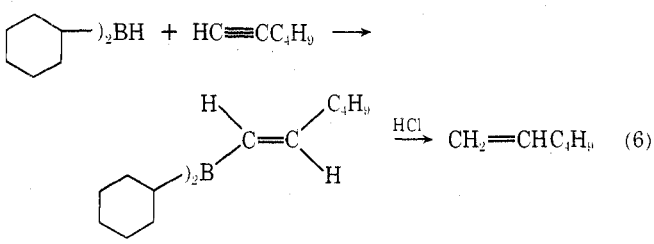
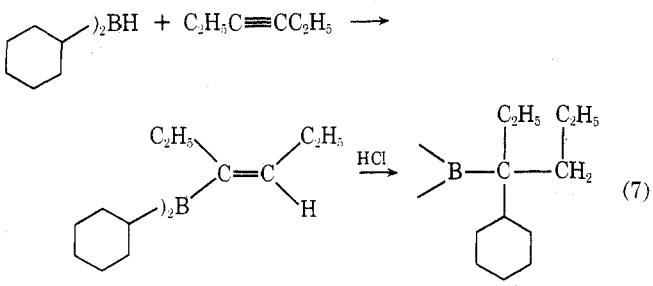
group migration). Since the second step involves the protonation of a vinylborane, the protonation of typical vinylboranes was briefly investigated. Hydroboration of 1-hexyne with dicyclohexylborane produces the terminal vinylborane (eq 6). The vinyl protons [NMR δ 6.70 (dt, J = 18



(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]

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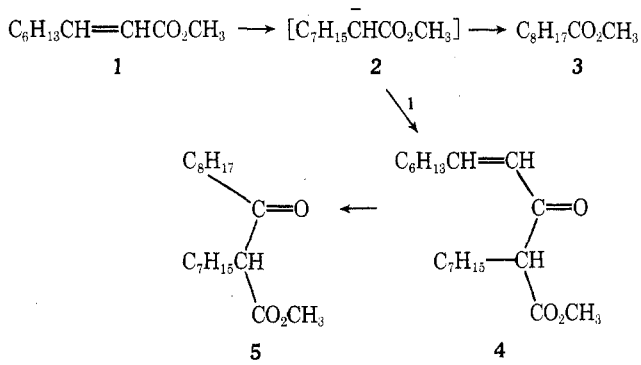
Unique Methodology for the Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Carboxylic Esters

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-

Table I
Reduction of α,β-Unsaturated Esters Using L-Selectride/*tert*-Butyl Alcohol

Enoate[a]	Time, min	Temp, °C	Product (% yield)[b]
1	20	−70	3 (92)
$CH_3CH{=}C(CH_3)CO_2CH_3$	20	−70	$C_2H_5CH(CH_3)CO_2CH_3$ (70)
	30	0	
$C_6H_{13}CH{=}C(CH_3)CO_2CH_3$	20	−70	$C_7H_{15}CH(CH_3)CO_2CH_3$ (90)
$(CH_3)_2C{=}CHCO_2C_2H_5$[c]	15	−70 → 0	$(CH_3)_2CHCH_2CO_2C_2H_5$ (70)
Methyl cinnamate	20	−70	starting material (29)
	30	0	$PhCH_2CH_2CO_2CH_3$ (27)
Ethyl *p*-nitrocinnamate	20	−70	*p*-$NO_2C_6H_4CH_2CH_2CO_2C_2H_5$ (62)

[a] Enoates were mixed with *t*-BuOH (2–2.5 equiv) and added to L-Selectride. [b] Reported yields represent isolated esters after oxidation of tri-*sec*-butylborane. Products were identified by comparison with authentic samples. [c] *tert*-Butyl alcohol was omitted in this experiment.

Table II
Reductive Alkylation of α,β-Unsaturated Esters

Enoate[a]	Alkylating agent	Time, min	Temp, °C	Product (% yield)[b]
1	CH_3I	20	0	$C_7H_{15}CH(CH_3)CO_2CH_3$ (60)
1	$CH_2{=}CHCH_2Br$	20	0	$C_7H_{15}CHCO_2CH_3$ (50), $CH_2CH{=}CH_2$
1	CH_3COCH_3	60	0	$C_7H_{15}CHCO_2CH_3$ (62), $CH_3{-}C(OH){-}CH_3$
1	C_4H_9I[c]	60	*d*	$C_7H_{15}CHCO_2CH_3$ (63), C_4H_9; 3 (19)
8	$PhCH_2Br$[c]	120	*d*	$(CH_3)_2CHCHCO_2C_2H_5$ (50), CH_2Ph

[a] Enoate was added to 1.0–1.1 equiv of L-Selectride™ in THF at −70° for 20 min. Alkylating agent was subsequently added and reaction completed as described in each case. Note the two exceptions. [b] Yields have not been optimized. All experiments using 1 also afforded 15–20% 5. [c] In these difficult alkylations, the enolate solution was added at room temperature to dry DMSO solutions of the alkylating agent (1.5–2 equiv); see ref 10. [d] Room temperature.

tride™ at −70° followed by careful oxidative work-up to remove tri-*sec*-butylborane afforded pure methyl nonanoate in 92% yield. No trace of 5 could be detected. Table I summarizes our results when this technique was applied to some structurally diverse enoates.

The reductions are quite clean and even sterically encumbered enoates such as methyl β,β-dimethylacrylate can be reduced in good yield. Whereas methyl cinnamate did not afford a worthwhile yield of β-phenylpropionic ester, ethyl *p*-nitrocinnamate was effectively reduced to the corresponding hydrocinnamate (mp 168°). Inverse hydride addition is possible in this system and we are presently investigating whether a nitro-stabilized benzylic anion is formed rather than an ester enolate.[8]

We have also observed that the intermediate enolates can be trapped with a reactive electrophile; in such procedures the enoate is added to L-Selectride in the absence of alcohol, followed later by the alkylating agent.[9] Overall yields are good and a summary of representative experiments is presented in Table II.

The yields of products in Table II are comparable to those of Rathke et al. who have generated and similarly alkylated ester enolates by low-temperature ester metalation.[10] It seems apparent that all the methodology developed by those workers should be applicable to anions arising from conjugate enoate reduction. Furthermore the remarkably nonbasic nature of L-Selectride™ makes it an especially attractive reagent for generating ester enolates under mild conditions.

The following is a typical experimental procedure.

Methyl-2-nonenoate (0.506 g, 2.98 mmol) and *tert*-butyl alcohol (0.55 g, 2,5 equiv) in dry THF (3 ml) was added dropwise down the side of a 50-ml round-bottomed flask containing stirred L-Selectride (3.0 ml of a 1*M* solution from Aldrich) under N_2 at −70°. After 20 min, methanol (0.2 ml) was injected and the reaction brought to room temperature, concentrated under reduced pressure, and diluted with hexane (20 ml). The flask was cooled in ice during addition of ice-cold aqueous 10% NaOH (1.2 ml, ~1 equiv) and 30% H_2O_2 (3 ml). After the mixture stirred overnight at room temperature, the aqueous layer was extracted twice with ether (10 ml) and the combined organic phases were worked up in the usual fashion to afford 0.46 g (92%) of methyl nonanoate, identical in every respect with an authentic sample.

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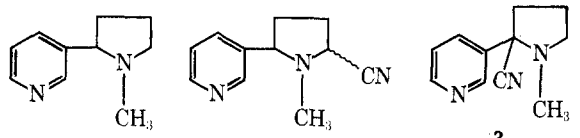
Nicotine Chemistry. 5′-Cyanonicotine

Summary: The synthesis of 5′-cyanonicotine is reported. An attempt to reproduce a literature preparation of this compound led to a mixture of isomeric cyanonicotines in which 2′-cyanonicotine predominated.

Sir: Murphy[1] has recently reported that oxidation of nicotine (1) with mercuric acetate, followed by treatment of the intermediate with potassium cyanide, results in the formation of a cyanonicotine. The product was assigned structure 2 on the basis of its mass and NMR spectra.

Repetition of Murphy's procedure[2] in our laboratory gave a compound which has been unequivocally characterized as 3 based on an independent synthesis of 2 and a detailed spectral analysis of 2 and 3.



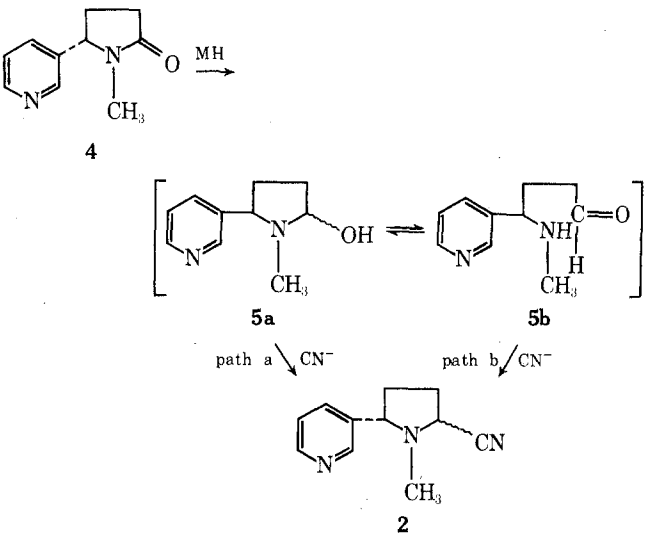
1 2 3

(*S*)-Cotinine (4)[3] was chosen as a logical starting point for the synthesis of 2 in that functionality is already present at the C-5′ position. Since tertiary amides have been reductively cleaved to secondary amines and aldehydes by metal hydrides,[4] introduction of the cyano group at C-5′ was envisaged as proceeding through a cyclic carbinolamine or an acyclic amino aldehyde as shown in Scheme I.[5]

When 4 was treated with 1.6 equiv of a fresh, standardized solution of sodium aluminum hydride[7] in dry tetrahydrofuran, a highly unstable product was isolated which exhibited an intense ir band at 1735 cm^{-1}, typical of a saturated aldehyde. Treatment of the partial reduction product with an excess of aqueous potassium cyanide and ammonium chloride gave an inseparable mixture of (2′*S*)-*cis*- and -*trans*-5′-cyanonicotine (2),[8] isolated in 75% yield (see Scheme I).

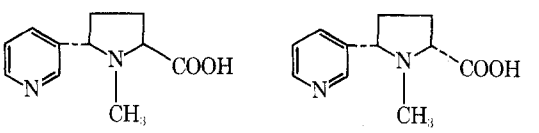
All spectral data for the mixture of the two nitriles were consistent with the assigned structure.[8] Acid hydrolysis of the mixture of nitriles gave a mixture of two nicotine-5′-carboxylic acids in a 2:1 ratio which were subsequently separated by fractional crystallization. The major isomer was

Scheme I



4 5a 5b 2

determined to be (2′*S*)-*trans*-nicotine-5′-carboxylic acid (6) based on the low field signal of the 5′ proton in its ^1H NMR spectrum,[9] while the minor isomer was assigned the cis configuration (7). In addition, ir and ^1H NMR spectra of



6 7

6 were identical with those of a racemic nicotine-5′-carboxylic acid of previously unassigned stereochemistry which was prepared by independent synthesis.[10]

The preparation of authentic 5′-cyanonicotine allowed us to investigate the structure of the product obtained from Murphy's procedure. Nicotine was treated with mercuric acetate in acetic acid. After addition of potassium cyanide to the neutralized (pH 7.0) solution, the components of the product mixture were found to be cotinine (~50%)[12] (4), unreacted 1, and a small amount of a nitrile. The crude product was distilled to give a 5% yield of an unstable oil which displayed a weak band at 2300 cm^{-1} in the ir. The ^1H NMR spectrum of the product, assigned structure 3, was significantly different from the spectrum of 2. The mass spectrum of 2 displayed a prominent molecular ion at *m/e* 187 and a base peak at *m/e* 109, whereas the spectrum of 3 had a barely detectable molecular ion, with a base peak at *m/e* 159.

The ^{13}C NMR spectrum of 3 upon SFOR decoupling is split into one quartet, three triplets, and a singlet [43.0 (q), 21.1, 36.2, and 53.7 (t), and 69.6 ppm (s)]. This pattern is consistent with an *N*-methylpyrrolidine containing a single tetrasubstituted carbon atom. The ^{13}C NMR spectrum of 2 shows a pair of peaks for each of the five saturated carbon atoms. The SFOR-decoupled spectrum displays a pair of quartets (36.5 and 38.1 ppm), a pair of triplets and a single triplet (33.6, 34.5, and 28.9 ppm), and two pairs of doublets (57.0 and 56.1 and 65.6 and 68.3 ppm) consistent with two isomeric *N*-methylpyrrolidines each containing two monosubstituted carbon atoms. Gas chromatography of 3 shows the presence of a small amount of 2 (~10%).[13]

The formation of 2′-cyanonicotine in our laboratory from the mercuric acetate dehydrogenation of nicotine establishes that its precursor is 8. This is consistent with the generalization[14] that mercuric acetate dehydrogenation of α-substituted cyclic amines results in the formation of the more substituted imminium salt. On the other hand, the