J=9.7 and 4.2 Hz), and 5.94 (dddd, 1H, J=9.7, 5.4, 2.2, and 2.0 Hz); ^{13}C NMR (125 MHz) δ=34.0 (d), 34.3 (t), 35.6 (t), 71.2 (d), 73.7 (t), 128.6 (d), and 130.6 (d). Found: C, 76.61; H, 9.27%. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15%.

1,4-Dimethyl-6-*exo*-phenylseleno-2-oxabicyclo[2.2.2]-octane(15). Method A. To a solution of 2.68 g (19.2 mmol) 1,4-dimethyl-3-cyclohexenemethanol(**13**)[8] and 3.06 g (25.3 mmol) of *s*-collidine in 100 ml of dry dichloromethane there was added drop-by-drop a solution of 4.05 g (21.2 mmol) of benzeneselenenyl chloride in 50 ml of dichloromethane for 2 h at −78 °C. The mixture was warmed to room temperature and stirred for 1.5 h. After removing the solvent, the residue was flash-chromatographed with hexane : dichloromethane (1 : 2) to give 3.83 g (68%) of **15**.

Method B. To a solution of 4.02 g (21.0 mmol) of benzeneselenenyl chloride in 100 ml of dry dichloromethane there was added at −78 °C solution of 3.75 g (17.6 mmol) of trimethylsilyl ether of **13**, prepared by the ordinary method; bp 87—89 °C/17 mmHg, in 50 ml of dichloromethane. The mixture was warmed to room temperature and the solvent evaporated. Flash-chromatography(hexane : dichloromethane=1 : 2) of the residue afforded 3.59 g (69%) of **15**.

15: ^{1}H NMR (500 MHz) δ=0.75 (s, 3H), 1.15 (s, 3H), 1.4—

1.6 (m, 2H), 1.7—1.8 (m, 2H), 2.0—2.2 (m, 2H), 3.55 (dd, 1H, J=8.4 and 3.0 Hz), 3.5—3.6 (m, 2H), 7.25 (m, 3H), and 7.53 (m, 2H). Found: C, 61.17; H, 6.86%. Calcd for $C_{15}H_{20}OSe$: C, 61.01; H, 6.83%.

1,4-Dimethyl-2-oxabicyclo[2.2.2]oct-5-ene(3). To an ice-cooled solution of 1.26 g (4.26 mmol) of **15** and 0.69 ml (7.96 mmol) of pyridine in 15 ml of dichloromethane was added a solution of 1.39 g of 30% aqueous H_2O_2 in 12 ml of H_2O (11.7 mmol); the mixture was stirred for 1.5 h while keeping the temperature below 30 °C. Dichloromethane (5 ml) and saturated sodium hydrogencarbonate (5 ml) were added and the products were taken in dichloromethane. The organic layer was washed with saturated aqueous $CuSO_4$ and brine, and was dried over anhyd Na_2SO_4. After removing CH_2Cl_2 under 100 mmHg at room temperature, the product was collected in a dry-ice trap under 5 mmHg. Kugelrohr distillation (70—80 °C/90 mmHg) gave 413 mg (70%) of **3**.

3: ^{1}H NMR (500 MHz) δ=1.08 (s, 3H), 1.27 (tdd, 1H, J=11.7, 4.2, and 3.5 Hz), 1.35 (ddd, 1H, J=12.4, 11.7, and 3.3 Hz), 1.51 (ddd, 1H, J=11.7, 9.5, and 3.3 Hz), 1.84 (ddd, 1H, J=12.4, 9.5, and 4.2 Hz), 3.04 (dd, 1H, J=7.0 and 3.5 Hz), 3.53 (d, 1H, J=7.0 Hz), 6.13 (d, 1H, J=8.2 Hz), and 6.16 (d, 1H, J=8.2 Hz); ^{13}C NMR δ=20.9 (q), 24.0 (q), 31.3 (t), 34.0 (t), 34.4 (s), 70.1 (s), 73.5 (t), 135.9 (d), and 138.3 (d). Found: C, 78.35; H, 10.57%. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21%.

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