Deuterium Incorporation *via* Zinc-Copper Couple Reductions of Halides

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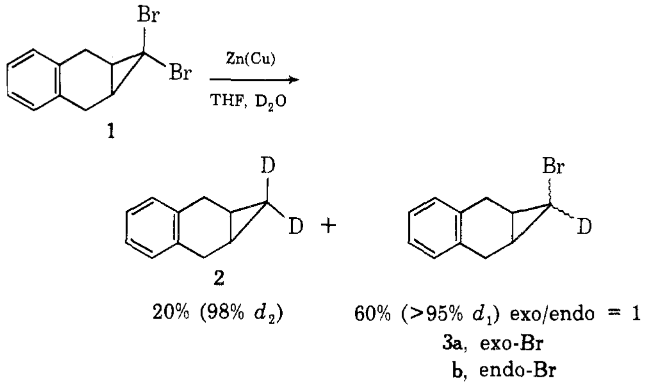
The need for a convenient, economical method for preparing various deuterium-labeled compounds in high isotopic purity for our photochemical studies prompted us to explore the zinc-copper couple reduction of appropriate halides.[2] We wish to note here the experimental details for a convenient introduction of deuterium into dibromocyclopropanes and α,α-dichlorocyclobutanones. The success of this method coupled with its potential general usefulness prompts this report.

We originally desired to prepare monodeuteriocyclopropane derivatives *via* monodeuteriobromocyclopropanes. While numerous reducing agents have been employed in converting dibromocyclopropanes to monobromocyclopropanes, tri-*n*-butyltin hydride,[3] methylsulfinyl carbanion,[4] Grignard reagent,[5] chromium sulfate,[6] sodium or lithium in alcohol,[7] alkyllithiums,[8] lithium aluminum hydride,[9] zinc,[10] catalytic hydrogenation,[11] and electrochemical reduction,[12] none of these constitutes a convenient, general method of obtaining high isotopic purity monodeuteriobromocyclopropanes. In those cases where high isotopic purity would be expected, the reagents and/or solvents used in the procedure would be expensive.[13]

We have found that freshly prepared zinc-copper couple in dry ether solvents with heavy water as the deuterium source effects clean reduction of dibromocyclopropanes 1 and 4 to their monobromo derivatives. In each case a minor yield of hydrocarbon was obtained. Since reduction of the monobromocyclopropane 3 does not occur at a moderate rate compared to that of 1 under these conditions, it appears that the hydrocarbon 2 (and presumably 5) does not arise from overreduction of the initial bromocyclopropane 3. The mild conditions employed for these reductions suggest their general utility for reaction with functionalized dibromocyclopropanes.



1

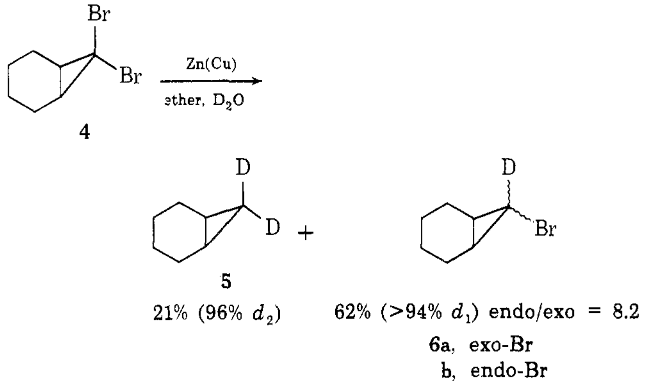
2

20% (98% d_2)

60% (>95% d_1) exo/endo = 1

3a, exo-Br

b, endo-Br



4

5

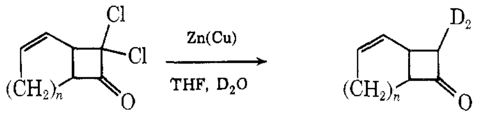
21% (96% d_2)

62% (>94% d_1) endo/exo = 8.2

6a, exo-Br

b, endo-Br

In a second system studied, dichloroketene adducts 7 and 8 underwent clean reductions to the corresponding cyclobutanones 9 and 10 in good yield and with a high degree of deuterium incorporation. Thus, here too, this method serves as an excellent alternative to tri-*n*-butyltin hydride[14a] or zinc-acetic acid reduction.[14b] Finally the recent report on β-chlorovinyl ketone reductions with zinc-silver couple prompted a brief examination of the reduction with zinc-copper couple.[15] Here reduction of 3-chloro-5,5-dimethylcyclohex-2-enone (11) produced 12 in 75% yield (greater than 98% vpc purity). Thus, in this instance the zinc-copper couple may serve as a convenient alternative to the zinc-silver couple.

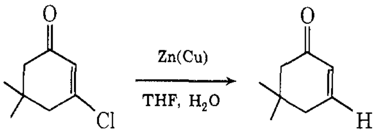


7, $n = 2$

8, $n = 1$

9, $n = 2$ 80% (>94% d_2

10, $n = 1$ 72% (>95% d_2)



11

12

In summary, zinc-copper reductions of appropriate halocarbons serve not only as an excellent procedure for introducing deuterium into organic substrates, but also as an alternative to the more commonly employed reducing reagents for halides.

Experimental Section

General. All compounds except 1 were prepared by literature procedures. Deuterium analyses were performed by nmr integration, as important P − 1 peaks in the mass spectra of the compounds prevented mass spectral deuterium assay. Work-up as usual refers to washing the organic phase with saturated ammonium chloride and saturated brine solution, drying over Drierite, and fractionation of the solvent. Structure assignments were made by spectroscopic (ir and nmr) comparison with the relevant data in the literature. All vpc analyses were performed on a Varian 1200 flame ionization gas chromatograph using a 5 ft × 0.125 in. column of 3% SE-30 on 100/120 Varaport 30.

Reduction of 7,7-Dibromo-3,4-benzobicyclo[4.1.0]heptane (1). To a stirred, heated solution (*ca.* 110°) of 200 ml of glacial acetic acid and 4 g of cupric acetate in a 1-l. erlenmeyer was added 40 g of zinc powder rapidly. The mixture was swirled for an additional 1 min and then filtered hot. The resulting couple was washed with acetic acid (2 × 50 ml) and anhydrous ether (2 × 50 ml) and heated under vacuum (120°, 1 mm) for 1 hr. After cooling, 250 ml of tetrahydrofuran was distilled from LiAlH$_4$ directly onto the couple. This mixture was magnetically stirred while 25 g (0.08 mol) of 1 and 20 ml of deuterium oxide were added rapidly. After the initial strongly exothermic reaction, the mixture was allowed to stir overnight. The reaction mixture was filtered through Celite, the filtrate was concentrated *in vacuo*, and the residue was extracted with ether (3 × 100 ml) and then worked up as usual. Distillation of this material through a 10-cm Vigreux column afforded first 2.4 g (20%) of 2 which solidified on standing, mp 30-33° (lit.[16] mp 31-33°), followed by the endo-exo epimers of 3, bp 110-130° (1 mm), 11.2 g (60%). The nmr spectra of the individual epimers were obtained from vpc isolation of the individual isomers from the distillate in a run using ordinary water. The exo-endo configuration was assigned from the magnitude of the cyclopropane hydrogen coupling constants.

The exo isomer **3a** showed nmr (100 MHz) τ 3.2 (m, 4 H), 6.88-7.15 (multiplet surrounding singlet at τ 7.0, 4 H), 7.52 (t, $J \cong 2.0$ Hz, 1 H), and 8.33 (br s, 2 H).

The endo isomer **3b** showed nmr (100 MHz) τ 3.2 (m, 4 H), 6.72 (t, $J = 7.2$ Hz, 1 H), 7.0 (center of a structural AB system, $J = 16$

Hz, 2 H), 7.52 (center of AB system, J = 16 Hz, 2 H), and 8.6 (br s, 2 H).

Analysis of the distilled mixture gave the following results.

Anal. Calcd for $C_{11}H_{11}Br$: C, 59.2; H, 4.93. Found: C, 59.6; H, 5.09.

Reduction of 7,7-Dibromobicyclo[4.1.0]heptane (4). In a manner analogous to the above, 15 g of zinc-copper couple, 10 g (0.04 mol) of **4**, and 5 ml of deuterium oxide in 200 ml of dry ether were stirred at room temperature for 24 hr. The solution was filtered through Celite, and the filtrate was worked up as usual. After distillation of the ether, the residue was vacuum fractionated to yield 0.70 g (18.5%) of **5**, bp 67-68° (110 mm) [lit.[17] bp 110° (760 mm)], and 4.20 g (62%), bp 83-86° (10 mm) [lit.[3] bp 96-99° (36 mm)], of an endo-exo mixture of **6a** and **6b**. Vpc analysis showed an endo/exo ratio of 8.2.

Reduction of 7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one (8). To 20 g of zinc-copper couple as prepared above in 80 ml of anhydrous tetrahydrofuran was added 4 g (0.023 mol) of **8** and 5 ml of deuterium oxide. The reaction mixture was stirred at 65° for 6 hr, filtered through Celite, and then diluted with 300 ml of water. The aqueous phase was extracted with pentane (6 × 75 ml) and the combined pentane extracts were worked up in the usual manner. Vacuum distillation yielded 1.8 g (72%) of **10**, bp 69-70° (30 mm) [lit.[14a] bp 62° (20 mm)]. Vpc analysis indicated >99% purity and nmr integration indicated a minimum of 95% dideuteration.

Reduction of 8,8-Dichlorobicyclo[4.2.0]oct-2-en-7-one (7). In a procedure analogous to the above, 12 g of zinc-copper couple, 95 ml of tetrahydrofuran, 2.07 g (0.01 mol) of **7**, and 5 ml of deuterium oxide were heated for 6 hr at 70°. Work-up as above followed by molecular distillation afforded 1.07 g (80%) of **9**, bp 64-65° (15 mm) [lit.[14a] bp 69-78° (5 mm)], homogeneous by vpc.

Reduction of 3-Chloro-5,5-dimethylcyclohex-2-enone (11). To a magnetically stirred solution of 4 g (0.025 mol) of **11** in 75 ml of tetrahydrofuran and 50 ml of ethyl ether was added 8 g of zinc-copper couple. The reaction mixture was stirred at room temperature for 6 hr and then filtered through Celite. The filtrate was poured into 200 ml of water followed by extraction with ether (4 × 100 ml). The combined ether layers were then worked up as usual. After distillation of the solvent, vacuum distillation yielded 2.2 g (75%) of 5,5-dimethylcyclohex-2-enone (**12**), bp 96-98° (34 mm) [lit.[18] bp 88° (32 mm)].

Preparation of 7,7-Dibromo-3,4-benzobicyclo[4.1.0]heptane (1). To a stirred mixture of 25.4 g (0.27 mol) of freshly prepared potassium *tert*-butoxide and 57 g (0.44 mol) of 1,4-dihydronaphthalene at 5-10° was added 58 g (0.23 mol) of bromoform dropwise over a period of 1 hr. The reaction mixture was then stirred at room temperature for 0.5 hr, 200 ml of water was added, and the solution was extracted with ether (3 × 100 ml). The combined ether extract was washed in 5% hydrochloric acid (100 ml) and then worked up as usual, yielding a red oil. The unreacted 1,4-dihydronaphthalene was distilled off and the product was collected as a yellow oil which solidified on standing, bp 104-110° (20 mm). Crystallization of this material from hexane yielded in several crops 36 g (52%) of **1** as a white, crystalline solid: mp 65-67°; ir (KBr) 6.58 (m), 6.89 (w), 7.02 (m), 7.69 (w), 9.63 (m), 10.52 (w), 11.02 (m), 13.28 (s), and 14.04 μ (s); nmr (CCl_4) τ 3.0 (s, 4 H), A_2B_2 centered at 7.1 with lower field component showing addition coupling (4 H), and 7.96 (m, 2 H).

Anal. Calcd for $C_{11}H_{10}Br_2$: C, 43.7; H, 3.31. Found: C, 43.9; H, 3.4.

Registry No.—1, 40467-32-1; **3a,** 51593-45-4; **3b,** 51703-88-9; **4,** 2415-79-4; **5,** 51592-70-2; **6a,** 51593-46-5; **6b,** 51593-47-6; **7,** 51592-71-3; **8,** 5307-99-3; **9,** 51592-72-4; **10,** 51592-73-5; **11,** 17530-69-7; **12,** 4694-17-1; 1,4-dihydronaphthalene, 612-17-9; bromoform, 75-25-2.

References and Notes

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(13) One possible exception to this is the use of *n*-butyllithium followed by quenching with heavy water. While this procedure has been utilized, no deuterium-incorporation data were given.[8b,c]

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Alternate Positions of Metalation of 1,2-Dimethylimidazole with Butyllithium

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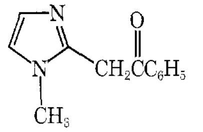
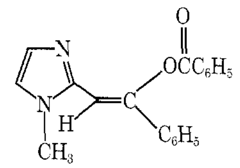
In conjunction with our studies of the preparation and solvolysis of imidazolylethanol derivatives,[1] the report by Tertov, Burykin, and Sadekov[2] that 1,2-dimethylimidazole (**1**) was metalated in the 5 position drew our interest. In our hands the course of the reaction is substantially different and more complex than indicated by the Russian authors. A recent report[3] of the reaction of 1,2-dimethylimidazole with benzoyl chloride to give rise to lateral substitution products (**2a, 2b**) prompts a report of our results at this time.

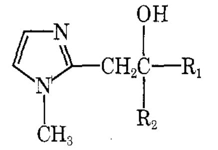


2a

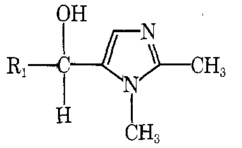


2b

At −80°, metalation of **1** proceeds slowly. The lithio derivative which is formed by addition of butyllithium to 1,2-dimethylimidazole reacts with benzaldehyde to give 1-phenyl-2-(1-methyl-2-imidazolyl)ethanol (**3**) in 28% yield, and not 1,2-dimethyl-α-phenylimidazole-5-methanol (**4**). Improved yields of **3** result at higher temperatures. When metalation is carried out in a normal fashion (addition of **1** to butyllithium at −15°) a mixture of **3** and **4** results, but in our hands the predominant product is **3**, not **4**, as reported by Tertov, *et al.*[2]



3, $R_1 = C_6H_5$; $R_2 = H$
5, $R_1 = CH_3$; $R_2 = H$
6, $R_1 = C_6H_5$; $R_2 = CH_3$



4, $R_1 = C_6H_5$

Results obtained under other experimental conditions are summarized in Table I.

We also prepared **5** and **6**. Using both normal and inverse conditions for the metalation of **1**, reaction of acetal-