Notes

Reduction as a Side Reaction Arising from the Thermal Decomposition of Lithium Organocuprates to Form Copper Hydride Derivatives[1]

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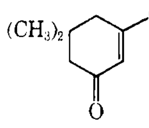
Earlier studies of the thermal decomposition of alkylcopper(I) derivatives[2] have indicated that, when possible, alkylcopper compounds 1 decompose by elimination of a copper hydride derivative 2 that may reduce an additional molar equivalent of the alkylcopper compound 1 to form copper(0). The copper(0) may catalyze further decomposition of the original organocopper compound.[2c] Except for derivatives [e.g., $(CH_3Cu)_n$] that cannot readily eliminate CuH, most organocopper compounds (including the lithium organocuprates) begin to undergo thermal decomposition somewhere within the temperature range −30 to 0°. This thermal decomposition problem [accompanied by formation of black colloidal Cu(0)] is aggravated by the fact that reaction of copper(I) salts with RLi reagents to form $(RCu)_n$ or $(R_2CuLi)_n$ reagents often fails to occur when the *temperature of the reaction mixture* is below the range −50 to −30°. Also, the cuprate reagents, $(R_2CuLi)_n$, often react only very slowly with other substrates at *reaction solution temperatures* below −20 to −30°. Thus, the reaction temperatures required to form and use $(R_2CuLi)_n$ reagents are often approximately the same as the temperatures where thermal decomposition becomes a serious competing reaction.[3]

$$\underset{\mathbf{1}}{(R{-}CH_2CH_2{-}Cu{-}\text{ligand})_n} \longrightarrow RCH{=}CH_2 + \underset{\mathbf{2}}{H{-}Cu{-}\text{ligand}}$$

We wish to call attention to the fact that when the reaction conditions selected permit competing thermal decomposition leading to a CuH derivative, a side reaction leading to reduction may also be observed. Such a competing reduction was observed during the conjugate addition of the mixed cuprate reagent, $t\text{-BuC}{\equiv}\text{CCu(Li)CH}{=}\text{CH}_2$, to isophorone (3).[3] In order to obtain a reasonable reaction rate for the conjugate addition, the reaction was run in a temperature range (−20 to 0°) where competing thermal decomposition of the cuprate reagent was occurring. The formation of the saturated ketone 4 as a by-product suggested that a copper hydride derivative had been formed by elimination from a vinylcopper species. In the reaction of several epoxides with $(n\text{-Bu})_2CuLi$ at 0–25°, by-products resulting from reduction of the epoxides were observed.[4] The authors surmised that these by-products were derived from CuH derivatives and found that this side reaction could be practically eliminated by performing the reactions in the presence of excess n-BuLi. In another instance where the saturated ketone 5 was stirred with $(n\text{-Bu})_2CuLi$ at 0° (a temperature where thermal decomposition is usually observed) for 1 hr, the authors observed that the only product formed was the alcohol 6.[5] These observations again suggest the occurrence of a reduction arising from a CuH derivative formed by thermal decomposition.



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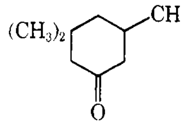

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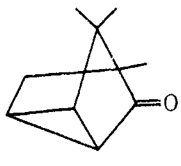

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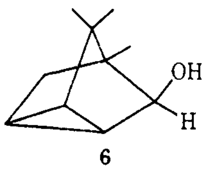

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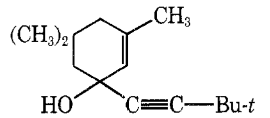
Several recent studies indicate that certain CuH derivatives may serve as reducing agents. Although polymeric $(CuH)_n$, prepared as an Et_2O-insoluble solid,[2a] is itself thermally unstable, decomposing to Cu(0) and H_2 at temperatures above −20°, the material does reduce various alkyl and aryl halides as well as organocopper compounds.[2a] A thermally stable, insoluble complex metal hydride having the stoichiometry $LiCuH_2$, prepared from Me_2CuLi in $LiAlH_4$,[6] may also be useful as a reducing agent. A reagent, presumed to be a CuH derivative, prepared by the reaction of CuI with $LiAlH(OMe)_3$ at 0° has been found to reduce various halides, sulfonates, and epoxides.[7] Also, solutions prepared by reaction of the insoluble $(CuH)_n$[2a] with 1 molar equiv of one of the RLi derivatives, LiOBu-*t*, LiSPh, $LiC{\equiv}CPr\text{-}n$, $LiC{\equiv}CBu\text{-}t$, or LiBu-*n*, in Et_2O, THF, or THF–HMP solution at −20 to −40°, have been found to reduce various halides, sulfonate esters, and the C=C of unsaturated carbonyl compounds.[8] These latter reagents were suggested[8] to have the stoichiometry LiCuHR.

To examine the question of what types of CuH derivatives were likely to reduce unsaturated carbonyl compounds, we treated the enone 3 with a cold, ethereal *suspension* of $(CuH)_n$,[2a] with a cold ethereal *solution* of the $n\text{-Bu}_3P$ complex[2a] of CuH, and with a PhH *solution* of the thermally more stable crystalline hexameric complex, $[Ph_3PCuH]_6$.[9] In no case did we observe formation of the dihydro ketone 4. Since the formation and separation of $(CuH)_n$ by the previously described[2a] reduction of CuBr with $i\text{-Bu}_2AlH$ in pyridine is tedious, we tried unsuccessfully to form comparable, well-defined material by reaction of the soluble complex, $(n\text{-Bu}_2S)_2CuI$, with $i\text{-Bu}_2AlH$ in cold heptane, Et_2O–heptane, or Et_2O–PhH. Although the solution, formed at −35°, decomposed (depositing either black colloidal Cu or a Cu mirror on the wall of the reaction vessel) when warmed suggesting the presence of some CuH derivative, we were unable to separate any well-defined product.

Preformed solid $(CuH)_n$ did not dissolve when treated with an Et_2O solution of $t\text{-BuC}{\equiv}CLi$. However, when the solvent was changed to THF, the $(CuH)_n$ dissolved upon treatment with ~0.3 molar equiv of $t\text{-BuC}{\equiv}CLi$ at −40° to form a brown solution. Because the original $(CuH)_n$ product contains a substantial amount (~25%)[2a] of pyridine that complicated measuring its weight, we treated the solid $(CuH)_n$ with just sufficient amounts of a cold (−40°) THF solution of $t\text{-BuC}{\equiv}CLi$ to obtain a solution and then analyzed aliquots of the solution for Cu and Li. The ratio Cu/Li determined for these solutions was 2.6, consistent with the formation of a reagent having a stoichiometry three CuH to one *t*-BuC≡CLi. This cold (−27°) THF solution reduced the enone **3** to the ketone **4** and the yield of **4** (46–48%) was approximately the same with or without added HMP (cf. ref 8a). If excess *t*-BuC≡CLi was used so that solutions of stoichiometry 1:1 CuH to *t*-BuC≡CLi were prepared, the yield of reduction product was lowered and higher boiling by-products were produced. Materials with comparable spectra and GLC behavior were formed by treatment of the enone **3** with *t*-BuC≡CLi, suggesting that these higher boiling by-products were formed from the 1,2 adduct **7**. This observation is compatible with our other observations indicating that the reducing agent formed from CuH and *t*-BuC≡CLi does not have a 1:1 stoichiometry, as would be the case for the formulation LiCuHR. Consequently, our data are consistent with the suggestion that the side reaction leading to reduction during a conjugate addition reaction can be attributed to partial decomposition of the cuprate reagent to form a CuH derivative, provided an organolithium reagent is present in the mixture. However, the CuH derivative formed in the presence of *t*-BuC≡CLi does not correspond to the previously described reagents, LiCuH(C≡CPr-*n*)[8] and LiCuHBu-*n*,[8b] either in its stoichiometry or in its response to added HMP.[8a]



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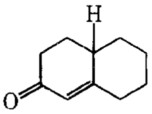
We also examined the reduction of the enone **8** with a cold (−27°) THF solution of the reagent *t*-BuC≡CLi-$(\mathrm{CuH})_3$. As with isophorone (**3**), reduction occurred slowly to form a mixture of saturated ketones **9** (87% of the mixture) and **10** (13% of the mixture). This same trend, favoring formation of the cis isomer, was also observed in reduction of the enone **11** with either *n*-PrC≡CCuHLi[8a] or *n*-BuCuHLi.[8b]



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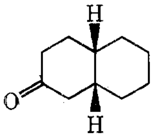

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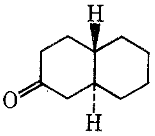

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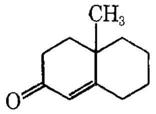

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To explore the seeming discrepancy in stoichiometry further we treated an excess of preformed[2a] $(\mathrm{CuH})_n$ with a THF solution of *n*-BuC≡CLi and analyzed the resulting solution for Cu content. Interestingly, with this *n*-alkylacetylide the stoichiometry was 1:1 *n*-BuC≡CLi to CuH, corresponding to the stoichiometry reported[8] when $(\mathrm{CuH})_n$ was treated with *n*-PrC≡CLi. Thus, for reasons we regard as obscure the THF solution formed from $(\mathrm{CuH})_n$ and *n*-BuC≡CLi has the stoichiometry LiCuH(C≡CBu-*n*) whereas the analogous solution formed from *t*-BuC≡CLi has the stoichiometry *t*-BuC≡CLi$(\mathrm{CuH})_3$.

Experimental Section[10]

Preparation of Reagents and Reactants. The preparations or sources and standardization procedures used for *t*-BuC≡CH,[3] *n*-BuC≡CH,[11b] ketones **4**, **9**, and **10**,[11a] and halide-free ethereal MeLi,[3] CuI,[3] CuBr,[3] and $(n\text{-Bu})_2\mathrm{SCuI}$[3] are described in earlier publications. Reaction of *t*-BuC≡CH with 1.0 equiv of MeLi at 0° in either $\mathrm{Et_2O}$ or THF was used to form solutions of *t*-BuC≡CLi. An analogous procedure was used to obtain a THF solution of *n*-BuC≡CLi. Commercial samples of $i\text{-Bu}_2\mathrm{AlH}$ were transferred in a drybox to give a 0.835 *M* solution in PhH or a 0.764 *M* solution in heptane. Previous directions[9] were followed to obtain $(\mathrm{Ph_3P}\cdot\mathrm{CuH})_6$ as red crystals, mp 105–107° (sealed capillary) (lit.[9] mp 111°). In a typical preparation of $(\mathrm{CuH})_n$,[2a] a cold (−40°) solution of 0.72 g (5.0 mmol) of CuBr in 50 ml of pyridine was treated with 7.2 ml of a heptane solution containing 5.5 mmol of $i\text{-Bu}_2\mathrm{AlH}_2$. After the mixture, which became red-brown in color, had been stirred at −40° for 10 min, it was diluted with $\mathrm{Et_2O}$ while keeping the temperature in the range −30 to −78°, and the resulting brown $(\mathrm{CuH})_n$ precipitate was separated by centrifugation. The solid was washed with three portions of cold (−40 to −78°) $\mathrm{Et_2O}$ before use. When the solid was treated with a cold (−40 to −78°) solution of 4 ml of $n\text{-Bu}_3\mathrm{P}$ in 15 ml of $\mathrm{Et_2O}$, practically all the solid dissolved to give a brown solution. This solution was treated with 0.70 g (5.1 mmol) of the enone **3** in 5 ml of $\mathrm{Et_2O}$ and the resulting solution was allowed to warm from −40 to 25° over several hours. The crude neutral product, recovered in the usual way, was distilled in a short-path still to separate 0.39 g (56%) of the starting enone **3** (GLC analysis, silicone SE-30 on Chromosorb P, retention time 9.8 min) that contained none of the saturated ketone **4** (6.9 min).

To examine the stoichiometry of solutions prepared from $(\mathrm{CuH})_n$, samples of $(\mathrm{CuH})_n$ were prepared[2a] at −30 to −40° from 1.44 g (10 mmol) of CuBr, 70 ml of pyridine, and a solution of 11 mmol of $i\text{-Bu}_2\mathrm{AlH}$ in 11.4 ml of heptane. Addition of excess cold $\mathrm{Et_2O}$ precipitated the $(\mathrm{CuH})_n$, which was washed in a centrifuge tube with three portions of cold (−40 to −78°) $\mathrm{Et_2O}$ before use. A portion of the $(\mathrm{CuH})_n$ was treated with a cold (−27°) solution of 4.02 mmol of *t*-BuC≡CLi in 14 ml of THF and the cold mixture was shaken and then centrifuged. Aliquots of the cold supernatant solution were withdrawn, and quenched in $\mathrm{H_2O}$. Each aliquot was analyzed for Li content by flame photometry and for Cu content by electrodeposition. The mole ratio of Cu/Li was 2.6 (average of three determinations). In a similar experiment a $(\mathrm{CuH})_n$ sample was treated with a cold solution of 4.99 mmol of *n*-BuC≡CLi in 25 ml of THF. After mixing and centrifugation, an aliquot of the supernatant solution was removed, quenched, and analyzed. The Cu/Li mole ratio was 1.2.

Reduction of Enone 3 with the CuH–*t*-BuC≡CLi Reagent. A solution of this reagent was obtained by treatment of the $(\mathrm{CuH})_n$, from 1.44 g (10.0 mmol) of CuBr and 11.0 mmol of $i\text{-Bu}_2\mathrm{AlH}$, with a solution of *t*-BuC≡CLi, from 0.32 g (3.9 mmol) of *t*-BuC≡CH, 3.85 mmol of MeLi, and 18 ml of THF, while the temperature of the reaction mixture was maintained at −40 to −78°. The solution of the CuH derivative was treated with 232 mg (1.68 mmol) of the enone **3** in 3 ml of THF, then stirred at −27° for 10 hr, and finally allowed to warm to 0°. The resulting solution was washed with aqueous $\mathrm{NH_4Cl}$, filtered through Celite, mixed with a known weight of $n\text{-C}_{12}\mathrm{H}_{26}$ (an internal standard), and analyzed employing a GLC apparatus (silicone SE-30 on Chromosorb P) calibrated with known mixtures of authentic samples. The components present were $n\text{-C}_{12}\mathrm{H}_{26}$ (retention time 15.4 min), ketone **4** (8.2 min, 48% yield), and enone **3** (11.6 min, 22% recovery). Collected (GLC) samples of ketones **3** and **4** were identified with authentic samples by comparison of GLC retention times and ir and mass spectra. In several cases the collected ketone **4** was contaminated with a few percent of the β,γ-unsaturated isomer of enone **3**.

When the same reaction was repeated except that 2 ml of HMP was added just before the addition of the enone **3**, there were obtained a 46% yield of ketone **4** and a 45% recovery of enone **3**. A comparable reaction was performed in which the $(\mathrm{CuH})_n$, from 10 mmol of CuBr, was treated with 10 mmol of *t*-BuC≡CLi before the addition of 1.68 mmol of the enone. In this case the GLC curve of the crude product exhibited peaks corresponding to $n\text{-C}_{12}\mathrm{H}_{26}$ (15.2 min), ketone **4** (8.6 min), enone **3** (12.4 min), and three additional higher boiling components (22.6, 24.4, and 26.8 min).

To obtain evidence concerning the nature of these higher boiling by-products, a cold (−27°) solution of *t*-BuC≡CLi, from 0.74 g (9.0 mmol) of *t*-BuC≡CH and 9.0 mmol of MeLi in 18 ml of THF, was treated with 0.41 g (3.0 mmol) of the enone **3** in 3 ml of THF. The reaction solution was stirred overnight while it was allowed to warm to 25° and then it was partitioned between $\mathrm{Et_2O}$ and aqueous $\mathrm{NH_4Cl}$ and the $\mathrm{Et_2O}$ solution was dried and concentrated. The crude neutral product, 0.63 g of yellow liquid, had ir absorption ($\mathrm{CCl_4}$) at 3600, 3450 (free and associated OH), 2240 (C≡C), and 1668 $\mathrm{cm^{-1}}$ (weak, conjugated C=O) indicating the presence of the adduct **7** accompanied by some unchanged enone **3**. The GLC curve of this crude product exhibited peaks corresponding to the unchanged enone **3** (11.9 min) and three partially resolved components with retention times (22.6, 24.5, and 26.8 min) corresponding to the three previously described by-products. A collected (GLC) sample of a mixture of these three components exhibited ir absorption at 2220 (conjugated C≡C), 1640, and 1610 $\mathrm{cm^{-1}}$ (C=C) and the mass spectrum of the mixture exhibited the following abundant peaks: *m/e* (rel intensity) 202 (82), 187 (100), 145 (34), 131 (23), 57 (81), and 41 (21). These spectroscopic properties are consistent with the formulation of these by-products (mol wt 202) as various double-bond isomers formed by dehydration of the alcohol **7** during the GLC analysis and separation.

Reduction of the Octalone 8 with the CuH-*t*-BuC$\equiv$CLi Reagent. The CuH, from 1.44 g (10.0 mmol) of CuBr and 11 mmol of *i*-$\mathrm{Bu_2AlH}$ in 12.4 ml of heptane, was dissolved in a cold (−40 to −78°) solution of 3.85 mmol of *t*-BuC$\equiv$CLi in 18 ml of THF and the resulting cold (−27°) solution was treated with a solution of 254 mg (1.69 mmol) of the octalone **8** in 3 ml of THF. The resulting solution was stirred at −27° for 10 hr and then allowed to warm to 0° and subjected to the previously described isolation procedure. The crude neutral product was mixed with 28.0 mg of *n*-$\mathrm{C_{14}H_{30}}$ (an internal standard) and subjected to analysis (GLC, Apiezon L on Chromosorb P) employing equipment that had been calibrated with known mixtures of authentic samples. The reaction product contained *n*-$\mathrm{C_{14}H_{30}}$ (retention time 11.5 min), the trans ketone **10** (16.9 min, yield 5%), the cis ketone **9** (19.0 min, yield 34%), and the starting ketone **8** (33.0 min, recovery 46%). Collected (GLC) samples of each of the ketone products **9** and **10** were identified with an authentic sample by comparison of ir and mass spectra and GLC retention times.

Registry No.—**3**, 78-59-1; **7**, 53783-16-7; **8**, 1196-55-0; $\mathrm{(CuH)}_n$, 53783-17-8; *t*-BuC$\equiv$CLi, 37892-71-0; *t*-BuC$\equiv$CLi$\mathrm{(CuH)_3}$, 53849-09-5.

References and Notes

(1) This research has been supported by Public Health Service Grant No. RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer.

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(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $\mathrm{MgSO_4}$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 NMR spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a $\mathrm{Me_4Si}$ internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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Stereoselectivity in the Base-Catalyzed Decarboxylation of 4-*tert*-Butylcyclohexane-1,1-dioic Acid[1]

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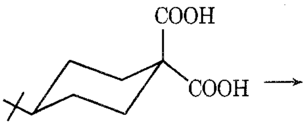
We recently reported the results of an investigation of the stereoselectivity of base-catalyzed decarboxylation of 5,5-dicarboxy-2-isopropyl-1,3-dioxane.[2] The product composition was found to be quite sensitive to the basic solvent chosen for the reaction. We were puzzled, however, by the apparent lack of sensitivity of the product composition in decarboxylation of 4-phenylcyclohexane-1,1-dioic acid to the solvent; 2,4,6-trimethylpyridine and 1,3,5-trimethylbenzene gave essentially the same result.[3] This prompted us to synthesize 4-*tert*-butylcyclohexane-1,1-dioic acid (**1**), study the diastereomeric composition of the product using a number of basic solvents, and compare these results to those of the 1,3-dioxane system.

Table I
Product Composition in the Decarboxylation of 4-*tert*-Butylcyclohexane-1,1-dioic Acid

Solvent	% 2 at 100.0°
Pyridine	70.7 ± 0.5[a]
2-Methylpyridine	70.3 ± 0.5
2,6-Dimethylpyridine	77.3 ± 0.6
N,*N*-Dimethylaniline	72.4 ± 0.6
N,*N*-Dimethylformamide	69.1 ± 1.3

[a] All errors are standard deviations.



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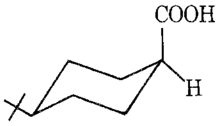

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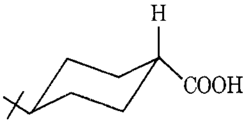

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A modified Birch reduction[4] of 4-*tert*-butylbenzoic acid produced 4-*tert*-butyl-1,5-cyclohexadien-1-oic acid (**4**). Two moles of hydrogen was consumed per mole of **4** using a palladium on carbon catalyst, and a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanoic acid was produced. Treatment of this mixture with diazomethane, carboxylation,[5] and hydrolysis gave **1**.

The results of base-catalyzed decarboxylation of **1** are given in Table I. The product composition is independent of the per cent yield. The investigation is limited by the fact that **1** was sparingly soluble in aniline and *N*-methylaniline. The diastereomeric product composition is indeed dependent on the choice of basic solvent. If the reasonable assumption is made that the step which controls the stereochemical outcome of decarboxylation of 5,5-dicarboxy-2-isopropyl-1,3-dioxane, *i.e.*, protonation of the enediol intermediate, also obtains in the present study, our results may be readily explained by comparing the steric hindrance encountered in approach of the conjugate acid of the basic solvent to the upper and lower faces of the intermediate. The syn-axial hydrogens render attack from above more difficult than attack at the lower face. As the bulk of the groups surrounding the acidic site increases, the selectivity increases. The identical product composition (within ex-