Cyclopropanation of Some Simple Olefinic Compounds. Byproduct Formation in Excess Simmons–Smith Reagent

Ioannis M. Takakis and Yorke E. Rhodes*

Department of Chemistry, New York University, New York, New York 10003

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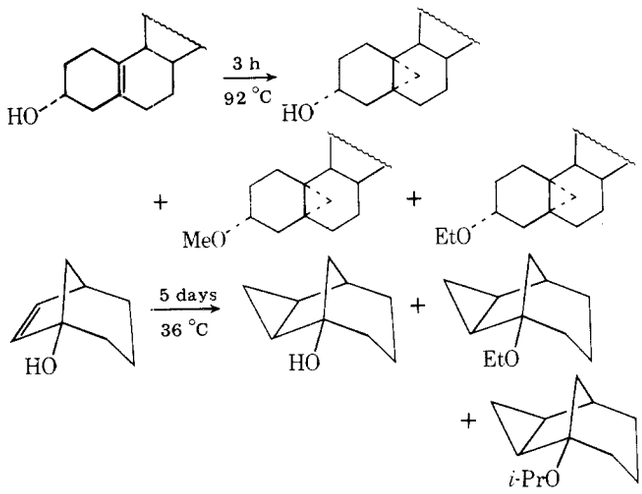
The Simmons–Smith reaction of certain unreactive alkenes of the types CH_2=$CHCH_2CO_2R$ (R = H, **1**; CH_3, **2**; CD_3, **3**) and CH_2=$CHCH_2CH_2OR'$ (R′ = $COCH_3$, **4**; CH_3, **5**; H, **6**) has been studied in excess diiodomethane and zinc–copper couple or zinc–mercury couple. In some cases the initially formed cyclopropane adducts reacted further to furnish ethers, formals, and transesterification byproducts. Ester **2** gave **10** and **11**; alcohol **6** afforded **12**, **9**, **14**, and **15**. Qualitatively, the order of reactivity of these compounds appears to follow the trend **6** ≥ **5** > **2** > **4** > **1**. A convenient procedure for the preparation of symmetrical formals is reported.

The reaction of alkenes with methylene iodide and zinc–copper couple, the Simmons–Smith reaction, has long been a useful synthetic tool for the preparation of cyclopropane compounds.[1] Vinylic alkyl substituents enhance the reaction rate, but excessive substitution brings about rate retardation.[1,2] Oxygen functions, particularly hydroxyl, in the vicinity of the double bond may enhance the reaction rate and direct the attack cis stereospecifically.[1,3] The nature of the "methylene transfer" intermediate has been discussed.[1]

Previous reports indicate that Simmons–Smith reactions of relatively unreactive alcohols furnish cyclopropyl alcohols, and in addition, ethers and formals when carried out under forcing conditions. For example, estr-5(10)-ene-3α,17β-diol gave not only the alcohol that results from direct cyclopropanation of the double bond but also the corresponding methyl and ethyl ethers.[4] Similarly, bicyclo[3.2.1]oct-6-en-1-ol afforded *exo*-tricylo[3.3.1.$0^{2,4}$]nonan-1-ol and the corresponding ethyl and isopropyl ethers.[5] In another work, Majerski and Schleyer[6] obtained symmetrical formals as side products during cyclopropanation reactions of allyl alcohols. In fact, depending upon reaction conditions, some of these alcohols furnished the corresponding formals predominantly.

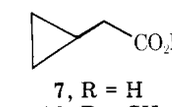


The above results prompted an investigation of terminal, unsubstituted alkenes **1–6**. These were prepared by standard methods and identified spectroscopically. All reactions were carried out in anhydrous ethyl ether using a large excess of diiodomethane and zinc–copper couple. Replacement of zinc–copper with amalgamated zinc (the use of which is unprecedented in Simmons–Smith reactions) afforded the same products, albeit in lower yields (Table I). Variation in the couple has also been reported by Conia,[7] who obtained higher yields with zinc–silver in lieu of zinc–copper couple. In this work, the use of zinc–mercury as a substitute for zinc–copper was not thoroughly explored.

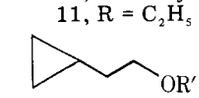
CH_2=$CHCH_2CO_2R$
1, R = H
2, R = CH_3
3, R = CD_3

CH_2=$CHCH_2CH_2OR'$
4, R′ = $COCH_3$
5, R′ = CH_3
6, R′ = H
16, R′ = $CH_2OCH_2CH_2CH$=CH_2

Cyclopropanation of **1**, **4**, and **5** gave the corresponding cyclopropane adducts **7**, **8**, and **9**, respectively. Similar treatment of **2**, prepared from **1** and diazomethane and uncontaminated by ethyl ester, yielded **10** as the major product contaminated by ethyl ester **11**. When **10** was subjected to the reaction conditions for 5 days, the crude mixture consisted of unreacted **10** (47%), ethyl ester **11** (40%), and two unidentified products (13%) of greater VPC retention times. Reduction of the mixture with lithium aluminum hydride afforded **12** as the only isolable product. These results might suggest C–H

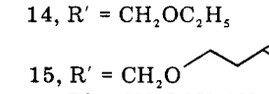


7, R = H
10, R = CH_3
13, R = CD_3
11, R = C_2H_5



8, R′ = $COCH_3$
9, R′ = CH_3
12, R′ = H

14, R′ = $CH_2OC_2H_5$



17, R′ = $CH_2OCH_2CH_2CH$=CH_2

insertion; however, analogous reaction of the trideuterated methyl ester **3** yielded the corresponding methyl ester **13** as well as the nondeuterated ethyl ester **11**, thus excluding a possible C–H insertion mechanism. It has been shown by Blanchard and Simmons[1] that if the reaction is carried out in ethyl ether, side products such as methyl iodide, ethoxyzinc iodide, and others are formed. Generation of these species is particularly favored here since excess reagent and longer reaction periods were employed. Therefore, it is conceivable that **11** may be formed via transesterification of **10** or **13** by ethoxyzinc iodide.

Cyclopropanation of **6** has been reported[8] as yielding only 25–26% of **12**. In this work, two additional products were obtained under various conditions and identified as **14** and **15** (Table I). Formal **15** was the major product in several runs, as suggested by Majerski and Schleyer,[6] who incidently were the first to obtain symmetrical formals in Simmons–Smith reactions (see above). On accasion, a third byproduct was obtained and identified as **9**. Structural elucidation of **14** presented initial difficulty due to the absence of the molecular ion in the mass spectrum and the superposition of the oxy-

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Table I. Cyclopropanation of Various Alkenes

Alkene	Alkene/CH_2I_2/Zn–Cu[a] (molar ratio)	Reaction period, h	% relative composition[b]			
			1	**7**	Unidentified	
1	1:3:5.4	84	72	12	16	
			6	**10**	**11**	
2	1:3:5.4	48	37	57	6	
	1:3:5.4[c]	48	63	35	2	
	1:3:6	24	19	78	3[d]	
	1:6:12	37	6	81[e]	13[e]	
			4	**8**		
4	1:3:5.4	48	50	50		
	1:3:5.4[c]	48	87	13		
	1:3:6	24	38	62[d]		
	1:2:2.5	60		23[f,g]		
			5	**9**		
5	1:3:3	48	3	97 87[f]		
	1:3:3[c]	48	16	84 77[f]		
			6	**12**	**14**	**15**
6	1:3:5.4	48	0	46	17	37
	1:3:5.4[c]	48	0	43	25	32
	1:2:2	48	23	71	4	3
	1:3:6	2	0	57	12	31
	1:3:6	24	0	46	11	43[d]

[a] A 0.05-mol amount of alkene was used in most experiments. [b] Determined from VPC peak areas. [c] Zinc–mercury was used instead of zinc–copper couple. [d] Percent relative yields were determined by use of cylooctane as an internal area standard. [e] Isolated yield of **10** and **11** combined is 50%. [f] Isolated yield. [g] Reference 10.

Table II. Product Analysis of 6 as a Function of Time

Time, h	% relative VPC area			
	6	**12**	**14**	**15**
1.00	100			
1.33	98	2		
1.83	79	19	3	
2.50	42	55	3	
3.00	30	63	7	
4.00	13	75	10	3
5.00	5	76	14	6
7.00		72	15	14
9.00		67	17	16
11.00		58	19	23
19.00		56	19	25
29.00		54	19	27
45.75		50	20	30
72.00		49	21	30
120.00		46	21	33

methylene protons of the two alkyl groups in the NMR spectrum. This accidental degeneracy resulted in a symmetrical heptet centered at δ 3.47 and was not removed by changing the solvent to benzene. Finally, elemental analysis and spin decoupling revealed the structure. Irradiation of the methyl protons (δ 1.13) caused the collapse of the heptet to a triplet ($C_3H_5CH_2C\mathbf{H}_2O$–) and a broad singlet (–$OC\mathbf{H}_2CH_3$). The structural assignments were confirmed by spectroscopic comparison with authentic samples.

The independent synthesis of **15** and **16** as well as the unsymmetrical **14** is worthy of mention as it provides a simple, convenient procedure for symmetrical formals. As a typical example, **6** was sealed in a tube with anhydrous calcium chloride powder and paraformaldehyde and heated at 98–100 °C for 3 days. Distillation gave starting **6** and **16** (56%). This eliminates the inconvenience associated with depolymerizing paraformaldehyde. Although there is an equilibrium involved between the alcohol and the formal, the large difference in boiling points affords a convenient separation by simple distillation. Authentic samples of **14** and **15** were prepared in the same manner from **12** and ethanol.

In an attempt to find optimum conditions for the formation of alcohol **12**, cyclopropanation of **6** was repeated and samples were withdrawn periodically and analyzed by VPC (Table II). A plot of the time course of the reaction (Figure 1) reveals the initial formation of **12**, which, being unstable under the reaction conditions, reacts further to yield formals **14** and **15** either directly or indirectly. Hydrolysis of **15** was carried out with an equivolume solution of 10% aqueous sulfuric acid and THF. Analysis of the mixture by VPC indicated starting **15** (4%) and **12** (96%). Thus, aqueous mineral acid hydrolysis of the reaction mixture of **6** could provide **12** in high yield. Partial cleavage of **15** was also effected by refluxing with zinc iodide, a strong Lewis acid byproduct in Simmons–Smith reactions, in anhydrous ethyl ether. VPC analysis revealed starting **15** (52%) and **12** (48%). Reaction of **12** alone with the Simmons–Smith reagent furnished starting **12** (27%), **9** (6%), **14** (19%), and **15** (48%). Under more vigorous conditions, it gave **12** (12%), **14** (68%), and **15** (20%). Interestingly, when **15** was subjected to the reaction conditions, it afforded **14** (48%) with the remainder being starting material. Reaction of **15** with diiodomethane in ethyl ether at the exclusion of zinc–copper couple failed, as analysis of the mixture revealed starting material only. Another interesting result was obtained during cyclopropanation of **16**, which also gave product **14** (29%) in addition to **17** (35%) and **15** (36%). These control reactions in conjunction with the results of Figure 1 suggest the following: (a) cyclopropanation of **6** occurs faster than formal generation; (b) alcohol **12** furnishes **14** and **15**; (c) symmetrical formal **15** is cleaved slowly under the reaction conditions to give unsymmetrical formal **14** via subsequent reactions; and (d) **14** seems to be the thermodynamically most stable product.

It should be emphasized that the various byproducts discussed above were obtained as a result of strenuous reaction conditions in an effort to increase the cyclopropane yields of unreactive olefinic compounds.

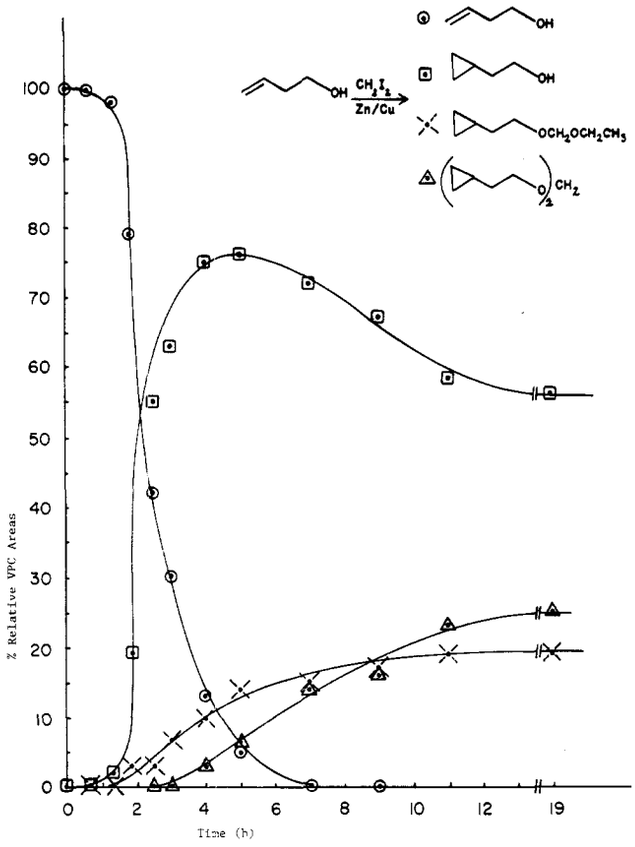

Figure 1. Product composition in the Simmons–Smith reaction of 3-buten-1-ol as a function of time.

Finally, a qualitative order of reactivity of the five compounds studied here may be inferred from the unreacted starting material obtained under similar reaction conditions (Table I). Thus, $6 \geq 5 > 2 > 4 > 1$. Since these substrates are not activated (inductive effect) or deactivated (steric effect) by alkyl substitution at the vinyl locants, the above order of reactivity may reflect the ability of the methylene transfer reagent to coordinate with the oxygen functional groups at the homoallylic positions.

Experimental Section

Materials and Equipment. Analytical VPC separations were carried out on an F and M Model 5750 gas chromatograph equipped with a flame ionization detector and a mechanical integrator using a 12 ft × ⅛ in stainless steel column packed with 7 g of 20% Carbowax 20M on 60–80 mesh Chromosorb P. Preparative VPC separations were performed on an F and M Model 700 gas chromatograph equipped with a thermal conductivity detector. An aluminum column packed with 40 g of 20% Carbowax 20M on 60–80 mesh Chromosorb P was employed. NMR spectra were obtained on Hitachi Perkin-Elmer R-20 and Varian Model A-60 spectrometers (60 MHz) in CCl_4 solution and are reported in units of δ (ppm) downfield from a Me_4Si in CCl_4 external reference. Infrared spectra (~5% CCl_4 solution) were recorded on a Perkin-Elmer Model 337 infrared spectrophotometer. Boiling points are uncorrected. Microanalyses were carried out by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. All solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4.

The ethyl ether used for Simmons–Smith reactions was distilled over lithium aluminum hydride. Freshly opened cans (Mallinckrodt) were also satisfactory. Commercial samples of diiodomethane and zinc–copper couple were used without further purification. 3-Buten-1-ol (**6**) was prepared by reduction of 3-butenoic acid (**1**) with lithium aluminum hydride: bp 28 °C (12 mm); n^{23}_D 1.4197 [lit.[9] bp 115 °C (770 mm), n^{25}_D 1.4182]. Treatment of **6** with acetic anhydride in pyridine gave 3-butenyl acetate (**4**): bp 120–123 °C; n^{23}_D 1.4240 [lit.[10] bp 121–123 and 126 °C, n^{25}_D 1.4104 and n^{20}_D 1.4105]. Reaction of **6** with diazomethane (prepared from *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide)[11] and a catalytic amount of boron trifluoride etherate in ethyl ether[12] afforded 4-methoxy-1-butene (**5**): bp 70–72 °C; n^{22}_D 1.3910 [lit.[13] bp 68–69 °C (750 mm), n^{20}_D 1.3976]. Methyl 3-butenoate (**2**) was obtained from **1** and diazomethane: bp 104–106 °C; n^{23}_D 1.4070 [lit.[13] bp 106 °C (745 mm)]. The compounds described above were at least 97% pure by VPC. Structural assignments were confirmed by IR and NMR spectroscopy.

Zinc–Mercury Couple for Simmons–Smith Reactions. Amalgamated zinc was prepared according to a procedure described in the literature[14a] except that zinc dust was used instead of mossy zinc. The couple was washed thoroughly first with water and then with ether. It was dried in a desiccator under vacuum.

Trideuteriomethyl 3-Butenoate (3). The trideuterated methyl ester was prepared according to the procedure of Sarett.[14b] A 250-mL round-bottom flask equipped with a condenser and drying tube was charged with anhydrous potassium carbonate (17.3 g, 0.151 mol) and purified acetone (80 mL). The mixture was heated at reflux for 3 h, at the end of which the heating source was removed and 3-butenoic acid (10.8 g, 0.125 mol) in dry acetone (25 mL) was added dropwise. Foaming occurred and a white slurry resulted. After heating for an additional 0.5 h, trideuteriomethyl iodide (15.5 g, 0.107 mol) in dry acetone (45 mL) was added dropwise, and the flask was heated at reflux for 20 h. The mixture was diluted with ethyl ether until potassium iodide precipitated out of solution. Filtration, drying, and removal of the solvents by distillation at atmospheric pressure gave a crude product which was purified by distillation to give 6.0 g (47%) of a colorless liquid: bp 107 °C; n^{28}_D 1.4050. The NMR spectrum is identical with that of the protio ester except that the singlet due to the methoxy protons at δ 3.52 is absent (0.0 H); IR 3095, 2990, 2260, 2200, 2125, 2080, 1745, 1645, 1420, 1410, 1335, 1292, 1270, 1192, 1093, 992, 922 cm^{-1}.

1,1-Di(3-butenoxy)methane (16). 3-Buten-1-ol (8.64 g, 0.120 mol), paraformaldehyde (1.80 g, 0.0599 mol), and powdered calcium chloride (3.33 g, 0.0300 mol), which was predried in an oven at 150 °C, were sealed in a tube and heated in an oil bath at 100 °C for 3 days. The mixture was diluted with ether (50 mL) and filtered. After drying and concentration, the residue was distilled to give starting material and 5.2 g (56%) of a colorless liquid: bp 65–68 °C (9 mm); NMR δ 2.27 (q, 4 H, allylic methylene), 3.49 (t, 4 H, oxymethylene), 4.54 (s, 2 H, methylenedioxy), 4.79–5.22 (m, 4 H, C-4 vinyl), 5.44–6.14 (m, 2 H, C-3 vinyl); IR 3080, 2985, 2930, 2875, 1740, 1640, 1425, 1375, 1180, 1124, 1078, 1040, 1000, 965, 921 cm^{-1}. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C,69.15; H, 10.25.

1-(2-Cyclopropylethoxy)-1-ethoxymethane (14) and 1,1-Di(2-cyclopropylethoxy)methane (15). 2-Cyclopropylethanol (**12**; 0.860 g, 0.0100 mol), absolute ethanol (0.460 g, 0.0100 mol), paraformaldehyde (0.300 g, 0.0100 mol), and anhydrous calcium chloride (0.555 g. 0.00500 mol) were sealed in a tube and heated as above. After workup of the reaction mixture and removal of ether, the crude product was separated by VPC (at 170 °C) to give four fractions with retention times of 1.7 (5%), 5.3 (55%), 6.5 (12%), and 19.8 (28%) min. The first fraction (5%) was not identified. The second fraction (55%) was shown to be **14**: n^{27}_D 1.4520; NMR δ −0.1 to 1.3 (cyclopropane), 1.13 (t, methyl), 1.39 (q, methylene at C-2; total measured area between δ −0.1 and 1.7 is 10 H), 3.47 (heptet, 4 H, $-CH_2OCH_2OCH_2-$), 4.51 (s, 2 H, methylenedioxy); IR 3070, 2975, 2870, 1375, 1192, 1122, 1103, 1087, 1053, 1041, 1021, 951 cm^{-1}. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.51; H, 11.02. The third fraction (12%) was identified as **12**. The fourth fraction (28%) was identified as **15**: n^{27}_D 1.4390; NMR δ −0.16 to 1.2 (m, 10 H, cyclopropane), 1.43 (q, 4 H, methylene at C-2), 3.53 (t, 4 H, methylene at C-1), 4.57 (s, 2 H, methylenedioxy); IR 3070, 3000, 2925, 2870, 1455, 1415, 1370, 1190, 1123, 1092, 1065, 1045, 1023, 963, 930, 885 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.56; H, 10.86.

General Cyclopropanation Procedure. To a 250-mL round-bottom flask equipped with a condenser, drying tube, and dropping funnel was added zinc–copper couple (0.10–0.60 mol) or zinc–mercury couple (0.15–0.27 mol), a few crystals of iodine, and anhydrous ethyl ether (50–75 mL). The stirred mixture was heated at reflux for 0.5 h. A solution of methylene iodide (0.10–0.30 mol) and the olefinic compound (ca. 0.05 mol) in anhydrous ethyl ether was added dropwise, and the mixture was refluxed for the specified time. The flask was cooled in an ice–water bath, and the mixture was hydrolyzed by the dropwise addition of a saturated ammonium chloride solution (100 mL). The aqueous layer was extracted several times with ether, and the combined ether extracts were washed with saturated potassium carbonate (100 mL) and then with brine (100 mL). The ether layer was dried, filtered, and concentrated at atmospheric pressure to give an oily mixture which was analyzed by VPC and purified either by preparative VPC or by distillation. Specific examples are given below, and repeated experiments using modifications of reagent ratios or reaction conditions are shown in Table I.

Cyclopropanation of 3-Butenoic Acid (1). Reaction of 5.4 g (0.05 mol) of **1** afforded 12% (by VPC) of cyclopropylacetic acid and 16% of an unidentified compound. The former was identified by comparison with an authentic sample.[15]

Cyclopropanation of 3-Buten-1-yl Acetate (4). Using the above procedure, 5.7 g (0.050 mol) of **4** afforded an oily mixture which upon VPC analysis gave two fractions. The first fraction (38%) was identified as **4** by coinjection with an authentic sample. The second fraction (62%) had bp 77 °C (56 mm), n^{23}_D 1.4220 [lit.[10a] n^{25}_D 1.4200]. Its NMR and IR spectra were identical with those reported for 2-cyclopropylethyl acetate.[16,17]

Cyclopropanation of 3-Buten-1-yl Methyl Ether (5). 3-Buten-1-yl methyl ether (4.30 g, 0.050 mol) was treated with the Simmons–Smith reagent, and the crude product was distilled and identified as 2-cyclopropylethyl methyl ether (**9**; 4.36 g, 87%): bp 97 °C (micro bp[18] 106 °C); n^{26}_D 1.4002; NMR δ −0.11 to 1.24 (m, 5 H, cyclopropane), 1.45 (q, 2 H, methylene at C-2), 3.28 [s, methoxy protons; overlapping with δ 3.37 (t, methylene at C-1); total area 5 H]; IR 3080, 3005, 2985, 2925, 2870, 2730, 1445, 1375, 1320, 1267, 1233, 1201, 1171, 1120, 1045, 1016, 997, 966, 926, 885, 820 cm^{-1}. Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.22; H, 11.82.

Cyclopropanation of Methyl 3-Butenoate (2). Cyclopropanation of **2** (5.0 g, 0.050 mol) followed by VPC (column temperature, 145 °C) yielded three fractions. The first fraction (retention time of 4.8 min; 19%) was identical with **2** by coinjection. The second fraction (retention time of 8.6 min; 78%) had identical NMR and IR spectra with those of methyl cyclopropylacetate[19] (**10**). The third fraction (retention time of 10.2 min; 3%) was identified as ethyl cyclopropylacetate (**11**): n^{22}_D 1.4205; NMR, the complex multiplet due to the five cyclopropane protons had a chemical shift between δ −0.05 and 1.3 and overlapped with the triplet due to the methyl protons between δ 1.0–1.4 (total area 8 H), δ 2.04 (d, 2 H, methylene at C-2), 4.02 (q, 2 H, ethoxy methylene); IR 3080, 2980, 1735, 1320, 1259, 1208, 1185, 1118, 1102, 1038, 1023, 989, 955, 912, 828 cm^{-1}. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.73; H, 9.67.

A mixture of the second and the third fractions was isolated by preparative VPC and reduced with lithium aluminum hydride. Only one product was obtained which had identical NMR and IR spectra with an authentic sample of 2-cyclopropylethanol (**12**).

Simmons–Smith Reaction of Methyl Cyclopropylacetate (10). Using the standard cyclopropanation procedure, a mixture of **10** (2.89 g, 0.0253 mol), diiodomethane (40.2 g, 0.150 mol), zinc–copper couple (20.0 g), and a catalytic amount of iodine in ethyl ether (100 mL) was heated at reflux for 5 days. After the usual workup procedure, the sample was analyzed by VPC and found to consist of starting **10** (47%), ethyl ester **11** (40%), and two unidentified, longer retention time products (13%). Other products of extremely short retention times were also observed and are probably the same as those observed and accounted for elsewhere.[1]

Cyclopropanation of Trideuteriomethyl 3-Butenoate (3). The Simmons–Smith reaction of the deuterated ester (same condition as for **2**) gave starting material and two other fractions which were isolated by preparative VPC and analyzed. The second fraction had n^{28}_D 1.4195. The NMR spectrum was similar to that of **10** as reported,[19] except that the singlet due to the methoxy groups at δ 3.6 was absent: NMR δ −0.3 to 1.4 (m, 5 H, cyclopropane), 2.10 (br d, 2 H, methylene at C-2); IR 3085, 3015, 2920, 2255, 2190, 2120, 2080, 1740, 1320, 1270, 1194, 1121, 1090, 1050, 1023, 998, 967, 938, 835 cm^{-1}. The NMR and IR spectra of the third VPC fraction were identical with those of **11**, indicating the complete absence of deuterium.

Cyclopropanation of 3-Buten-1-ol (6). A. Under Various Conditions. The Simmons–Smith reaction of **6** (10.8 g, 0.150 mol), when carried out under various conditions (Table I), furnished four fractions. The first fraction was observed in small amount after several repetitions of the reaction. It was tentatively identified as 2-cyclopropylethyl methyl ether (**9**) by comparison of its VPC retention time with that of the sample isolated from cyclopropanation of **5**. The second fraction (retention time of 8.4 min at 158 °C; 11%), n^{27}_D 1.4520, was identified as **14** by comparison of its spectral properties with those of the authentic sample prepared above. The third fraction (retention time of 10.8 min at 158 °C; 46%) had NMR and IR spectra identical with those of 2-cyclopropylethanol (**12**). The fourth fraction (retention time of 38.2 min at 158 °C; 43%), n^{27}_D 1.4390, was identified as **15** by spectroscopic comparison with an authentic sample.

B. Product Analysis as a Function of Time. Using the general procedure, a mixture of **6** (7.2 g, 0.10 mol), diiodomethane (80.4 g, 0.30 mol), and zinc–copper couple (22.2 g, 0.30 mol) in anhydrous ethyl ether (100 mL) was heated at reflux. Samples (1 mL) were withdrawn with a syringe at appropriate intervals and analyzed by VPC. Weight percent relative amounts of products calculated from VPC areas are given in Table II. Molar response corrections were not made (see Figure 1).

Cleavage of 1,1-Di(2-cyclopropylethoxy)methane (15). A. With Mineral Acid. Ketal **15** (1.0 g, 0.0054 mol) was dissolved in tetrahydrofuran (30 mL). A 10% aqueous sulfuric acid solution (30 mL) was added, and the heterogeneous solution was heated with vigorous stirring for 21 h. The solution was extracted several times with 50 mL portions of ether, and the combined ether extracts were washed successively with water, potassium carbonate, and brine. Drying, filtration, and removal of ether gave a crude product which on VPC analysis showed starting formal (4%) and **12** (96%).

B. With Zinc Iodide. A mixture of **15** (1.84 g, 0.010 mol), zinc iodide (6.38 g, 0.202 mol), and a few crystals of iodine in anhydrous ether (30 mL) was heated at reflux for 48 h. Analysis by VPC indicated starting **15** (52%) and **12** (48%).

Simmons–Smith Reaction of 2-Cyclopropylethanol (12). 2-Cyclopropylethanol (2.15 g, 0.025 mol), methylene iodide (6.70 g, 0.025 mol), zinc–copper couple (3.7 g, 0.05 mol), and a few crystals of iodine were dissolved in ether (25 mL), and the mixture was heated at reflux for 24 h. VPC of the crude mixture revealed the following composition: **12** (27%), **9** (6%), **14** (19%), and **15** (48%). In a second reaction, a mixture of **12** (1.00 g, 0.012 mol), methylene iodide (20.1 g, 0.075 mol), zinc–copper couple (10.0 g, 0.135 mol), and a few crystals of iodine in ether (100 mL) was heated at reflux for 84 h. The following compounds were observed upon VPC analysis: **12** (12%), **14** (68%), and **15** (20%). Other shorter retention time peaks were also observed in small amounts but were not identified.

Simmons–Smith Reaction of 1,1-Di(2-cyclopropylethoxy)-methane (15). Using the general procedure, a mixture of **15** (1.84 g, 0.010 mol), methylene iodide (8.04 g, 0.030 mol), zinc–copper couple (4.44 g, 0.061 mol), and a catalytic amount of iodine in ether (30 mL) was heated at reflux for 48 h. Analysis by VPC gave starting **15** (52%) and **14** (48%). When the reaction was repeated using the same materials as above, but not using zinc–copper couple, **15** was recovered unreacted.

Cyclopropanation of 1,1-Di-(3-butenoxy)methane (16). Using the general procedure, a mixture of **16** (3.9 g, 0.025 mol), diiodomethane (40.2 g, 0.15 mol), zinc–copper couple (20.0 g, 0.27 mol), and a catalytic amount of iodine in ether (100 mL) was heated at reflux for 5 days. Analysis of the crude product mixture by VPC revealed three fractions. The first fraction (29%) had an identical NMR spectrum with that of **14**. The second fraction (35%), n^{26}_D 1.4278, was identified as 1-(3-butenoxy)-1-(2-cyclopropylethoxy)methane (**17**) on the basis of the following data: NMR δ −0.2 to 1.2 (m, 5 H, cyclopropane), 1.36 (q, 2 H, cyclopropylcarbinyl protons), 2.24 (q, 2 H, allylic protons), 3.46 (t, 4 H, $-CH_2OCH_2OCH_2-$), 4.50 (s, 2 H, methylenedioxy), 4.73–5.22 (br d, 2 H, terminal vinyl protons), 5.27–5.98 (m, 1 H, internal vinyl proton); IR 3075, 3005, 2930, 2870, 1640, 1460, 1420, 1370, 1178, 1115, 1083, 1037, 1017, 950, 914, 882 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.39; H, 10.47. The third fraction (36%) had an NMR spectrum identical with that of **15**.

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Registry No.—**1**, 625-38-7; **2**, 3724-55-8; **3**, 66688-09-3; **4**, 1576-84-7; **5**, 4696-30-4; **6**, 627-27-0; **7**, 5239-82-7; **8**, 66688-05-9; **9**, 66688-06-0; **10**, 34108-21-9; **11**, 53432-87-4; **12**, 2566-44-1; **13**, 66688-11-7; **14**, 66688-07-1; **15**, 66688-08-2; **16**, 48057-46-1; **17**, 66688-10-6; trideuteriomethyl iodide, 865-50-9.

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Reduction of *gem*-Dihalocyclopropanes with Zinc. Monoreductive Dehalogenation of *gem*-Dihalocyclopropyl Methyl Ketones and Dioxolanes

Roger Barlet

Laboratoire de Chimie Organique, Université Scientifique et Médicale de Grenoble, 38041 Grenoble, Cedex, France

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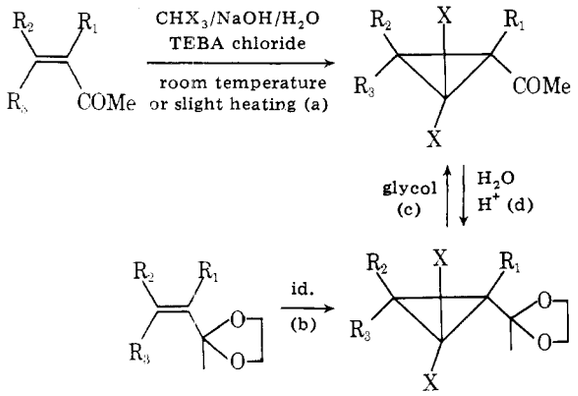
The monoreduction, by means of zinc powder in alcoholic potassium hydroxide, of 11 *gem*-dihalocyclopropyl methyl ketones and six *gem*-dihalocyclopropylmethyldioxolanes was reported and gave satisfactory yields. With ketones, contrary to dioxolanes, the monoreduction occurred without general stereoselectivity, but required critical temperature control and precise reaction times to prevent total reduction. α-Alkylated ketones ($R_2 = R_3 = H$; R_1 = Me, *i*-Pr, or *t*-Bu) led predominantly to cis isomers, especially with bulky R_1, while α,β- ($R_3 = H$; R_1 = Me; R_2 = Me or *i*-Pr) and β,β′-dialkylated ketones ($R_1 = H$; $R_2 = R_3$ = Me) gave steric preference depending on the nature of the halogen. In all cases, dioxolanes gave a stereoselective formation of the trans isomers. These results were rationalized by postulating a predominant initial zinc attack at the less hindered C–X bond. With dioxolanes, the second step would be a high inversion of the resulting α-halocyclopropyl radicals. With ketones, intermediates could be carbanions and results explained by an easier inversion of the α-chlorocyclopropyl carbanions relative to the α-bromocyclopropyl carbanions.

A large variety of reagents can bring about reductive monodehalogenation of *gem*-dihalocyclopropanes.[1,2] Furthermore, recent studies examined the stereoselectivity of such a monoreduction with organotin hydride,[3-5] lithium aluminum hydride ($LiAlH_4$),[6,7] or related hydrides.[8,9] Moreover,



zinc powder in acetic acid[10] or ethanol–acetic acid[11] was revealed as an efficient and cheap means for reducing dihalocyclopropanes. The recent reduction with zinc in alcoholic potassium hydroxide appeared particularly attractive as a stereoselective and easy method.[2]

We wish now to report the monoreduction of *gem*-dihalocyclopropyl methyl ketones and their corresponding dioxolanes with this latter reagent. It was of interest to test the generality of the monoreduction, with a free or a protected carbonyl group as ring substituent, and to check its stereoselectivity especially with a crowded group such as a dioxolane.

The substrates were easily available by dihalocarbenic addition to olefinic ketones (a) or to dioxolanes (b) with subsequent ketalization (c) or hydrolysis (d) if needed.[12] The two-step procedure (a + c) for dioxolane synthesis was preferred to the direct addition (b). Conversely, for ketones, the direct method (a) was better except for compounds with $R_1 = H$, which required steps b and d.

Results

Results are summarized in Tables I and II. Our experimental conditions (method m_1) gave monoreduced rings as major products with satisfactory yields.

Ketones A–K (Table I) underwent reduction more easily than dioxolanes L–Q (Table II) with the exception of the dichloro ketone F, which was not reduced in boiling ethanol but required boiling propanol or butanol. It is also noteworthy that dibromo ketones underwent monoreduction more readily than dichloro ketones. In both cases formation of fully reduced cyclopropanes was difficult to avoid.

For ketones the extent of the reduction was greatly dependent on the temperature. In order to limit the reduction and to obtain preferably monoreduced ketones each substrate required specific temperature conditions and reaction time. Furthermore, for a few ketones we determined a critical temperature below which the extent of the reduction was considerably reduced and above which the complete reduction occurred rapidly. In all cases stereoisomeric pairs of cis and trans monoreduced compounds (cis and trans refer to the position of the halogen relative to the acetyl group) were obtained without general selection.

For dioxolanes, with careful temperature and reaction time controls we obtained a stereoselective monoreduction, giving predominantly the trans isomer.

Identification and Characterization

Identification and configurational assignments of the reduced compounds were easily achieved by comparison with halocarbenoid adducts of olefinic dioxolanes previously prepared.[13] Halocyclopropanation by halogen exchange gave both chloro- and bromodioxolanes which were converted, when

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