Improved Preparations of 3-Chloro-2-(chloromethyl)-1-propene and 1,1-Dibromo-2,2-bis(chloromethyl)cyclopropane: Intermediates in the Synthesis of [1.1.1]Propellane

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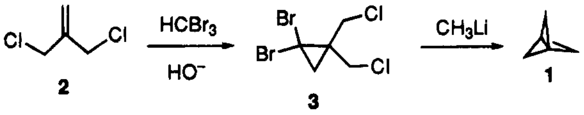
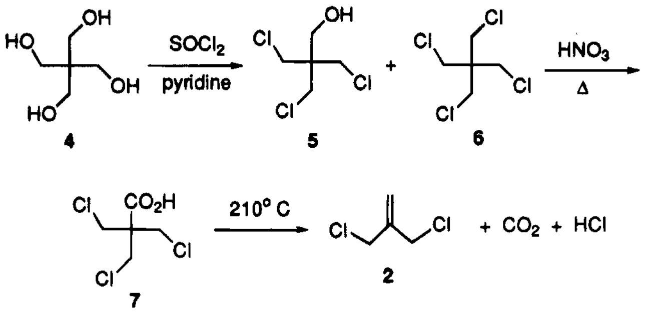
The remarkably direct Szeimies synthesis[1] of [1.1.1]-propellane (**1**) has allowed the investigation of many reactions of this compound on a preparative scale.[2] The Szeimies method involves addition of dibromocarbene to commercially available 3-chloro-2-(chloromethyl)-1-propene (**2**) followed by methyllithium induced ring closure of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (**3**).



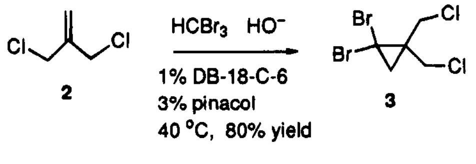
While this method is brief, yields for the dibromocarbene addition reaction are modest (30% of recrystallized material[2b]), and the workup is time-consuming due to emulsions. Additionally, 3-chloro-2-(chloromethyl)-1-propene is expensive.[3] Very recently, Della and Taylor[4] reported an improved procedure for the addition of dibromocarbene to 3-chloro-2-(chloromethyl)-1-propene. In our hands their new procedure provided a more convenient workup than previous ones,[1,2] but no significant increase in yield. We were unable to approach their reported yields (70%) even with several attempts on the same scale. This has prompted us to report our modified procedures that allow the preparation of large quantities of **2** and **3** in good yields.

The synthesis of 3-chloro-2-(chloromethyl)-1-propene (**2**) can be accomplished by the direct chlorination of methallyl chloride but the yields are low and purification involves a tedious spinning band distillation.[5] A much more satisfactory method is based on our modifications of two previously published procedures[6] and starts with pentaerythritol (**4**). Pentaerythritol is converted to a 2.8:1 mixture of trichloride **5** and tetrachloride **6** using 3.08 equiv each of pyridine and thionyl chloride. Without purification, the crude mixture of chlorides is oxidized with hot nitric acid. Unreacted tetrachloride **6** may be recovered unchanged from the oxidation while the trichloride **5** is converted to the carboxylic acid **7**. Heating the crude acid **7** to 210 °C allows for smooth decarboxylation and elimination of HCl and gives a virtually quantitative yield of pure alkene **2**.



Our modified procedure as compared with previous preparations[6] results in a safer, more convenient preparation of 3-chloro-2-(chloromethyl)-1-propene on a large scale from inexpensive materials. In the thionyl chloride/pyridine procedure, the ratio of reagents has been adjusted to allow for the formation of only pentaerythrityl tetrachloride (**6**) and trichlorohydrin (**5**); none of the dichlorinated product is produced. This provides an easier work up procedure; the product can be filtered rather than extracted, and the crude products are used in the nitric acid oxidation procedure, thereby avoiding a tedious distillation. The nitric acid oxidation procedure has been modified to make it much safer and more convenient. Previously, the authors noted that after the nitric acid was added in one portion and the mixture was heated, "a reaction became apparent, whereupon the flask was rapidly lowered into a waiting bath of cold water and the operator withdrew."[6a] The pyrolysis of acid **7** is a more detailed modification of a procedure reported[6b] as an improvement to the original method. Originally[6a] a large amount of quinoline was used to catalyze the conversion of 3-chloro-2,2-bis(chloromethyl)propanoic acid to 3-chloro-2-(chloromethyl)propene. It has since been reported[6b] that heating neat **7** to a higher temperature cleanly affords the final product **2**. The present procedure allows for the pyrolysis of the crude acid **7** obtained in the nitric acid oxidation reaction.

Optimization of the conditions for the dibromocarbene addition to alkene **2** required many trials. Finally a set of conditions were found that afforded high yields of **3** with easy workup. These conditions involve the combination of a catalytic amount of pinacol and dibenzo-18-crown-6 together with bromoform and 50% aqueous sodium hydroxide solution at 40 °C. In this way pure crystalline cyclopropane can be obtained in yields of up to 80%.



The cocatalytic effects of pinacol in the phase transfer catalysis of dihalocarbene additions to alkenes were noted by Dehmlow and co-workers who showed that pinacol accelerates the phase transfer deprotonation of substrates up to pK_a 27.[7] Dehmlow also studied the effects of various crown ethers as phase transfer catalysts in the

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(1) (a) Semmler, K.; Szeimies, G.; Belzner, J. *J. Am. Chem. Soc.* **1985**, *107*, 6410. (b) Belzner, J.; Bunz, U.; Semmler, K.; Szeimies, G.; Opitz, K.; Schlüter, A.-D. *Chem. Ber.* **1989**, *122*, 397.

(2) See, for instance: (a) Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2194. (b) Kaszynski, P.; Friedli, A. C.; Michl, J. *J. Am. Chem. Soc.* **1992**, *114*, 601.

(3) Available from Aldrich Chemical Co. at a current cost of $40 for 10 g.

(4) Della, E. W.; Taylor, D. K. *J. Org. Chem.* **1994**, *59*, 2986.

(5) Gragson, J. T.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Am. Chem. Soc.* **1953**, *75*, 3344.

(6) (a) Mooradian, A.; Cloke, J. *J. Am. Chem. Soc.* **1945**, *67*, 942. (b) Gafarov, A. N., Kharasova, T. S.; Nikol'skaya, V. F. *J. Org. Chem., USSR*, **1980**, *16*, 2173.

(7) Dehmlow, E. V.; Raths, H-C.; Soufi, J. *J. Chem. Res. (S)* **1988**, 334.

0022-3263/95/1960-4666$09.00/0

addition of dibromocarbene to allylic bromides.[8] In Dehmlow's study, elevated temperature (40 °C) and dibenzo-18-crown-6 did not give the highest ratio of addition/substitution with allyl bromide. However with 3-chloro-(2-chloromethyl)-1-propene, these were the optimal conditions that we found for dibromocarbene addition.

This preparation of 1,1-dibromo-2,2-bis(chloromethyl)-cyclopropane is a modification of the method reported by Szeimies and co-workers[1] and represents a significant improvement in both the convenience of the workup and the yield of the reaction. In the present method, dilution and filtration of the reaction mixture leave behind a mostly solid residue from which the product is easily obtained. Most significantly, the problematic emulsion which forms in the Szeimies method is effectively eliminated. In our hands, the recent modification reported by Della and Taylor,[4] while eliminating the emulsion problem, did not give a significantly better yield than the original Szeimies procedure. In contrast, the present procedure routinely produces 60–80% yields of pure crystalline **3**.

Experimental Section

3-Chloro-2,2-bis(chloromethyl)propan-1-ol (5). A 5-L, four-necked round-bottomed flask equipped with an efficient mechanical stirrer, addition funnel, thermometer adapter, and a condenser is charged with 417 g (3.00 mol) of pentaerythritol and 730 g (9.24 mol) of pyridine. With vigorous stirring 1134 g (9.24 mol) of thionyl chloride is added dropwise over the course of 4–5 h so that the temperature of the yellow-orange reaction mixture is maintained between 65–95 °C. When the addition is complete, the reaction mixture is heated overnight to 120–130 °C until no more sulfur dioxide is evolved. After gas evolution ceases, the flask is cooled slightly, and 2 L of cold water is added with stirring. The brown-yellow product precipitates, is filtered, and is washed with 2–3 L of water. The dried, crude product (461 g) is approximately a 1:2.8 mixture of pentaerythrityl tetrachloride and pentaerythrityl trichlorohydrin. This crude material is used directly in the next step.

Pentaerythrityl trichlorohydrin (**5**) may be separated from pentaerythrityl tetrachloride (**6**) by fractional distillation under reduced pressure. Pentaerythrityl tetrachloride is collected from 95–120 °C at 10–12 mmHg. It may be recrystallized from cyclohexane to yield small white crystals with mp 95–96 °C (lit.[6a] 97 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 8H). Pentaerythrityl trichlorohydrin is collected from 125–130 °C at 10–12 mmHg. It may be recrystallized from cyclohexane to obtain long, fine, white needles, mp 63–65 °C (lit.[6a] 65.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 2H), 3.66 (s, 6H), 2.0 (br, 1H).

3-Chloro-2,2-bis(chloromethyl)propanoic Acid (7). *(Caution: Nitrogen oxides are highly toxic. This procedure should be carried out in a well-ventilated hood!)* The crude mixture (461 g) of pentaerythrityl tetrachloride (**5**) and pentaerythrityl trichlorohydrin (**6**) obtained from the above reaction is transferred to a 3-L round-bottomed flask equipped with an efficient mechanical stirrer, reflux condenser, thermometer adapter, and addition funnel. The transfer is most easily accomplished by melting the solid over a steam bath and pouring the mixture through a funnel directly into the reaction flask. The flask and its contents are heated to 70–80 °C with a heating mantle, and a small portion (10–15 mL) of concentrated nitric acid (70%) is added with vigorous stirring to initiate the reaction. As the reaction begins, a large amount of dark orange-brown vapor appears. Stirring is continued, and the addition of nitric acid is resumed after the initial exothermic reaction subsides (usually within 15 min). The remaining nitric acid (660–680 mL) is added in 20–30 mL aliquots over 4–6 hours such that the nitrogen oxides are continually evolved but the reaction does not become violent. After the addition is completed, the reaction mixture is heated at 70–80 °C until the evolution of nitrogen oxides is no longer evident (12–24 h). The warm reaction mixture is poured into a 4-L beaker, and 2-L of cold water is added to precipitate the tetrachloride/carboxcylic acid product mixture. The beaker and its contents are allowed to stand for several hours at room temperature to ensure complete precipitation of the product, the crude product mixture is filtered and washed with water, and the carboxcylic acid is extracted as follows. The solid is pulverized and transferred to a 4 L beaker, and 2.5 L of 1 M NaOH is added with stirring. Stirring is continued for 30–60 min after which the insoluble material is filtered and washed well with water. The combined washings and yellow, aqueous filtrate are acidified to pH 1 with concentrated HCl (~250 mL). The carboxylic acid **7** precipitates as a white solid which is easily filtered and dried to yield a fine white powder (153 g, 43% yield). The aqueous filtrate is extracted with methylene chloride and the organic extracts are dried with magnesium sulfate and concentrated to provide an additional 50–60 g of the desired acid. The crude, combined product **7** (55% yield) may be used directly in the next step, mp 107–109 °C. Recrystallization from cyclohexane yields long needles, mp 109–111 °C (lit.[6a] 112.8–113° C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.87 (br 1H), 3.85 (s, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.5, 55.3, 42.7 ppm.

3-Chloro-2-(chloromethyl)-1-propene (2). Crude 3-chloro-2,2-bis(chloromethyl)propanoic acid (**7**) (205 g, 1.00 mol) from the previous procedure is transferred to a 500 mL, two necked round-bottomed flask along with a football magnetic stir bar (1.25 × 0.5 in.). A short path still head is attached, and the flask is immersed in a high temperature oil bath which has been preheated to a stable 210 °C. Moderate stirring is maintained throughout the reaction. Within 30–60 min, gas evolution becomes apparent, the reaction mixture turns brown and then black, and the product begins to distill. As the reaction proceeds, a black, tarry residue begins to build up on the bottom and sides of the flask. The product begins to distill, slowly at first and then quite steadily at which point the head temperature rises to 138 °C. The product **2** (115 g, 92% yield) thus obtained is a clear, colorless liquid (bp 136–138 °C) which is >92% pure by GC and ^{1}H NMR analysis. If desired, the product may be further purified by simple distillation which gives a sharp bp at 137–138 °C (lit.[6a] 138–138.3 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (s, 2H), 4.18 (s, 4H).

1,1-Dibromo-2,2-bis(chloromethyl)cyclopropane (3). Into a 1-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, and a condenser equipped with a potassium hydroxide drying tube, are placed 54.1 g (0.403 mol) of 3-chloro-2-(chloromethyl)-1-propene (**2**), 212 g (0.807 mol) of bromoform, 1.70–2.00 g (14.4 mmol) of pinacol, and 1.45 g (3.94 mmol) of dibenzo-18-crown-6. With very vigorous stirring, 312 g of a 50% aqueous sodium hydroxide solution which has been cooled to 15 °C is added in one portion. The reaction mixture turns orange, brown, and then black within 5 min, and the temperature of the reaction mixture begins to rise. Within 20 min, the internal reaction temperature is 49–50 °C at which point the reaction flask is cooled with a room temperature water bath, and the reaction temperature decreases to *ca.* 20 °C. After 1 h, the bath is removed and the reaction mixture is heated to 40 °C (internal temperature). The vigorously stirred mixture is maintained at this temperature for four days. The reaction mixture is cooled to room temperature, diluted with 500 mL of water, and filtered through a pad of Celite on a glass fritted funnel (pore size C), using a water aspirator. Up to an additional 1 L of water is used to rinse the thick black reaction mixture from the flask. The resulting golden-yellow filtrate is discarded. The black, solid residue in the frit, and any material remaining in the reaction flask are transferred to a 1-L beaker with pentane, acetone, and a glass rod, and the mixture is vigorously stirred with an additional 500 mL of a 1:1 (v/v) solution of acetone and pentane for 30 min. This mixture is filtered through a glass fritted funnel using a minimal layer of Celite. The Celite pad is washed thoroughly with 1:1 pentane/acetone solution, and the resulting brown filtrate is dried over magnesium sulfate. Concentration using

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(8) Dehmlow, E. V.; Wilkenloh, J. *Ann. Chem.* **1990**, 125.

a rotary evaporator, followed by distillation under vacuum (bp 75–85 °C/0.4 mmHg), and low temperature (*ca.* −20 °C) recrystallization from pentane (*ca.* 1 mL/g product) provides 95 g (80% yield based on 92% pure **2**) of the product **3** as small, white crystals, mp 47.5–50 °C (lit.[1b] 45–46 °C). Yields are consistently between 60 to 80%. Spectroscopic data matched those previously reported.[1b]

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Additions and Corrections

Vol. 59, 1994

Leo A. Paquette,* Timothy J. Watson, Dirk Friedrich, Roger Bishop, and Eric Bacque. Is Through-Bond Dihomoaromaticity Attainable? Preparation of [4,5]Dihomotropone, Investigation of Its Ground-State Properties, and an Attempt To Generate the Dihomotropylium Cation.

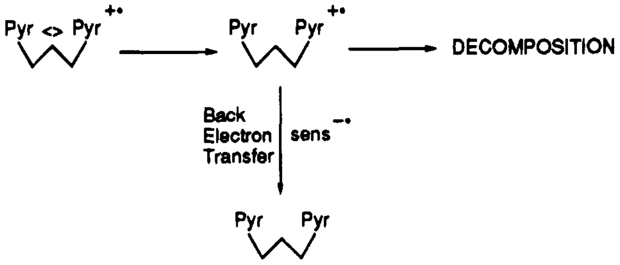
Page 5700 The word *dihydro*aromaticity in the title should read *dihomo*aromaticity.

JO954006W

Vol. 60, 1995

David J. Fenick, Heather S. Carr, and Daniel E. Falvey*. Synthesis and Photochemical Cleavage of Cis-Syn Pyrimidine Cyclobutane Dimer Analogs.

Page 629, column 2, Scheme 6 should be as shown below.



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