A Facile Double Migration in the Protonation of Lithium Alkynyltrialkylborates with Acid

Summary: Protonation of lithium alkynyltrialkylborates, $(R_3BC{\equiv}CR')Li$, with acid can be directed to achieve a double migration of alkyl groups from boron to carbon.

Sir: Monolithium acetylide reacts rapidly with trialkylboranes to produce the lithium ethynyltrialkylborate (eq 1). The protonation of such compounds with hydrochloric acid may be controlled to produce the Markovnikov alkenylborane[1] (eq 2). However, the use of excess acid causes a facile second migration of an alkyl group from boron to carbon (eq 3). Oxidation with alkaline hydrogen peroxide then

$$R_3B + LiC{\equiv}CH \longrightarrow (R_3BC{\equiv}CH)Li \quad (1)$$

$$(R_3BC{\equiv}CH)Li \xrightarrow[-78°]{HCl/H_2O} \begin{matrix} R \\ \diagdown \\ C{=}CH_2 \\ \diagup \\ R_2B \end{matrix} + LiCl \quad (2)$$

$$\begin{matrix} R \\ \diagdown \\ C{=}CH_2 \\ \diagup \\ R_2B \end{matrix} \xrightarrow[\Delta]{HCl/H_2O} R{-}\underset{HO}{\overset{}{B}}{-}\underset{R}{\overset{R}{C}}{-}CH_3 \quad (3)$$

produces the tertiary alcohol in high yield. Such a migration during the protonation of simple vinylboranes has hitherto been unobserved. This unusual migration is quite broadly applicable and has now been observed in the protonation of a considerable number of lithium alkynyltrialkylborates (eq 4).

$$(R_3BC{\equiv}CR')Li \xrightarrow{H^+} \xrightarrow{[O]} HO{-}\underset{R}{\overset{R}{C}}{-}CH_2R' \quad (4)$$

Alkali metal alkynyltrialkylborates are readily protonated under mild conditions to give a mixture of isomeric alkenylboranes[2] (eq 5). These vinylboranes may be cleaved

$$(R_3BC{\equiv}CR')M \xrightarrow{H^+} R_2BCR{=}CHR' \quad (5)$$

with acetic acid to give a cis–trans mixture of internal olefins[2] or they may be oxidized to regiospecific ketones.[2b] No double migration has been observed in these reactions. Indeed, Zweifel has shown that vinylboranes are cleaved to olefin upon protonation with mineral acid. Only when the vinylborane is first complexed with methyllithium does protonation cause an alkyl group to migrate.[3]

However, protonation of lithium ethynyltri-*n*-butylborate (5 mmol) with concentrated hydrochloric acid (5 mmol) at −78°, followed by oxidation with alkaline hydrogen peroxide at room temperature, produces the unexpected product, 5-methyl-5-nonanol, in 20% yield, along with 55% expected 2-hexanone. The use of excess acid results in exclusive carbinol formation (80% yield).

The reaction is quite general. The complexes from monolithium acetylide[4] or monolithium acetylide–ethylenediamine (EDA)[2c,5] and a variety of trialkylboranes react quite readily upon warming to room temperature with adequate hydrochloric acid. As a general procedure, these complexes are refluxed for 1 hr in tetrahydrofuran (THF) with 2 mol of concentrated hydrochloric acid following the initial protonation at −78°. The complexes from trialkylboranes and 1-hexyne or cyclohexylethyne are somewhat more sluggishly protonated. These require 1–2 hr of reflux. The highly hindered complexes from 3,3-dimethyl-1-butyne require somewhat more drastic conditions, such as 4–8 hr in refluxing 1-butanol. In the case of these more hindered boranes, the yields of carbinol also decrease. The results are summarized in Table I.

Table I
The Protonation of Lithium Alkynyltrialkylborates for the Synthesis of *tert*-Alcohols

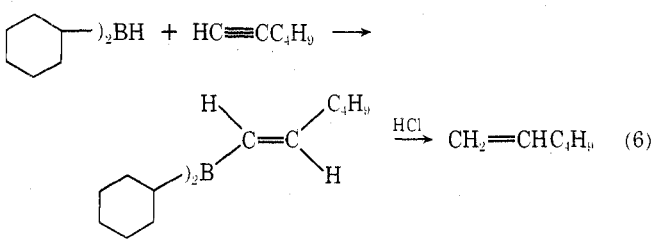
Trialkylborane, R	Yield,[a] %, of $R_2C(OH)CH_2R'$, R'					
	H	H·EDA	*n*-Butyl	*tert*-Butyl	Cyclohexyl	Phenyl
n-Butyl	82	80	86	86	74	73
Isobutyl	72	72	81	75	77	86
sec-Butyl	68	55	86	30[c]	78	30[d]
Cyclopentyl	72	72	84[b]		75	
Cyclohexyl	72	86	80	15[c]	63	0[d]

[a] By VPC. All reactions were run on a 5-mmol scale. The products were isolated by preparative VPC and characterized by spectroscopy. [b] Isolated yield. [c] The main product was unreacted starting material. [d] The reaction took a different course which is presently under investigation.

The following procedure for the preparation of 1,1-dicyclopentyl-1-hexanol is representative. A dry 500-ml flask equipped with a septum-capped inlet, a reflux condenser, and magnetic stirring bar was connected to a bubbler and flushed with nitrogen. The flask was charged with THF (65 ml) and cyclopentene (300 mmol, 26.5 ml). The flask was cooled to 0° and borane–THF (100 mmol, 35.6 ml of 2.81 *M*) was added dropwise. The solution was then stirred at room temperature for 1 hr, then cooled to 0°. A dry 250-ml flask was flushed with nitrogen and charged with THF (80 ml) and 1-hexyne (100 mmol, 12.0 ml). The flask was cooled to 0° and *n*-butyllithium in hexane (100 mmol, 44 ml of 2.27 *M*) was added dropwise. After 10 min, the contents were transferred dropwise by a double-ended needle[6] to the 500-ml flask containing the tricyclopentylborane. After completion of the addition, the solution was stirred for 10 min and then cooled to −78°. Concentrated hydrochloric acid (~240 mmol, 20 ml) was added, and the solution was warmed to room temperature by removing the Dry Ice–acetone bath. The solution was heated at reflux for 1 hr. The solution was then cooled and neutralized to the phenolphthalein end point with 40% potassium hydroxide (~25 ml). Ethanol (100 ml) and sodium hydroxide (24 g) were added to the flask. Hydrogen peroxide (40 ml of 30%) was added at such a rate as to keep the temperature at 50°. After the addition, the solution was heated to 50° for 2 hr and then cooled, and the aqueous layer was saturated with potassium carbonate. The THF phase was separated, and the water layer was extracted with 2 × 50 ml of ether. The combined organic phase was dried over magnesium sulfate and distilled. There was collected 20.1 g (84%) of 1,1-dicyclopentyl-1-hexanol, bp 118–120° (0.01 mm), $n^{20}D$ 1.4876.

The protonation of lithium alkynyltrialkylborates may thus be controlled to give either the alkenylborane[1] (monoalkyl group migration) or the *tert*-alkylborane (dialkyl

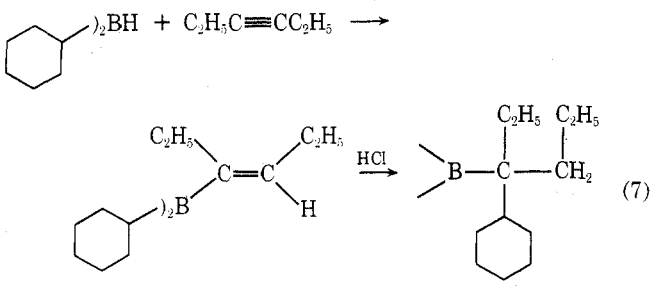
group migration). Since the second step involves the protonation of a vinylborane, the protonation of typical vinylboranes was briefly investigated. Hydroboration of 1-hexyne with dicyclohexylborane produces the terminal vinylborane (eq 6). The vinyl protons [NMR δ 6.70 (dt, J = 18



(6)

Hz, J = 5.6 Hz), 6.15 (d, J = 18 Hz)] disappear upon treatment with concentrated hydrochloric acid and protons due to 1-hexene appear. Oxidation produces none of the expected 1-cyclohexyl-1-hexanol. These results thus confirm previous investigations of mineral acid protonations of vinylboranes.[3]

Hydroboration of 3-hexyne with dicyclohexylborane produces the internal vinylborane (eq 7). The vinyl protons [δ



(7)

5.72 (m)] disappear upon protonation. Oxidation produces 3-cyclohexyl-3-hexanol in 96% yield.

Thus, there is a major difference in the behavior of dialkylvinylboranes toward hydrochloric acid, depending upon whether the vinyl group is terminal (eq 6) or internal (eq 7). The former undergoes simple protonolysis of the B–C bond; the latter undergoes proton addition to the double bond with B–C alkyl group migration.

The protonation of lithium alkynyltrialkylborates may now be controlled to give either alkenylboranes or organoboranes containing bulky *tert*-alkyl groups. Such organoboranes are becoming increasingly important in the formation of complex structures.[6,7] Furthermore, the present reaction suggests that other reactions of lithium alkynyltrialkylborates may be controlled to produce double migrations.[8]

References and Notes

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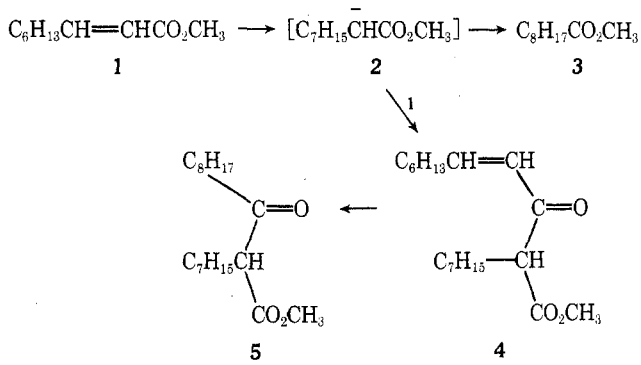
Unique Methodology for the Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Carboxylic Esters

Summary: A wide variety of α,β-unsaturated esters undergo 1,4 reduction and reductive alkylation to afford saturated esters in preparatively useful yields through the agency of lithium tri-*sec*-butylborohydride.

Sir: Recently we reported that α,β-unsaturated cyclohexenones, unlike their acyclic counterparts,[1] undergo exclusive 1,4 reduction to ketone enolates when treated with potassium tri-*sec*-butylborohydride (K-Selectride™, Aldrich).[2] These enolates can subsequently be protonated or alkylated in excellent yield. We became intrigued with the possibility that such borohydride reagents might similarly convert α,β-enoates to saturated esters by way of saturated ester enolates, since no present synthetic methodology generally accomplishes this transformation. Solutions of alkali metals in amines have been used to reduce the double bond of α,β-unsaturated acids,[3] but chemical reduction of the corresponding esters becomes a low yield process commonly leading to saturated alcohols.[4] This communication describes how trialkylborohydrides can successfully be employed to convert α,β-unsaturated esters directly to saturated esters in excellent yield. Furthermore the intermediate ester enolates which are generated can be alkylated in situ, thus accomplishing in a one-pot procedure for the first time what is usually a four-step series of reactions.[5]

When methyl-2-nonenoate **1** was subjected to K-Selectride™ in ether or THF at −70°, rapid disappearance of enoate was accompanied by formation of methyl nonanoate **3** in low yield as well as preponderant amounts of a single, high-molecular weight ester shown by ir, NMR, and mass spectroscopy to be the keto ester **5**.[6] This substance apparently resulted from initial 1,4 reduction to saturated ester enolate **2**, then attack by **2** on **1** to form the unsaturated keto ester **4**. Conjugate reduction of **4** produced **5**, whose structural assignment was also supported by its positive $FeCl_3$ test.[7]



By substituting the corresponding lithium trialkylborohydride (L-Selectride™) we hoped to retard the dimerization and, indeed, **1** with L-Selectride™ afforded a 4:1 mixture of methyl nonanoate and **5** in 80% yield. However, efforts to eradicate the yield-lowering self-condensation by varying solvent, temperature, and ester type, or by using cosolvents such as hexamethylphosphoric triamide, were uniformly unsuccessful; the best yield of **3** obtainable (−70°, 20 min) seemed to be 75%.

Other experiments in our laboratory had revealed appreciable lifetimes of Selectride™ reagents in the presence of alcohol solvents, and suggested that such a reducing medium might avoid Claisen condensation by rapidly protonating the first-formed ester anions. In fact, addition of **1** and *tert*-butyl alcohol (2 equiv) to a THF solution of L-Selec-