1 H, J = 6 Hz), 6.90 (s, 1 H), 10.7 (br s, 1 H); ^{13}C NMR δ 21.0 (t), 21.9 (q), 41.4 (t), 68.9 (d), 108.8 (d), 127.7 (s), 130.5 (s), 161.3 (s), 197.9 (s); exact mass 207.0893 (calcd for $C_{11}H_{13}NO_3$ 207.0894). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.76; O, 23.19. Found: C, 63.71; H, 6.37; N, 6.95; O, 23.45].

Irradiation of 2h. A solution of **2h** (E/Z = 50/50; 1.4 g, 0.0096 M) in ether was irradiated for 30 min to give **3h** as a mixture of isomers (trans/cis 50:50) which was separated by column chromatography [*trans*-**3h** 32% yield; ^{1}H NMR δ 1.28 (t, 3 H, J = 6.75 Hz), 1.35 (d, 3 H, J = 6.75 Hz), 2.20–2.90 (m, 4 H), 3.25 (dq, 1 H, J = 6 Hz, J = 6.75 Hz), 4.22 (q, 2H, J = 6.75 Hz), 4.35 (d, 1 H, J = 6 Hz), 7.30 (br s, 1 H); ^{13}C NMR δ 14.1 (q), 20.1 (q), 21.6 (t), 37.1 (d), 40.1 (t), 61.6 (t), 74.3 (d), 120.5 (s), 172.2 (s), 186.1 (s), 194.8 (s); *cis*-**3h** 18% yield; ^{1}H NMR δ 1.20 (t, 3 H, J = 7.5 Hz), 1.35 (d, 3 H, J = 7.5 Hz), 2.20–2.90 (m, 4 H), 3.40 (dq, 1 H, J = 7.5 Hz, J = 10.5 Hz), 4.25 (q, 2 H, J = 7.5 Hz), 5.0 (d, 1 H, J = 10.5 Hz), 7.10 (br s, 1 H); ^{13}C NMR δ 14.2, 14.4, 21.6, 34.6, 40.1, 61.3, 70.9, 120.7, 170.4, 186.3, 194.9] and **4h** [12% yield; mp 192–194 °C (lit.[18] mp 172–174 °C); ^{1}H NMR (DMSO-d_6) δ 1.33 (t, 3 H, J = 7.2 Hz), 2.34 (s, 3 H), 2.80 (s, 4 H), 4.30 (q, 2 H, J = 7.2 Hz), 12 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 12.5 (q), 16.2 (q), 22.2 (t), 43.2, 61.8 (t), 124.2 (s), 127.0 (s), 128.4 (s), 161.9 (s), 163.1 (s), 198.8 (s); exact mass 207.08949 (calcd for $C_{11}H_{13}NO_3$ 207.0894). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.52; H, 6.29; N, 6.52].

Irradiation of 2i and 2j. A solution of **2i** or **2j** (0.4 g) in ether (250 mL) was irradiated for 20 min to yield polymers.

Irradiation of 2k. A solution of **2k** (1.3 g, 0.0197 M) in ether (290 mL) was irradiated for 3 h to give **4k** [31% yield; ^{1}H NMR δ 1.38 (d, 6 H, J = 6.5 Hz), 1.40 (t, 3 H, J = 6.6 Hz), 4.3 (q, 2 H, J = 6.6 Hz), 5.25 (septet, 1 H), 7.30 (m, 1 H), 7.58 (m, 1 H); ^{13}C NMR δ 14.4 (q), 22.0 (q), 60.2 (t), 68.5 (d), 116.0 (d), 117.9 (s), 124.2 (s), 127.5 (d), 161.0 (s), 164.4 (s). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.67; N, 6.22; O, 28.44. Found: C, 58.61; H, 6.89; N, 6.50; O, 28.21].

Irradiation of 2l. A solution of **2l** (1.2 g, 0.0196 M) in ether (290 mL) was irradiated for 1 h to give **4l** [22% yield; mp 134–136 °C; ^{1}H NMR δ 1.38 (d, 6 H, J = 6.5 Hz), 2.43 (s, 3 H), 2.60 (s, 3 H), 5.22 (septet, 1 H, J = 6.5 Hz), 7.23 (s, 1 H); ^{13}C NMR δ 14.0, 22.0, 28.3, 68.4, 117.3, 120.7, 122.3, 139.8, 161.1, 195.0. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.16; H, 7.18; N, 6.70; O, 22.97. Found: C, 63.25; H, 7.12; N, 6.71; O, 23.02].

Irradiation of 2m. A solution of **2m** (0.8 g, 0.0168 M) in ether (210 mL) was irradiated for 20 min to give **4m** [20% yield; mp 70–72 °C (C_6H_6); ^{1}H NMR δ 1.30 (t, 6 H, J = 7 Hz), 2.60 (s, 3 H), 4.30 (q, 2 H, J = 7 Hz), 4.35 (q, 2 H, J = 7 Hz), 7.5 (d, 1 H, J = 3 Hz), 10.35 (br s, 1 H); ^{13}C NMR δ 11.4, 14.2, 14.5, 59.8, 60.5, 116.7, 121.0, 127.5, 129.9, 162.0, 165.0. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.67; N, 6.22; O, 28.44. Found: C, 58.59; H, 6.78; N, 5.90; O, 28.24].

Irradiation of 2n. A solution of **2n** (0.7 g, 0.0157 M) in ether (210 mL) was irradiated for 30 min to give **4n** [57% yield; mp 140–142 °C (C_6H_6) (lit.[21] mp 142 °C); ^{1}H NMR δ 1.25 (t, 3 H, J = 7 Hz), 2.35 (s, 3 H), 2.45 (s, 3 H), 2.52 (s, 3 H), 4.28 (q, 2 H, J = 7 Hz), 10.3 (br s, 1 H); ^{13}C NMR δ 12.7, 14.5, 15.1, 31.3, 60.4, 118.1, 122.7, 123.6, 129.6, 138.7, 162.1, 195.8] and **5** [14% yield; ^{1}H NMR δ 1.40 (t, 3 H, J = 7.4 Hz), 2.30 (s, 3 H), 2.48 (s, 3 H), 2.50 (s, 3 H), 4.42 (q, 2 H, J = 7.4 Hz), 6.90 (s, 1 H); ^{13}C NMR δ 14.3, 19.5, 23.0, 24.3, 61.3, 122.3, 126.8, 145.3, 154.7, 154.7, 158.5, 169.1].

Irradiation of 6l. A solution of **6l** (Z configuration of the α,β-olefinic bond; 1 g) in ether (700 mL) was irradiated for 1 h to give **6l** (E configuration of the olefinic α,β-bond; 90% yield).

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Selective Reductions. 39. Partial Reduction of Carboxylic Acids with Thexylchloroborane–Methyl Sulfide. A Direct and Simple Aldehyde Synthesis

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A systematic study of the direct partial reduction of carboxylic acids to the corresponding aldehydes with thexylchloroborane–methyl sulfide (ThxBHCl·SMe_2) under practical conditions (methylene chloride, room temperature) has been carried out. The reaction is quite general, and the yields of aldehydes are very good, almost quantitative in the aliphatic series. Many other readily reducible functional groups tolerate these reaction conditions. Furthermore, aliphatic carboxylic acids can be reduced selectively in the presence of aromatic acids. The aldehyde products are readily isolated in high yields either by forming the sodium bisulfite adduct, followed by regeneration with formaldehyde, or by using steam distillation to remove the byproduct.

During the past 70 years, numerous efforts have been made to find simple and general synthetic routes to aldehydes from carboxylic acids.[2] In the early years, both the Rosenmund's catalytic hydrogenation of acid chlorides[3] and Stephen's procedure[4] were widely utilized. However, these procedures suffered from limited applicability. The discovery of lithium aluminum hydride[5] led to its application for the preparation of aldehydes by reduction of various carboxamides.[6,7]

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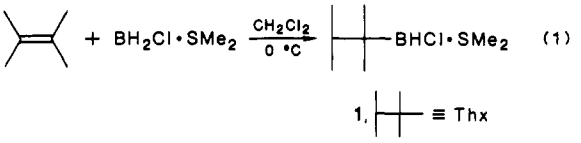
Modified reagents of lithium aluminum hydride such as lithium di- and triethoxyaluminum hydride or lithium tri-*tert*-butoxyaluminum hydride prepared from the addition of 2 or 3 equiv of alcohols to the parent compound appear to be very useful reagents for the synthesis of aldehydes from esters or lactones,[8] carboxamides,[9] acid chlorides,[10] or even nitriles.[11] The conversion of carboxylic acid derivatives into aldehydes can also be carried out with diisobutoxyaluminum hydride,[12] sodium borohydride in dimethylformamide,[13] diaminoaluminum hydride,[14] complex copper borohydride salts,[15] anionic iron carbonyl complexes,[16] and others.[17] Alternatively, reduction of carboxylic acids with borane–methyl sulfide to the corresponding trialkylboroxines, followed by oxidation with pyridinium chlorochromate, gives the desired aldehydes.[18]

A number of methods for the direct transformation of carboxylic acids into aldehydes by using lithium in methylamine,[19] diisobutylaluminum hydride,[20] thexylborane,[21] bis(4-methylpiperazinyl)aluminum hydride,[22] the Grignard reagent catalyzed by dichloro-bis(π-cyclopentadienyl)titanium,[23] or *N,N*-dimethylchloromethyleniminium chloride and lithium tri-*tert*-butoxyaluminum hydride[24] have been reported. However, none of these methods offers a simple, general, direct procedure for the reduction process. Moreover, in most cases, the yields reported are based only on the analysis with (2,4-dinitrophenyl)hydrazine or other analytical methods. No practical isolations of the aldehyde products from the reaction mixture have been demonstrated.

Recently we examined the hydroborating characteristics of thexylchloroborane–methyl sulfide (ThxBHCl·SMe_2, 1) and its application to the synthesis of unsymmetrical ketones.[25] The approximate rates and stoichiometry of the reaction with selected organic compounds containing representative functional groups under standardized conditions (methylene chloride, 0 °C) were studied.[26] The reagent is a mild reducing agent. Excess ThxBHCl·SMe_2 in methylene chloride at 0 °C does not reduce esters, epoxides, aromatic nitriles, and nitro compounds. However, unexpectedly, treatment of aliphatic and aromatic carboxylic acids with the reagent results in the almost instantaneous utilization of 1 equiv of hydrogen, coupled with the evolution of hydrogen, followed by the rapid utilization of a second equivalent of hydride. A third equivalent of hydride is utilized only slowly. This suggested the possibility of achieving a direct synthesis of aldehydes from carboxylic acids, even in the presence of other readily reducible groups. In this respect, this reagent is similar to thexylborane (ThxBH_2).[21] However, ThxBHCl·SMe_2 appears to be more selective for the reduction of functional groups and much more reactive to carboxylic acids than ThxBH_2 itself. The reagent, ThxBHCl·SMe_2 (1), is readily prepared by the hydroboration of 2,3-dimethyl-2-butene with monochloroborane–methyl sulfide in methylene chloride (eq 1).[25-28]



This reagent is quite stable and a useful hydroborating and reducing agent. Unfortunately, the byproduct produced in the hydrolysis of the intermediate, thexylboronic acid, is often relatively difficult to remove from the reduction mixture. One method that has been utilized in the past is its oxidation by alkaline hydrogen peroxide to the corresponding alcohol and boric acid, following the reduction. However, this is not a desirable procedure, particularly in cases where the reduction products, such as aldehydes, are quite sensitive to oxidation. In these cases, the development of another simple procedure for isolation of the product is desirable. Hence, we undertook to examine the physical and chemical properties of thexylboronic acid and its derivatives.[29] Consequently, we were now ready to investigate the reduction of carboxylic acids, ThxBHCl·SMe_2, in the hope of establishing a simple, general synthetic route to aldehydes with convenient procedures for isolation of the products.[30]

Results and Discussion

Reaction Conditions. ThxBHCl·SMe_2 (1) in methylene chloride reacts with all of the carboxylic acids examined to evolve 1 equiv of hydrogen immediately and quantitatively at 0 °C. In early experiments, the effect of the mode of addition of the reagent on the aldehyde yield was examined with hexanoic acid and benzoic acid. It was observed that there was no significant difference in the yield whether the hydride reagent solution was added to the solution or slurry of acid in methylene chloride (reverse addition) or whether the solution of acid in methylene chloride was added to the hydride solution (normal addition) at 0 °C. The former procedure is obviously preferable since it permits a higher concentration of the reaction mixture, more desirable for a practical synthesis, because of the generally low solubility of carboxylic acids in methylene chloride. It was demonstrated that the addition of the reagent solution to a slurry of carboxylic acid in methylene chloride at 0 °C (for cases where the carboxylic acids were not quite soluble in methylene chloride

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at 0 °C) was quite satisfactory, since the slurry becomes clear as the hydrogen evolves. However, the addition of the reagent at room temperature, rather than 0 °C, resulted in partial liberation of hydrogen chloride from a reaction between the carboxylic acid hydrogen and the chlorine of the reagent, resulting in a somewhat lower yield of aldehyde. Therefore, reverse addition at 0 °C was adopted as the preferred procedure.

The effect of the ratio of reagent to compound was also examined. No significant difference in results was noted, even with the use of excess reagent (up to 200% excess), either at 0 °C or at room temperature. Therefore, it was concluded that the slow addition of 2.2 equiv of the reagent (10% excess) to 1 equiv of compound in methylene chloride at 0 °C for the hydrogen evolution stage, followed by reduction at room temperature, is optimum for the reduction to aldehyde. Under these reaction conditions, the reduction was complete within 15 min for aliphatic carboxylic acids, but required 24 h for aromatic carboxylic acids.

Finally, we considered preferred conditions for the hydrolysis of the reaction intermediate. Because the reagent itself possesses a chlorine atom, hydrogen chloride is generated when the reaction mixture is treated with water. Therefore, it was concluded that the transfer of the reaction mixture to a stirred flask containing precooled water (i.e., the use of 50 mL of water for a 50-mmol-scale reaction forms a solution that is 2.2 M hydrochloric acid) should be satisfactory for the hydrolysis without liberating gaseous hydrogen chloride.

We were concerned whether subjecting the aldehyde in the methylene chloride to the 2.2 M hydrochloric acid might be deleterious. Accordingly, we tested a modification of the procedure, hydrolyzing the reaction intermediate with 4.4 M aqueous sodium acetate. There was no significant difference in the isolated yield of hexanal. Evidently the aldehyde in the methylene chloride is protected from the action of the 2.2 M hydrochloric acid by the insolubility of the solvent (methylene chloride) in which it is contained. Even the monoethyl ester of adipic acid was converted into the corresponding aldehyde without serious hydrolysis of the ester group. In cases where the aldehyde is quite sensitive to the action of acids, it is probable that the use of an aqueous buffer, such as sodium acetate, for the hydrolysis of the intermediate would be helpful.

Scope of the Reaction. The above experiments led to the following general procedure. In the usual setup is placed an appropriate quantity of the carboxylic acid and methylene chloride (15 mL for a 50-mmol-scale reaction). To the slurry maintained at ~0 °C with an ice water bath is added dropwise with vigorous stirring the appropriate quantity of the reagent (2.2 equiv). The hydrogen eliminated is conducted safely away. Following addition of the reagent, the ice water bath is removed, and the reaction mixture is stirred for 15 min in the case of aliphatic carboxylic acids and 24 h in the case of aromatic carboxylic acids, both at room temperature. The reaction mixture is then transferred to a flask containing 50 mL of water rapidly stirred to achieve hydrolysis of the intermediate. The methylene chloride layer is separated and treated with sodium bisulfite for isolation of the bisulfite addition adduct of the aldehyde, followed by regeneration of the aldehyde. Alternatively, an aliquot is treated with (2,4-dinitrophenyl)hydrazine in cases where the yield of aldehyde was established by analysis. This standard procedure was then applied to 15 representative carboxylic acids, and the results are summarized in Table I.

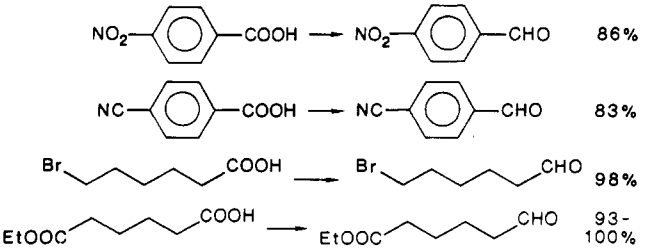
Table I. Yields of Aldehydes in the Reduction of Representative Carboxylic Acids with Thexylchloroborane–Methyl Sulfide in Methylene Chloride at Room Temperature[a]

acid	yield of aldehyde,[b] %: by analysis with (2,4-dinitrophenyl)-hydrazine	yield of aldehyde,[b] %: by isolation with sodium bisulfite adduct
benzoic	59	47
α-naphthoic	56	48
p-methoxybenzoic	51	46
p-nitrobenzoic	86	71, 78[c]
m-cyanobenzoic	83	67
terephthalic	72	59
hexanoic	99	83[d] (75)[e]
decanoic	97	89, 45[c]
stearic	98	92, 95[c]
neopentanoic	62(98)[f]	(71)[d,f]
diphenylacetic	91(93)[f]	83
cyclohexanecarboxylic	91(94)[f]	80
1,10-decanedicarboxylic	97	93
6-bromohexanoic	98	86
adipic acid monoethyl ester	93–100[g]	81[g], 72[d,h]

[a] Reacted with 10% excess reagent (2.2 equiv for monocarboxylic and 4.4 equiv for dicarboxylic acid) for 24 h with aromatic and for 15 min with aliphatic carboxylic acids, both at room temperature after the hydrogen evolution at 0 °C. [b] Yields are based on the analytically pure products after evaporation of solvent. [c] Isolated yield by using a steam-distillation technique. [d] Yield on distillation of the regenerated product. [e] Reaction intermediate hydrolyzed with 4.4 M aqueous sodium acetate. [f] Reacted for 3 h at room temperature. [g] A mixture of acid and ester of (2,4-dinitrophenyl)-hydrazone, indicating partial hydrolysis of the carbethoxy group. [h] No solid sodium bisulfite adduct formed (see the Experimental Section).

Generally the yields in the aromatic series were lower than those in the aliphatic series. Examining the results for the aromatic series more closely, a significant influence of substituents upon the yield appears to exist. Thus, the yields realized for the unsubstituted aromatic carboxylic acids (i.e., benzoic acid and α-naphthoic acid) and those substituted with an electron-donating group (i.e., *p*-methoxybenzoic acid) are significantly lower than the yields realized in the case of the aromatic acids substituted with an electron-withdrawing group (i.e., *p*-nitrobenzoic, *m*-cyanobenzoic, and terephthalic acid). However, in the case of the aliphatic compounds, it appears that the yields of aldehydes are almost quantitative, with no observable dependence on the structure of the acid. Even the aliphatic dicarboxylic acids are reduced to the corresponding dialdehydes in essentially quantitative yields.

Furthermore, many other readily reducible groups in the acid undergoing reduction appear to be tolerant to these reaction conditions. Thus, aromatic carboxylic acids with a substituent of methoxy, cyano, or nitro are reduced chemoselectively to the corresponding aldehydes without attack of the substituent. Aliphatic carboxylic acids with a bromo or ester group are also reduced cleanly and quantitatively to the corresponding aldehyde without attack on the substituent.



Isolation of Aldehydes. The reagent ThxBHCl·SMe_2 appears to be an excellent reducing agent to achieve the conversion of carboxylic acids into aldehydes. However, the convenient isolation of the aldehyde products from the reaction mixture provided another important problem to be solved. The byproduct, thexylboronic acid, is relatively difficult to remove from the reaction mixture. The usual method used in the past was its oxidation by alkaline hydrogen peroxide to the corresponding alcohol and boric acid. However, in the case of the aldehyde synthesis, this appeared to be undesirable because of the possible sensitivity of aldehydes to such oxidation. Accordingly, we sought for some other simple, practical methods to separate the aldehydes in pure form from the thexylboronic acid.

On the basis of the results of a study of the chemical and physical characteristics of thexylboronic acid,[29] we explored a number of procedures for the isolation of aldehydes: distillation, steam distillation, column chromatographic separation, separation as the Schiff base, removal of thexylboronic acid as its derivatives, etc. None of these methods provided the simple, general, and practical procedure we desired.

Finally, we examined the classical procedure, the sodium bisulfite method.[31] Fortunately, the separation of aldehydes as the sodium bisulfite adducts from the reaction mixture, followed by the regeneration of aldehydes from the adducts with formaldehyde, provided a highly convenient, general, and practical method.[31] It was found that the formation of a solid adduct was remarkably fast, general, and quite independent of the structure of the aldehydes in the reaction mixture, with only one exception (vide infra, Table I, footnote *g*).

Furthermore, the typical regeneration procedure with formaldehyde appeared to be general for the simple aldehydes, and the recovered yields were quite satisfactory. However, the rate of regeneration of aldehydes appears to be dependent on the solubility of the solid adduct in aqueous medium. In the case of adducts of low solubility in the saturated magnesium sulfate solution employed, such as the adducts of diphenylacetaldehyde, *m*-cyanobenzaldehyde, etc., a slightly modified procedure, which involves reaction with formaldehyde in water instead of in the saturated magnesium sulfate solution, followed by subsequent saturation with magnesium sulfate, gave a faster regeneration of aldehyde. Especially in the case of the adduct of stearaldehyde, which is almost insoluble and hence essentially inert to the treatment with formaldehyde under the usual conditions, raising the temperature for the reaction of formaldehyde with the adduct to 90–95 °C gave an almost quantitative regeneration of the aldehyde.

Although the bisulfite adduct formation appeared, from our study, to be a general characteristic of aldehydes, the formation of solid adducts did not appear to be nearly as general. In some cases, such as 5-carbethoxy-1-pentanal and some of the lower molecular weight aldehydes, the adducts could be quite soluble in the saturated sodium bisulfite solution employed. However, in such cases, extraction of the saturated bisulfite solution with ether easily removes thexylboronic acid and other impurities. The aldehyde is then readily recovered in pure form by regeneration with formaldehyde.

The conditions for regeneration of aldehydes are summarized in Table II, and the yields isolated by this method are listed in Table I.

(31) (a) Cornforth, J. W. *Organic Syntheses*; Wiley: New York, 1963; *Collect.* Vol. IV, p 757. (b) Coleman, R. A. Ph.D. Thesis, Purdue University, 1970.

Table II. Regeneration of Aldehydes from the Corresponding Sodium Bisulfite Adducts with Formaldehyde Solution

aldehyde	regenerating procedure[a]	rctn time, h	remarks
benzaldehyde	A	1	*b*
α-naphthaldehyde	A	1	*c*
p-methoxybenzaldehyde	B	1	*b*
p-nitrobenzaldehyde	A	1	*b, d*
m-cyanobenzaldehyde	B	1	*b, d*
terephthalaldehyde	A	1	*b, d*
hexanal	A	1	*b*
decanal	A	1	*e*
stearaldehyde	C	1	*f*
trimethylacetaldehyde	C	0.5	*f*
diphenylacetaldehyde	C	1	*f*
cyclohexanecarboxaldehyde	A	2	*g*
1,10-decanedicarboxaldehyde	C	0.5	*f*
6-bromohexanal	A	1	*b*
5-carbethoxy-1-pentanal	D	1	*h*

[a] See the procedures described in the Experimental Section. [b] Fast for both adduct formation and the regeneration of aldehyde. [c] Adduct formation requires 5 h. [d] Product is not quite soluble in pentane, so THF was used to extract the aldehyde. [e] Adduct formation required 3 h. [f] Fast for adduct formation, but very slow for the regeneration of aldehyde at room temperature. [g] Fast for adduct formation, but slow for the regeneration of aldehyde. [h] No solid adduct formed, but fast for both reactions.

Table III. Selective Reduction of Aliphatic Carboxylic Acid in the Presence of Aromatic Carboxylic Acid with Thexylchloroborane–Methyl Sulfide in Methylene Chloride at Room Temperature[a,b]

compound used	product	mol %[c]
hexanoic acid + benzoic acid	hexanal benzaldehyde	92 (74)[d] 6[e]
cyclohexanecarboxylic acid + benzoic acid	cyclohexanecarboxaldehyde benzaldehyde	93 trace

[a] 3.1 equiv of the reagent per mixture of 1 equiv in each of the compounds was utilized. 1.6 M in the reagent, 0.5 M in each of the compounds. [b] Reacted for 1 h at room temperature. [c] Determined by GC analysis from the response ratios determined for authentic samples. [d] Isolated yield by the sodium bisulfite method. [e] 90% of benzoic acid was recovered.

An alternative method for isolating aldehydes of relatively high boiling point (i.e., low volatility) such as *p*-nitrobenzaldehyde and stearaldehyde, with steam distillation, also proved practical. Thexylboronic acid is relatively volatile.[29] Hence, it distills out relatively rapidly of the reaction mixture under steam distillation conditions, leaving the aldehyde behind. The isolated yields by this method were 78% for *p*-nitrobenzaldehyde and 95% for stearaldehyde, but only 45% for decanal (evidently a borderline case in volatility). Consequently, this simple isolation procedure should be especially advantageous for the partial reduction of the carboxylic group in complex molecules.

Selective Reduction of Aliphatic Carboxylic Acid in the Presence of Aromatic Carboxylic Acid. The reduction of aliphatic carboxylic acids is much faster than the reduction of aromatic carboxylic acids. The former reduction is complete within 15 min, whereas, the latter requires some 24 h, both at room temperature. The remarkable difference in the rate of reduction of aliphatic and aromatic carboxylic acids suggested the possibility of achieving the selective reduction of aliphatic carboxylic acids in the presence of aromatic carboxylic acids under preparative conditions. Indeed, we achieved up to 92–93% reduction of aliphatic carboxylic acids in mixtures with

Table IV. Reaction Rates of Hexanoic Acid with Thexylchloroborane–Methyl Sulfide in Methylene Chloride[a] and Thexylborane in Tetrahydrofuran[b] at Room Temperature[c]

reaction time,[d] h	yield of hexanal,[e] %	
	ThxBHCl·SMe_2	$ThxBH_2$
0.25	99.5	8
1.0	99	17
3.0		26
24.0		66

[a] 1.75 M in ThxBHCl; 0.8 M in compound in methylene chloride. [b] 0.88 M in $ThxBH_2$; 0.8 M in compound in THF. [c] 2.2 equiv of hydride to compound was utilized. [d] Reaction time at room temperature after the evolution of hydrogen at 0 °C. [e] Determined by GC analysis from the response ratios with an authentic sample.

benzoic acid, with only minor reduction of the benzoic acid. In one typical experiment, 74% of hexanal was isolated by the sodium bisulfite method, and 90% of unreacted benzoic acid was recovered from the reaction mixture. The results are summarized in Table III.

Comparison of Rates of Aldehyde Formation between $ThxBH_2$ in THF and ThxBHCl·SMe_2 in Methylene Chloride. The partial reduction of carboxylic acids with $ThxBH_2$ in THF was previously observed in this laboratory.[21] However, no systematic study of the reaction was carried out. However, a 98% of hexanal from hexanoic acid and an 82% yield of benzaldehyde from benzoic acid were achieved by using 2.5 mmol of $ThxBH_2$/mmol of acid under refluxing THF. We undertook to compare these two methods for the synthesis of aldehydes. We compared both reagents for the rates of aldehyde formation for the same carboxylic acid under identical preparative conditions. The results are summarized in Table IV.

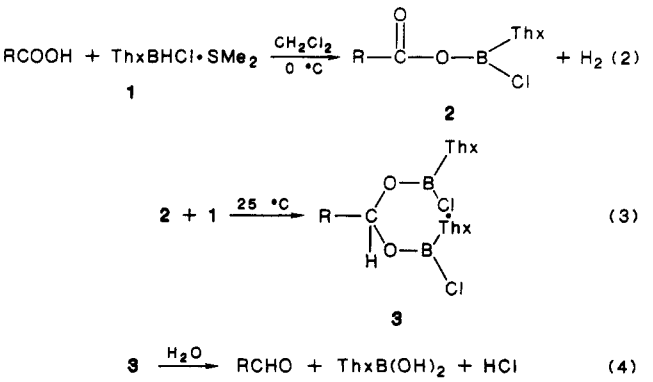
As shown in Table IV, it is evident that the rate of aldehyde formation with ThxBHCl·SMe_2 in methylene chloride is much faster than with $ThxBH_2$ in THF. In view of the fact that the reaction with $ThxBH_2$ requires refluxing of the THF solution and a considerable excess of the reagent (3 equiv excess) to obtain a high yield of aldehyde, the reagent ThxBHCl·SMe_2 appears preferable for practical purposes.

Mechanistic Considerations. The reaction of both aromatic and aliphatic carboxylic acids with ThxBHCl·SMe_2 evolves 1 equiv of hydrogen immediately and quantitatively. The subsequent reduction stage is much faster for aliphatic carboxylic acids than for aromatic carboxylic acids. The yields of aldehydes were almost quantitative for aliphatic, but somewhat lower for aromatic.

Although study of the reaction mechanism was not a primary objective of this investigation, the results suggest the following mechanism. The first step is the rapid formation of the thexyl(acyloxy)borane **2** from the reaction of the carboxylic acid with the reagent **1**. Then transfer of a hydride to the (acyloxy)borane **2** from a second mole of the reagent **1** gives the corresponding aldehyde intermediate **3**, which appears to be quite stable to further reduction. Subsequent hydrolysis gives the desired aldehyde (eq 2–4). The reason for the lower yields in the aromatic series is not clear. A possible explanation is that the thexyl(acyloxy)borane **2** might undergo redistribution to a less reactive species, such as thexylbis(acyloxy)borane, during the slow reduction process.

Conclusion

From this systematic study, a convenient procedure for the direct partial reduction of carboxylic acids to the corresponding aldehydes under practical conditions in very good yields is now available. Moreover, it is possible to reduce selectively aliphatic carboxylic acids in the presence of aromatic carboxylic acids and/or other readily reducible functional groups. Convenient methods for isolating the aldehyde products add an additional advantage to this useful procedure, which should find valuable application for organic synthesis.



Experimental Section

All glassware used was dried thoroughly in a drying oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air- and moisture-sensitive materials were carried out under a dry nitrogen atmosphere. Further special experimental techniques are described elsewhere.[32]

All chemicals were commercial products of the highest purity, which were carefully purified by standard method before use. The carboxylic acids were commercial products and were purified either by distillation or by recrystallization. Tetrahydrofuran (THF) was distilled from benzophenone–sodium ketyl and all other solvents (methylene chloride, *n*-pentane, and diethyl ether) were thoroughly dried over molecular sieves and distilled. Borane–methyl sulfide (BMS) and 2,3-dimethyl-2-butene were used directly as received from Aldrich. Boron trichloride in a cylinder was used as received from Matheson. Methyl sulfide was distilled from a small quantity of 9-BBN prior to use.

All of the compounds prepared have been fully characterized by ^1H and ^{11}B NMR spectra. Yields reported in all cases are of analytically pure compounds unless otherwise specified. Melting points and boiling points reported here are uncorrected. ^1H NMR spectra were recorded on a Varian T-60 instrument. ^{11}B NMR spectra were recorded on a Varian FT-80A spectrometer. ^{11}B NMR chemical shifts are with reference to BF_3·OEt_2 (δ 0) and are assigned as positive with the resonances downfield from BF_3·OEt_2. GC analyses were carried out using a Varian Model 1400 FID chromatograph equipped with a Hewlett-Packard 3390A integrator/plotter.

Preparation of Thexylchloroborane–Methyl Sulfide (ThxBHCl·SMe_2) in Methylene Chloride.[25-27] To an oven-dried, tared, 2-L flask fitted with a sidearm and a stopcock leading to a mercury bubbler was added ca. 1.5 L of pentane (*n*-pentane), and the contents were cooled to −20 °C with a dry ice–water–ethylene glycol bath. The gaseous boron trichloride was condensed to the volume of 170 mL (2.0 mol) in a graduated cylinder, which was placed in a −78 °C bath, and then the liquified boron trichloride was transferred to the precooled pentane with a double-ended needle. To this was added 200 mL of methyl sulfide dropwise (a strongly exothermic reaction) and a white precipitate, presumably the boron trichloride–methyl sulfide complex, was formed immediately. After the complete addition of methyl sulfide, the mixture was stirred for an additional hour and then brought to room temperature. The pentane was removed via reverse flow through a gas dispersion tube, the precipitate was washed three times with 500 mL of pentane, and the pentane was removed. The slurry of the complex was first dried by using an

(32) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.

aspirator and then dried further under vacuum. An off-white solid weighing 359 g (2.0 mol) of boron trichloride–methyl sulfide complex (BCl_3·SMe_2) was obtained. No further purification was performed, and the material was used to prepare monochloroborane–methyl sulfide.

Assuming that boron trichloride–methyl sulfide is only about 90% pure, 360 mL of a 10.0 M borane methyl sulfide (BMS) was added to the neat BCl_3·SMe_2 (359 g, 2.0 mol). The solid dissolved in ca. 20 min, and the solution became clear. The solution was stirred for 6 h at room temperature, followed by heating to 55 °C for 6 h. The ^{11}B NMR spectrum of the solution showed a mixture of BCl_3·SMe_2, BH_2Cl·SMe_2, $BHCl_2$·SMe_2, and BMS. The remaining BMS was added in 10-mL portions. After the addition of each portion, the solution was heated to 55 °C for 2 h and examined by ^{11}B NMR. The final solution examined by ^{11}B NMR was found to be a mixture of $BHCl_2$·SMe_2 (15.8%), BH_2Cl·SMe_2 (68.4%), and BMS (15.8%) in equilibrium. Throughout the reaction, 396 mL of a 10.0 M BMS (3.96 mol) was utilized.

To this precooled mixture of boranes was added 260 mL of methylene chloride and 70 mL of methyl sulfide. A 555.5-g sample of 2,3-dimethyl-2-butene (6.6 mol) was added dropwise via a double-ended needle, and the solution was stirred for 2 h at 0 °C, followed by stirring at room temperature for 5 h. The resulting thexylchloroborane–methyl sulfide (ThxBHCl·SMe_2) solution in methylene chloride was found to be 3.0 M, and the ^{11}B NMR spectrum of the solution showed a clean doublet centered at δ 7.17 (J_{B-H} = 125.2 Hz).

Reduction of Carboxylic Acids. The following reductions are typical of the procedure utilized in the quantitative analysis with (2,4-dinitrophenyl)hydrazine.

p-Nitrobenzoic acid (9.02 g, 54 mmol) was placed in an oven-dried, 100-mL flask fitted with a sidearm and a bent adaptor, which was connected to a mercury bubbler. The contents were dried under vacuum, and the flask was flushed with dry nitrogen. The flask was immersed in an ice water bath and to this was added 16 mL of methylene chloride. The precooled 39.6 mL of 3.0 M solution of ThxBHCl·SMe_2 (118.8 mmol, 10% excess) in methylene chloride was added dropwise with vigorous stirring. After the complete evolution of hydrogen, the ice water bath was removed, and the reaction mixture was stirred for 24 h at room temperature. An aliquot (4 mmol) of the reaction mixture was withdrawn and subjected to analysis with (2,4-dinitrophenyl)hydrazine, showing a yield of 86%: mp of the hydrazone 317–319 °C dec (lit.[33] mp 320 °C). The rest of the reaction mixture (50 mmol) was further treated for isolating the aldehyde.

Terephthalic acid (8.97 g, 54 mmol) in 16 mL of methylene chloride was treated with 237.6 mmol of the reagent and reacted for 24 h at room temperature in the same manner described above. By estimation as the (2,4-dinitrophenyl)hydrazone, the yield was 72%: mp of the hydrazone 115–117 °C (lit.[33] mp 116 °C).

Stearic acid (15.36 g, 54 mmol) in 16 mL of methylene chloride was reacted with 118.8 mmol of the reagent at 0 °C for the hydrogen evolution and reduced at room temperature for 15 min. An aliquot of the reaction mixture was analyzed with (2,4-dinitrophenyl)hydrazine (a yield of 98%): mp of the hydrazone 102 °C (lit.[33] mp 101 °C).

Similarly, 1,10-decanedicarboxylic acid (12.44 g, 54 mmol) was treated with 237.6 mmol of the reagent and reacted for 15 min at room temperature. Estimation of an aliquot of the reaction mixture with (2,4-dinitrophenyl)hydrazine gave the hydrazone, mp 100–101 °C, in a yield of 97%.

6-Bromohexanoic acid (10.53 g, 54 mmol) was also converted into the corresponding aldehyde by the reaction with 118.8 mmol of the reagent for 15 min at room temperature. Estimation as the (2,4-dinitrophenyl)hydrazone, mp 92–93 °C, indicated a yield of 98%. Anal. Calcd: C, 40.12; H, 4.21; N, 15.60; Br, 22.25. Found: C, 39.97; H, 4.23; N, 15.59; Br, 22.07.

Adipic acid monoethyl ester (9.41 g, 54 mmol) was reduced in the usual manner. The aliquot of the reaction mixture (4.0 mmol) was subjected to the usual analysis by (2,4-dinitrophenyl)-hydrazine, providing 1.26 g of the hydrazone. The ^1H NMR spectrum of the hydrazone (DMSO-d_6) showed the presence of the hydrazone of 5-carbohydroxy-1-pentanal in a significant amount, formed by partial hydrolysis of the ester group in the very strong acidic medium of the (2,4-dinitrophenyl)hydrazine reagent. From this fact, we can estimate that the yield is in the range of 93–100%. (If the weighed hydrazone comes from the pure ester aldehyde, the 1.26 g isolated corresponds to a yield of 93%; assuming that the hydrazone comes from the pure acid aldehyde, the yield corresponds to a yield of 100%.)

In fact, the isolated yield of 5-carbethoxy-1-pentanal was quite satisfactory under the standard workup conditions for isolation of the product (procedure D).

A number of carboxylic acids were reduced in the same manner described above, and the yields of aldehydes were established by the quantitative estimation of the corresponding 2,4-dinitrophenylhydrazone. The identity of the hydrazones was checked through their melting points. The yields of the hydrazones are listed in Table I.

Sodium Bisulfite Adduct Formation of Aldehydes. The procedure for the adduct formation of 6-bromohexanal in the reaction mixture is representative. After reaction of 6-bromohexanoic acid (54 mmol) with the reagent for 15 min at room temperature (vide ante), an aliquot of the reaction mixture was withdrawn for analysis with (2,4-dinitrophenyl)hydrazine. Then the remaining reaction mixture was transferred with a double-ended needle to the flask containing 50 mL of cold water in an ice water bath and hydrolyzed with vigorous stirring for 1 h at room temperature. The mixture was then saturated with sodium chloride, and the organic layer was separated. After being neutralized with a small quantity of sodium bicarbonate, the organic layer was poured into 75 mL of a saturated aqueous sodium bisulfite solution, and 170 mL of THF was added. The mixture was stirred for 1 h. At this time the crystalline bisulfite adduct of 6-bromohexanal was apparent. The solution was cooled in an ice water bath to ensure complete crystallization of the adduct. The adduct was then collected by filtration, washed with 3 × 25 mL of pentane, and dried. The solid adduct was then subjected to the procedure for regeneration of aldehyde.

Formation of a solid adduct was general for most cases examined in this study, with one exception. The reaction mixture of adipic acid monoethyl ester was treated with a sodium bisulfite solution in the usual manner. However, no solid bisulfite adduct was evident at this time. In this case, the aqueous sodium bisulfite layer was separated, washed with 3 × 25-mL portions of diethyl ether, and then subjected to the procedure for regeneration of aldehyde.

Usually the adduct formation was complete within 1 h. However, in some cases, the rate of the adduct formation was quite slow. The conditions for adduct formation are noted in Table II.

Regeneration of Aldehydes. The following four different procedures for the regeneration of aldehydes are listed in Table II.

Procedure A. Regeneration of 6-bromohexanal from the corresponding adduct is representative. The solid adduct of 6-bromohexanal collected (vide ante) was placed in 50 mL of a saturated aqueous magnesium sulfate solution, and then 50 mL of pentane and 8 mL of a 37% formaldehyde solution were added. The mixture was stirred for 1 h. The pentane layer was separated and dried with anhydrous magnesium sulfate. Evaporation of all volatile materials gave an 86% yield of the almost pure product. Distillation of the crude product gave 6.8 g of pure 6-bromohexanal (76%): bp 106–107 °C (14 mm); n^{20}_D 1.4788. Anal. Calcd: C, 40.24; H, 6.19; Br, 44.63. Found: C, 40.12; H, 5.89; Br, 44.35.

In cases where the product was not quite soluble in pentane, such as *p*-nitrobenzaldehyde and terephthalaldehyde, THF was used to extract the product.

Procedure B. The regeneration of *m*-cyanobenzaldehyde is illustrative. The solid adduct collected was placed in 40 mL of water, and then 50 mL of THF and 8 mL of a 37% formaldehyde solution were added. The mixture was stirred for 1 h and saturated with magnesium sulfate heptahydrate. The organic layer was separated and dried. Evaporation of all volatile materials gave 3.0 g of almost pure *m*-cyanobenzaldehyde (67%): mp 77–78 °C (lit.[33] mp 75–78 °C). The ^1H NMR spectrum agreed with that of an authentic sample.

Procedure C. This is suitable for regeneration of high molecular weight aldehydes. Application to stearaldehyde is rep-

(33) *CRC Handbook of Tables for Organic Compound Identification*, 3rd ed.; CRC Press, Inc.: Cleveland, 1967.

resentative. The procedure was actually the same as in procedure B, except for the reaction temperature. Thus, the mixture was heated to 90–95 °C for 1 h with stirring. The solid disappeared. The mixture was cooled to room temperature and saturated with magnesium sulfate heptahydrate. The organic layer was separated and dried, and on removal of the solvent, almost pure stearaldehyde (12.35 g, 92%) was obtained: mp 37–38 °C (lit.[33] mp 38 °C). The ^{1}H NMR spectrum agreed with that of an authentic sample.

Procedure D. This is a procedure that can be used when no solid bisulfite adduct is formed. 5-Carbethoxy-1-pentanal was regenerated by this procedure. To the separated aqueous sodium bisulfite adduct layer following washing with diethyl ether was added 50 mL of a 37% formaldehyde solution. Then magnesium sulfate heptahydrate was added until saturation had been achieved. A 50-mL portion of pentane was added, and the mixture was stirred for 1 h. The pentane layer was separated and dried, and on evaporation of all solvent, an 81% yield of almost pure aldehyde (n^{20}_D 1.4269) was obtained. The further purification by distillation gave pure 5-carbethoxy-1-pentanal (5.70 g, 72%): bp 117–118 °C (13 mm); n^{20}_D 1.4268; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3 H, CH_3), 1.6 (m, 4 H, CH_2), 2–2.6 (m, 4 H, CH_2), 4.1 (q, 2 H, CH_2O), 10 (m, 1 H, CHO). Anal. Calcd: C, 60.74; H, 8.92. Found: C, 60.35; H, 9.21.

Isolation of Aldehydes by Distillation. Isolation of stearaldehyde is illustrative. In the usual setup, 30 mmol of stearic acid was reduced with 66 mmol of the reagent in methylene chloride at room temperature for 15 min, the same as the procedure described previously. The reaction mixture was transferred with a double-ended needle to the flask containing 40 mL of cold water in an ice water bath and hydrolyzed with vigorous stirring for 1 h at room temperature. The acidic solution was neutralized with 20 mL of 3 N aqueous sodium hydroxide solution, followed by adding a small quantity of sodium bicarbonate powder. The mixture with water was then subjected to distillation directly. The distillation was continued until the total 95 mL of distillate was collected. Almost all of the thexylboronic acid was distilled out, along with water. A 30-mL portion of pentane was added to the residue, and the organic layer was separated and dried. On removal of solvent, the crude product was obtained in a yield of 102%: mp 34 °C (lit.[33] mp 38 °C). The ^{11}B NMR spectrum of the crude product indicated the presence of some thexylboronic acid. The product was further purified by passing through an alumina column with diethyl ether as an eluent, providing pure stearaldehyde (7.65 g, 95%): mp 38 °C (lit.[33] mp 38 °C). The ^{1}H NMR spectrum agreed with that of an authentic sample.

Selective Reduction of Aliphatic Carboxylic Acid in the Presence of Benzoic Acid. The competitive reaction between hexanoic acid and benzoic acid is representative. In the usual setup, a 100-mL flask was charged with 0.61 g of benzoic acid (5 mmol), 0.93 g of hexanoic acid (5 mmol), and 3 mL of methylene chloride. The mixture was cooled to 0 °C. To this stirred mixture was then added 5.17 mL of 3.0 M thexylchloroborane in methylene chloride (15.5 mmol) dropwise. After the hydrogen evolution was complete, the mixture was brought to room temperature and stirred for 1 h. The reaction was then quenched with 5 mL of water, and *n*-nonane was added as an internal standard. GC analysis of the organic layer indicated a 92% yield of hexanal and 6% yield of benzaldehyde.

In the larger scale reaction (50 mmol of each carboxylic acid), a 74% yield of hexanal was isolated by using the sodium bisulfite method in the usual manner, and a 90% yield of benzoic acid was recovered by using the potassium carbonate extraction.

Registry No. 1, 75067-06-0; benzoic acid, 65-85-0; benzaldehyde, 100-52-7; α-naphthoic acid, 86-55-5; α-naphthaldehyde, 66-77-3; *p*-methoxybenzoic acid, 100-09-4; *p*-methoxybenzaldehyde, 123-11-5; *p*-nitrobenzoic acid, 62-23-7; *p*-nitrobenzaldehyde, 555-16-8; *m*-cyanobenzoic acid, 1877-72-1; *m*-cyanobenzaldehyde, 24964-64-5; terephthalic acid, 100-21-0; terephthalaldehyde, 623-27-8; hexanoic acid, 142-62-1; hexanal, 66-25-1; decanoic acid, 334-48-5; decanal, 112-31-2; stearic acid, 77-92-9; stearaldehyde, 638-66-4; neopentanoic acid, 75-98-9; trimethylacetaldehyde, 630-19-3; diphenylacetic acid, 117-34-0; diphenylacetaldehyde, 947-91-1; cyclohexanecarboxylic acid, 98-89-5; cyclohexanecarboxaldehyde, 2043-61-0; 1,10-decanedicarboxylic acid, 693-23-2; 1,10-decanedicarboxaldehyde, 38279-34-4; 6-bromohexanoic acid, 4224-70-8; 6-bromohexanal, 57978-00-4; adipic acid monoethyl ester, 626-86-8; 5-carbethoxy-1-pentanal, 27983-42-2.

Selective Reductions. 40. A Critical Examination of the Relative Effectiveness of Various Reducing Agents for the Asymmetric Reduction of Different Classes of Ketones

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Among a wide variety of highly promising asymmetric reducing agents recently reported in the literature, 20 promising reagents were selected for critical examination. All of the data for the asymmetric reductions of prochiral ketones by these 20 reagents were compiled. The various ketones were organized into 10 distinct classes. However, direct comparison of the relative effectiveness of these 20 reagents for individual classes of ketones proved not possible because of the wide variation in the individual ketones used to test each reagent. In the hope of making possible such comparison, we selected one representative ketone for each of the 10 different classes of ketones. Then, six of the most promising reagents were selected: *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, *B*-Ipc-9-BBN (neat); diisopinocampheylchloroborane, Ipc_2BCl; a mixed reagent of 2 equiv of BH_3 with (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol, BH_3–AMDPB (2:1); NB-Enantride; K-Glucoride; and Binal-H. These six reagents were applied to the 10 selected standard ketones. On the basis of results obtained for the six reagents and the 10 selected ketones, preferred reagents are suggested for the asymmetric reduction of individual classes of ketones.

Chiral modifications of complex metal hydride reagents with a wide variety of chiral auxiliaries for the asymmetric reduction of carbonyl compounds have been studied actively during the last 2 decades. However, asymmetric

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