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The Chemistry of Cyclopropanols. II. Synthetic Methods[1-3]

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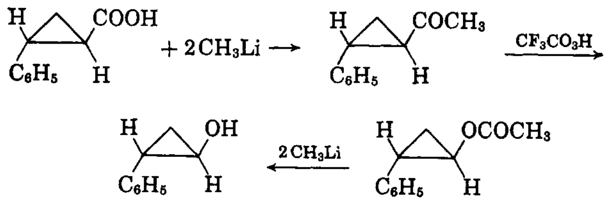
General methods are described for the synthesis of cyclopropanols. A wide variety of these alcohols may be prepared from substituted cyclopropane carboxylic acids by way of substituted cyclopropyl acetates. 1-Methylcyclopropanol may be obtained from 2-methylepichlorohydrin in a manner analogous to Cottle's original synthesis of cyclopropanol. Many 1-substituted cyclopropanols may be prepared by reaction of 1,3-dichloroacetone with Grignard reagents. The synthesis of 1-methylcyclopropanol in low yield from isopropenyl acetate is also reported.

Our interest in an investigation of the chemistry of cyclopropanols was aroused by the discovery that cyclopropanol itself could be prepared in reasonable yield by the hydrolysis or reduction of cyclopropyl acetate,[1] and that in pure form it could be kept for long periods of time without serious decomposition. In this paper we report several synthetic methods which we have developed for the preparation of alkyl- and aryl-substituted cyclopropanols which, together with methods which have been developed subsequently in other laboratories, make the synthesis of a variety of cyclopropanols a relatively routine matter and are allowing a systematic study of their chemistry to be carried out.

Synthesis from Cyclopropyl Acetates.—The most general method for the synthesis of cyclopropanols, particularly those of known stereochemistry, appears to be by way of their acetates, prepared in turn from an appropriately substituted cyclopropanecarboxylic acid. The synthesis of *trans*-2-phenylcyclopropanol is outlined in Chart I. Each step proceeds in approximately 75% yield and the final alcohol may be distilled and crystallized if due caution is exercised to prevent ring opening. Arylcyclopropanols are even more sensitive to base than cyclopropanol itself,[1] and great caution must be exercised in working up the final reaction to prevent conversion to aldehydes. Yields of pure alcohol were much lower when lithium aluminum hydride was used as the reducing agent in place of methyllithium.

CHART I



From Epichlorohydrins.—Concurrent with the investigation of the synthesis of cyclopropanols from the acetates we had been attempting to determine if the Cottle[5] procedure for the synthesis of cyclopropanol could be improved and generalized. In that method, epichlorohydrin is allowed to react with anhydrous magnesium bromide in ether; ferric chloride is added, and then ethyl Grignard reagent. Cyclopropanol prepared by this method may be purified by gas chromatography and while yields are low (20–30%) the simplicity of the procedure and the availability of starting materials make this the method of choice for the preparation of the parent alcohol.

From Cottle's original work and from subsequent work on the formation of cyclopropanes by ring closure with Grignard reagents and ferric ions,[6] the reaction sequence shown in Chart II seemed a reasonable one. Considering the number of possible side reactions, we were pleasantly surprised to discover that the reaction worked as well for the synthesis of 1- and 2-methylcyclopropanols as it did for cyclopropanol itself. In fact, 1-methylcyclopropanol was prepared in 36% yield from 2-methylepichlorohydrin, and a mixture of *cis*- and *trans*-2-methylcyclopropanol was obtained in 23% yield from 3-methylepichlorohydrin.

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[1] Part I: C. H. DePuy and L. R. Mahoney, *J. Am. Chem. Soc.*, **86**, 2653 (1964).

[2] This work was supported by a grant from the National Science Foundation. Preliminary reports of some of this work have appeared previously.[3]

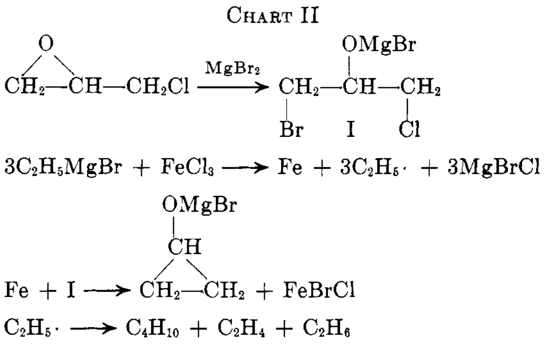
[3] (a) C. H. DePuy, L. R. Mahoney, and K. L. Eilers, *J. Org. Chem.*, **26**, 3616 (1961); (b) C. H. DePuy, R. A. Klein, and G. M. Dappen, *ibid.*, **27**, 3742 (1962).

[4] (a) Alfred Sloan Fellow, 1960-1964. (b) Ohio Oil Co. Fellow, 1960-1961; Procter and Gamble Summer Fellow, 1961. (c) Ohio Oil Co. Fellow, 1961-1962.

[5] (a) J. K. Magrane and D. L. Cottle, *J. Am. Chem. Soc.*, **64**, 484 (1942); (b) C. W. Stahl and D. L. Cottle, *ibid.*, **65**, 1782 (1943).

[6] M. S. Kharasch, M. Weiner, W. Nudenberg, A. Bhattacharya, T. Wang, and N. C. Yang, *ibid.*, **83**, 3232 (1961).

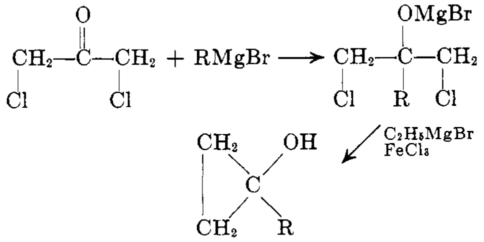
Chart II



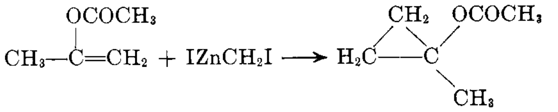
An attempt was made to extend the method to the synthesis of arylcyclopropanols. In the case of the methylcyclopropanols the requisite chloro olefins were commercially available but this was not the case for the aryl olefins, and their synthesis and epoxidation were tedious. Application of the Cottle procedure to these epoxides led to the isolation of small amounts of product which could be shown by n.m.r. to contain the desired 1- and 2-phenylcyclopropanols, but the length of the isolation procedure and the difficulty of preparing the starting epoxides makes this an unattractive route to these alcohols.

From Dichloroacetone.—The starting chloro epoxides for use in the Cottle procedure are usually difficult to prepare, and it is hypothesized that these are ring opened in the very first step of the reaction. We next turned our attention to another way of preparing these same, ring-opened intermediates. Addition of a Grignard reagent to commercially available 1,3-dichloroacetone (Chart III) should generate the magnesium salt of a 1,3-dichloro alcohol which, if our suggested reaction sequence is correct, would ring close to a 1-substituted cyclopropanol. In fact, using this method 1-arylcyclopropanols have been prepared in yields up to 55%. When an attempt was made to prepare 1-methylcyclopropanol by this same sequence the yield was only 29%. We believe that the lower yield in this case is due to the difficulty of isolating the relatively volatile alcohol from the large amount of ether.

Chart III



From Enol Acetates.—Cyclopropyl acetates could be prepared easily, at least in theory, by the addition of zinc iodomethylene to enol acetates. Simmons and Smith[7] obtained a 30% yield of cyclopropyl acetate from vinyl acetate, but in our hands substituted enol acetates gave only very small yields of substituted cyclopropyl acetates. As an example, isopropenyl acetate and zinc iodomethylene gave 1-methylcyclopropyl acetate in 2.5% yield. Further investigation of this method appears worthwhile since a number of interesting bi- and tricyclic cyclopropanols could be formed easily from these reagents.



Experimental

Ethyl *cis*- and *trans*-2-Phenylcyclopropanecarboxylate.—These esters were obtained by a modification of the procedure of Burger and Yost.[8] A mixture of styrene (167 g., 1.61 moles) and ethyl diazoacetate[9] (183 g., 1.61 moles), cooled to 0°, was added dropwise to styrene (83.5 g., 0.8 mole) heated at 150° under a nitrogen atmosphere. The reaction was exothermic and complete within 3 hr. The excess styrene was removed *in vacuo* and the residue was distilled to yield 242 g. (79% yield) of a mixture containing 65% *trans* and 35% *cis* esters, b.p. 79–92° (0.1 mm.), lit.[8a] b.p. 105–110° (1–2 mm.).

Distillation of the mixture of *cis* and *trans* esters through a spinning band column yielded fractions boiling between 65.5 and 95.5° (0.35–0.65 mm.). The pure *trans* isomer had b.p. 94–95.5° (0.65 mm.), m.p. 35–36° (from pentane); lit.[10] b.p. 105–106° (0.2 mm.), m.p. 38°. The ester had $n^{25}\text{D}$ 1.5191 (undercooled). The pure *cis* isomer could be obtained in good yield by redistillation through the spinning-band column of the lower boiling fractions. The pure *cis* isomer had b.p. 88.5–89° (0.7 mm.), $n^{25}\text{D}$ 1.5131.

***cis*-2-Phenylcyclopropanecarboxylic Acid.**—A mixture of the *cis* ester (35.0 g., 0.184 mole), sodium hydroxide (11.2 g., 0.28 mole), 120 ml. of ethanol, and 60 ml. of water was heated under reflux for 18 hr. The reaction mixture was cooled, diluted with ice, and acidified by slow addition of hydrochloric acid. The acid was collected and recrystallized from pentane to give the pure *cis* acid, 23 g. (77% yield), m.p. 106.5–107°, lit.[8a] m.p. 106–107°.

***trans*-2-Phenylcyclopropanecarboxylic Acid.**—This acid, prepared in an analogous way and recrystallized from water, had m.p. 90.5–91.5°, lit.[8a] m.p. 93.0°.

***trans*-2-Phenylcyclopropyl Methyl Ketone.**—Into a 5000-ml., round-bottom flask equipped with a reflux condenser and a mechanical stirrer was charged *trans*-2-phenylcyclopropanecarboxylic acid (189 g., 1.2 moles) and 200 ml. of anhydrous ether. Methyllithium in ether (approximately 2.5 moles), prepared from 400 g. (2.8 moles) of methyl iodide and 43 g. (6.1 g.-atoms) of lithium metal in 1500 ml. of anhydrous ether and filtered through a coarse glass-wool plug into an addition funnel, was added dropwise at such a rate so as to maintain steady reflux, suitable precautions being taken to vent the methane formed. When the addition was complete, saturated aqueous ammonium chloride was added dropwise with vigorous stirring to destroy any excess methyllithium. When two clear layers had formed, the ether layer was separated, washed with saturated ammonium chloride solution and twice with water, and dried over anhydrous magnesium sulfate. The ether was removed and the residue was distilled to yield 140 g. (75% yield) of *trans*-2-phenylcyclopropyl methyl ketone, b.p. 85–87° (0.25 mm.). A 2,4-dinitrophenylhydrazone was prepared with m.p. 137–138°.

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.98; H, 4.80; N, 16.61.

***trans*-2-Phenylcyclopropyl Acetate.**—Peroxytrifluoroacetic acid[11] from trifluoroacetic anhydride (460 g., 2.2 moles) and 90% hydrogen peroxide (57 ml., 2.2 moles) in 500 ml. of methylene chloride was added dropwise over a 2-hr. period to a stirred slurry of *trans*-2-phenylcyclopropyl methyl ketone (140 g., 0.88 mole), 600 g. (4.2 moles) of disodium hydrogen phosphate, and 500 ml. of methylene chloride in a 5-l., round-bottom flask. The reaction was moderated at reflux temperature by an ice bath. When addition was complete, the reaction was allowed to stir an additional 2 hr.; the solids were filtered, washed with methylene chloride,

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(7) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959).

(8) (a) A. Burger and W. L. Yost, *ibid.*, **70**, 2198 (1948); (b) E. Buchner and J. Geronimus, *Ber.*, **36**, 3782 (1903); (c) A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost, *J. Am. Chem. Soc.*, **71**, 3307 (1949).

(9) N. E. Searle, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 424.

(10) M. Julia, S. Julia, and B. Bemont, *Compt. rend.*, **245**, 2304 (1957).

(11) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

and discarded. The methylene chloride solution was washed with water, saturated aqueous sodium bicarbonate solution until free of acid, and again with water. The methylene chloride was removed by careful distillation and the residue was distilled to give 109 g. (77% yield) of *trans*-2-phenylcyclopropyl acetate, b.p. 84–85° (0.25 mm.).

trans-**2-Phenylcyclopropanol.**—2-Phenylcyclopropanols are extremely sensitive to basic solutions, and for best results the alcohol should be worked up, recrystallized, and stored in acid-washed glass or, preferably, polyethylene flasks. *trans*-2-Phenylcyclopropyl acetate (10.0 g., 0.057 mole) was dissolved in 50 ml. of anhydrous ether in a three-necked flask equipped with a magnetic stirrer, reflux condenser, and pressure-compensated dropping funnel. Methyllithium (180 ml. of 0.631 *M* solution, 0.11 mole) was added over a period of 0.5 hr.; the mixture was stirred an additional 0.5 hr. and then transferred to a dropping funnel. A large excess of boric acid was added to 200 ml. of water in a 500-ml. flask equipped with a stirrer and reflux condensor. With maximum stirring, the acetate reduction solution was added as rapidly as practical to the boric acid suspension. The solution was transferred to a separatory funnel along with enough water to dissolve the remaining boric acid, the aqueous layer was extracted twice with ether, and the ether extracts were washed with saturated salt solution and dried. The ether was removed, finally *in vacuo* at room temperature, and the residue was distilled to give 6 g. (79% yield) of *trans*-2-phenylcyclopropanol, b.p. 73–74° (0.25 mm.). Recrystallization from ether–pentane at low temperature gave pure alcohol, m.p. 41.5–42°.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56, H, 7.51. Found: C, 80.17; H, 7.67.

A *p*-toluenesulfonate, prepared in the usual manner and recrystallized from ether–pentane, had m.p. 62–63°.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.7; H, 5.61; S, 11.1. Found: C, 66.2; H, 5.7; S, 11.3.

Cyclopropanol.—Cyclopropanol was prepared by the procedure of Magrane and Cottle[5a] utilizing the modifications described by Stahl and Cottle[5b] and by Roberts and Chambers.[12] Magnesium bromide was prepared by the addition of bromine (48 g., 0.3 mole) to magnesium (7.2 g., 0.3 g.-atom) in 200 ml. of anhydrous ether in a three-necked flask equipped with a reflux condenser, stirrer, and addition funnel. Ferric chloride hexahydrate (0.3 g., 0.0012 mole) was added, and to this mixture was added, over a period of 30 min., epichlorohydrin (28 g., 0.3 mole) in 30 ml. of ether. Stirring was continued for 1 hr. and then ethyl Grignard [in 800 ml. of ether from 98 g. (0.9 mole) of ethyl bromide and 21.6 g. (0.9 g.-atoms) of magnesium metal] was added slowly over a period of 2 hr. Gas evolution was complete after an additional 2 hr., but stirring was continued overnight. The reaction mixture was hydrolyzed by pouring into an iced ammonium chloride solution and filtered, and the ether layer was separated and extracted with eight 100-ml. portions of water. The combined aqueous extracts were extracted continuously with ether for 2 days, the ether extract was dried, and most of the ether was removed by careful distillation through a 12-in. packed column. The residual cyclopropanol was purified by preparative g.p.c. on a 2 m. × 15 mm. column of 30% Ucon LB55OX on 60–80-mesh firebrick at 80° to give 5.9 g. (34% yield) of cyclopropanol, b.p. 101°, lit.[1] b.p. 100.5–101°.

1-Chloro-2-methyl-2,3-epoxypropane.—This epoxide was prepared by reaction of commercially available 3-chloro-2-methyl-1-propene with perbenzoic acid to give a 78% yield of epoxide, b.p. 75° (200 mm.), lit.[13] b.p. 46° (50 mm.).

1-Methylcyclopropanol.—This alcohol was prepared in 36% yield after g.p.c. separation by the same sequence as for cyclopropanol. It had b.p. 103.5°.

Anal. Calcd. for C_4H_8O: C, 66.67; H, 11.10. Found: C, 66.54, 66.62; H, 11.30, 11.20.

A *p*-toluenesulfonate, prepared in the usual way, was an oil at room temperature but could be purified by low-temperature crystallization from ether–pentane.

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.4; H, 6.2; S, 14.2. Found: C, 58.2; H, 6.2; S, 14.2.

1-*p*-Methylphenylcyclopropanol.—*p*-Methylphenylmagnesium bromide was prepared from *p*-bromotoluene (35 g., 0.216 mole) and magnesium metal (5.76 g., 0.216 g.-atom) in 200 ml. of anhydrous ether. Dichloroacetone (25 g., 0.2 mole) in 200 ml. of ether was added slowly, with stirring. Next a solution of ethylmagnesium bromide in 800 ml. of ether [from ethyl bromide, 129 g. (1.2 moles) and magnesium 30 g. (1.25 g.-atoms)] was added dropwise, simultaneously with the addition of anhydrous ferric chloride (2.5 g., 0.015 mole) in 200 ml. of ether. There was a copious evolution of gas during the addition, which required 2 hr. After stirring overnight the reaction mixture was poured onto a slurry of ice and 2 *M* hydrochloric acid saturated with ammonium chloride. The ether layer was separated and the water layer was extracted several times with fresh ether. The ether extracts were combined, dried, and removed by distillation. The residue was distilled to give 1-*p*-methylphenylcyclopropanol, 16 g. (55% yield), b.p. 70–80° (0.4 mm.). The product usually crystallized on distillation and was recrystallized from pentane to give pure alcohol, m.p. 39–40°.

A *p*-toluenesulfonate, prepared in the usual manner, had m.p. 87.5–88°.

1-Methylcyclopropanol.—This alcohol was obtained in an analogous manner from methylmagnesium iodide and dichloroacetone. In this case the alcohol could be purified by distillation through a 12-in. column packed with tantalum Helipak; the yield was 27%.

1-Methylcyclopropyl Acetate.—Zinc iodomethylene,[10] from methylene iodide (53 g., 0.2 mole) was prepared in 150 ml. of anhydrous ether, and isopropenyl acetate (40 g., 0.4 mole) was added. The mixture was heated under reflux for 60 hr. The reaction mixture was cooled and washed with 100 ml. of 5% ammonium chloride and 150 ml. of 1:1 ammonium hydroxide solution. After drying, the ether was removed by distillation and the residual liquid was distilled *in vacuo*. Gas chromatography on a Ucon LB550-X column gave 0.7 g. (2.5% yield) of 1-methylcyclopropyl acetate, b.p. 112.5–113°.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.10; H, 8.84. Found: C, 62.53; H, 9.10.

The ester was converted by reduction with lithium aluminum hydride into 1-methylcyclopropanol whose infrared and n.m.r. spectra were identical with those of an authentic sample.

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[12] J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 3176 (1951).

[13] Union Carbide and Carbon Corp., British Patent 735,974 (1956); *Chem. Abstr.*, **50**, 8730 (1956).