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Selective Reductions. 26. Lithium Triethylborohydride as an Exceptionally Powerful and Selective Reducing Agent in Organic Synthesis. Exploration of the Reactions with Selected Organic Compounds Containing Representative Functional Groups[1,2]

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The approximate rates, stoichiometry, and products of the reaction of lithium triethylborohydride ($LiEt_3BH$) with selected organic compounds containing representative functional groups under standard conditions (tetrahydrofuran, 0 °C) were examined in order to explore the reducing characteristics of this reagent and to establish the utility of the reagent as a selective reducing agent. Primary and secondary alcohols, phenols, and thiols evolve hydrogen rapidly and quantitatively, whereas the reaction with 3-ethyl-3-pentanol is slow. *n*-Hexylamine is inert to this reagent. Aldehydes and ketones are reduced rapidly and quantitatively to the corresponding alcohols. Even the highly hindered ketone 2,2,4,4-tetramethyl-3-pentanone is reduced within 30 min. The stereoselectivities achieved with this reagent in the reduction of mono- and bicyclic ketones are better than those realized with lithium aluminum hydride, lithium alkoxyaluminohydrides and lithium borohydride; thus norcamphor is reduced to 1% *exo*- and 99% *endo*-2-norbornanol. The reagent rapidly reduces cinnamaldehyde to the cinnamyl alcohol stage, with further addition to the double bond being sluggish. Anthraquinone is cleanly reduced to 9,10-dihydro-9,10-dihydroxyanthracene. The diol was isolated in 77% yield. Carboxylic acids evolve hydrogen rapidly and quantitatively (1 equiv); further reduction is very slow. Acyclic anhydrides utilize 2 equiv of hydride to give an equimolar mixture of acid and alcohol after hydrolysis. Utilizing this procedure, we converted phthalic anhydride to phthalide in 90% yield. Acid chlorides, esters, and lactones are rapidly and quantitatively reduced to the corresponding carbinols. Epoxides undergo rapid reduction with the uptake of 1 equiv of hydride. In the case of unsymmetrical epoxides, exclusive Markovnikov ring opening was observed. Acetals, ketals, and ortho esters are inert to this reagent. Primary amides evolve 1 equiv of hydrogen rapidly. Further reduction of caproamide is slow, whereas benzamide is not reduced. Tertiary amides are rapidly and quantitatively reduced by $LiEt_3BH$ exclusively to the corresponding alcohols. Such a clean transformation has not been observed with any other hydride reagent currently available. Benzonitrile rapidly utilizes 2 equiv of hydride to go to the amine stage, whereas capronitrile takes only 1 equiv. Hydrolysis of the latter reaction mixture did not give the expected caproaldehyde, but *n*-hexylamine and the starting material were obtained in equal amounts. It appears possible to selectively reduce tertiary amides and aromatic nitriles to aldehydes in excellent yields by utilizing stoichiometric quantities of the reagent. 1-Nitropropane utilizes only 1 equiv of hydride for hydrogen evolution without any reduction. Nitrobenzene, azobenzene, and azoxybenzene are rapidly reduced. Cyclohexanone oxime rapidly evolves hydrogen but no reduction is observed. Phenyl isocyanate readily consumes 1 equiv of hydride in going to the formanilide stage. Pyridine is rapidly reduced to the tetrahydropyridine stage, followed by further slow reduction. Pyridine *N*-oxide also undergoes rapid reaction with this reagent. Disulfides are rapidly reduced to the thiol stage, whereas sulfoxide, sulfonic acid, and sulfides are practically inert toward this reagent. Cyclohexyl tosylate is slowly reduced to give a mixture of cyclohexane (80%) and cyclohexene (20%). Diphenyl sulfone slowly reacts to give an unexpected product, ethylbenzene, in excellent yield. The nature of the intermediates of representative reactions was also studied. Products of the reaction of the reagent with simple primary and secondary alcohols, *tert*-butyl alcohol, and most ketones exist as weak triethylborane complexes, whereas those of 3-ethyl-3-pentanol, phenols, carboxylic acids, thiols, and 1-nitropropane exist as their lithium salts without coordinating with the triethylborane formed.

The discovery[4] of the exceptional characteristics of lithium trialkylborohydrides in 1972 in the course of a study of the carbonylation of organoboranes aroused considerable interest in the exploration of their utility for

(1) Based upon a thesis submitted by S. C. Kim in December 1976 in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Presented at the 168th National Meeting of the American Chemical Society, Atlantic City, NJ, Sept 1974.

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organic functional-group reductions. As a result of such explorations, a number of trialkylborohydrides have emerged in recent years as highly attractive reducing agents to achieve chemo-, regio-, and stereoselective transformations in organic synthesis.[5,6] Unlike the parent compound, lithium borohydride, trialkylborohydrides are exceptionally powerful nucleophilic reducing agents capable of cleaving cyclic ethers[7] and reducing hindered halides,[8] epoxides,[9] *p*-toluenesulfonate esters of hindered and cyclic alcohols,[10,11] quaternary ammonium salts,[12] activated olefins,[13] etc., rapidly and cleanly to the desired products. They have been recognized as the most powerful simple nucleophiles available for S_N2 displacements. Even more important, hindered and highly hindered trialkylborohydrides possess the remarkable ability to introduce major steric control into the reduction of cyclic and bicyclic ketones.[14-16] In this respect, these reagents are unequalled by any other reagents currently available. Many of these reagents are finding attractive applications in the stereoselective synthesis of prostaglandins.[17] Further, trialkylborohydrides containing an asymmetric alkyl group reduce unsymmetrical ketones to optically active secondary alcohols.[18]

In view of these remarkable properties, it was desirable to undertake a systematic exploration of the reducing characteristics of trialkylborohydrides. We have recently described such systematic studies of the approximate rates, stoichiometry, and products of the reactions of lithium aluminum hydride,[19] lithium trimethoxyaluminohydride,[20] lithium tri-*tert*-butoxyaluminohydride,[21] aluminum hydride,[22] diborane,[23] disiamylborane,[24] thexylborane,[25] and 9-BBN[26] all in tetrahydrofuran (THF) solution at 0 °C (with one exception, 9-BBN, which was carried out at 25 °C) with a standard list of organic compounds representative of the more common functional groups. Because of the commercial availability[27] and the easier method of preparation, lithium triethylborohydride (Super-Hydride 1 M, $LiEt_3BH$) was chosen as the reagent of choice in the present study.

We undertook a detailed study of the rate, stoichiometry, and products of the reaction of $LiEt_3BH$ with representative functional groups and its applicability for selective reductions in organic synthesis. The results of these investigations are reported in the present paper.

Results and Discussion

Preparation of Standard Solutions of Lithium Triethylborohydride in THF. Solutions of lithium triethylborohydride in THF were conveniently prepared by stirring at 25 °C 1 equiv of triethylborane with an excess of finely divided lithium hydride (usually in moderate excess) in THF for approximately 24 h, followed by refluxing for 2–3 h. Filtration removed the excess lithium hydride and gave crystal clear solutions. The concentration was determined by hydrolyzing a known aliquot of the solution with a water–glycerine–THF (1:1:1) mixture at 25 °C and measuring the hydrogen evolved. The yields were quantitative (eq 1).

$$LiH + Et_3B \xrightarrow{THF} \underset{100\%}{LiEt_3BH} \quad (1)$$

Under an inert atmosphere, solutions of lithium triethylborohydride in THF appear to be stable indefinitely—with no change observed in months at room temperature and in days at 65 °C.

Procedure for Rate and Stoichiometry Studies. The general procedure adopted was to add 10 mmol of the organic compound under investigation to 40 mmol of lithium triethylborohydride in sufficient tetrahydrofuran to give 40 mL of solution. The mixtures were maintained at 0 °C (ice bath). This made the reaction mixture 1.0 M in $LiEt_3BH$ and 0.25 M in compound. Any hydrogen evolved was noted. Aliquots were then removed at appropriate intervals of time and analyzed for "residual hydride" by hydrolysis.[28] Simultaneously, a blank was run, in which 10 mL of THF was added, in place of the 10 mL of the THF solution of the compound, all other conditions being the same. In some cases, where the hydrogen evolution is continuous or a precipitate is formed, individual experiments were conducted on a 5-mmol scale to measure the hydrogen evolution and to determine the residual hydride with different time intervals, without removing aliquots.

In this manner it was possible to establish both the rate at which reduction proceeds and the stoichiometry of the reactions (number of hydrides utilized per mole of the compound) when the reaction proceeds to essential completion under the reaction conditions.

Product Analysis by GLC. Having established the approximate rate and stoichiometry of the reaction, we desired to establish the nature of the products wherever

(3) Graduate research assistant on Research Grant No. DA-ARO-D-31-124-73-G148, supported by the U.S. Army Research Office (Durham, NC).

(4) For extensive review of the discovery and applications of trialkylborohydrides, see: Krishnamurthy, S. *Aldrichimica Acta* **1974**, *7*, 55 and references cited therein.

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(17) For example, see: (a) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491. (b) Corey, E. J.; Varma, R. K. *Ibid.* **1971**, *93*, 7319. (c) Corey, E. J.; Becker, K. B.; Varma, R. K. *Ibid.* **1972**, *94*, 8616. (d) Schaub, R. E.; Weiss, M. J. *Tetrahedron Lett.* **1973**, 129. (e) Grudzinska, C. V.; Weiss, M. J. *Ibid.* **1973**, 141. (f) Miyano, M.; Stealey, M. A. *J. Chem. Soc., Chem. Commun.* **1973**, 180. (g) Poleto, J. F.; Bernady, K. F.; Kupfer, D.; Partridge, R.; Weiss, M. J. *J. Med. Chem.* **1975**, *18*, 359.

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(22) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.

(23) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637.

(24) Brown, H. C.; Bigley, D. B.; Arora, S. K.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 7161.

(25) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Org. Chem.* **1972**, *37*, 2942.

(26) Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem.* **1975**, *40*, 1864.

(27) Lithium triethylborohydride (Super-Hydride) is now commercially available as a 1 M solution in THF from the Aldrich Chemical Co., Milwaukee, WI 53233.

(28) It is convenient to discuss the utilization of the reagents in terms of moles of hydride taken up per mole of the compound. However, it should not be confused that free "hydride" ion is the active species. An "active hydride" refers to one B–H bond, 1 equiv of $LiEt_3BH$.

it appeared of interest, offering a valuable possibility for selective reduction.

Accordingly, separate reactions on a smaller scale (~5 mmol) were carried out by using either a stoichiometric amount of the reagent or an excess amount, depending upon the nature of the reaction. Analyses were carried out after hydrolyzing the reaction mixture with water or dilute hydrochloric acid when necessary. The products were identified by comparison with authentic samples, and the yields were usually determined by GC utilizing internal standards and standard synthetic mixtures.

Determination of the Nature of the Intermediates. It was also of interest to determine whether the intermediates (reaction products prior to hydrolysis) exist as triethylborane "ate" complexes or as lithium salts without coordinating with the triethylborane formed.

The method involved preparation of representative reaction mixtures in THF using a stoichiometric amount of lithium triethylborohydride at room temperature. After the reaction was complete, the reaction mixture, without hydrolysis, was injected into a gas chromatograph where the injection port was maintained at 25–30 °C and the column at 50 °C. The shape of the peak corresponding to triethylborane and the yield were noted and compared with that for a standard solution of triethylborane in THF.

The results fall into three categories: (i) formation of strong complexes—for those reactions where no triethylborane peak was observed; (ii) formation of weak complexes—for those reactions where varying degrees of tailing in the triethylborane peak was observed (this was interpreted as the slow dissociation of the complex at the injection port); (iii) no complex formation—for those reactions where a clean symmetrical peak was observed (in this case, the yield of triethylborane was also quantitative).

Rate and Stoichiometry. Alcohols, Phenols, Amines, and Thiols. All of the alcohols examined liberated hydrogen rapidly and quantitatively, with the exception of 3-ethyl-3-pentanol, which evolved only 0.91 equiv of hydrogen in 24 h. The rate of hydrogen evolution for alcohols decreases in the order primary ≥ secondary > tertiary. This is in agreement with the usual interpretation that the acidity of the hydroxylic hydrogen in these alcohols decreases in this order.[29] Such a trend was also observed with diborane and 9-BBN but not with the aluminohydrides, all of which evolved hydrogen instantly. On the other hand, sodium borohydride readily reacts only with methanol.[30]

The products of the reactions of primary and secondary alcohols appear to exist as weak triethylborane complexes of the corresponding lithium alkoxides (eq 2). The

$$\mathrm{ROH + LiEt_3BH \longrightarrow [RO{-}BEt_3]^-Li^+ + H_2} \quad (2)$$

$$\downarrow \mathrm{H_2O}$$

$$\mathrm{ROH}$$

R = primary of secondary alkyl

product of the reaction with *tert*-butyl alcohol also exists as a weak complex of triethylborane. However, the reaction product of 3-ethyl-3-pentanol shows no evidence of coordination with triethylborane. This is attributed to the high steric requirements of lithium triethylcarboxide.

Phenol, 2,6-di-*tert*-butylphenol, and both of the thiols evolved hydrogen rapidly and quantitatively. The corresponding lithium salts produced did not coordinate with the triethylborane.

Surprisingly, *n*-hexylamine proved to be inert to this reagent under the experimental conditions.

Simple hydrolysis regenerates the starting materials quantitatively.

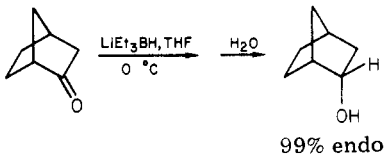
The experimental results for the reaction of the reagent with representative alcohols, phenols, amines, and thiols are summarized in Table I.

Aldehydes and Ketones. The aldehydes and ketones examined rapidly utilize 1 equiv of hydride to proceed to the alcohol stage, according to eq 3. Even the highly

$$\mathrm{RR'CO + LiEt_3BH \rightarrow [RR'CHO{-}\overline{B}Et_3]Li^+ \xrightarrow{H_2O} \underset{>95\%}{RR'CHOH}} \quad (3)$$

hindered ketone 2,2,4,4-tetramethyl-3-pentanone undergoes reduction with remarkable ease.

Hydrolysis of the reaction products provides the corresponding alcohols in quantitative yield. Norcamphor is reduced with excellent stereoselectivity, yielding 99% *endo*- and 1% *exo*-norborneol (eq 4). Similarly, 2-



(4)

99% endo

methylcyclohexanone is quantitatively reduced to give a mixture of 75% *cis*- and 25% *trans*-2-methylcyclohexanol.

Table I. Reaction of Lithium Triethylborohydride with Representative Alcohols, Phenols, Amines, and Thiols in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
1-hexanol	5 min	0.96		
	1 h	0.96	0.98	0.02
benzyl alcohol	5 min	1.04		
	1 h	1.04	1.04	0.00
3-hexanol	5 min	0.91		
	0.25 h	0.93		
	3 h	0.94		
	6 h	0.96		
	24 h	0.96	1.00	0.04
3-ethyl-3-pentanol	5 min	0.04		
	0.25 h	0.11		
	0.5 h	0.20		
	1 h	0.38		
	3 h	0.76		
	6 h	0.87		
	12 h	0.90		
	24 h	0.91	0.91	0.00
phenol	5 min	1.02		
	1 h	1.02	1.08	0.06
2,6-di-*tert*-butylphenol[c]	5 min	1.02		
	1 h	1.02	1.0	0.00
n-hexylamine	1 h	0.00	0.0	0.00
benzenethiol	5 min	0.99		
	1 h	0.99	1.05	0.06
1-hexanethiol	5 min	0.98		
	1 h	0.98	0.98	0.00

[a] Ten millimoles of compound was added to 40 mmol of $LiEt_3BH$ in 40 mL of solution (0.25 M in compound and 1.0 M in $LiEt_3BH$). [b] In mmol/mmol of compound. [c] Immediate white precipitate.

(29) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: New York, 1965; Chapter 7.

(30) The formation of the allylic alcohol from cinnamaldehyde does not appear to apply to cyclic α,β-unsaturated ketones. Our preliminary study showed that the reaction of 2-cyclohexen-1-one with an equimolar amount of the reagent at 0 °C gave, after hydrolysis, 46% cyclohexanone and 32% 2-cyclohexen-1-ol. A similar observation was recently made with potassium tri-*sec*-butylborohydride: Ganem, B. *J. Org. Chem.* **1975**, *40*, 146.

Table II. Reaction of Lithium Triethylborohydride with Representative Aldehydes and Ketones in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
caproaldehyde	5 min	0.04	1.06	1.02
	1 h	0.04	1.06	1.02
benzaldehyde	5 min	0.01	0.99	0.98
	1 h	0.01	0.99	0.98
2-heptanone	5 min	0.06	1.08	1.02
	1 h	0.06	1.08	1.02
norcamphor	5 min	0.03	1.02	0.99
	1 h	0.03	1.02	0.99
acetophenone	5 min	0.05	1.06	1.01
	1 h	0.05	1.06	1.01
benzophenone	5 min	0.03	1.06	1.03
	1 h	0.02	1.06	1.04
2,2,4,4-tetramethyl-3-pentanone	5 min	0.00	0.84	0.84
	0.25 h	0.00	0.94	0.94
	0.5 h	0.00	1.01	1.01
	1 h	0.00	1.01	1.01
cinnamaldehyde	5 min	0.01	1.04	1.03
	0.25 h	0.01	1.02	1.01
	0.5 h	0.01	1.04	1.03
	1 h	0.01	1.04	1.03
	3 h	0.01	1.10	1.09
	6 h	0.01	1.28	1.27
	24 h	0.01	1.55	1.54

[a,b] See the corresponding footnotes in Table I.

Recent developments in our laboratories clearly reveal that these stereoselectivities are greatly enhanced by increasing the steric requirements of the alkyl substituents on the boron atom. Thus, the reduction of 2-methylcyclohexanone yields 85% of *cis*-2-methylcyclohexanol with lithium tri-*n*-butylborohydride,[14] 97% with lithium perhydro-9b-boraphenalylhydride (PBPH),[14] 99.3% with lithium tri-*sec*-butylborohydride,[15] and 99.7% with lithium trisiamylborohydride.[16]

Cinnamaldehyde utilizes 1 equiv of hydride rapidly, with a slow uptake of the second hydride. This corresponds to a rapid initial reduction to the cinnamyl alcohol stage, followed by a slow addition of the reagent to the double bond. In fact, hydrolysis of a reaction mixture, utilizing an equimolar amount of the reagent, gave a quantitative yield of cinnamyl alcohol.[30] A detailed study of the addition of the reagent to the double bond of cinnamyl alcohol, as well as to other aromatically conjugated olefins, has been completed and will be published shortly. Cinnamyl alcohol was also realized in the reduction of cinnamaldehyde with 9-BBN[31] and with lithium tri-*tert*-butoxyaluminohydride,[21] whereas the reduction with both lithium aluminum hydride[20] and lithium trimethoxyaluminohydride[21] can involve simultaneous attack on the double bond.

The results for the reaction of lithium triethylborohydride with representative aldehydes and ketones are summarized in Table II.

Quinones. As was pointed out earlier,[20] the reduction of a quinone to a hydroquinone should utilize 2 equiv of hydride, one for reduction and one for hydrogen evolution. On the other hand, reduction to the 1,4-dihydroxycyclohexadiene stage should utilize 2 equiv of hydride for reduction, without hydrogen evolution.

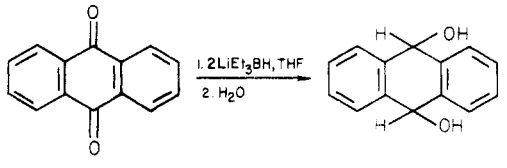
p-Benzoquinone rapidly consumed 1.19 equiv of hydride, of which 0.33 equiv was utilized for hydrogen evolution, with only slow further uptake of hydride. An immediate formation of a gelatinous precipitate was observed. This changed its color from an initial violet to brownish orange within 2 min. The value observed for the hydride uptake does not correspond to clean reduction to either stage.

Table III. Reaction of Lithium Triethylborohydride with Representative Quinones in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
p-benzoquinone[c,d]	0.25 h	0.33	1.19	0.86
	0.5 h	0.35	1.25	0.90
	1 h	0.33	1.29	0.96
	3 h	0.35	1.32	0.97
	6 h	0.32	1.37	1.05
	24 h	0.35	1.42	1.07
anthraquinone[e,f]	5 min	0.03	2.01	1.98
	1 h	0.03	2.01	1.98

[a,b] See the corresponding footnotes in Table I. [c] Each measurement was done separately on a 2-mmol scale and by hydrolyzing the reaction mixture in a reaction flask. [d] Immediate violet gellike substance and a color change into orange-brown in 1–2 min. After hydrolysis, the color changes into yellowish orange. [e] Reverse addition (solution of reagent added to suspension of anthraquinone). [f] Immediate color change to dark green, then to reddish violet, and finally to red, all within 5 min.

Anthraquinone, on the other hand, rapidly utilizes 2 equiv of hydride without significant hydrogen evolution, indicating a clean reduction to 9,10-dihydro-9,10-dihydroxyanthracene. Indeed, the diol was isolated following hydrolysis in a yield of 77% (eq 5). This diol has been



(5)

previously prepared from anthraquinone by utilizing 9-BBN[26] (79%) and sodium borohydride[32] (65%). The corresponding reactions with lithium aluminum hydride and lithium trimethoxyaluminohydride are not clean, giving a mixture of products. The results for these reactions of quinone with this reagent are summarized in Table III.

Carboxylic Acids and Acyl Derivatives. Carboxylic acids instantly evolve 1 equiv of hydrogen to form their lithium salts (eq 6). Even after 24 h, no further hydride

$$\mathrm{RCOOH} + \mathrm{LiEt_3BH} \xrightarrow{\text{fast}} \mathrm{RCOOLi} + \mathrm{Et_3B} + \mathrm{H_2} \quad (6)$$
$$\xrightarrow[\text{very slow}]{\mathrm{LiEt_3BH}} \mathrm{RCH_2OH}$$

uptake was observed with both caproic acid and benzoic acid. The reaction mixture of caproic acid immediately turned milky after the addition of the carboxylic acid to the reagent; it became more and more thick with time. However, the corresponding reaction mixture of benzoic acid remained clear. The starting material, the carboxylic acid, can be regenerated by simple hydrolysis and is formed quantitatively, as revealed by GLC analysis in the case of caproic acid.

The inertness of carboxylic acids to reduction by $LiEt_3BH$ is quite surprising. Such behavior for carboxylic acids has been noted for mild reducing agents, such as sodium borohydride[33] and lithium tri-*tert*-butoxy-

(31) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1975**, *40*, 1864. (b) *Ibid.* **1977**, *42*, 1197.

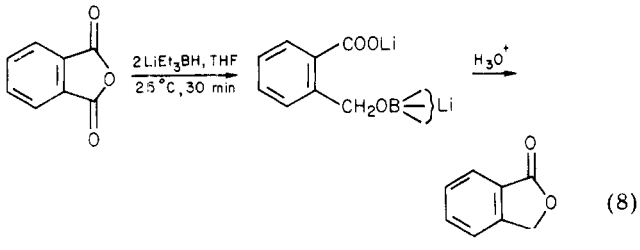
(32) (a) Criswell, T. R.; Klenderman, B. H. *J. Org. Chem.* **1974**, *39*, 770. (b) Meek, J. S.; Koh, L. L. *Ibid.* **1968**, *33*, 2942.

aluminohydride.[21] The reagent, therefore, should be highly useful for the selective reduction of many other reducible functional groups in the presence of the carboxylic acid grouping.

Acid anhydrides rapidly consume 2 equiv of hydride without further uptake, corresponding to reduction to the carboxylic acid and alcohol stages (eq 7). It should be

$$CH_3COCCH_3 + LiEt_3BH \xrightarrow{THF} CH_3COOLi + CH_3CHO + Et_3B \quad (7)$$
$$\downarrow LiEt_3BH$$
$$CH_3CH_2OH$$

possible to utilize this characteristic for the in situ conversion of cyclic anhydrides to lactones. In fact, a 90% yield of phthalide was realized in the reduction of phthalic anhydride with 2 equiv of the reagent, followed by acid hydrolysis (eq 8).



(8)

90% (76% isolated)

Procedures have been developed for the conversion of cyclic acid anhydrides to lactones by utilizing sodium borohydride and lithium aluminum hydride and its alkoxy derivatives.[34,35] Lithium triethylborohydride exhibits exceptional promise for such transformations under very mild reaction conditions.

Acid chlorides utilize 2 equiv of hydrides rapidly, yielding the corresponding alcohol in quantitative yield (eq 9). In the case of caproyl chloride, some hydrogen evolution was observed, and the yield of the alcohol (1-hexanol) was somewhat low, only 83%. Possibly there is some attack at the reactive α position.

$$RCOCl + 2LiEt_3BH \xrightarrow{THF} \xrightarrow{H_2O} RCH_2OH \quad (9)$$

In order to test the possibility that lithium triethylborohydride might be capable of bringing about a partial reduction to the aldehyde stage either of acid chlorides at low temperatures or of carboxylic acids at higher temperatures, reductions using stoichiometric amounts of the reagent (1 molar equiv for the acid chloride and 2 molar equiv for the carboxylic acid) were tried. For caproyl chloride, the reagent was slowly added to the compound (reverse addition) at −78 °C and maintained there. After 2 h, the reaction mixture was allowed to warm to room temperature, hydrolyzed, and analyzed by GLC. There was present 1-hexanol in 20–23% yield and a small amount of *n*-hexyl hexanoate; no caproaldehyde could be detected. A 2,4-DNP test also failed to indicate the formation of any aldehyde. The reagent failed to reduce either caproic or benzoic acid even after 24 h at reflux (65 °C). GLC analysis of these reaction mixtures, following hydrolysis, indicated the formation of only a trace amount of the corresponding alcohols. In neither case was formation of aldehyde detected.

Table IV. Reaction of Lithium Triethylborohydride with Representative Carboxylic Acids and Acyl Derivatives in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total H_2 used[b]	hydride used for redn[b]
caproic acid[c]	5 min	1.03	1.03	0.00
	24 h	1.02	1.05	0.03
benzoic acid	5 min	1.02	1.03	0.01
	1 h	1.02	1.03	0.01
acetic anhydride	5 min	0.03	1.99	1.96
	24 h	0.03	1.99	1.96
succinic anhydride	5 min	0.11	2.07	1.96
	1 h	0.11	2.07	1.96
phthalic anhydride	5 min	0.10	2.01	1.91
	24 h	0.10	2.01	1.91
caproyl chloride	5 min	0.10	1.93	1.83
	1 h	0.10	1.95	1.85
benzoyl chloride	5 min	0.03	1.98	1.95
	1 h	0.03	2.01	1.98

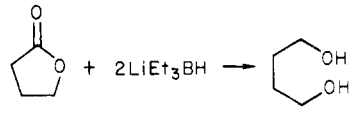
[a, b] See the corresponding footnotes in Table I. [c] The solution turns milky and gets thicker with time.

The experimental results for the reaction of the reagent with representative carboxylic acids, anhydrides, and acid chlorides are summarized in Table IV.

Esters and Lactones. Esters and lactones rapidly take up 2 equiv of hydride, undergoing reduction to the alcohol and diol stage, respectively. Hydrolysis of the reaction mixture from ethyl caproate with 2 equiv of the reagent provided a 100% yield of 1-hexanol (eq 10). Similarly,

$$CH_3(CH_2)_4COOC_2H_5 + 2LiEt_3BH \xrightarrow[25\ °C,\ 2\ min]{THF} \xrightarrow{H_2O} CH_3(CH_2)_4CH_2OH + C_2H_5OH \quad (10)$$

1,4-butanediol was formed in 94% yield in the reduction of γ-butyrolactone (eq 11). Isopropenyl acetate rapidly



(11)

utilized 3 equiv of hydride. Presumably, the acetate group is reduced to the ethanol stage (two hydrides) and the isopropenyl group to the isopropyl alcohol stage (one hydride).

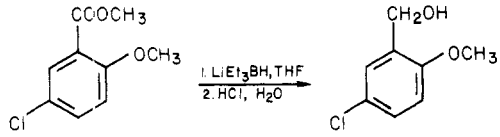
The possibility of selectively reducing a carboxylic acid ester to the corresponding aldehyde with lithium triethylborohydride was also explored. Accordingly, an equimolar amount of the reagent was slowly added to a solution of ethyl caproate in THF at −78 °C. After 1 h, the reaction mixture was allowed to warm to room temperature and hydrolyzed. GLC analysis revealed the absence of caproaldehyde and a 49% yield (based on the ester) of 1-hexanol. Also, 50% of the original ester was recovered. This suggests that the initial reaction product, the tetrahedral intermediate, breaks down approximately as rapidly as it is formed.

The exceptionally high reactivity of $LiEt_3BH$ toward ester groups is demonstrated by the selective reduction of esters of aromatic carboxylic acids to alcohols in the presence of other functional groups[36] (eq 12 and 13).

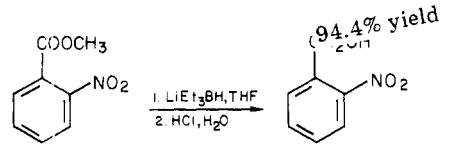
The experimental data for the reaction of lithium triethylborohydride with representative esters and lactones

(33) Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122.
(34) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574.
(35) (a) Bloomfield, J. J.; Lee, S. H. *J. Org. Chem.* **1967**, *32*, 3919. (b) Crose, B. E.; Stewart, J. C. *Tetrahedron Lett.* **1968**, 3589. (c) Birckelbaw, M. E.; LeQuesne, P. M.; Wocholski, C. K. *J. Org. Chem.* **1970**, *35*, 558.

(36) Lane, C. F. *Aldrichimica Acta* **1974**, *7*, 32.



(12)



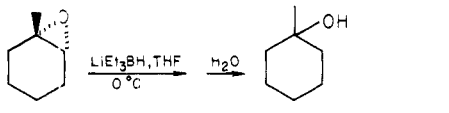
(94.4% yield)

(13)

99.7% yield

are summarized in Table V.

Epoxides, Acetals, Ketals, and Ortho Esters. All of the epoxides examined utilized 1 mol of hydride, undergoing rapid and quantitative reduction to the corresponding alcohols. The opening of the epoxide ring with this reagent proceeds with exceptional regio- and stereoselectivity, yielding the Markovnikov alcohol exclusively. Thus, 1,2-epoxybutane gives 2-butanol, and 1-methylcyclohexene oxide gives 1-methylcyclohexanol exclusively (eq 14). The only exception to such exclusive formation



(14)

100% (100% tertiary)

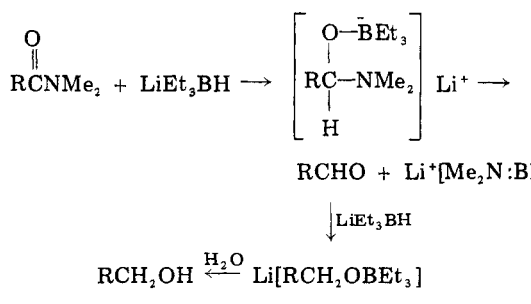
of the Markovnikov alcohol appears to be the reduction of styrene oxide, which proceeds to yield a mixture of 97% of 1-phenylethanol and 3% of 2-phenylethanol. Similar behavior has been noted for this system with other hydride reagents previously examined.

The acetal, ketal, and ortho ester[37] examined proved to be inert toward the reagent under the experimental conditions. Following treatment with the reagent for 24 h, 90% recovery of 2-phenyldioxolane from the reaction mixture was achieved. Consequently, aldehyde or keto groups can be readily protected from the reagent by converting them to the corresponding acetals or ketals. These results are summarized in Table VI.

Amides and Nitriles. Primary amides react almost instantly to evolve 1 equiv of hydrogen; further hydrogen evolution does not occur even over extended periods of time. While caproamide then undergoes a sluggish reduction, the corresponding reduction of benzamide is even slower. On the other hand, the reactions with tertiary amides are much faster. *N,N*-Dimethylcaproamide rapidly utilizes only 1.46 equiv of hydride within 5 min, with further uptake of hydride being relatively slow and incomplete.[38] On the other hand, *N,N*-dimethylbenzamide consumes 2 equiv of hydrides within 5 min. *N,N*-Dimethylpivalamide also utilizes 2 equiv of hydride but requires between 3 and 6 h for completion. The slower rate observed for the pivalic acid derivatives is attributed to the higher steric requirements of this compound.

Unlike most other hydride reducing agents, which react with tertiary amides to give amines as major products (if not the only product), $LiEt_3BH$ reduces these tertiary amides to the corresponding alcohols. Thus, by treating the tertiary amides with two equiv of the reagent, we obtained an 80% yield of 1-hexanol, a 97% yield of benzyl alcohol, and a 95% yield of neopentyl alcohol. No evidence was obtained for the presence of the corresponding tertiary amines.

The mechanism of this reaction is probably similar to that proposed by Weygand for reductions with lithium aluminum hydride[39] (eq 15).



(15)

The possibility of achieving partial reduction of tertiary amides to the corresponding aldehydes[40] was examined

Table V. Reactions of Lithium Triethylborohydride with Representative Esters and Lactones in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
ethyl	5 min	0.01	2.02	2.01
caproate	1 h	0.01	2.02	2.01
ethyl	5 min	0.01	1.98	1.97
benzoate	1 h	0.01	2.00	1.99
phenyl	5 min	0.07	2.09	2.02
acetate	1 h	0.07	2.10	2.03
γ-butyro-	5 min	0.02	2.00	1.98
lactone	1 h	0.02	2.02	2.00
phthalide	5 min	0.03	2.03	2.00
	0.5 h	0.03	1.97	1.95
isopropenyl	5 min	0.01	2.94	2.93
acetate	1 h	0.01	2.98	2.97

[a,b] See the corresponding footnotes in Table I.

Table VI. Reaction of Lithium Triethylborohydride with Representative Epoxides, Acetals, Ketals, and Ortho Esters in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
1,2-butylene	5 min	0.02	1.03	1.01
oxide	1 h	0.02	1.03	1.01
styrene	5 min	0.00	1.02	1.02
oxide	1 h	0.00	1.00	1.00
cyclohexene	5 min	0.03	1.04	1.01
oxide	1 h	0.03	1.03	1.00
1-methyl-1,2-	5 min	0.01	1.00	0.99
cyclohexene	1 h	0.01	1.04	1.03
oxide				
2-phenyl-	5 min	0.03	0.02	0.00
dioxolane	6 h	0.03	0.06	0.03
	24 h	0.05	0.10	0.05
2-methyl-2-ethyl-	5 min	0.05	0.08	0.03
dioxolane	24 h	0.05	0.08	0.03
triethyl	5 min	0.01	0.01	0.00
orthoformate	24 h	0.01	0.03	0.02

[a,b] See the corresponding footnotes in Table I.

(37) Ortho esters are readily reduced to the corresponding acetals with lithium aluminum hydride: Claus, C. J.; Morganthau, J. L., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 5005.

(38) It is probable that the incomplete hydride uptake observed with *N,N*-dimethylcaproamide is due to the formation of $LiNMe_2$ according to this mechanism. $LiNMe_2$ (or its triethylborane complex) thus formed may metalate the intermediate aldehyde or the still unreacted amide at the α position to form the corresponding lithium salt which would resist further reaction with lithium triethylborohydride. For the other two tertiary amides, no such complication should be involved, because of the absence of any α-hydrogen.

(39) Weygand, F.; Linde, H.; Schäfer, F.; Eigen, I. *Angew. Chem.* **1953**, *65*, 525.

with *N,N*-dimethylcaproamide by using the same procedure previously described for caproyl chloride. Indeed, GLC analysis of the reaction mixture following hydrolysis revealed the presence of 67% of caproaldehyde, 12% of 1-hexanol, and 21% of residual amide. No attempt was made to maximize the yield in this promising new approach to an aldehyde synthesis. However, further study is planned.

The reaction of nitriles with triethylborohydride is unique. Aliphatic nitriles, such as capronitrile, utilize 1 equiv of hydride but fail to show any further hydride uptake with time. No hydrogen evolution is observed in this reaction. This stoichiometry appeared to indicate the formation of a stable imine derivative which, upon hydrolysis, would yield caproaldehyde. Contrary to this expectation, analysis of the reaction product following hydrolysis revealed the presence of approximately half of the initial nitrile. Moreover, no aldehyde was present. Further, the acid-assisted hydrolysis of this reaction mixture resulted in the formation of *n*-hexylamine in a yield of 40%. These unexpected results can be accounted for in terms of the mechanism[41] shown in eq 16–19.

$$CH_3(CH_2)_4CN + 2LiEt_3BH \rightarrow \underset{\mathbf{1}}{[CH_3(CH_2)_4CH_2N(BEt_3)_2]^{2-}(Li^+)_2} \quad (16)$$

$$\mathbf{1} + CH_3(CH_2)_4CN \rightarrow \underset{\mathbf{2}}{[CH_3(CH_2)_4CH_2NH{-}\bar{B}Et_3]Li^+} + \underset{\mathbf{3}}{[CH_3(CH_2)_3CH{=}C{=}N{-}\bar{B}Et_3]Li^+} \quad (17)$$

$$2 \xrightarrow{H_3O^+} CH_3(CH_2)_4CH_2NH_2 \quad (18)$$

$$3 \xrightarrow{H_2O} CH_3(CH_2)_4CN \quad (19)$$

Benzonitrile, on the other hand, utilizes 2 equiv of hydride within 5 min under standard conditions (4 molar equiv of reagent), indicating a clean reduction to the benzylamine stage. However, when 2 molar equiv of the reagent was used, the hydride uptake decreased to 1.7 equiv. GLC analysis of this reaction mixture following hydrolysis indicated the formation of 80% of benzylamine and 8.5% of benzaldehyde. Furthermore, addition of an equimolar amount of the reagent (1:1) to benzonitrile in THF at 0 °C or 25 °C produced an 85–97% yield of benzaldehyde following hydrolysis of the reaction mixture. Further study revealed that the 1:1 adduct **4** is in equilibrium with 2:1 adduct **5** (eq 20 and 21).

$$PhC{\equiv}N + LiEt_3BH \rightarrow \underset{\mathbf{4}}{[PhCH{=}N{-}\bar{B}Et_3]Li^+} \quad (20)$$

$$\mathbf{4} + LiEt_3BH \rightleftharpoons \underset{\mathbf{5}}{[PhCH_2N(BEt_3)_2]^{2-}(Li^+)_2} \quad (21)$$

Further studies on these unusual reactions of nitriles[41] and their potential applications for the synthesis of aldehydes are currently underway.[42] The experimental results of these studies of the reactions of the reagent with amides and nitriles are summarized in Table VII.

Table VII. Reaction of Lithium Triethylborohydride with Representative Amides and Nitriles in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
caproamide	5 min	1.04	1.13	0.09
	0.25 h	1.04	1.15	0.11
	0.5 h	1.04	1.20	0.16
	1 h	1.04	1.21	0.17
	3 h	1.04	1.27	0.23
	6 h	1.04	1.27	0.23
	24 h	1.04	1.45	0.41
benzamide	5 min	1.05	1.03	0.00
	6 h	1.05	1.03	0.00
	24 h	1.05	1.11	0.06
N,N-dimethyl-caproamide[c]	5 min	0.00	1.46	1.46
	0.25 h	0.00	1.46	1.46
	0.5 h	0.00	1.48	1.48
	1 h	0.00	1.54	1.54
	4 h	0.00	1.82	1.82
	6 h	0.00	1.86	1.86
	24 h	0.00	1.86	1.86
N,N-dimethyl-benzamide	5 min	0.00	2.01	2.01
	1 h	0.00	1.99	1.99
N,N-dimethyl-pivalamide	0.25 h	0.01	0.83	0.82
	0.5 h	0.01	1.14	1.13
	1 h	0.01	1.51	1.50
	3 h	0.02	1.90	1.88
	6 h	0.03	2.10	2.07
	12 h	0.03	2.12	2.09
capronitrile	5 min	0.00	1.03	1.03
	24 h	0.00	1.03	1.03
benzonitrile[d]	5 min	0.01	2.00	1.99
	1 h	0.01	2.00	1.99
	0.25 h[e]	0.00	1.68	1.68
	1 h[e]	0.00	1.72	1.72
	7 h[e]	0.00	1.70	1.70

[a,b] See the corresponding footnotes in Table I. [c] White precipitate. [d] Immediate color change to red-violet and then to pale greenish yellow within 5 min. [e] 0.5 M in hydride (hydride/compound ratio = 2).

Nitro Compounds and Their Derivatives. 1-Nitropropane rapidly evolves 1 equiv of hydrogen, forming a white precipitate, with no hydride consumed for reduction. Presumably, the active α-hydrogen is involved in this reaction (eq 22). The starting material can be recovered

$$CH_3CH_2CH_2NO_2 + LiEt_3BH \longrightarrow CH_3CH_2CH{=}\overset{+}{N}(O^-)(OLi) \downarrow + Et_3B \quad (22)$$

quantitatively by careful hydrolysis. This observation suggests the possibility of reducing other functional groups selectively in the presence of an aliphatic nitro group. Exploration of the applicability of this reaction for the synthesis of aldehydes by a Nef-type reaction[43] would also be interesting.

Nitrobenzene rapidly utilizes 2 equiv of hydride for reduction with slight hydrogen evolution, and the values do not change significantly with time. The amount of the hydrogen evolved in a series of experiments varied from 0.25 to 0.5 equiv. Although the amount of the hydride utilized corresponds to reduction to the azobenzene stage, the amount of hydrogen evolved is not in accord with this

(40) Partial reduction of tertiary amides to aldehydes has been successful with lithium aluminum hydride, lithium di- and triethoxyaluminohydride, lithium diisobutylaluminohydride, and disiamylborane.[15] See: Staab, H. A.; Braeunling, H. *Justus Liebigs Ann. Chem.* **1962**, *654*, 119. Brown, H. C.; Tsukamoto, T. *J. Am. Chem. Soc.* **1961**, *83*, 4549. *Ibid.* **1964**, *86*, 1089. Duhamel, P.; Duhamel, L.; Siret, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1970**, *270*, 1750.

(41) Kim, S. C. Ph.D. Thesis, Purdue University, West Lafayette, Indiana, 1976.

(42) Currently, the aldehyde synthesis by partial reduction of nitriles is best carried out with lithium triethoxyaluminohydride: Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085.

(43) For a review, see: Noland, W. E. *Chem. Rev.* **1955**, *55*, 137.

Table VIII. Reduction of Representative Nitro Compounds and Their Derivatives with Lithium Triethylborohydride in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
nitro-	5 min	1.04	1.03	0.00
propane[c]	3 h	1.04	1.05	0.01
nitro-	5 min	0.26	2.06	1.80
benzene[d,e]	0.25 h	0.26	2.12	1.86
	0.5 h	0.26	2.16	1.90
	1 h	0.26	2.16	1.90
	3 h	0.26	2.18	1.92
	6 h	0.26	2.24	1.98
	24 h	0.29	2.36	2.07
	1 h[f]	0.52	2.44	1.92
	3 h[f]	0.52	2.52	2.00
azo-	5 min	0.01	0.18	0.17
benzene[g]	0.25 h	0.02	0.25	0.23
	0.5 h	0.03	0.45	0.42
	1 h	0.05	0.73	0.68
	3 h	0.07	0.97	0.90
	6 h	0.10	1.09	0.99
	24 h	0.14	1.15	1.01
azoxy-	5 min	0.05	1.26	1.21
benzene[h]	0.25 h	0.05	1.51	1.46
	0.5 h	0.05	1.63	1.58
	1 h	0.05	1.73	1.68
	3 h	0.08	1.90	1.82
	6 h	0.14	2.09	1.95
	24 h	0.30	2.17	1.87
	1 h[f]	0.62	2.57	1.95
	3 h[f]	0.67	2.72	2.05

[a,b] See the corresponding footnotes in Table I. [c] Immediate white precipitate. [d] Color changes to green, then to dark red, and finally to orange, all within 5 min. [e] The value of hydrogen evolution was observed to be 0.26–0.5 with a series of experiments. [f] At 25 °C. [g] Color changes to dark red and slowly to dark green. [h] Initial color changes to dark orange and then to brown in 5 min.

possible reaction. Consequently, a decision as to the course of reaction is best deferred until it is possible to explore this reaction in greater detail.

Azobenzene is slowly reduced, utilizing 1 equiv of hydride for reduction in 6 h accompanied by slow but continuous hydrogen evolution. This corresponds to reduction to the hydrazobenzene stage.

Azoxybenzene utilizes 1.21 equiv of hydride rapidly; further hydride uptake is sluggish and is accompanied by slow hydrogen evolution. This indicates that the initial reduction to the azobenzene stage is rapid, followed by slow reduction to the hydrazobenzene stage.

Interesting color changes are observed in those reactions involving nitrogen compounds with $LiEt_3BH$. With nitrobenzene, the solution became green immediately, changing to dark red and finally to orange—all occurring within 5 min. The azobenzene solution became dark red and slowly changed to dark green. Azoxybenzene, on the other hand, showed an immediate color change to dark orange and then to brown within 5 min.

It is interesting to note that lithium tri-*tert*-butoxyaluminohydride, while inert to nitrobenzene, azobenzene, and azoxybenzene, gives the same results with 1-nitropropane, evolving 1 equiv of hydrogen without reduction taking place. Aluminum hydride is inert to these compounds, whereas lithium aluminum hydride and lithium trimethoxyaluminohydride reduce all of the four compounds relatively slowly.

The results of these experiments are summarized in Table VIII.

Table IX. Reaction of Lithium Triethylborohydride with Representative Other Nitrogen Compounds in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
cyclohexanone	5 min	1.03	1.01	0.00
oxime[c]	24 h	1.04	1.01	0.00
phenyl	5 min	0.01	1.05	1.04
isocyanate	24 h	0.01	1.03	1.02
pyridine[d]	5 min	0.00	2.12	2.12
	0.25 h	0.00	2.12	2.12
	0.5 h	0.00	2.10	2.10
	1 h	0.00	2.14	2.14
	3 h	0.00	2.20	2.20
	6 h	0.00	2.28	2.28
	24 h	0.00	2.40	2.40
	1 h[e]	0.00	2.23	2.23
	24 h[e]	0.00	2.30	2.30
pyridine	5 min	0.07	2.50	2.43
N-oxide[f]	0.25 h	0.11	2.68	2.57
	0.5 h	0.17	2.72	2.55
	1 h	0.26	2.85	2.59
	3 h	0.43	2.93	2.50
	6 h	0.52	3.01	2.49
	24 h	0.64	3.07	2.43

[a,b] See the corresponding footnotes in Table I. [c] Thick white milky solution. [d] Color changes to pale yellowish green, then to light orange, and finally to yellowish green, all within 5 min. After 6 h, the color changes to yellowish orange. [e] At 25 °C. [f] Color changes to light green, then to yellowish orange, and finally to orange in 5 min. This slowly changes to red and then to dark red.

Other Nitrogen Compounds. Cyclohexanone oxime rapidly liberates 1 equiv of hydrogen, without undergoing reduction under the standard conditions. Consequently, the formation of oximes would provide another means for protecting carbonyl groups toward $LiEt_3BH$, permitting selective reduction of other reactive functional groups in the same molecule.

Phenyl isocyanate is rapidly reduced, utilizing 1 equiv of hydride, corresponding to reduction to the formanilide stage. Although the formation of formanilide was confirmed by product analysis, this does not appear to be a practical procedure, since hydrolysis of the initial reaction product required acid, converting the formanilide intermediate into aniline.

Lithium triethylborohydride reacts with pyridine with remarkable ease. Two equivalents of hydride are utilized within 5 min, indicating conversion of the pyridine ring to a tetrahydropyridine derivative. Further reaction, presumably to the piperidine stage, is quite slow and incomplete. More detailed investigation of the actual positions of addition with varying amounts of the hydride appears quite attractive. Pyridine *N*-oxide also reacts rapidly, utilizing a puzzling 2.5 equiv of hydride rapidly, with slow subsequent hydrogen evolution.

These experimental results are summarized in Table IX.

Oximes are rapidly reduced to the amine stage by both lithium aluminum hydride and aluminum hydride.[44] On the other hand, diborane reduces oximes to the corresponding hydroxylamines.[45] Both reagents also reduce phenyl isocyanate to the *N*-methylaniline stage. Lithium trimethoxyaluminohydride reduces phenyl isocyanate to the same stage, whereas the product with lithium tri-

(44) Aluminum hydride was shown to give a better yield of amines from oximes than lithium aluminum hydride: Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1968**, *90*, 2927.

(45) Feuer, H.; Vincent, B. F., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3771. Feuer, H.; Vincent, B. F., Jr.; Bartlett, R. S. *J. Org. Chem.* **1965**, *30*, 2877.

tert-butoxyaluminohydride appears to be the formanilide.

Sulfur Compounds. Disulfides are rapidly reduced to the thiol stage, utilizing 2 equiv of hydride, one for reduction and one for hydrogen evolution (eq 23). Thus,

$$RSSR + 2LiEt_3BH \rightarrow 2RSLi + 2Et_3B + H_2 \quad (23)$$

diphenyl sulfide undergoes reduction to benzenethiol rapidly and quantitatively.

Methyl *p*-tolyl sulfide and dimethyl sulfoxide are essentially inert to the reagent under reaction conditions. While di-*n*-butyl sulfone is inert to the reagent, the reaction with diphenyl sulfone takes an entirely different course. It utilizes 1 equiv of hydride (6 h), forming a white precipitate. Following heating of the reaction mixture at reflux, ethylbenzene was detected in 75% yield. Consequently, we are achieving an alkylation of the benzene ring (eq 24). In this reaction, any formation of the corresponding sulfoxide or sulfide was not detected by GLC. A detailed study of this reaction is underway and will be reported shortly.

$$PhSO_2Ph \xrightarrow[THF,\ reflux]{LiEt_3BH} PhCH_2CH_3 \quad (24)$$

Sulfonic acids rapidly evolve the theoretical amount of hydrogen, but no significant hydride uptake for reduction is observed. Cyclohexyl tosylate reacts slowly, accompanied by slow hydrogen evolution under the experimental conditions. The reaction gives a mixture of products: 76% cyclohexane and 20% cyclohexene.[11] This yield of cyclohexane is significantly higher than that achieved by lithium aluminum hydride, which gives 54.1% of cyclohexane, along with 25.4% of cyclohexene and 19.5% of cyclohexanol.[19]

The inertness of dimethyl sulfoxide to lithium triethylborohydride is somewhat of a surprise. This behavior is only comparable to that of lithium tri-*tert*-butoxyaluminohydride among the aluminohydrides and boron hydrides previously examined.[19-26]

These experimental results with representative sulfur compounds are summarized in Table X.

Table X. Reaction of Lithium Triethylborohydride with Representative Sulfur Compounds in Tetrahydrofuran at 0 °C

compd[a]	time	H_2 evolved[b]	total hydride used[b]	hydride used for redn[b]
di-*n*-butyl disulfide	5 min	1.03	2.00	.097
	1 h	1.03	2.02	0.99
diphenyl disulfide	5 min	1.02	2.01	0.99
	1 h	1.02	1.99	0.97
methyl *p*-tolyl sulfide	5 min	0.00	0.00	0.00
	24 h	0.00	0.02	0.02
dimethyl sulfoxide	5 min	0.00	0.00	0.00
	1 h	0.01	0.02	0.01
	3 h	0.04	0.09	0.05
	6 h	0.07	0.09	0.02
	24 h	0.14	0.21	0.07
di-*n*-butyl sulfone	5 min	0.04	0.04	0.00
	24 h	0.04	0.04	0.00
diphenyl sulfone[c]	5 min	0.01	0.04	0.03
	0.25 h	0.01	0.04	0.03
	0.5 h	0.01	0.11	0.10
	1 h	0.01	0.17	0.16
	6 h	0.01	0.58	0.57
	24 h	0.01	0.94	0.93
methanesulfonic acid[d]	5 min	1.05	1.03	0.00
	1 h	1.05	1.05	0.00
	24 h[e]	1.03	1.06	0.03
p-toluenesulfonic acid monohydrate	5 min	2.05	2.06	0.01
	1 h	2.05	2.03	0.00
	3 h	2.05	2.05	0.00
	6 h	2.05	2.08	0.03
	24 h	2.05	2.22	0.17
cyclohexyl tosylate	5 min	0.01	0.00	0.00
	0.5 h	0.02	0.00	0.00
	1 h	0.04	0.17	0.13
	6 h	0.17	0.65	0.48
	24 h	0.30	1.04	0.74

[a,b] See the corresponding footnotes in Table I. [c] Color changes to pale green, then to light orange, and finally to red orange after 15 min. Color slowly fades away with formation of white precipitate after 6-24 h. [d] White precipitate. [e] At 25 °C.

Synthetic Possibilities of Lithium Triethylborohydride. It was previously demonstrated that lithium triethylborohydride is an exceptionally powerful nucleophile in S_N2 displacement reactions with alkyl halides, far more powerful than lithium aluminum hydride and lithium borohydride. Thus, the replacement of the four hydrogens in the parent lithium borohydride molecule with three ethyl groups enhances the hydride transfer ability by some 10000 times ($k_{Et_3BH^-/BH_4^-} = 10^4$).[8] The present study reveals that lithium triethylborohydride is in fact a very powerful reducing agent, capable of reducing many functional groups with great ease in a manner not observed with any of the previously examined reducing agents. Yet, lithium triethylborohydride exhibits remarkable selectivity with many functional groups, a characteristic usually associated with relatively mild reducing agents, such as sodium borohydride and lithium tri-*tert*-butoxyaluminohydride. Consequently, it is desirable at this point to point out the most promising areas of possible applications of lithium triethylborohydride, as well as other trialkylborohydrides.

Lithium triethylborohydride reacts rapidly with primary or secondary alcohols and phenols, but the reactions with tertiary alcohols are relatively slow. Primary (and presumably secondary) amines are inert to this reagent. This suggests the use of lithium triethylborohydride to react preferentially with the primary or secondary alcohol group in a molecule containing a tertiary hydroxyl group or amino groups. In this manner, the tertiary hydroxyl or amino group could be operated upon by suitable reactions as the reagent blocks the primary or secondary hydroxyl group as the complex, $-OBEt_3]^-Li^+$.

Lithium triethylborohydride reduces aldehydes and ketones rapidly and quantitatively (at 0 °C or even −78 °C). Even hindered ketones such as di-*tert*-butyl ketone, camphor, etc., undergo relatively rapid reduction. The corresponding alcohols can be easily isolated in excellent yields. The unusually high stereoselectivity achieved in the reduction of cyclic and bicyclic ketones with hindered and highly hindered trialkylborohydrides is one of the most attractive characteristics of these derivatives. This has found numerous applications.[8,9] Protection of such carbonyl compounds may be conveniently achieved by converting them to acetals, ketals, or oximes, thus making possible the selective reduction of other less readily reducible functional groups in the presence of such aldehyde or keto groups.

Lithium triethylborohydride and potassium tri-*sec*-butylborohydride add cleanly in a conjugate fashion (1,4-addition) to α,β enones and α,β enoates. This provides a facile and efficient route to lithium and potassium enolates.[30,46] Such enolates are versatile intermediates in the synthesis of carbon structures as they react with a variety of electrophiles.[46,47]

The rapid and clean reduction of anthraquinone to

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9,10-dihydro-9,10-dihydroxyanthracene with lithium triethylborohydride serves as a convenient alternative to other reagents, which have previously been demonstrated to achieve this reduction, such as 9-BBN[26] and aluminum hydride.[22]

The inertness or the nonreducibility (for those which evolve only hydrogen and can be recovered quantitatively by hydrolysis) exhibited toward the reagent by carboxylic acids, primary amides, aliphatic nitro compounds, oximes, sulfides, alkyl sulfones, sulfonic acids, and aryl halides[8] should be especially useful for the selective reductions of other reducible functional groups in the presence of these "inert" groups. For instance, reduction of the keto group without affecting the carboxylic group in the same molecule would be possible. For this purpose, sodium borohydride, lithium tri-*tert*-butoxyaluminohydride, 9-BBN, and disiamylborane have been utilized in the past. The reagent should be especially valuable in permitting a rapid reduction of carboxylic ester groups in the presence of carboxylic acid groups.[36] The reverse selective reduction is readily achieved with borane in THF.[23]

Lactone synthesis from cyclic anhydrides appears to be another promising area for lithium triethylborohydride, requiring further exploration. Examination of the regio- and stereoselectivity achievable in the case of unsymmetrical cyclic anhydrides with various trialkylborohydrides would also be highly interesting.

Lithium triethylborohydride in tetrahydrofuran possesses an exceptional capability for the facile regio- and stereospecific reductive opening of hindered and labile epoxides to give the Markovnikov alcohol in excellent isomeric purity.

Similarly, quaternary ammonium salts are reduced rapidly and cleanly to the corresponding amines in quantitative yield. Even more interesting is the fact that the reagent is capable of discriminating between methyl and ethyl groups.[48]

The reduction of tertiary amides exclusively to the corresponding alcohols is also one of the unique features of lithium triethylborohydride. The reagent appears at this stage to be advantageous over other conventional reagents for this purpose.

Aldehyde synthesis by partial reduction of tertiary amides and aromatic nitriles deserves further exploration with respect to its generality and applicability.

The formation of ethylbenzene in the reaction of lithium triethylborohydride with diphenyl sulfone not only is mechanistically interesting but also indicates a promising possibility for the convenient preparation of various alkylbenzenes, especially for the synthesis of pure *n*-alkylbenzenes.

Triethylborohydride provides an advantageous and convenient procedure for the deoxygenation of alcohols through the reduction of their *p*-toluenesulfonate esters. The reaction is applicable to tosylates derived from acyclic, cyclic, and hindered alcohols.

Finally, our recent study revealed that lithium triethylborohydride is capable of adding to various olefins under relatively mild conditions.[49] These reactions not only provide a simple hydrogenation of olefins but also lead to formation of trialkylboranes of unusual structures.

Conclusions

A systematic exploration of the reaction of representative organic functional groups with lithium triethylborohydride in tetrahydrofuran has now been completed. This study has led to an overall understanding of the unusual characteristics of this new reducing agent. The data clearly reveal that lithium triethylborohydride is an exceptionally powerful hydride reducing agent, far more powerful than lithium borohydride and apparently even more powerful than lithium aluminum hydride in many cases. Thus the reagent appears to be the most powerful nucleophile available to organic chemists for displacement reactions of alkyl halides, alkyl tosylates, and epoxides. Yet the reagent exhibits a remarkable selectivity toward a number of organic functional groups—a property normally considered to be characteristic of relatively mild reducing agents, such as sodium borohydride. It is evident that lithium triethylborohydride possesses unique and exceptional reducing characteristics not present in other hydride reagents and should therefore find many useful applications in organic synthesis.

Experimental Section

Materials. Tetrahydrofuran was distilled over lithium aluminum hydride under nitrogen and stored over 5 Å molecular sieves. Lithium hydride (Alfa Inorganics) and triethylborane (Callery Chemical Co.) were used without further purification.

Most of the organic compounds utilized in this study were commercial products of the highest available purity. They were further purified by distillation or recrystallization when necessary. Some compounds were synthesized by using standard procedures. In all of the cases, physical constants agreed satisfactorily with constants in the literature. All glassware was dried thoroughly in a drying oven and cooled under a dry stream of nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere, and hypodermic syringes were used to transfer the solutions.

Standard Solution of Lithium Triethylborohydride.[49] In a dry 500-mL flask fitted with a side arm, a rubber syringe cap, and a magnetic stirring bar, 7.2 g (900 mmol, 50% excess) of lithium hydride was placed, and a reflux condenser connected to a mercury bubbler was attached. After 314.8 mL of THF was introduced, the system was flushed with nitrogen. While the mixture was vigorously stirred, 85.2 mL (600 mmol, total volume of the solution 400 mL) of triethylborane was introduced slowly. Generally, an exothermic reaction begins some 5–15 min following the addition. At this stage, an ice bath was placed under the flask to control the reaction and to avoid overflow of the reaction mixture through the condenser. After this vigorous reaction was over, the reaction mixture was refluxed for 2–3 h in order to ensure completion. The resulting solution was filtered through a filter chamber fitted with a sintered-glass (fine-grade) filter under slight positive pressure of nitrogen in order to remove excess lithium hydride. The resulting clear solution was standardized by removing an aliquot, hydrolyzing it with a water–glycerine–THF (1:1:1) mixture, and measuring the hydrogen evolved. With a series of preparations, the concentrations were determined to be in the range of 1.45–1.55 M in $LiEt_3BH$.

The THF solution of lithium triethylborohydride is characterized by a strong, broad absorption in the IR at 2060 cm^{-1} (BH).[49] If the solution was maintained under a dry nitrogen atmosphere, no change in composition was detected in months at room temperature or in days at 65 °C (refluxing THF).

Procedure for Study of the Rate and Stoichiometry. The reduction of ethyl benzoate is representative. The lithium triethylborohydride solution, 26.7 mL of a 1.50 M solution (40 mmol), and 3.3 mL of THF were introduced into a dried, 100-mL flask fitted with a rubber syringe cap on an inlet port, a magnetic stirring bar, and a reflux condenser connected to a gas buret through a dry ice vapor trap. The flask was immersed in an ice bath, the stirring solution was brought to 0 °C, and 10 mL (10 mmol) of a 1 M solution of ethyl benzoate in THF was injected rapidly. Hydrogen evolution was monitored. In this way, a solution was obtained which was 1.0 M in lithium triethylborohydride and 0.25 M in ethyl benzoate.

Upon addition of the compound, 1.0 mL of hydrogen was evolved, corresponding to 0.01 mmol/mmol of compound. No

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more hydrogen evolution was observed throughout the reaction. After 5 min, a 4.0-mL aliquot of the reaction mixture was removed and injected into a hydrolyzing mixture of water–glycerine–THF (1:1:1). The hydrogen evolved was measured. It amounted to 1.96 mmol, as compared to 3.98 mmol for a blank experiment (in which 10 mL of THF had been substituted for the 10 mL of the ethyl benzoate solution). The difference, 2.02 mmol, represents the number of millimoles of hydride used per millimole of the compound (ester). Therefore, the number of millimoles of hydride used for reduction per millimole of compound is the number of millimoles of hydride used per millimole of compound minus the number of millimoles of hydride used for hydrogen evolution, or 2.02 – 0.01 = 2.01. Aliquots were also removed and hydrolyzed after 0.25, 0.5, and 1.0 h of reaction time. The amounts of hydrogen evolved in these experiments were 1.98, 1.96, and 1.96 mmol, indicating 1.99, 2.01, and 2.01 to be the numbers of millimoles of hydride used for reduction per millimole of compound in 0.25, 0.5, and 1.0 h, respectively. Obviously, the reaction was complete within 5 min.

Procedure for Determining the Nature of the Intermediates. For this purpose, 1-hexanol, cyclohexanol, *tert*-butyl alcohol, 3-ethyl-3-pentanol, phenol, 2,6-diisopropylphenol, butanethiol, cyclohexanone, caproic acid, benzoic acid, 1-nitropropane, and water were selected. The reactions of 1-hexanol and 3-ethyl-3-pentanol are representative.

In a typical reaction flask were placed 3.3 mL (5 mmol) of a 1.51 M solution of lithium triethylborohydride and 2 mL (5 mmol) of a 2.5 M solution of *n*-octane (as internal standard), both in THF, and 5 mL (5 mmol) of a 1 M solution of 1-hexanol in THF was injected at room temperature. After 10 min, 4.92 mmol of hydrogen was evolved, indicating the reaction was complete. This reaction mixture was injected into a gas chromatograph where the injection port was maintained at 25–30 °C and the column (5% SE-30, 8 ft × 0.125 in.) at 50 °C. This analysis showed considerable tailing of the peak corresponding to triethylborane. On the other hand, the standard solution of triethylborane showed a clean symmetrical peak.

The procedure for 3-ethyl-3-pentanol followed that described for 1-hexanol. Twelve hours following the addition, hydrogen evolution was complete (5.01 mmol). GLC analysis of the reaction solution showed the presence of triethylborane, with a peak comparable to that of the standard solution of triethylborane. The amount detected was 96% of the calculated quantity.

Analysis of the 1-hexanol reaction mixture indicates that the product must exist as a weak triethylborane complex which undergoes relatively slow dissociation at the injection port. The corresponding products formed by the reagent with cyclohexanol, *tert*-butyl alcohol, cyclohexanone, and water all behaved similarly.

The results with the 3-ethyl-3-pentanol solution indicated the formation of lithium triethylcarboxide and free triethylborane, without significant complex formation. The products of the reagent with phenol, 2,6-diisopropylphenol, butanethiol, caproic acid, benzoic acid, and 1-nitropropane all exhibited the same behavior.

Procedure for Product Analysis by GLC. The reduction of cinnamaldehyde to cinnamyl alcohol is representative. In a 50-mL flask, fitted with a rubber syringe cap on an inlet port, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, were placed 5.8 mL (8.8 mmol) of a 1.52 M solution of lithium triethylborohydride solution, 2 mL (4 mmol) of a 2 M solution of ethylbenzene (as internal standard), both in THF, and 2.2 mL of THF. A water bath was placed under the flask. A 2-mL (8 mmol) sample of a 4 M solution of cinnamaldehyde in THF was introduced while the mixture was vigorously stirred at room temperature. After 15 min, hydrolysis of an aliquot established that 1.01 mmol of hydride had reacted per mmol of compound. The reaction mixture was stirred further for 15 min and hydrolyzed with 2 mL of water. The triethylborane formed was oxidized with 3 mL of 30% hydrogen peroxide followed by heating the mixture at 40–50 °C for 1 h. The aqueous layer was saturated with potassium carbonate, and the dry THF layer was subjected to GLC analysis on a 5% Carbowax 20M column, 6 ft × 0.125 in., indicating the presence of 97% of cinnamyl alcohol.

Preparative Procedures for Reduction of Organic Compounds with Lithium Triethylborohydride. In most cases, the identities of the products were established by GLC analysis, as described above. However, in some cases, the products were isolated and characterized, as described for the following two examples.

Reduction of Anthraquinone to 9,10-Dihydro-9,10-dihydroxyanthracene. In a 500-mL flask, typically equipped as above, 5.59 g (26.8 mmol) of anthraquinone was placed, and 50 mL of THF was introduced. An ice bath was placed under the flask, and 44 mL (59 mmol) of a 1.34 M solution of lithium triethylborohydride was slowly added with vigorous stirring. A small amount of hydrogen (10 mL, 0.01 mmol/mmol of compound) was evolved. After 1 h, the reaction mixture was hydrolyzed with 50 mL of water (vigorous reaction!), which resulted in the evolution of 130 mL (5.13 mmol) of hydrogen, indicating 2.0 mmol of hydride had been utilized per mmol of compound. The mixture was neutralized with dilute hydrochloric acid, and triethylborane, THF, and most of the water were removed under vacuum. The resulting precipitate (unevenly colored, red and white) was dissolved in warm benzene (~300 mL) and recrystallized to give 4.36 g (77%) of 9,10-dihydro-9,10-dihydroxyanthracene as a white solid (needles and plates), mp 175–178 °C, preceded by signs of decomposition at ~110 °C (lit.[50] mp 195 °C).

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.45; H, 5.66.

A diacetate derivative of this diol was prepared from a small portion of the product with acetic anhydride in pyridine. After recrystallization (methanol), the diacetate was obtained as a white solid, mp 172–173 °C (lit.[51] mp 172–173 °C).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.95; H, 5.44. Found: C, 72.93; H, 5.54.

Reduction of Phthalic Anhydride to Phthalide. In a 300-mL flask was placed 4.8 g (32.4 mmol) of phthalic anhydride in 50 mL of THF. The flask was immersed in an ice bath, and 48.2 mL (71.3 mmol) of a 1.48 M solution of lithium triethylborohydride was introduced with vigorous stirring. After 1 h, 10 mL of water was added to hydrolyze the reaction mixture. The hydrogen evolved indicated 1.97 mmol of hydride/mmol of compound had been consumed. The resulting mixture was oxidized by the slow addition of 25 mL of 30% hydrogen peroxide, followed by heating at 40–50 °C for 1 h. Then 40 mL of 6 N hydrochloric acid was added slowly, with cooling, followed by heating the mixture to a gentle reflux of THF for 3 h. After the mixture was cooled, the THF layer was separated, the aqueous layer was extracted with ether (50 mL), and the combined organic layer was dried over anhydrous magnesium sulfate. The solvents were removed under vacuum, and the crude product was dissolved in methanol, followed by evaporation of the solvent under vacuum to eliminate a small quantity of boric acid present. Vacuum distillation of the resulting oil (which solidified upon standing) gave 3.51 g (76%) of phthalide: mp 69.5–71 °C (lit.[49] mp 72–73 °C); NMR ($CDCl_3$, Me_4Si) δ 5.3 (s, 2, CH_2), 7.5–7.9 (m, 4, aromatic).

A comparable yield of phthalide was also obtained by using a procedure similar to that described for the reduction of anthraquinone. In this case, the reaction mixture was hydrolyzed by the slow addition of 40 mL of 6 N hydrochloric acid, followed by gentle reflux of the THF solution for 1 h. After the volatile materials were evaporated under vacuum, the crude material was recrystallized from water to give phthalide as a white solid (65% yield), mp 72–73 °C.

Reduction of Various Representative Functional Groups to Aldehydes with the Stoichiometric Amount of $LiEt_3BH$. The selective reduction of *N,N*-dimethylcaproamide to caproaldehyde is described as representative. Into a 50-mL flask, 2 mL (2 mmol) of a 1 M solution of *N,N*-dimethylcaproamide, 1 mL (1 mmol) of a 1 M solution of *n*-dodecane (as internal standard), both in THF, and 3.6 mL of THF were injected and cooled to −78 °C with a dry ice bath. To this vigorously stirred soltuion was added 1.35 mL (2 mmol) of a 1.48 M solution of lithium triethylborohydride over 15 min. After 2 h at this temperature, the flask was allowed to come to room temperature and hydrolyzed with 2 mL of water. The water layer was saturated with potassium carbonate, and the dry THF layer was subjected

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to GLC analysis (5% Carbowax 20M, 6 ft × 0.125 in.), which showed the presence of 67% caproaldehyde, 12% 1-hexanol, and 21% unreacted amide.

Registry No. Lithium triethylborohydride, 22560-16-3; 1-hexanol, 111-27-3; benzyl alcohol, 100-51-6; 3-hexanol, 623-37-0; 3-ethyl-3-pentanol, 597-49-9; phenol, 108-95-2; 2,6-di-*tert*-butylphenol, 128-39-2; hexylamine, 111-26-2; benzenethiol, 108-98-5; 1-hexanethiol, 111-31-9; caproaldehyde, 66-25-1; benzaldehyde, 100-52-7; 2-heptanone, 110-43-0; norcamphor, 497-38-1; acetophenone, 98-86-2; benzophenone, 119-61-9; 2,2,4,4-tetramethyl-3-pentanone, 815-24-7; cinnamaldehyde, 104-55-2; *p*-benzoquinone, 106-51-4; anthraquinone, 84-65-1; caproic acid, 142-62-1; benzoic acid, 65-85-0; acetic anhydride, 108-24-7; succinic anhydride, 108-30-5; phthalic anhydride, 85-44-9; caproyl chloride, 142-61-0; benzoyl chloride, 98-88-4; ethyl caproate, 123-66-0; ethyl benzoate, 93-89-0; phenyl acetate, 122-79-2; γ-butyrolactone, 96-48-0; phthalide, 87-41-2; isopropenyl acetate, 591-87-7; 1,2-butylene oxide, 106-88-7; styrene oxide, 96-09-3; cyclohexene oxide, 286-20-4; 1-methyl-1,2-cyclohexene oxide, 1713-33-3; 2-phenyldioxolane, 936-51-6; 2-methyl-2-ethyldioxolane, 126-39-6; triethyl orthoformate, 122-51-0; caproamide, 628-02-4; benzamide, 55-21-0; *N,N*-dimethylcaproamide, 5830-30-8; *N,N*-dimethylbenzamide, 121-69-7; *N,N*-dimethylpivalamide, 24331-71-3; capronitrile, 628-73-9; benzonitrile, 100-47-0; nitropropane, 108-03-2; nitrobenzene, 98-95-3; azobenzene, 103-33-3; azoxybenzene, 495-48-7; cyclohexanone oxime, 100-64-1; phenyl isocyanate, 103-71-9; pyridine, 110-86-1; pyridine *N*-oxide, 694-59-7; dibutyl disulfide, 629-45-8; diphenyl disulfide, 882-33-7; methyl *p*-tolyl sulfide, 623-13-2; dimethyl sulfoxide, 67-68-5; dibutyl sulfone, 598-04-9; diphenyl sulfone, 127-63-9; methanesulfonic acid, 75-75-2; *p*-toluenesulfonic acid, 104-15-4; cyclohexyl tosylate, 953-91-3; cyclohexanol, 108-93-0; *tert*-butyl alcohol, 75-65-0; cyclohexanone, 108-94-1; water, 7732-18-5; 2,6-diisopropylphenol, 2078-54-8; butanethiol, 109-79-5; cinnamyl alcohol, 104-54-1; 9,10-dihydro-9,10-dihydroxyanthracene, 58343-58-1; 9,10-dihydro-9,10-dihydroxyanthracene diacetate, 6938-79-0; *endo*-2-norbornanol, 497-36-9; 1,4-butanediol, 110-63-4; 1-methylcyclohexanol, 590-67-0; neopentyl alcohol, 75-84-3; benzylamine, 100-46-9; ethylbenzene, 100-41-4.

Regiospecific Synthesis of Islandicin Methyl Ether

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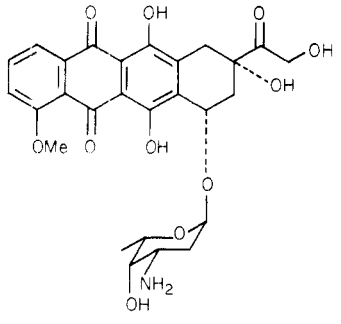
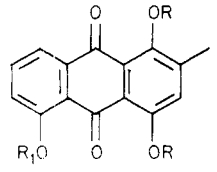
This paper presents a novel approach to the construction of highly functionalized anthraquinones. It involves an aryl cuprate–benzyl halide coupling followed by cycloacylation under mild conditions to an anthracenone. Several novel byproducts were encountered.

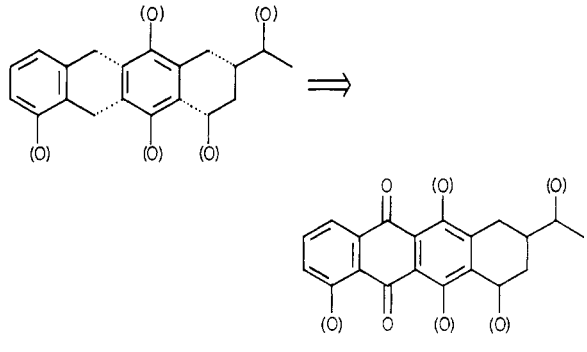
There is considerable interest in developing efficient synthetic routes to the aglycones of adriamycin and related anthracyclinone antibiotics.[1-15] Our general approach to this involves construction of suitably substituted anthracenes and subsequent elaboration of the D ring.[16]





1a, R = R_1 = CH_3
b, R = $CH_2C_6H_5$; R_1 = CH_3
c, R = R_1 = H
d, R = H; R_1 = CH_3
e, R = Ac; R_1 = CH_3

To this end we have devoted some attention to the development of a regiospecific synthesis of unsymmetrically substituted anthracenes as per eq 1. We selected islan-



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