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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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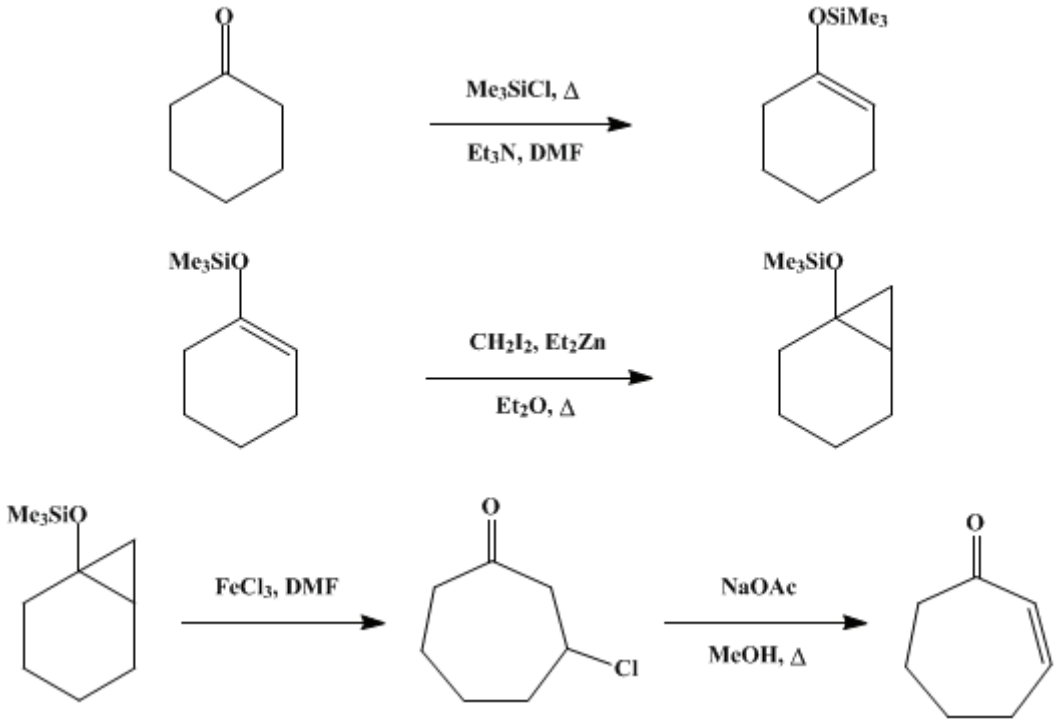
ONE-CARBON RING EXPANSION OF CYCLOALKANONES TO CONJUGATED CYCLOALKENONES: 2-CYCLOHEPTEN-1-ONE



Submitted by Yoshihiko Ito, Shotaro Fujii, Masashi Nakatuska, Fumio Kawamoto, and Takeo Saegusa[1].
Checked by Peter Senter, William F. Burgoyne, and Robert M. Coates.

1. Procedure

Caution! Diethylzinc, which is used in Part B of this procedure, is highly pyrophoric. Accordingly, this reagent must be kept under a nitrogen atmosphere; exposure to air must be avoided during transfers.

A. 1-*Trimethylsilyloxycyclohexene*. A 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser protected with a calcium chloride tube, and a rubber septum is charged with 100 ml. of *N,N*-dimethylformamide (Note 1) and 60.6 g. (0.600 mole) of triethylamine (Note 2). The solution is stirred while 32.6 g. (0.300 mole) of chlorotrimethylsilane (Note 3) and 24.5 g. (0.250 mole) of cyclohexanone are injected in succession through the septum into the flask. The resulting mixture is stirred and heated under reflux for 6 hours, cooled to room temperature, and diluted with 300 ml. of pentane. The triethylamine hydrochloride that precipitates is removed by filtering through a coarse, sintered-glass Büchner funnel, and the filter cake is washed with three 100-ml. portions of pentane. The filtrates are combined and washed with three 300-ml. portions of ice-cold sodium hydrogen carbonate solution. The organic layer is washed rapidly with 100 ml. of ice-cold 3% hydrochloric acid and 100 ml. of ice-cold sodium hydrogen carbonate in succession. The pentane solution is washed with 50 ml. of sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated. The residual liquid is distilled at reduced pressure through a 10-cm. Vigreux column, affording, after separation of a small forerun, 33–35.5 g. (78–84%) of 1-trimethylsilyloxycyclohexene, b.p. 74–75° (20 mm.) ((Note 4)).

B. 1-*Trimethylsilyloxybicyclo*[4.1.0]*heptane*. A 250 ml., three-necked, round-bottomed flask is

equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a reflux condenser bearing a nitrogen inlet at its top, and a rubber septum. The apparatus is purged with nitrogen, flamed dry, and allowed to cool (Note 5). The flask is charged with 130 ml. of diethyl ether (Note 6), 17.0 g. (0.100 mole) of 1-trimethylsilyloxycyclohexene, and 18.5 g. (0.146 mole) of diethylzinc (Note 7), each being added through the septum with a syringe. The solution is stirred and maintained at room temperature with a water bath while 40.2 g. (0.150 mole) of diiodomethane (Note 8) is added slowly from the dropping funnel over a 1-hour period (Note 9). The reaction mixture is stirred and heated under reflux for 8 hours (Note 10). After the reaction is complete (Note 11), the contents of the flask are stirred and cooled in an ice-water bath as 5.4 ml. of concentrated aqueous ammonium chloride is added over *ca.* 30 minutes. A large amount of gas is evolved, and a white solid is formed during the hydrolysis. The salts are separated by filtering through a sintered-glass Büchner funnel and washed with 100 ml. of a 1:1 (v/v) ether–pentane solution. The combined filtrates are washed with four 50-ml. portions of ice-cold saturated aqueous ammonium chloride and two 100-ml. portions of ice-cold aqueous sodium chloride. The solution is filtered through a pad of anhydrous sodium sulfate and evaporated. The residual liquid is distilled through a 17.5-cm. Vigreux column under reduced pressure, affording a forerun of 2.1–3.5 g., b.p. 65–80° (12 mm.), and 14.2–15.2 g. (77–83%) of 1-trimethylsilyloxybicyclo[4.1.0]heptane, b.p. 80–82° (12 mm.) (Note 12).

C. 2-*Cyclohepten*-1-*one*. A 250-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel bearing a nitrogen inlet at its top, and a thermometer is charged with 17.9 g. (0.110 mole) of anhydrous iron(III) chloride (Note 13). The flask is immersed in an ice-water bath, stirring is begun, and 70 ml. of *N,N*-dimethylformamide (Note 1) is added slowly (Note 14). When all the iron(III) chloride has dissolved, a solution of 9.2 g. (0.050 mole) of 1-trimethylsilyloxybicyclo[4.1.0]heptane in 20 ml. of *N,N*-dimethylformamide is added dropwise through the dropping funnel over 1 hour while the internal temperature is maintained at 0–5°. After the addition is complete, the brown solution is stirred at room temperature for 2 more hours, then poured into *ca.* 200 ml. of ice-cold 1 *N* hydrochloric acid. The aqueous solution is extracted with three 50-ml. portions of chloroform. The combined chloroform extracts are washed successively with 50-ml. portions 1 *N* hydrochloric acid, saturated sodium hydrogen carbonate, and sodium chloride solution. The solution is dried by filtration through a pad of anhydrous sodium sulfate and evaporated. The remaining liquid (Note 15) is dissolved in 50 ml. of methanol saturated with sodium acetate and heated at reflux for 3 hours. The volume is reduced to *ca.* 25 ml. by evaporation under reduced pressure, 50 ml. of water is added, and the mixture is extracted with three 30-ml. portions of ether. The combined extracts are dried over anhydrous sodium sulfate, the ether is evaporated, and the residual liquid is distilled under reduced pressure through a 17.5-cm. Vigreux column, yielding after separation of a 0.4–1.0 g. forerun, 4.3–4.5 g. (78–82%) of 2-cyclohepten-1-one as a colorless liquid, b.p. 73–76° (18 mm.) (Note 16).

2. Notes

1. *N,N*-Dimethylformamide was purified by distillation from calcium hydride under a nitrogen atmosphere and stored over Linde type 4A molecular sieves.
2. Triethylamine was distilled from lithium aluminum hydride.
3. Chlorotrimethylsilane is available from Aldrich Chemical Company, Inc. The reagent was distilled before use.
4. The product has the following spectral properties: IR (neat) cm.$^{-1}$: 1675 (C=C); ^{1}H NMR, δ (multiplicity, number of protons, assignment): 0.16 (s, 9H, Si(CH_3)$_3$), 1.3–2.1 (m, 8H, 4CH_2), 4.78 (m, 1H, vinyl *H*).
5. A slight positive pressure of nitrogen is maintained in the apparatus throughout this procedure.
6. Anhydrous diethyl ether from Mallinckrodt Chemical Works was distilled from sodium and benzophenone before use.
7. Diethylzinc in a cylinder pressurized with nitrogen was purchased from Alfa Division, Ventron Corporation, and distilled at atmospheric pressure under a nitrogen atmosphere before use, b.p. 118°. The distillate was collected in a two-necked receiver fitted with a rubber septum and kept under a nitrogen atmosphere. Aliquots of diethylzinc were withdrawn with a gas-tight syringe. The checkers destroyed excess or waste reagent by injecting it cautiously beneath the surface of ice-cold water through which argon was vigorously bubbled.

8. Diiodomethane from both Eastman Organic Chemicals and Aldrich Chemical Company, Inc., was used by the checkers after distillation under reduced pressure, b.p. 68–70° (12 mm.).
9. The solution becomes somewhat cloudy as the diiodomethane is added.
10. The checkers found considerable variation in the rate of the reaction in different runs, the time required for its completion ranging from 3 to 10 hours. It is therefore advisable to monitor the progress of the reaction. For this purpose small aliquots (*ca.* 0.05 ml.) were withdrawn from the flask with a syringe and hydrolyzed by injection into a vial containing ether and saturated ammonium chloride. The relative amounts of enol silane and cyclopropoxy silane were determined by GC on an 0.6 cm. × 3.7 m. column of 3% OV-17 coated on 100–120 mesh Chromosorb W. With a column temperature of 120° and a carrier gas flow rate of 20 ml. per minute, the retention times for the enol silane and the cyclopropoxy silane are *ca.* 1.9 and 2.3 minutes, respectively.
11. In one run that was particularly slow, an additional 9.9 g. of diiodomethane was added. The reaction then proceeded quickly to completion.
12. The spectral properties of the product are as follows: IR (neat) $cm.^{-1}$: 1250, 1209, 1010, 900, 865, 840; 220-MHz. ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.13 [s, 9H, $Si(CH_3)_3$], 0.29 (t, *J* = 5, 1H, *endo* cyclopropyl *H* at C-7), 0.84 (d of d, *J* = 5 and *J* = 11, 1H, *exo* cyclopropyl *H* at C-7), 0.98–1.70 (m, 6H, cyclohexyl *H*), 1.82–2.18 (m, 3H, cyclohexyl *H*). A GC analysis as described in (Note 10) indicated the purity of the product to be *ca.* 95–98%, the remainder being 3–5% of unreacted enol silane.
13. Anhydrous iron(III) chloride was purchased by the submitters from Merck & Company, Inc. The checkers obtained the reagent from Aldrich Chemical Company, Inc. The reagent was dried at 60–70° under reduced pressure for several hours before use.
14. The dissolution of iron(III) chloride in *N,N*-dimethylformamide is exothermic.
15. A GC analysis on the liquid by the submitters using a Carbowax 20 M (polyethylene glycol) column at 170° showed a major peak assigned to 3-chlorocycloheptanone and minor peak for 2-cycloheptenone. The spectral properties of 3-chlorocycloheptanone are as follows: IR (neat) $cm.^{-1}$: 1705 (C=O); ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.4–2.3 [m, 6H, $(CH_2)_3$-CHCl], 2.3–2.6 (m, 4H, CH_2COCH_2), 4.1–4.4 (m, 1H, CHCl); mass spectrum, *m/e* (intensity ratio): *M*+, 146 and 148 (3:1).
16. A GC analysis by the submitters as described in the preceding note indicated that the purity of the product was 98%. The purity of the product obtained by the checkers was estimated at 95% by a GC analysis at 140° as described in (Note 10). 2-Cyclohepten-1-one has the following spectral properties: IR (neat) $cm.^{-1}$: 1700 (C=O), 1660 (C=C), 1445, 1090, 888; ^1H NMR, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.75 [m, 4H, $CH_2(CH_2)_2CH_2$], 2.45 [m, 4H, $CH_2(CH_2)_2CH_2$], 5.90 (d, *J* = 13, 1H, CH=CHCO), 6.52 (d of t, *J* = 5 and *J* = 13, 1H, CH=CHCO).

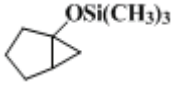
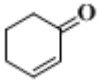
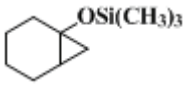
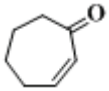
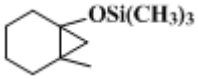
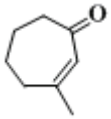
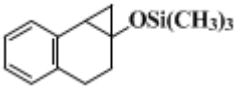
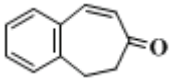
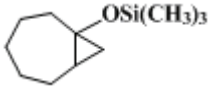
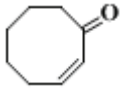
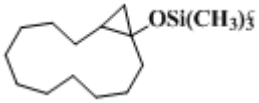
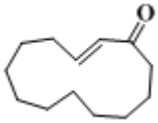
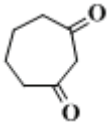
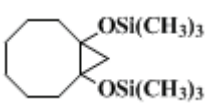
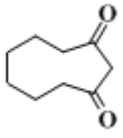
3. Discussion

This procedure illustrates a new three-step reaction sequence for the one-carbon ring expansion of cyclic ketones to the homologous α,β-unsaturated ketones.[2] The key step in the sequence is the iron(III) chloride-induced cleavage of the central bond of trimethylsilyloxycyclopropanes which are obtained by cyclopropanation of trimethylsilyl enol ethers. The procedure for the preparation of 1-trimethylsilyloxycyclohexene from cyclohexanone described in Part A is that of House, Czuba, Gall, and Olmstead.[3]

The cyclopropanation of 1-trimethylsilyloxycyclohexene in the present procedure is accomplished by reaction with diiodomethane and diethylzinc in ethyl ether.[4] This modification of the usual Simmons–Smith reaction[5,6] in which diiodomethane and activated zinc are used has the advantage of being homogeneous and is often more effective for the cyclopropanation of olefins such as enol ethers which polymerize readily. However, in the case of trimethylsilyl enol ethers, the heterogeneous procedures with either zinc–copper[7 8 9] or zinc–silver couple[10 11 12] are also successful. Attempts by the checkers to carry out Part B in benzene or toluene at reflux instead of ethyl ether afforded the trimethylsilyl ether of 2-methylenecyclohexanol, evidently owing to zinc iodide-catalyzed isomerization of the initially formed cyclopropyl ether.[13] The preparation of 1-trimethylsilyloxybicyclo[4.1.0]heptane by cyclopropanation with diethylzinc and chloroiodomethane in the presence of oxygen has been reported.[14]

The ring-opening reaction with iron(III) chloride in *N,N*-dimethylformamide is effective with a series of 1-trimethylsilyloxybicyclo[*n*.1.0]alkanes, as shown by the examples presented in Table I.[2] The corresponding 3-chlorocycloalkanones are usually isolable intermediates which are separately subjected to dehydrochlorination with sodium acetate in methanol, as in the preparation of 2-cyclohepten-1-one described here. However, the reaction of 1-trimethylsilyloxybicyclo[3.1.0]hexane with iron(III) chloride at 0–5° afforded 2-cyclohexen-1-one directly. The slower ring opening of 1-trimethylsilyloxybicyclo [10.1.0]tridecane was carried out at 80°, conditions which also effected spontaneous dehydrochlorination to *trans*-2-cyclotridecenone. The regiospecific ring enlargement of the unsymmetrical ketones, 2-methylcyclohexanone and β-tetralone, are of particular interest in view of the diversity of synthetic routes to trimethysilyl enol ethers.[15]

TABLE I
PREPARATION OF 2-CYCLOALKENONES AND CYCLOALKANE-1,3-DIONES BY IRON(III) CHLORIDE-INDUCED RING OPENING OF 1-TRIMETHYLSILYLOXY-AND 1,2-BIS(TRIMETHYLSILYOXY)BICYCLO[*n*.1.0] ALKANES

Silyloxybicyclo-[*n*.1.0]alkane	2-Cycloalkenone or Cycloalkane-1,3-dione	Yield (%)[a]
		98
		80[b]
		83
		83
		92
		81[c]
		68
		72

[a]The scale was 0.002–0.005 mole except as noted.
[b]This reaction was conducted on a 0.05-mole scale.
[c]This compound was a mixture of *cis* and *trans* isomers.

The present procedure for ring expansion has also been applied to 1,2-bis(trimethylsilyloxy)bicyclo[*n*.1.0]alkanes,[2,16] which are prepared by cyclopropanation of 1,2-bis(silyloxy)cycloalkenes.[17] The latter are readily available from acyloin condensations in the presence of chlorotrimethylsilane.[18] This reaction provides a new route to cyclic 1,3-diketones and macrocyclic compounds containing two 1,3-diketone units in the ring. It has been reported[19] that methylcyclopropanation of 1,2-bis-(trimethylsilyloxy)cyclohexene by 1,1-diiodoethane with zinc–copper couple or diethylzinc and the subsequent iron(III) chloride-induced ring expansion afforded 2-methylcycloheptane-1,3-dione in moderate yield.

The regiospecificity of the iron(III) chloride-induced ring cleavage contrasts with that observed in reactions of 1-silyloxybicyclo[*n*.1.0]alkanes with bromine[9] and potassium *tert*-butoxide.[11] Although the mechanism of the reaction is not known with certainty, it is reasonable to suppose that an alkoxy radical is involved, that this radical undergoes homolytic scission of the more highly substituted carbon–carbon bond of the cyclopropane ring, and that the resulting carbon radical abstracts a chlorine atom from iron (III) chloride.[20]

2-Cyclohepten-1-one has been prepared from cycloheptanone by dehydrohalogenation of the ethylene ketals of 2-chloro- and 2-bromocycloheptanone and subsequent hydrolysis.[21] [22] The α,β-dehydrogenation of cycloheptanone has also been effected *via* the α-phenylthio[23] and α-phenylseleno[24] ketones which were subjected to oxidation and thermal elimination. Another route to the title compound starts with cycloheptene, which is subjected to allylic bromination, hydrolysis, and chromic acid oxidation.[25]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 414
- Org. Syn. Coll. Vol. 9, 643

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silver couple

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether,
ethyl ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

copper (7440-50-8)

toluene (108-88-3)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

chromic acid (7738-94-5)

iron(III) chloride (7705-08-0)

Triethylamine hydrochloride (554-68-7)

Pentane (109-66-0)

diiodomethane (75-11-6)

diethylzinc (557-20-0)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

2-methylcyclohexanone (583-60-8)

Cycloheptanone (502-42-1)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

zinc iodide

β-Tetralone (530-93-8)

2-cyclohexen-1-one (930-68-7)

CHLOROTRIMETHYLSILANE (75-77-4)

2-Cyclohepten-1-one,
2-cycloheptenone (1121-66-0)

1-trimethylsilyloxycyclohexene (6651-36-1)

1-Trimethylsilyloxybicyclo[4.1.0]heptane (38858-74-1)

3-chlorocycloheptanone

cyclopropyl ether

chloroiodomethane (593-71-5)

1-trimethylsilyloxybicyclo[3.1.0]hexane

1-trimethylsilyloxybicyclo[10.1.0]tridecane

1,2-bis-(trimethylsilyloxy)cyclohexene

1,1-diiodoethane (594-02-5)

2-methylcycloheptane-1,3-dione

2-bromocycloheptanone

cycloheptene

potassium tert-butoxide (865-47-4)

trans-2-cyclotridecenone

trimethylsilyl ether of 2-methylenecyclohexanol

2-chlorocycloheptanone