Reaction of Chloromethylcarbene with Trimethylsilyl Enol Ethers; Conversion of Cycloalkanones into Higher α-Methylcycloalkenones

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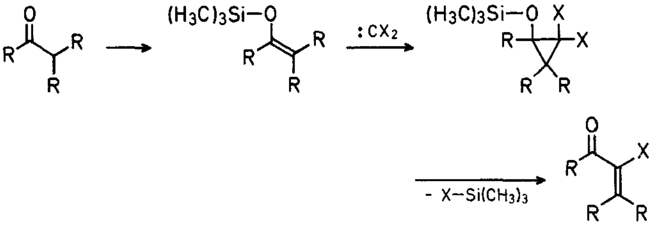
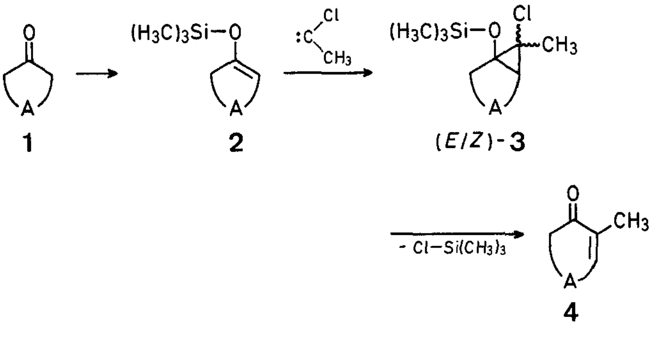
It is known that saturated aldehydes and ketones are readily converted into higher α-halo-α-ethylenic homologues on addition of a dihalocarbene CX_2 to enol ethers and acetates[1,2], to enamines[3], and particularly to trimethylsilyl enol ethers[4,5], followed by opening of the C_3 ring which accompanies any acid or thermal elimination of halotrimethylsilane; for some earlier reviews and general information, see Ref.[6].



The present paper describes the cycloaddition of chloromethylcarbene to trimethylsilyl enol ethers **2** of cycloalkanones **1**; by eliminating chlorotrimethylsilane from the chloro-siloxy-methylcyclopropanes (*Z*/*E*)-**3** thus formed, the higher α-methylcycloalkenones **4** are produced (Table 1). This short sequence is obviously interesting from the point of view of synthesis.



The reaction of chloromethylcarbene with enol ethers **2** gives a mixture of two stereoisomeric cyclopropane derivatives (*Z*/*E*)-**3**, the isolation and in particular separation (owing to their instability) of which present difficulties, in addition to lacking any interest from the preparative point of view. However, they have been differentiated and identified by examination of their chlorocyclopropanol derivatives (*Z*/*E*)-**5**, which were separated by chromatography on silica gel. The stereoisomer (*Z*)-**5** (the hydroxy and chloro groups in the *cis*-configuration) is actually eluted before (*E*)-**5**. Their I.R. spectra in tetrachloromethane solution are particularly significant. Those of the (*E*)-**5** chlorocyclopropanols have a medium-intensity band at $\nu = 3600\ \text{cm}^{-1}$ due to the free hydroxy vibration and a second very high-intensity band, in concentrated solution, at $\nu = 3400\ \text{cm}^{-1}$, due to intermolecularly bonded hydroxy groups, this band disappears on dilution. Those of the (*Z*)-**5** chlorocyclopropanols do not have the free hydroxy band around $\nu = 3600\ \text{cm}^{-1}$ but do present a fairly thin large band (due to intramolecularly bonded hydroxy groups) around $\nu = 3570\ \text{cm}^{-1}$, besides a low-intensity band around $3400\ \text{cm}^{-1}$ (intermolecularly bonded hydroxy groups), the second only disappearing on dilution. The ^{1}H-N.M.R. spectra of each of the cyclopropanols (*E*)-**5** and (*Z*)-**5** that were isolated confirm these structures. The effect, on the signal of the methyl group, of the addition of the shift reagent $Eu(fod)_3$ to the sample is greater in the (*E*)-series, in which the hydroxy and the methyl groups have the *cis*-configuration, than in the (*Z*)-series.

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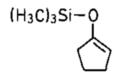
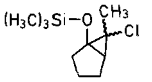
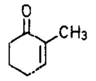
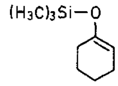
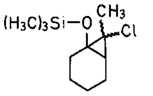
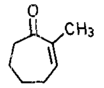
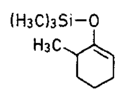
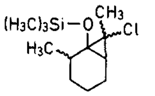
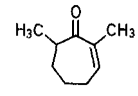
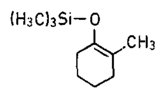
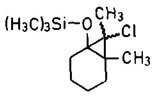
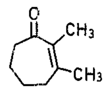
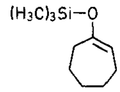
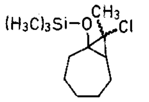
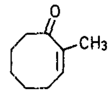
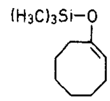
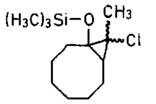
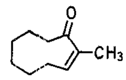
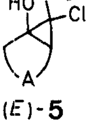
Table 1. Higher α-Methylcycloalkenones 4 from Cycloalkanones 1 via Silyl Enol Ethers 2 and Cyclopropanes 3

Entry	Silyl Enol Ether 2[a]	Chlorosilyloxy-cyclopropane 3[b]	(*E*/*Z*) ratio	Reaction Conditions solvent/reflux time	Product 4[c]	Yield [%]
a			69/31	see text		66
b			67/33	toluene/1 day methanol/$(C_2H_5)_3N$/3 days		65 62
c			···	toluene/5 days methanol/$(C_2H_5)_3N$/3 days		57 56
d			87/13	toluene/4.5 days methanol/$(C_2H_5)_3N$/1.5 days		78 71
e			74/26	xylene/6 days methanol/$(C_2H_5)_3N$/3 days		82 83
f			64/36	toluene/6 days methanol/$(C_2H_5)_3N$/3 days		91 77

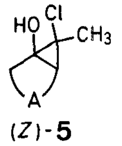
[a] Prepared from the cycloalkanones **1** according to Ref.[7].

[b] The yields of the crude (*E*/*Z*)-**3** mixtures (for their identification see text) were in the range 80–95% (determined by N.M.R.) but by-products of the reaction of *n*-butyllithium with 1,1-dichloroethane were also present. The (*E*/*Z*)-mixture can be roughly purified by rapid distillation under high vacuum (see Table 2) except in the case of (*E*/*Z*)-**3d** where rearrangement occurs on distillation.

[c] Ketones **4** were isolated by chromatography on silica gel and their purities as checked by V.P.C. on carbowax 20M and SE30 were higher than 95%. The yields of ketone **4** were based on trimethylsilyl enol ethers **2**.



(*E*)-**5**



(*Z*)-**5**

The crude mixture of (*E*/*Z*)-**3** was used in every case to obtain the higher ring 2-methyl-cycloalkenone **4**; it was heated either in toluene (or xylene) under reflux, or in methanol containing triethylamine. Among the chloro-siloxy-cyclopropane derivatives of the cycloalkanones (**3a–e**), the rate of the rearrangement of the (*E*)-isomer, in which the chloro and trimethylsilyloxy groups have the *trans*-configuration, is greater than that of the (*Z*)-isomer [(*E*)-**2a** is particularly unstable, even at 0 °C, and difficult to isolate, vide infra]. However, another difference appeared in the chloro-siloxy-cyclopropane derivatives of cyclooctanone: thus, (*E*)-**3f** reacts more quickly than (*Z*)-**3f** on heating in methanol/triethylamine, whereas the opposite is true in toluene. In any case, the (*E*)- and (*Z*)-isomers **3** essentially gave one and the same product, namely the higher 2-methyl-2-cycloalkenone **4**.

The reaction of chloromethylcarbene with the *silyl enol ether of cyclopentanone* (**2a**) (the first entry in Table 1) and the production of 2-methylcyclohex-2-enone (**4a**) should be brought about in a particular way. In effect, chloro-siloxy-methylcyclopropane (*E*)-**3a** rapidly undergoes conversion, even at low temperature, into the enone **4a** with the elimination of chlorotrimethylsilane, as a result of the water added for the work-up (see footnote [b] of Table 1), to bring about hydrolysis of the trimethylsilyloxy group in (*Z*)-**3a**. To avoid the formation of the corresponding chlorocyclopropanol (*Z*)-**5a** by this hydrolysis, triethylamine is first added beforehand to the reaction medium. It is preferable to first separate the intact chlorocyclopropane (*Z*)-**3a** by distillation under high vacuum (55 °C/0.6 torr; yield: 22%) from the enone **4a** and to treat it more energetically on its own, i.e. to heat it for 4 h under reflux in acetonitrile containing silver acetate (1 equivalent). One thus obtains the enone **4a** in an overall yield of 66%, after purification by chromatography on silica gel.

These preparations of chlorosiloxycyclopropanes **3** were performed on a 0.01 molar scale; the chloromethylcarbene was prepared from 1,1-dichloroethane (4 g, 0.04 mol) and *n*-butyllithium (0.03 mol) according to Ref.[8] in the presence of the enol ether **2** (0.01 mol) in anhydrous ether at a temperature of −30° to −40 °C (the addition of *n*-butyllithium was made during 1.5 h). The conversion of the chlorosiloxycyclopropanes **3** into methylcycloalkenones **4** was achieved by heating the crude (*E*/*Z*)-mixture as reported in Table 1. After evaporation of the solvents, ketones **4** were isolated by chromatography on silica gel. The preparation of enone **4e** was also performed on 0.1 molar scale and purification conducted by distillation.

2-Methyl-2-cyclooctenone (4e):

1-Trimethylsiloxy-1-cycloheptene (**2e**): this compound is prepared from cycloheptanone, chlorotrimethylsilane, and triethylamine in dimethylformamide according to the procedure reported[7]; yield: 77%; b.p. 73–74 °C/8 torr.

8-Chloro-8-methyl-1-trimethylsiloxybicyclo[5.1.0]octane [(*E*/*Z*)-**3e**]: A solution of *n*-butyllithium in hexane (0.3 mol) is added over a period of 7 h, to a stirred mixture of the silyl enol ether **2e** (18.4 g, 0.1 mol) and 1,1-dichloroethane (40 g, 0.4 mol) in anhydrous ether (50 ml) at a temperature of −40 to −30 °C. The stirred mixture is then allowed to warm to 0 °C over 2 h and is washed with water (to pH = 7). The organic layer is separated, dried with sodium sulfate, and the solvents are removed under vacuum at ambient temperature. The crude product (33.1 g) is rapidly distilled under high vacuum with a short column; yield: 24.9 g; b.p. 47–49 °C/0.03 torr; yield determined by ^{1}H-N.M.R.: 90%.

Table 2. Spectral Data for Products **3** and **4**

Product	b.p. [°C]/torr (Lit. b.p. [°C]/torr)	I.R. (CCl_4) [cm^{-1}]		^{1}H-N.M.R. (CCl_4, 60 MHz) δ [ppm]	U.V. (i-C_8H_{18}) λ_{max} [nm] (ε)	2,4-dinitrophenylhydrazone of **4**	
		$\nu_{C=O}$	$\nu_{C=C}$			Molecular formula[a]	m.p. [°C] (Lit. m.p.)
(*Z*)-**3a**	55°/0.6	—	—	0.14 (s, 9H); 0.8–2.4 (m, 7H); 1.60 (s, 3H)	—	—	—
(*E*)-**3b**	36–38°/0.03	—	—	0.15 (s, 9H); 0.9–2.6 (m, 9H); 1.62 (s, 3H)	—	—	—
(*Z*)-**3b**		—	—	0.12 (s, 9H); 0.8–2.5 (m, 9H); 1.54 (s, 3H)	—	—	—
(*E*)-**3e**	47–49°/0.03	—	—	0.14 (s, 9H); 0.6–2.3 (m, 11H); 1.64 (s, 3H)	—	—	—
(*Z*)-**3e**		—	—	0.16 (s, 9H); 0.5–2.4 (m, 11H); 1.53 (s, 3H)	—	—	—
(*E*)-**3f**	56–58°/0.03	—	—	0.17 (s, 9H); 0.6–2.1 (m, 13H); 1.63 (s, 3H)	—	—	—
(*Z*)-**3f**		—	—	0.18 (s, 9H); 0.6–2.2 (m, 13H); 1.48 (s, 3H)	—	—	—
4a	73–74°/20 (77–78°/24)[12]	1673	—	1.72 (br. s, 3H); 1.8–2.6 (m, 6H); 6.7 (m, 1H)	227.5 (10550); 327 (22)	$C_{13}H_{14}N_4O_4$ (290.3)	208.5° (207.5–209°)[9]
4b	84–85°/20 (85–86°/20)[13]	1667	—	1.6–2.0 (m, 4H); 1.77 (br. s, 3H); 2.1–2.7 (m, 4H); 6.49 (br. t, 1H, J=6 Hz)	230.5 (8410); 327.5 (42)	$C_{14}H_{16}N_4O_4$ (304.3)	125° (121–122°)[10]
4c	92–93°/20 (110°/45)[14]	1672	—	1.07 (d, 3H, J=7 Hz); 1.2–3.0 (m, 7H); 1.8 (br. s, 3H); 6.4 (m, 1H)	230.5 (8200); 324.5 (46)	$C_{15}H_{18}N_4O_4$ (318.3)	76.5°[b]
4d	104–105°/20	1665	1635 (sh)	1.2–1.9 (m, 4H); 1.73 (br. s, 3H); 1.91 (br. s, 3H); 2.2–2.7 (m, 4H)	240 (10120); 323.3 (65)	$C_{15}H_{18}N_4O_4$ (318.3)	156.5° (146–147°)[11]
4e	101–102°/20 (73°/2.8)[15]	1681	1659	1.4–2.2 (m, 6H); 1.79 (br. s, 3H); 2.2–2.7 (m, 4H); 6.03 (m, 1H)	232 (16580); 312.5 (53)	$C_{15}H_{18}N_4O_4$ (318.3)	149°
4f[c]	115–116°/20	1696	1660	1.2–2.1 (m, 8H); 1.82 (br. s, 3H); 2.1–2.8 (m, 4H); 5.9 (m, 1H)	233.5 (7850); 321.5 (43)	$C_{16}H_{20}N_4O_4$ (332.5)	108.5°

[a] The structure of these 2,4-dinitrophenylhydrazones is in accord with their I.R. and N.M.R. spectra and their microanalyses (C, H, N ±0.30%).

[b] Mixture of *syn*- and *anti*-isomers.

[c] $C_{10}H_{16}O$ (152.2) calc. C 78.89 H 10.59; found 78.9 10.60

2-Methyl-2-cyclooctenone (**4e**): The mixture of cyclopropane derivatives (*E/Z*)-**3e** (24.9 g, ~0.1 mol) is refluxed in xylene (300 ml) for 6 days. The xylene is evaporated and the residual oil is distilled under vacuum; yield: 11.05 g (80%); purity: 92% (G.L.C. on carbowax 20M and SE30); b.p. 101–102 °C/20 torr.

$C_9H_{14}O$ (138.2); M.S.: m/e = 138.

I.R. (CCl_4): ν = 1681 (C=O); 1659 cm^{-1} (C=C).

^{1}H-N.M.R. (CCl_4): δ = 6.03 ppm (m, 1H, C=CH—).

The same product can be obtained on heating for 3 days a solution of the cyclopropanes **3e** in a boiling mixture (300 ml for 0.1 mol) of methanol and triethylamine (85:15). After evaporation of the solvents, the enone is dissolved in pentane, the triethylamine hydrochloride is removed by filtration. The pentane is evaporated and the enone is purified by chromatography on silica gel.

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