Regioselective route to sterically hindered cyclopropylcarbinyl halides

Robert T. Hrubiec, and Michael B. Smith

J. Org. Chem., **1984**, 49 (3), 431-435• DOI: 10.1021/jo00177a008 • Publication Date (Web): 01 May 2002

Regioselective Route to Sterically Hindered Cyclopropylcarbinyl Halides[1a]

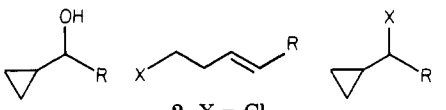
Robert T. Hrubiec[1b] and Michael B. Smith*

Department of Chemistry, U-60, University of Connecticut, Storrs, Connecticut 06268

Received August 22, 1983

Reaction of cyclopropylcarbinyl alcohols 1 with hexachloroacetone and triphenylphosphine resulted in 80–90% yields of the corresponding cyclopropylcarbinyl chlorides 4 regioselectively, with no trace of the homoallylic chloride 2 or the chlorocyclobutane derivative **6a**. Similar reaction of 1 with bromine and triphenylphosphine, in dimethylformamide, gave 65–80% yields of the cyclopropylcarbinyl bromide 5 with trace amounts of the homoallylic bromide 3 but no detectable bromocyclobutane derivative **6b**. These reactions are amenable to the preparation of very sterically hindered cyclopropylcarbinyl halides, heretofore inaccessible, regioselectively and in a facile manner.

The transformation of cyclopropylcarbinyl alcohols such as 1 into the corresponding homoallylic halide 2 or 3 under



1 2, X = Cl; 3, X = Br; 10, X = I 4, X = Cl; 5, X = Br; 11, X = I

a, R = H; b, R = Me; c, R = Et; d, R = *n*-Pr; e, R = *n*-Bu; f, R = *i*-Pr; g, R = *t*-Bu

electrophilic conditions is a useful reaction which had received considerable attention.[2] This conversion has been accomplished with great efficiency by treatment of **1a** or **1b** with hydrogen bromide,[2c] zinc bromide,[2f,g] phosphorus pentachloride[3,4] and magnesium halides.[2a,b] The facility of this reaction has usually thwarted the use of **1a** or **1b** for the preparation of 1-halo-1-cyclopropylalkanes. Although both 1-bromo-1-cyclopropylethane (**5b**)[3] and 1-chloro-1-cyclopropylethane (**4b**)[3,4] have been prepared, the approaches were of limited utility and products often of questionable purity. The conversion of more hindered and more labile alcohols to the corresponding halide have not been previously reported. We have recently shown[5] that treatment of **1b** with triphenylphosphine and hexachloroacetone, used by Magid for the conversion of allylic alcohols to the corresponding chloride,[6] resulted in an 84% isolated yield of **4b**. Likewise, reaction of **1b** with bromine and triphenylphosphine, analogous to work reported by Kirmse for the preparation of bromocyclopropylmethane (**5a**),[7] gave 66% of **5b**.[5] An essential feature of these transformations was the isolation of **4a** and **5b** uncontaminated by the homoallylic rearrangement products, **2** or **3**, always observed with other reagents. We can now report further on the scope of this reaction and its generality to the synthesis of 1-cyclopropyl-1-haloalkanes (cyclopropylcarbinyl halides) **4** and **5**, possessing a variety of alkyl groups.

Results and Discussion

Our recent interest in nucleophilic, homoallylic substitution reactions on unactivated cyclopropylcarbinyl derivatives required a synthetic approach to halides such as **4** or **5** compatible with systematic insertion of alkyl groups which would effectively block approach of a nucleophile to the halogen-bearing carbon. More importantly, we required that **4** or **5** be prepared without contamination by the homoallylic halides **2** and or **3** or by halocyclobutane derivatives **6**. It became evident that the literature contained nothing relevant to the preparation of such compounds. Our success in the conversion of 1-cyclopropyl-1-ethanol (**1b**) to **4b** and **5b** suggested application of this method to the synthesis of the desired halies, and we initially focused on the preparation of the requisite alcohols. It has been reported that alcohols **1b–f** could be prepared in good yield by lithium aluminum hydride reduction of the corresponding ketone.[8-11] The ketones were prepared by reaction of cyclopropyl cyanide or cyclopropanecarboxylic acid chloride with the appropriate Grignard reagent.[12] In this manner, 1-cyclopropyl-1-ethanone was converted to **1b**, 1-cyclopropyl-1-propanone to **1c**, 1-cyclopropyl-1-butanone to **4d**, 1-cyclopropyl-1-pentanone to **1e**, 1-cyclopropyl-2-methyl-1-propanone to **1f**, and 1-cyclopropyl-2,2-dimethyl-1-propanone to **1g**. Alcohol **1a** was obtained by lithium aluminum hydride reduction of cyclopropanecarboxylic acid chloride. A summary of the preparation of 1 via the alkyl cyclopropyl ketones is presented in Table I.

As noted in our preliminary study, the conditions employed by Magid consisted of addition of triphenylphosphine to a solution of hexachloroacetone and the alcohol.[6] This technique, when applied to **1b**, afforded only 45% of a 3:2 mixture of **4b** and **2b**, respectively. The

(1) (a) Presented, in part, at the 13th Northeast Regional Meeting of the American Chemical Society, Hartford, CT, June 1983; ORGN 149 (Hrubiec, R. T.; Smith, M. B.). (b) Abstracted, in part, from the Ph.D. thesis of R.T.H.

(2) (a) McCormick, J. P.; Fitterman, A. S.; Barton, D. L. *J. Org. Chem.* **1981**, *46*, 4708. (b) McCormick, J. P.; Barton, D. L. *Ibid.* **1980**, *45*, 2566. (c) Julia, M.; Julia, S.; Guegan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072. (d) Hoffsommer, R. D.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1962**, *278* 4134. (e) Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 577. (f) Brady, S. F.; Ilton, M., Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882. (g) Johnson, W. S.; Li, T.; Faulkner, D. J.; Campbell, S. F. *Ibid.* **1968**, *90*, 6225. (h) Mori, K.; Ohki, M.; Sato, A.; Matsui, M. *Tetrahedron* **1972**, *28*, 3739. (i) Julia, M.; Paris, J.-M., *Tetrahedron Lett.* **1974**, 3445. (j) Santelli, C. *Ibid.* **1979**, 1165. (k) Corey, E. J.; Long, A. K. *J. Org. Chem.* **1978**, *43*, 2209.

(3) Bruce, W. F.; Mueller, G.; Seifter, J.; Grove, W.; Szabo, J. L. U.S. Patent 2 494 084; *Chem. Abstr.* **1951**, *45*, 177*d*.

(4) (a) Julia, M.; Mouzin, G.; Descoins, C. *C. R. Hebd. Seances Acad. Sci.* **1967**, *264*, 330. (b) Olah, G.; Jewell, C. L.; Kelly, D. P.; Porter, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 146. (c) Sneen, R. A.; Born, A. L. *Ibid.* **1961**, *83*, 614. (d) Conia, J. M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 578. (e) Servis, K. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *73*, 2509.

(5) Hrubiec, R. T.; Smith, M. B. *Synth. Commun.* **1983**, *13*, 593.

(6) (a) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J Org. Chem.* **1979**, *44*, 359. (b) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *Tetrahedron Lett.* **1977**, 2999.

(7) Kirmse, W.; Kapps, M.; Hager, R. B. *Chem. Ber.* **1966**, *99*, 2855.

(8) (a) Landgrebe, J. A.; Becker, L. W. *J. Am. Chem. Soc.* **1968**, *90*, 395. (b) Hanack, M.; Ensslin, H. M. *Justus Liebigs Ann. Chem.* **1968**, *713*, 49. (c) Julia, S.; Julia, M.; Brasseur, L. *Bull. Soc. Chim. Fr.* **1962**, 1634.

(9) (a) Norman, H. *C. R. Hebd. Seances Acad. Sci.* **1951**, *232*, 1358. (b) Julia, M.; Julia, S.; Yu, T. S. *Bull. Soc. Chim. Fr.* **1961**, 1849.

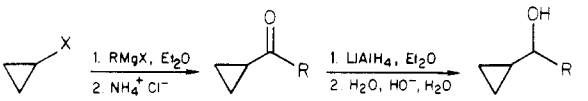
(10) Lillien, I.; Doughty, R. A. *J. Org. Chem.* **1968**, *33*, 3841.

(11) Pierre, J. L.; Perraud, R.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1969**, 1322.

(12) (a) Hanack, M.; Ensslin, H. M. *Justus Liebigs Ann. Chem.* **1966**, *100*, 697. (b) Hanack, M.; Bocher, S.; Herteirch, I.; Hummel, K.; Voetl, V. *Ibid.* **1970**, *733*, 5.

0022-3263/84/1949-0431$01.50/0

Table I. Preparation of Cyclopropylcarbinyl Alcohols 1

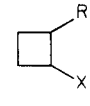


1

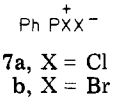
X	reflux time, h	R	% yield of ketone[a]	bp (mmHg), °C	% yield of 1[a]	bp (mmHg), °C
		CH_3[b]		114 (760)	72	121-122 (760) [lit.[8] 76 (67)]
CN	6	Et	68	53-54 (45) [lit.[12,20d] 131 (760)]	78	67-69 (45) [lit.[8,9] 75-77 (49)]
CN	6	*n*-Pr	73	64-66 (38) [lit.[12] 75-78 (50)]	76	78-80 (37) [lit.[8] 85 (20)]
CN	8	*n*-Bu	78	57-60 (11) [lit.[12] 66-67 (13)]	97	81-82 (37) [lit.[9] 155-157 (760)]
CN	13	*i*-Pr	71	57-59 (11) [lit.[20] 140-141 (760)]	86	72-73 (36) [lit.[10] 144 (760)]
COCl	22	*t*-Bu	35	68-75 (30) [lit.[20d,21] 147-149 (76)]	69	73-75 (33)

[a] Identification based upon satisfactory infrared and ^1H NMR analyses. [b] Commercially available.

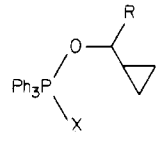
"reverse addition" technique which we reported consisted of slow addition of the alcohol to a slurry of hexachloroacetone and triphenylphosphine and gave **4** exclusively.[5] When we added alcohols **1a–g** to a slurry of hexachloroacetone and triphenylphosphine, we found that the corresponding 1-chloro-1-cyclopropylalkanes, **4a–g**, were isolated in 80–90% yield. We were gratified to find that **4a–g** were uncontaminated by the homoallylic chlorides **2a–g** or the 2-alkyl-1-chlorocyclobutanes **6a**. This confirmed the high regioselectivity of our technique for conversion of **1** to **4**, even with such remarkable steric impedance as exhibited by **1g**. In addition, we did not observe the elimintion products which Magid had noted in some allylic systems.[6]



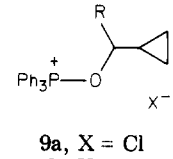
6a, X = Cl
b, X = Br



7a, X = Cl
b, X = Br



8a, X = Cl
b, X = Br
c, X = I



9a, X = Cl
b, X = Br
c, X = I

Our results are summarized in Table II. It is clear that the purity and yield of chloride **4** was essentially independent of the steric congestion about the hydroxyl-bearing carbon in **1**. An examination of the intermediates proposed for this reaction appears to explain this interesting result. As noted by Magid and others,[5,6] chlorotriphenylphosphonium chloride (**7a**), formed in situ, appears to be the species which reacts with the alcohol. Magid has also shown that intermediates such as **8a** or **9a** are formed in the reaction of **7a** with alcohols,[13] although it was not known which dominated the reaction. Our observations suggest that mild thermolysis of **8a**/**9a** is required to liberate the halide, **4**, and triphenylphosphine oxide since workup of the reaction mixture prior to distillation afforded only starting material, **1**. Magid has noted that allylic alcohols containing a chiral hydroxyl-bearing carbon are converted to the chloride with nearly quantitative inversion.[6] This result implies an S_N2-type displacement by chloride ion which is clearly impossible with such a sterically hindered system as **1g**. The facile reaction of **1g** and the independence of the intermediate to the steric bulk at the hydroxyl-bearing carbon suggests a thermal P → C transfer of chlorine from **8a**, via a concerted process or via **9a**, if **9a** is a tight ion pair. This has been previously suggested to explain the conversion of tertiary alcohols to chlorides with **7a**.[6]

We next turned our attention to the more labile bromides **5a–g**. In Kirmse's study, 1-cyclopropylmethanol (**1a**), upon treatment with bromotriphenylphosphonium bromide (**7b**) gave a mixture of 89% of **5a**, 9% of **6a** (R = H), and 2% of **3a**.[14] Our method had afforded a 66% yield of **5b**, however, with only 3% of **3b** and no 2-alkyl-1-bromocyclobutane (**6b**).[5] Likewise, treatment of a mixture of **1a** and triphenylphosphine, in dimethylformamide cooled to −10 °C, with bromine afforded 72% of **5a** with no trace of **3a** or **6b**. With our method, **7b** was formed in situ in the presence of the dimethylformamide solvent and the alcohol. This modification apparently suppressed formation of the side products noted by Kirmse. We found that **1a–g** were converted to the corresponding bromides **5a–g** in 65–80% yields as summarized in Table II. We also noted that workup of the mixture prior to flash distillation, as with the chlorides, gave back **1** unchanged.

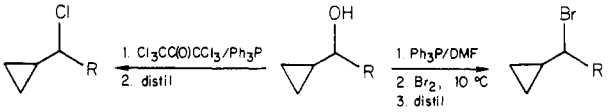
We have assumed the presence of a complex such as **8b** or **9b**, analogous to **8a** or **9a**, in which the bromine was transferred from phosphorous to carbon upon mild thermolysis without rearrangement of the cyclopropylcarbinyl substrate. We noted two important differences, however, when compared to the chloride reaction. Production of **5** from **1** proceeded with reduced regioselectivity and 3–8% of the homoallylic bromide, **3a–g**, was observed,[15] in contrast to the clean reactions observed with hexachloroacetone and triphenylphosphine. In addition, reaction of **1** with bromine exhibited a marked temperature dependence. When bromine was added to **1** at ambient temperatures, rather than at −10 °C, isomerization to **3** oc-

(13) (a) Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 810. (b) Appel, R.; Knoll, F.; Michel, W.; Morbach, W.; Wihler, W.-D.; Veltman, H. *Chem. Ber.* **1976**, *109*, 58. (c) Appel, R.; Wihler, H.-D. *Ibid.* **1976**, *109*, 3446. (d) Appel, R.; Veltmann, H. *Tetrahedron Lett.* **1977**, 399. (e) Appel, R.; Scholer, H. *Chem. Ber.* **1977**, *110*, 2382. (f) Appel, R.; Milker, R.; Ruppert, I. *Ibid.* **1977**, *110*, 2385. (g) Appel, R.; Morbach, W. *Synthesis* **1977**, 699. (h) Tömösközi, I.; Gruber, L.; Radics, L. *Tetrahedron Lett.* **1975**, 2473. (i) Castro, B.; Chapleur, Y.; Gross, B. *Ibid.* **1974**, 2313.

(14) Wiley, G. A. *J. Am. Chem. Soc.* **1964**, *86*, 964.

(15) The relatively constant amount of **3** formed, apparently independent of the steric hindrance in **1**, suggests that **3** is formed by thermal decomposition of **5** during distillation and not at the time of reaction with triphenylphosphine and bromine. This would suggest regioselectivity on a par with that noted for formation of chlorides **4** but suggests greater lability for the bromide, **5**.

Table II. Yields, Boiling Points, and Spectral Data of Cyclopropylcarbinyl Halides 4 and 5



4 1 5

halide	R	% yield[a]	bp (mmHg), °C	IR (neat, film)[b]	^{1}H NMR ($CDCl_3$),[c]
4a	H	87	86-88 (760) [lit.[7] 86-88 (760)]	3100, 3120, 3000-2880, 1500, 1375, 1030, 980, 925, 800	0.10-0.90 (m, 4 H), 0.95-1.68 (m, 1 H), 3.50 (d, J = 3.5 Hz, 2 H)
4b	Me	84	100-101.5 (760) [lit.[3-5] 100-102 (760)]	3100, 3000-2880, 1455, 1370, 1030, 920, 820	0.10-0.70 (m, 4 H), 0.70-1.85 (m, 1 H), 1.52 (d, J = 3.5 Hz, 3 H), 2.90-3.60 (m, 1 H)
4c	Et	85	55-56 (55)[d] [lit.[9a] 125-126 (760)]	3085, 3020, 3000-2860, 1460, 1380, 1020, 920, 830	0.10-0.70 (m, 4 H), 0.70-1.55 (m, 1 H), 1.10 (dist t, J = 3.0 (Hz, 3 H), 1.78 (dist q, J = 3.0 (Hz, 2 H), 2.82-3.30 (m, 1 H)
4d	n-Pr	87	79-81 (54)[d]	3085, 3020, 3000-2845, 1470, 1390, 1020, 935, 800	0.10-2.10 (complex m, 9 H), 0.83 (dist t, J = 3.0 Hz, 3 H), 2.82-3.30 (m, 1 H)
4e	n-Bu	93	108-110 (55)[d]	3100, 3020, 3000-2860, 1470, 1395, 1030, 995, 830	0.10-2.20 (complex m, 14 H), 2.90-3.45 (m, 1 H)
4f	i-Pr	79	72-73 (55)[d]	3100, 3025, 3000-3870, 1465, 1390, 1025, 940, 810	0.20-0.85 (m, 4 H), 0.85-1.55 (m, 1 H), 1.10 (d, J = 3.5 Hz, 6 H), 1.70-2.65 (m, 1 H), 2.85-3.20 (m, 1 H)
4g	t-Bu	80	77-79 (34)[d]	3100, 3020, 3000-2885, 1485, 1375, 1030, 980, 980, 835, 760, 730	0.20-1.25 (m, 5 H), 1.60 (s, 9 H), 3.00 (d, J = 4.5, 1 H)
5a	H	72	49-50 (84) [lit.[7] 109-110 (760)]	3100, 3020, 3000-2965, 1445, 1375, 1025, 965, 905, 835, 790	0.10-0.90 (m, 4 H), 0.95-1.68 (m, 1 H), 3.22 (d, J = 3.5, 2 H)
5b	Me	66[e]	58-60 (79) [lit.[3] 57-58 (70)]	3100, 3020, 3000-2880, 1370, 1025, 905, 790	0.10-1.80 (m, 4 H), 0.80-1.60 (m, 1 H), 1.65 (d, J = 3.5, 3 H), 2.98-3.65 (m, 1 H)
5c	Et	77[f]	51-52 (22)[d] [lit.[22] 151-153 (760)]	3080, 3010, 3000-2840, 1460, 1380, 1150, 1020, 905, 820, 790	0.15-1.65 (m, 5 H), 1.05 (dist t, J = 3.0, 3 H), 1.95 (dist q, J = 3.0, 2 H), 3.00-3.50 (m, 1 H)
5d	n-Pr	77[g]	67-68 (20)[d]	3090, 3010, 3000-2840, 1380, 1150, 1020, 935, 820	0.15-2.15 (complex m, 9 H), 0.82 (dist t, J = 3.0, 3 H), 3.10-3.65 (m, 1 H)
5e	n-Bu	73[h]	72-74 (11)[d]	3100, 3020, 3000-2870, 1470, 1395, 1030, 950, 820	0.15-2.20 (complex m, 14 H), 3.00-3.45 (m, 1 H)
5f	i-Pr	79[i]	62-64.5 (20)[d]	3100, 3025, 3000-2860, 1470, 1380, 1020, 950, 805	0.20-1.60 (m, 5 H), 1.05 (d, J = 3.5, 6 H), 1.65-2.30 (m, 1 H), 3.10-3.45 (m, 1 H)
5g	t-Bu	72[j]	73-73.2 (19)[d]	3100, 3020, 3000-2880, 1480, 1375, 1150, 1035, 980, 920, 830, 750, 690	0.20-1.30 (m, 5 H), 1.13 (s, 9 H), 3.28 (d, J = 4.5 Hz, 1 H)

[a] Isolated yields. [b] Reported in reciprocal centimeters. [c] Reported in δ values (parts per million downfield from tetramethylsilane); J values are reported in hertz. [d] Satisfactory elemental analysis obtained for this compound. [e] Plus 3% of **3c**. [f] Plus 6% of **3c**. [g] Plus 7% of **3d**. [h] Plus 5% of **3e**. [i] Plus 7% of **3f**. [j] Plus 2% of **3g**.

curred as the major process. Transfer of the bromine was independent of the steric impedance about the hydroxyl-bearing carbon, however, and we did not observe formation of the bromocyclobutane derivative **6b**. The reduced regioselectivity and thermal instability of the reaction of **1** with bromine clearly suggests that **8b/9b** are more labile than **8a/9a**. It is not clear if this increased lability is due to thermal instability or to increased concentration of halonium ion with bromine as compared to hexachloroacetone. In both cases, release of the cyclopropylcarbinyl cation from **8b** or **9b** would allow equilibration and the usual products of electrophilic reactions of **1**. The lack of **6b**, however, suggests a tight ion pair rather than a "free" cyclopropylcarbinyl cation. Once again, the facility of the conversion of **1g** to **5g** precludes a S_N2-type displacement by bromide in **9b**.

The relatively small amount of **3** could be easily removed in each case by fractional distillation and posed no problems in the isolation of pure **5** on preparative scales. It was noted that the more hindered bromides undergo thermal decomposition if heated too vigorously neat. Careful distillation in vacuo, however, afforded clean, stable products.

We have defined a preparative route to a very useful and heretofore inaccessible class of compounds. The lack of homoallylic and cyclobutyl contaminants in the cyclopropylcarbinyl halide products is evidence of the high regioselectivity of this reaction. This should be of great value to those studies requiring such halides in a high state of purity. 1-Cyclopropyl-1-haloalkanes containing virtually any alkyl substitutent at the halogen-bearing carbon can be easily prepared. This method also allows preparation of very sterically hindered halides such as **4f,g** and **5f,g** inaccessible by other methods, in a facile manner. Unfortunately, as we have previously noted,[5] this method is not conducive to the formation of the corresponding iodides, **11**. Although the cyclopropylcarbinyl iodide was observed in the reaction of **1** with iodine and triphenyl-

phosphine in dimethylformamide, the yield was low, and the major product was always the homoallylic iodide **10**. Presumably, this is due to isomerization or ionization of the initially formed complex **8c** or **9c**. We were unable to control this isomerization under a variety of conditions, rendering the method useless for the preparation of 1-cyclopropyl-1-iodoalkanes. The method is, however, facile and clean for the preparation of simple as well as sterically hindered cyclopropylcarbinyl chlorides and bromides.

Experimental Section

All ^{1}H NMR spectra were obtained with a Varian Associates EM-360 NMR spectrometer at 60 MHz with tetramethylsilane as an internal standard. Chemical shifts were recorded in δ units downfield from tetramethylsilane. The infrared spectra were recorded on a Perkin-Elmer IR-283 instrument. Analytical VPC was accomplished by using a Perkin-Elmer 3820-B gas chromatograph and VPC/MS analyses with a Hewlett-Packard HP-5987 instrument. The cyclopropyl methyl ketone, cyclopropylmethanol, cyclopropyl cyanide, cyclopropanecarbonyl chloride, triphenylphosphine, hexachloroacetone, and all alkyl halides were obtained from Aldrich Chemical Co. Diethyl ether was distilled from sodium/benzophenone or from lithium aluminum hydride. Microanalyses were performed by MicAnal, Tucson, AZ.

General Procedure for Preparation of Cyclopropyl Alkyl Ketones.[12a] In a typical procedure, magnesium turnings (130 mmol) were added to a flame-dried, three-necked, round-bottomed flask fitted with pressure-equalizing addition funnel, magnetic stirrer, and reflux condenser, followed by slow addition of a solution of dry ether and the appropriate alkyl halide (130 mmol). After formation of the Grignard reagent was complete, the slurry was cooled to ambient temperature and a solution of cyclopropyl cyanide (132 mmol) or cyclopropanecarbonyl chloride (132 mmol) in ether was added, dropwise, and the solution was refluxed for several hours. Hydrolysis with saturated aqueous ammonium chloride was followed by stirring at 25 °C for 20–24 h. The solution was decanted, the solids were washed with ether and dried ($MgSO_4$), and the solvents were removed under reduced pressure. The resultant cyclopropylalkyl ketones, summarized in Table I, were distilled through a 15-cm Vigreux column at reduced pressure.

General Procedure for Lithium Aluminum Hydride Reduction to Cyclopropylalkylcarbinols (1).[8-11] In a typical procedure, a slurry of lithium aluminum hydride (130 mmol) in anhydrous ether was treated, dropwise, with an ether solution of the cyclopropylalkyl ketone (78.8 mmol) at 0 °C. The resulting slurry was refluxed 1–3 h, cooled to 0 °C and treated, dropwise, with water, 15% NaOH, and water.[16] The solids were filtered and washed with ether, the solution was dried ($MgSO_4$), and the solvents were removed at reduced pressure. The alcohols **1**, summarized in Table I, were isolated by distillation through a 15-cm Vigreux column. Alcohol **1g** was purified by flash chromatography (silica gel, ether/pentane) prior to distillation.

General Procedure for the Preparation of 1-Chloro-1-cyclopropylalkanes (4). Hexachloroacetone was added to a round-bottomed-flask followed by triphenylphosphine. The resultant slurry was cooled to 15–20 °C (ice), and the appropriate alcohol **1** was added, dropwise, such that the temperature of the mixture was maintained below 20 °C. The slurry was then stirred at ambient temperatures for the indicated time, the contents of the flask were then flash distilled (in vacuo, 0.2 mmHg) into a 1-L round-bottomed flask chilled to −78 °C (acetone/CO_2), and all distillates below 35 °C were collected. The collected liquid was warmed slightly and distilled through a 15-cm Vigreux column to obtain the desired 1-chloro-1-cyclopropylalkane (**4**). The yield, boiling point, infrared, and ^{1}H NMR data for **4a–g** are shown in Table II.

1-Chloro-1-cyclopropylmethane (4a). A slurry of 24.4 g (92.2 mmol) of hexachloroacetone and 4.5 g (17.2 mmol) of triphenylphosphine, treated with 1.1 g (15.3 mmol) of **1a** and stirred for 3 h, afforded 1.2 g (13.3 mmol 87%) of **4a**.[7,17]

1-Chloro-1-cyclopropylethane (4b). A slurry of 52.3 g (197.5 mmol) of hexachloroacetone and 23.0 g (87.7 mmol) of triphenylphosphine, treated with 7.0 g (8.1 mmol) of **1b** and stirred for 45 min, afforded 7.0 g (6.7 mmol, 83%) of **4b**.[3,4]

1-Chloro-1-cyclopropylpropane (4c). A slurry of 24.4 g (92.2 mmol) of hexachloroacetone and 4.5 g (17.2 mmol) of triphenylphosphine, treated with 1.5 g (15 mmol) of **1c** and stirred for 3 h, afforded 1.5 g (12.7 mmol, 85%) of **4c**. Anal. Calcd for $C_6H_{11}Cl$: C, 60.76; H, 9.35; Cl, 29.89. Found: C, 61.01; H, 9.57; Cl, 29.56.

1-Chloro-1-cyclopropylbutane (4d). A slurry of 21.8 g (82.3 mmol) of hexachloroacetone and 4.0 g (15.3 mmol) of triphenylphosphine, treated with 1.5 g (13.1 mmol) of **1d** and stirred for 3 h, afforded 1.5 g (11.3 mmol, 86%) of **4d**. Anal. Calcd for $C_7H_{13}Cl$: C, 63.39; H, 9.88; Cl, 26.73. Found: C, 63.38; H, 10.11; Cl, 26.69.

1-Chloro-1-cyclopropylpentane (4e). A slurry of 34.9 g (131.8 mmol) of hexachloroacetone and 6.6 g (25.2 mmol) of triphenylphosphine, treated with 2.8 g (21.8 mmol) of **1e** and stirred for 2 h, afforded 3.0 g (20.5 mmol 94%) of **4e**. Anal. Calcd for $C_8H_{15}Cl$: C, 65.52; H, 10.31. Found: C, 65.62; H, 10.08.

1-Chloro-1-cyclopropyl-2-methylpropane (4f). A slurry of 34.9 g (131.8 mmol) of hexachloroacetone and 6.9 g (26.3 mmol) of triphenylphosphine, treated with 2.5 g (21.9 mmol) of **1f** and stirred for 3 h, afforded 2.3 g (17.3 mmol, 79%) of **4f**. Anal. Calcd for $C_7H_{13}Cl$: C, 63.39; H, 9.88; Cl, 26.73; mol wt 132.0707. Found: C, 63.82; H, 10.06; Cl, 26.62; mol wt 132.0704.

1-Chloro-1-cyclopropyl-2,2-dimethylpropane (4g). A slurry of 20.9 g (78.9 mmol) of hexachloroacetone and 3.3 g (12.6 mmol) of triphenylphosphine, treated with 1.5 g (11.7 mmol) of **1g** and stirred for 3 h, afforded 1.3 g (8.9 mmol, 76%) of **4g**. Anal. Calcd for $C_8H_{15}Cl$: C, 65.52; H, 10.31; Cl, 24.17. Found: C, 65.81; H, 10.56; Cl, 24.02.

General Procedure for the Preparation of 1-Bromo-1-cyclopropylalkanes (5). The appropriate alcohol **1** was added to a three-necked round-bottomed flask fitted with magnetic stirrer and pressure-equalizing addition funnel, containing triphenylphosphine in dimethylformamide (from BaO/KOH). The solution was stirred at 25 °C for 30 min and then cooled to −10 °C (ice/salt). Bromine was added, dropwise, such that the solution temperature was maintained between −5 and −10 °C. The solution was warmed slightly and flash distilled in vacuo (0.5 mmHg) into a 1-L round-bottomed flask chilled to −78 °C, and all the distillate below 50 °C was collected. The distillate was warmed slightly and poured into 0.15 L of ice-cold water to which 20 mL of saturated $NaHCO_3$ had been added. The bromide **5** settled to the bottom, was separated, dried ($CaCl_2$), and distilled through a 15-cm Vigreux column. Alternatively, the aqueous solution was extracted with pentane (3 × 50 mL), and dried ($CaCl_2$), the solvents were removed under reduced pressure, and **5** was distilled. The alkene content of the distillate was determined by VPC and ^{1}H NMR analyses and by comparison with authentic samples of **3**.[18] The yield, boiling point, infrared, and ^{1}H NMR data for **5a–g** are shown in Table II.

1-Bromo-1-cyclopropylmethane (5a). A solution of 27.7 g (105.6 mmol) of triphenylphosphine and 7.0 g (97.1 mmol) of **1a** in 0.125 L of DMF was treated with 15.8 g (98.9 mmol) of bromine and afforded 9.5 g (70.4 mmol, 73%) of **5a**.[7,17a,19]

(16) Fieser, L. F.; Fieser, M. A. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 584.

(17) (a) deMeijere, A.; Leuttke, W. *Chem. Ber.* **1966**, *99*, 2155. (b) Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 2149. (c) Walling, C.; Fredericks, P. S. *Ibid.* **1962**, *84*, 3326.

(18) The authentic homoallylic bromide, **3**, was obtained by reaction of **1** with 48% HBr and zinc bromide. Comparison and identification were made by VPC, VPC/MS, and ^{1}H NMR analyses, but isolation of the material from reaction of **1** was impossible due to the minute amounts present.

(19) Miller, B.; Lai, K. H. *J. Chem. Soc. D* **1971**, 334.

(20) (a) Hanack, M.; Bocher, S.; Inge, H.; Klaus, H.; Volker, V. *Justus Liebigs Ann. Chem.* **1970**, *733*, 5. (b) Van Wijnen, W. T.; Steinberg, H.; DeBoer, T. J. *Tetrahedron* **1972**, *28*, 5422. (c) Monti, S. A.; Ward, C. K. *Tetrahedron Lett.* **1971**, 697. (d) Bunce, S. C. *J. Am. Chem. Soc.* **1955**, *77*, 6616.

(21) (a) Van Wijnen, W. T.; Steinberg, H.; DeBoer, T., *J. Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 844. (b) Bravo, P.; Guadiamo, G.; Ticozzi, C.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1970**, *100*, 566.

(22) Braker, W.; Pribyl, E. J.; Loth, W. A. *J. Am. Chem. Soc.* **1947**, *69*, 866.

1-Bromo-1-cyclopropylethane (5b). A solution of 28.0 g (106.8 mmol) of triphenylphosphine and 8.6 g (99.8 mmol) of **1b** in 0.12 L of DMF was treated with 16.0 g (100.1 mmol) of bromine and afforded 9.8 g (65.8 mmol, 66%) of **5b**.[3,5]

The initial distillate contained 3% alkenes which we assume was 5-bromo-2-pentene (**3b**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropylpropane (5c). A solution of 11.4 g (43.5 mmol) of triphenylphosphine and 4.0 g (39.9 mmol) of **1c** in 50 mL of DMF was treated with 6.6 g (41.3 mmol) of bromine and afforded 5.0 g (30.7 mmol, 77%) of **5c**. Anal. Calcd for $C_6H_{11}Br$: C, 44.20; H, 6.80; Br, 49.01. Found: C, 44.38; H, 6.68; Br, 48.72.

The initial distillate contained 6% of alkenes which we assume was 1-bromo-3-hexene (**3c**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropylbutane (5d). A solution of 12.5 g (47.7 mmol) of triphenylphosphine and 5.0 g (43.8 mmol) of **1d** in 60 mL of DMF was treated with 7.2 g (45.1 mmol) of bromine and afforded 6.0 g (33.9 mmol 77%) of **5d**. Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40; Br, 45.12. Found: C, 47.80; H, 7.61; Br, 45.39.

The initial distillate contained 7% of alkenes which we assume was 1-bromo-3-heptene (**3d**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropylpentane (5e). A solution of 8.7 g (33.2 mmol) of triphenylphosphine and 4.0 g (31.2 mmol) of **1e** in 40 mL of DMF was treated with 5.0 g (31.3 mmol) of bromine and afforded 4.3 g (22.5 mmol, 72%) of **5e**. Anal. Calcd for $H_8H_{15}Br$: C, 50.28; H, 7.91; Br, 41.81. Found: C, 50.39; H, 7.94; Br, 41.52.

The initial distillate contained 5% of alkenes which we assume was 1-bromo-3-octene (**3e**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropyl-2-methylpropane (5f). A solution of 25.0 g (95.3 mmol) of triphenylphosphine and 10.1 g (88.4 mmol) of **1f** in 0.115 L of DMF was treated with 14.3 g (89.5 mmol) of bromine and afforded 12.3 g (69.5 mmol, 79%) of **5f**. Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40; Br, 45.12. Found: C, 47.32; H, 7.24; Br, 45.34.

The initial distillate contained 7% of alkenes which we assume was 1-bromo-5-methyl-3-hexene (**3f**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropyl-2,2-dimethylpropane (5g). A solution of 12.3 g (46.9 mmol) of triphenylphosphine and 5.5 g (42.9 mmol) of **1g** in 50 mL of DMF was treated with 7.1 g (44.4 mmol) of bromine and afforded 5.9 g (30.9 mmol, 72%) of **5g**. Anal. Calcd for $C_8H_{15}Br$: C, 50.28; H, 7.91; Br, 41.81; mol wt 190.0359. Found: C, 50.76; H, 8.05; Br, 40.74; mol wt 190.0351.

The initial distillate contained 2% of alkenes which we assume was 1-bromo-5,5-dimethyl-3-hexene (**3g**) by comparison with an authentic sample.[18]

Acknowledgment. We thank the Leo H. Baekeland Fund of the Research Corp. for funding of this work. We thank Gary Lavigne and Marvin Thompson, who performed the mass spectral analyses.

Registry No. **1a**, 2516-33-8; **1b**, 765-42-4; **1b** (ketone), 765-43-5; **1c**, 18729-46-9; **1c** (ketone), 6704-19-4; **1d**, 4426-61-3; **1d** (ketone), 6705-46-0; **1e**, 4379-16-2; **1e** (ketone), 14113-86-1; **1f**, 17393-35-0; **1f** (ketone), 6704-20-7; **1g**, 24382-76-1; **1g** (ketone), 20845-95-8; **4a**, 5911-08-0; **4b**, 10524-06-8; **4c**, 88106-23-4; **4d**, 88106-24-5; **4e**, 88106-25-6; **4f**, 88106-26-7; **4g**, 88106-27-8; **5a**, 7051-34-5; **5b**, 80204-20-2; **5c**, 88106-28-9; **5d**, 88106-29-0; **5e**, 88106-30-3; **5f**, 88106-31-4; **5g**, 88106-32-5; $Cl_3CCOCCl_3$, 116-16-5; Ph_3P, 603-35-0; Br_2, 7726-95-6; cyclopropyl cyanide, 5500-21-0; cyclopropanecarbonyl chloride, 4023-34-1.

Energetics of Carbonyl Addition and Elimination. Methoxide Ion with Esters[1]

Stephen C. Hoops, Joan van Oosterdiep, and Richard L. Schowen*

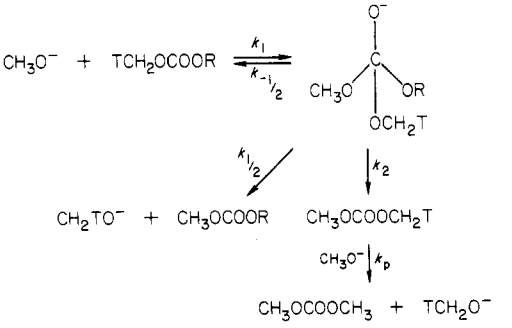
Department of Chemistry, University of Kansas, Lawrence, Kansas 66045-2112

Received July 19, 1983

Tritium-labeled methyl benzoates, $CH_2TO_2CC_6H_4X$, lose the labeled methoxyl group in methoxide-containing methanol with $\Delta H^* = 11$–16 kcal mol^{-1}, $\Delta S^* = -17$ to −25 eu, $\rho_p = -2.4$, and retardation by ortho substituents. The similar exchange of dimethyl carbonate gives $\Delta H^* = 11$ kcal mol^{-1}, $\Delta S^* = -26$ eu. (−)-Menthyl methyl carbonate undergoes relatively rapid exchange and slow conversion to dimethyl carbonate ($k_{-1}/k_2 = 16$ at 45 °C and 18 at 36 °C), with $\Delta H^* = 16$ kcal mol^{-1}, $\Delta S^* = -17$ eu, for addition of methoxide ion, $\Delta H^* = 19$ kcal mol^{-1}, $\Delta S^* = -15$ eu, for overall formation of the transition state for elimination of menthoxide ion. It is concluded that the dominant transition states are for bond formation and fission and that these are characterized by ΔH^* around 10–20 kcal mol^{-1}, ΔS^* around −15 to −30 eu.

The reaction of strong nucleophiles with carbonyl substrates to produce displacement of a leaving group commonly occurs in a two-step manner, in which formation of the nucleophilic bond results in a tetrahedral intermediate (addition step), and the leaving group is then expelled with return of the carbonyl group to its trigonal form (elimination step).[2] Isotope exchange has been a useful technique in elucidating the relative importance of these two processes in limiting the rate. Especially straightforward in this regard is the exchange of a labeled methoxyl group of carbonate esters in basic methanol solution,[3]

Scheme I



as in Scheme I. As opposed to ^{18}O exchange of carbonyl labeled esters in water, this system involves no ambiguities about the rapidity of proton switching among oxygens in the tetrahedral adduct. Thus it was possible to show that,

(1) This research was supported by the National Institutes of Health and the National Science Foundation.

(2) Guthrie, J. P. *Acc. Chem. Res.* **1983**, *16*, 122 and references cited therein.

(3) Mitton, C. G.; Schowen, R. L.; Gresser, M.; Shapley, J. *J. Am. Chem. Soc.* **1969**, *91*, 2036.

0022-3263/84/1949-0435$01.50/0