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SELECTIVE INTRODUCTION OF HYDROGEN ISOTOPES BY ELECTROLYTIC REDUCTION OF THE CARBON-HALOGEN BOND

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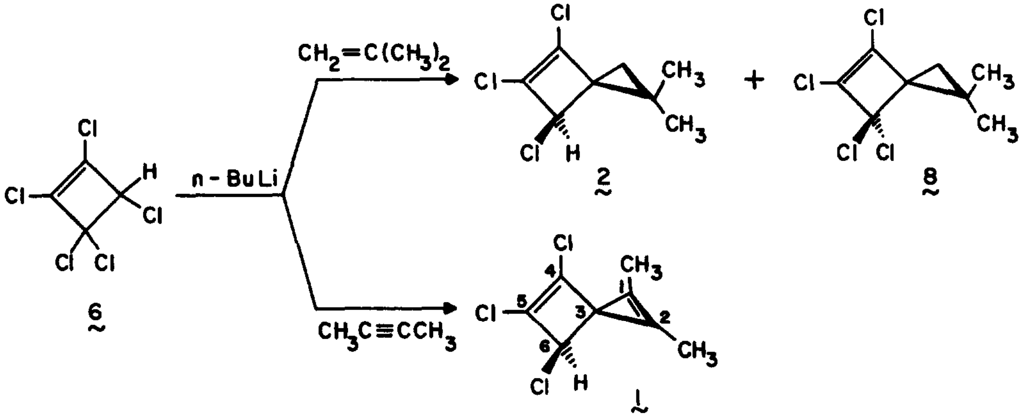
In a report appearing elsewhere,(1) our preliminary results on the kinetic acidity of the spiro[2.3]-hexadienes are detailed. These studies required a method of preparation of the spirocycles 1-5 with the proton at C-6 enriched with tritium. We have found electrolytic reduction at controlled potential in the presence of tritium-enriched water to be the method of choice.

Direct synthesis of the unlabeled trichloro derivatives 1 and 2 is possible by reaction of 3-H-pentachlorocyclobutene (6) with n-butyllithium in the presence of isobutylene or 2-butyne. The n-butyllithium, reacting with 6 predominantly via halogen-metal exchange instead of by proton abstraction, produces 1,2-dimethyl-4,5,6-trichlorospiro[2.3]hexadiene(2,3) (1) from 2-butyne in ca. 35% crude yield; preparative gas chromatography affords 1 in high purity but with considerable loss due to thermal decomposition. With isobutylene, the major product is 1,1-dimethyl-4,5,6-trichlorospiro[2.3]hex-4-ene(2) (2, 45% yield), accompanied by 5% of 1,1-dimethyl-4,5,6,6-tetrachlorospiro[2.3]hex-4-ene(5) (8). However, this method was not employed on a large scale for two reasons: (1) the product mixtures are complex and require tedious isolation procedures which are not efficient considering the thermal lability of spirodiene 1 and, to a lesser extent, the spiroenes 2-5; (2) attempts to introduce tritium into compounds 1-5 by heterogeneous base-catalyzed exchange using sodium hydroxide in tritium-enriched water/dimethylsulfoxide mixtures at 25° results in low incorporation of tritium and significant thermal decomposition of the spirocycles. It is clear that tritium must be introduced using a rapid reaction under mild conditions, and with simple isolation techniques.

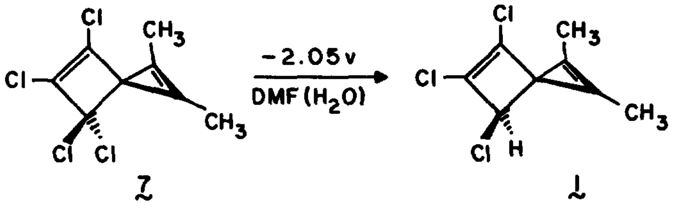


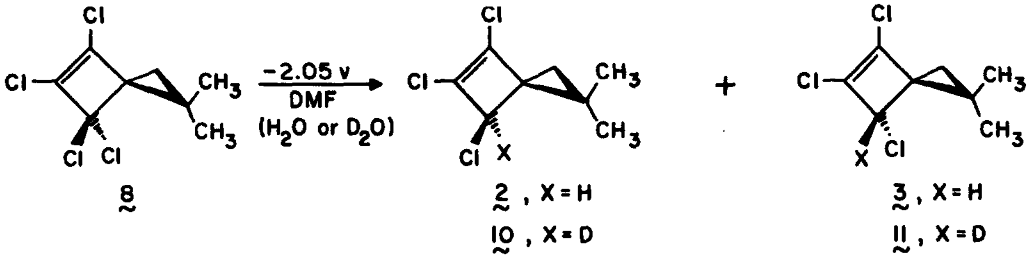
Attractive starting materials are the easily available$^{(5)}$ spirocycles 7-9 which would give the desired compounds if the allylic chlorine at C-6 is replaced by hydrogen (tritium). Preliminary experiments using tri-*n*-butyltin hydride$^{(6)}$ and lithium aluminum hydride did not lead to selective reduction of one allylic chlorine. However, electrolytic reduction, a technique observed to effect selective reduction of one halogen in polyhalogen compounds,$^{(7)}$ was much more promising, as polarographic studies indicated half-wave potentials for the spirocycles 7-9 lay in the easily accessible range -1.58 to -1.70 v *vs* the saturated calomel electrode.$^{(1)}$

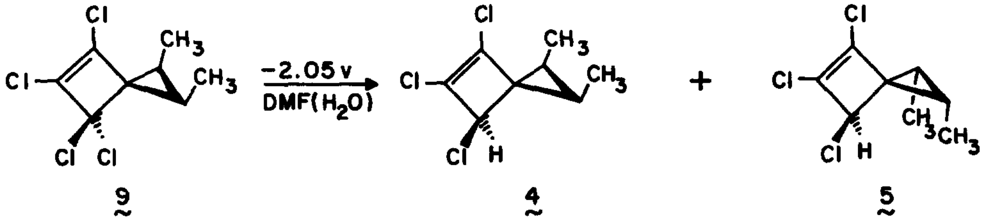
A typical preparative electrolysis is carried out with a Wenking Model 68-FR-0.5 potentiostat in a water-jacketed three-compartment cell. The working electrode is a stirred mercury pool, the counter electrode is a platinum wire, and the reference electrode is a saturated calomel electrode making contact with the electrolyte through a capillary opening. The reference and counter electrode compartments are each isolated from the working electrode compartment via a fritted glass disc (coarse). With the three compartments filled to equal height with the electrolyte solution (0.2 M lithium perchlorate in dimethylformamide), the tetrachlorospirocycle (*eg.*, 7, 3-5 mmoles) is added to the working electrode compartment, and argon is bubbled through the solution for 10-15 min to remove oxygen. Then the potentiostat is engaged to maintain the potential between the reference and working electrode at 2.05 ± 0.01 v. The initial current of 150-200 ma decreases over 2-3 hr, reaching a constant background current of 5-10 ma. The contents of the working electrode compartment are diluted with water and washed repeatedly with pentane. The combined pentane washes are washed with water, dried, concentrated at aspirator pressure and finally distilled in a short path apparatus at 25°/0.01 torr to afford the desired trichlorospirocycle (*eg.*, 1) in 87% yield and > 95% purity. The source of the proton is apparently adventitious water in the dimethylformamide as evidenced by the isotopic labeling experiments described below.

By this method, reduction of 8 produces equal amounts of epimers 2 and 3, in 95% combined yield. The stereochemical assignment is based on H^1nmr double resonance studies of the pure isomers$^{(1)}$ obtained by preparative gas chromatography. Irradiation at the methyl proton resonance frequency (1.33 δ) for 3 causes an 18% enhancement in the area of the signal from the proton at C-6 (4.72 δ), due to an internal nuclear Overhauser effect, thus indicating that the proton at C-6 is on the average *ca.* 2.9 Å from a methyl group.$^{(8)}$ No internal nuclear Overhauser effect could be detected in the other epimer, 2; therefore, the C-6 proton is a greater distance from the methyl groups. In the same way, reduction of 9 affords a mixture of 4 and 5 in a ratio of 3:1, respectively, but separation of the isomers has not yet been achieved. The H^1nmr and ir spectral data from the mixture are in complete accord with the proposed structures; quantitative estimation of the amounts of the two isomers is obtained by integration of the H^1nmr signals for the C-6 proton (4.55δ for 4 and 4.80δ for 5).

Addition to the electrolysis mixture of small amounts (6-8 mmoles) of water enriched in a heavy isotope of hydrogen leads to the trichlorospirocycles 1-5 with the heavy isotope incorporated efficiently at C-6. For example, addition of 100% excess (6 mmoles) of deuterium oxide to the dimethylformamide/-lithium perchlorate mixture during electroreduction of 8 (3.0 mmoles) produces a mixture containing 60%







10 and 40% 11 in 88% yield and 98% isotopic purity at C-6. Similarly, in the presence of 150 µl of tritium-enriched water (100 mc/ml), electrolysis of 7 (3.0 mmoles) affords 1 in 88% yield with activity of $>10^6$ cpm/mg. In this way, tritium-enriched samples of spirocycles 1-5 were prepared in high yield, high purity, and high specific activity.

This method of introduction of hydrogen isotopes should have wide applicability because many types of carbon-halogen bonds are electroreducible.(9) It has a unique combination of advantages: it employs the most convenient source of the isotopes, proceeds selectively at the most easily reduced halogen, requires only a small excess of the labeled water, and proceeds in essentially aprotic neutral media at 25°. The scope of this technique, especially as a simple means of introducing three isotopes of hydrogen at one carbon atom, is currently under study.

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(2) The H^1 nmr, ir, and mass spectral data for this compound are in complete accord with the proposed structure. The composition has been verified by high resolution mass spectrometry (AEI-MS-902).

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