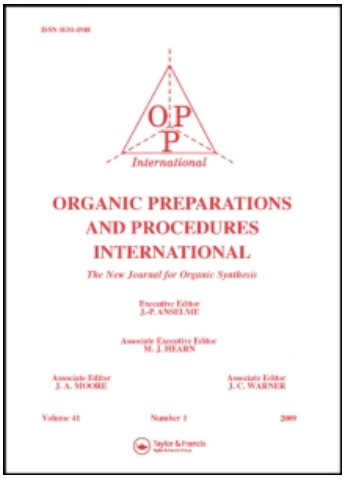

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REDUCTION OF ORGANIC COMPOUNDS WITH THEXYL-*S*-BUTOXYBORANE

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REDUCTION OF ORGANIC COMPOUNDS WITH THEXYL-*s*-BUTOXYBORANE

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Very recently, we communicated the reaction of carboxylic acids with thexylalkoxyboranes (ThxBHOR: Thx = 2,3-dimethyl-2-butyl, R = Et, *i*-Pr, *i*-Bu, *s*-Bu, *t*-Bu, Ph).[1,2] Among these derivatives, ThxBHO^{i}Pr and ThxBHO^{s}Bu efficiently reduced various carboxylic acids to the corresponding aldehydes in good yields. Such unique reducing action intrigued us, because the reagents seem to be a new class of selective reducing agents. Accordingly, we began a systematic study of their reducing properties. Thexyl-*s*-butoxyborane (ThxBHO^{s}Bu) was chosen for this initial study. We examined the possibility for selective reductions of representative organic compounds with use of the reagent in limiting amount.

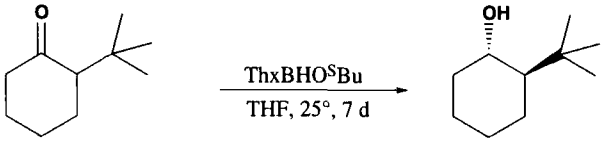
The alcohols and phenols listed in Table 1 evolved hydrogen incompletely with stoichiometric amount of ThxBHO^{s}Bu. After initial rapid evolution of some hydrogen, no further release of gas was apparent. Virtually no hydrogen evolution was noticed with primary amines and thiols. None of these compounds underwent reduction by the reagent.

Aldehydes were cleanly reduced to the corresponding alcohols with one equivalent of ThxBHO^{s}Bu in 2 or 3 days, whereas the reduction of ketones was very slow and incomplete. Even after 5 days at 25°, a maximum of only about 80% of the theoretical amount of alcohol was produced. The stereoselectivity of ThxBHO^{s}Bu reductions of substituted cycloalkanones indicates that the ThxBHO^{s}Bu behaves like unhindered hydride reagents to produce the thermodynamically more stable alcohol epimers preferentially. Thus, the reduction of 2-*t*-butylcyclohexanone using two equivalents of ThxBHO^{s}Bu gave 99% *trans*-2-*t*-butylcyclohexanol in a total 92% yield in 7 days at 25° (*Eq. 1*). The results are presented in Table 2.

TABLE 1. Reaction of ThxBHO^{s}Bu with "Active Hydrogen Compounds" in THF at 25°[a]

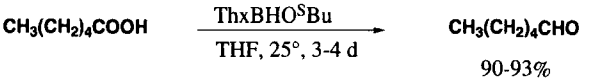
Cmpd	Time (hrs)	Ratio of rgt/cmpd	Hydride used for Hydrogen evolution[b,c]
1-Hexanol	0.5	1.00	0.46
	1.0	1.00	0.48
	3.0	1.00	0.48
Benzyl alcohol	0.5	1.00	0.61
	1.0	1.00	0.61
Phenol	0.5	1.00	0.24
	1.0	1.00	0.25
	3.0	1.00	0.25
n-Hexylamine	0.5	2.00	0.03
	1.0	2.00	0.03
1-Hexanethiol	0.5	1.00	0.00
	1.0	1.00	0.00
Benzenethiol	0.5	1.00	0.00
	1.0	1.00	0.00

a) Solutions being 0.8 M in reagent and 2.0 M in compound examined both in THF were utilized for reactions. b) Mmoles of reagent per mmol of compound. c) Determined gasometrically.



99%, *trans* (1)

The reaction of carboxylic acids was examined with two or three equivalents of ThxBHO^{s}Bu at 25°. Both hexanoic acid and benzoic acid reacted with this reagent to evolve one equivalent of hydrogen instantly and quantitatively, and consumed another equivalent of hydride for reduction and further hydride uptake was very slow. This relatively rapid consumption of one equivalent of hydride for reduction suggests the possibility of aldehyde formation. In fact, the reaction of hexanoic acid with three equivalents of ThxBHO^{s}Bu provided hexanal in 93% yield in 4 days at 25° (Eq 2). However, the reaction of benzoic acid gave somewhat lower yield of benzaldehyde (68%) (Table 3). The initially formed aldehyde intermediate seems to be so sterically hindered that it survived even in the presence of extra reagent under these reaction conditions.



(2)

TABLE 2. Reaction of ThxBHO^{s}Bu with Aldehydes and Ketones in THF at 25°[a]

Cmpd	Time (hrs)	Ratio of Rgt/cmpd	Hydride[b,c]	Product	Yield[d] (%)
Hexanal	1	1.00	0.67	1-Hexanol	65
	6	1.00	0.75	1-Hexanol	73
	24	1.00	0.87	1-Hexanol	89
	48	1.00	0.98	1-Hexanol	98
	72	1.00	1.00	1-Hexanol	100
Benzaldehyde	1	1.00		Benzyl alcohol	62
	6	1.00		Benzyl alcohol	79
	24	1.00	0.96	Benzyl alcohol	95
	48	1.00	1.00	Benzyl alcohol	100
2-Heptanone	48	1.00		2-Heptanol	50
	120	1.00	0.82	2-Heptanol	79
Acetophenone	48	1.00		1-Phenylethanol	41
	120	1.00	0.64	1-Phenylethanol	65
Benzophenone	48	1.00		Benzhydrol	42
	120	1.00	0.61	Benzhydrol	60
2-Methylcyclohexanone	48	1.00		2-Methylcyclohexanol	34
	168	2.00	0.99	2-Methylcyclohexanol[e]	96
3-Methylcyclohexanone	168	2.00	1.01	3-Methylcyclohexanol[f]	98
4-Methylcyclohexanone	168	2.00	1.00	4-Methylcyclohexanol[g]	99
2-*t*-Butylcyclohexanone	168	2.00	0.94	2-*t*-Butylcyclohexanol[h]	92
4-*t*-Butylcyclohexanone	168	2.00	0.97	4-*t*-Butylcyclohexanol[i]	98
3,3,5-Trimethylcyclohexanone	168	2.00	0.98	3,3,5-Trimethylcyclohexanol[j]	95
2-Methylcyclopentanone	168	2.00	0.99	2-Methylcyclopentanol[k]	97
Norcamphor	48	1.00		Norborneol	32
	168	1.00		Norborneol	74
	168	2.00	0.94	Norborneol[l]	93

a-c) See corresponding footnotes in Table 1. d) Determined by GC analysis with an internal standard and authentic samples. e) A 30:70 ratio of *cis*- and *trans*-2-methylcyclo hexanols. f) A 96:4 ratio of *cis*- and *trans*-3-methylcyclohexanols. g) A 6:94 ratio of *cis*- and *trans*-4-methylcyclohexanols. h) A 1:99 ratio of *cis*- and *trans*-2-*t*-butylcyclo hexanols. i) A 7:93 ratio of *cis*- and *trans*-4-*t*-butylcyclohexanols. j) A 56:44 ratio of *cis*- and *trans*-3,3,5-trimethylcyclohexanols. k) A 59:41 ratio of *cis*- and *trans*-2-methylcyclopentanols. l) A 1:99 ratio of *endo*- and *exo*-norborneols.

The most outstanding feature of ThxBHO^{s}Bu as a reducing agent is its ability to convert carboxylic acids to the corresponding aldehydes. Such conversion with various alkoxy derivatives has already been reported.[1] In this respect, thexylalkoxyboranes[1] and thexylhaloboranes[3,4] are very promising reagents for the reduction of carboxylic acids to aldehydes. However, the alkoxy derivatives are much milder and hence more selective reducing agents than the halo derivatives. A simple,

TABLE 3. Reaction of ThxBHO^{s}Bu with Carboxyl Acids in THF at 25°[a]

Cmpd	Time (hrs)	Ratio of rgt/cmpd	Hydride[b,c,d]	Product	Yield[e] (%)
Hexanoic acid	6	2.00	1.69		
	48	2.00	1.78		
	72	2.00	1.91		
	96	2.00	1.98	Hexanal	90
	6	3.00	1.72		
	48	3.00	1.98		
	72	3.00	2.05	Hexanal	93
	96	3.00	2.08		
Benzoic acid	6	2.00	1.66		
	48	2.00	1.81		
	72	2.00	1.88		
	96	2.00	1.94	Benzaldehyde	64
	6	3.00	1.72		
	48	3.00	1.95		
	72	3.00	2.01		
	96	3.00	2.04	Benzaldehyde	68

a-c) See corresponding footnotes in Table 1. d) Along with immediate evolution of 1 equivalent of hydrogen. e) Analyzed as 2,4-dinitrophenylhydrazones.

TABLE 4. Reaction of ThxBHO^{s}Bu with Acid Chlorides in THF at 25°[a]

Cmpd	Time (hrs)	Ratio of rgt/cmpd	Hydride	Product	Yield[d] (%)
Hexanoyl Chloride	6	2.00	0.58		
	48	2.00	0.88		
	72	2.00	0.97		
	96	2.00	0.98	Hexanal	83
Trimethylacetyl Chloride	96	2.00	0.97	Trimethylacetaldehyde	60
Cyclopropanecarbonyl Chloride	96	2.00	0.96	Cyclopropanecarboxaldehyde	70
Adipoyl Chloride	96	4.00	1.86	Adipaldehyde	61
Sebacoyl Chloride	96	4.00	1.96	Sebacaldehyde	76
Benzoyl Chloride	6	2.00	0.51		
	48	2.00	0.74		
	72	2.00	0.82		
	96	2.00	0.87		
	120	2.00	0.92	Benzaldehyde	61
o-Toluoyl Chloride	120	2.00	0.94	*o*-Tolualdehyde	50
m-Toluoyl Chloride	120	2.00	0.91	*m*-Tolualdehyde	56
p-Toluoyl Chloride	120	2.00	0.93	*p*-Tolualdehyde	54
Phthaloyl Chloride	120	4.00	1.78	Phthalic dicarboxaldehyde	51

a-c) See corresponding footnotes in Table 1. d) Analyzed as 2,4-dinitrophenylhydrazones.

convenient procedure involved the sodium bisulfite adduct formation and the regeneration of aldehydes using formaldehyde is also efficiently applicable for the isolation of the aldehydes produced in this reaction.[1,3]

The reaction of acid chlorides with two equivalents of ThxBHO^{s}Bu consumed only less than one equivalent of hydride for reduction relatively rapidly and no further hydride consumption was noticed. We examined the possibility of aldehyde formation. The aliphatic acid chlorides listed in Table 4 were reduced to the corresponding aldehydes with two equivalents of ThxBHO^{s}Bu in yields of 60-83%. α,ω-Diacid chlorides, such as adipoyl chloride and sebacoyl chloride, were also converted to dialdehydes with excess reagent in yields of 61-76%. However, the reaction of aromatic acid chlorides provided the corresponding aldehydes in yields of only around 50%.

Little or no reaction was observed between ThxBHO^{s}Bu and esters under the experimental conditions used. The reagent also showed no reactivity toward *N,N*-dimethylcarboxamides. The actual data are given in Table 5. As shown in Table 6, all epoxides and nitriles examined were totally inert to ThxBHO^{s}Bu.

TABLE 5. Reaction of ThxBHO^{s}Bu with Esters and *N,N*-Dimethylcarboxamides in THF at 25°[a]

Cmpd	Time (hrs)	Ratio of Rgt/cmpd	Hydride[b,c]	Product	Yield[d] (%)
Ethyl benzoate	96	2.00	0.00		
Ethyl hexanoate	48	2.00	0.18		
	96	2.00	0.30	1-Hexanol	27
N,N-Dimethylbenzamide	96	2.00	0.01		
N,N-Dimethylhexanoamide	96	2.00	0.02		

a-c) See corresponding footnotes in Table 1. d) Determined by GC analysis.

TABLE 6. Reaction of ThxBHO^{s}Bu with Epoxides and Nitriles in THF at 25°[a]

Cmpd	Time (hrs)	Ratio of rgt/cmpd	Hydride[b,c]
1,2-Butylene oxide	96	1.00	0.00
Cyclohexene oxide	96	1.00	0.00
Styrene oxide	96	1.00	0.00
Hexanenitrile	96	2.00	0.00
Benzonitrile	96	2.00	0.00

a-c) See corresponding footnotes in Table 1. d) Determined by GC analysis.

The nitro compounds, disulfides and sulfones listed in Table 7 all failed to indicate any reaction with ThxBHO^{s}Bu; however, surprisingly, dimethyl sulfoxide was reduced to dimethyl sulfide quantitatively at a relatively rapid rate. Slow hydrogen evolution was also observed as reduction proceeded, perhaps the hydrogen being evolved from the boronic acid intermediate.[5] The relatively

rapid reduction of dimethyl sulfoxide with ThxBHO^{s}Bu and the relative inertness of the reagent towards many other functional groups suggests the possibility of using this reagent for the selective deoxygenation of sulfoxides to sulfides under mild conditions. The results are summarized in Table 7.

TABLE 7. Reaction of ThxBHO^{s}Bu with Nitrogen and Sulfur Compounds in THF at 25°[a]

Cmpd	Time (hrs)	Ratio of Rgt/cmpd	Hydride[b,c]	Product	Yield[d] (%)
1-Nitropropane	48	2.00	0.00		
Nitrobenzene	48	2.00	0.00		
Di-*n*-butyl disulfide	72	2.00	0.00		
Diphenyl disulfide	72	2.00	0.00		
Dimethyl sulfoxide	12	2.00	0.95[e]	Dimethyl sulfide	73
	24	2.00	1.20[f]	Dimethyl sulfide	86
	48	2.00	1.48[g]	Dimethyl sulfide	100
Diphenyl sulfone	48	2.00	0.00		

a-c) See corresponding footnotes in Table 1. d) Determined by GC analysis. e) Along with 0.21 equivalent of hydrogen evolution. f) Along with 0.32 equivalent of hydrogen evolution. g) Along with 0.41 equivalent of hydrogen evolution.

EXPERIMENTAL SECTION

All operations were carried out under a dry nitrogen atmosphere. All glassware, syringes, and needles were oven-dried at 140° and cooled to room temperature with nitrogen gas before use. All the compounds examined were commercial products of the highest purity which were further purified by standard methods before use. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl. 2,3-Dimethyl-2-butene (tetramethylethylene) was purchased from the Aldrich Chemical Co. and distilled from lithium aluminum hydride. Sodium borohydride was also purchased from the Aldrich Chemical Co. and dried in a hot desiccator under reduced pressure before use. Dimethyl sulfate was freshly distilled. ^{11}B NMR spectra were obtained on a Bruker AMX 300 spectrometer; the chemical shifts are in δ relative to BF_3•OEt_2 with downfield assigned as positive. Gas chromatographic analyses were carried out with Donam DS 6200 and Varian 3300 FID chromatographs using Carbowax 20 M and Methylsilicone 3300 capillary columns.

Preparation of Thexylborane (ThxBH$_2$) in THF.[6]- The following procedure for the preparation of a 0.9 M THF solution of ThxBH$_2$ is representative. An oven-dried, 1-L round-bottom flask equipped with a magnetic stirring bar and fitted a rubber-capped side-arm was charged by cannula with 454.5 mL of a 1.1 M solution of BH_3•THF[7] (500 mmol) in THF, and the flask was immersed in an ice-salt bath under nitrogen. 2,3-Dimethyl-2-butene (44.2 g, 525 mmol) was added dropwise with stirring, keeping the temperature below 0°. The reaction mixture was stirred for an additional 3 h at that temperature. An aliquot of the ThxBH$_2$ solution in THF so prepared was quenched in a glycerol-water hydrolyzing mixture and the hydrogen gas evolved was measured volumetrically to indicate the

concentration of the $ThxBH_2$ solution being 0.90 M. The solution was further utilized for preparation of ThxBHOR.

Preparation of Thexyl-*s*-butoxyborane (ThxBHO^{s}Bu) in THF.- A 250-mL round-bottom flask equipped with a magnetic stirring bar and fitted with a rubber septum was charged by cannula with 110 mL of a 0.90 M solution of $ThxBH_2$ (99 mmol) in THF and cooled under nitrogen to -25° with use of a cooling bath. *s*-Butyl alcohol (7.8 g, 105 mmol) was added dropwise with vigorous stirring. After the hydrogen evolution ceased, the reaction mixture was stirred for an additional 1 h at 0° to afford a 0.8 M of ThxBHO^{s}Bu solution. ^{11}B NMR (THF): δ 50 (d, J = 125 Hz). The solution of ThxBHO^{s}Bu thus prepared was stable when stored under a static pressure of dry nitrogen at 0°.

General Procedure Used for Hydride Reductions.- The following procedure was used for quantitative studies. The reduction of hexanal is described as an example of the experimental procedure. The ThxBHO^{s}Bu solution, 30.0 mL of 0.8 M (24.0 mmol), was introduced into a dried, 100-mL flask fitted with a rubber syringe cap on an inlet port, a magnetic stirring bar, and a bent adapter connected to a gas buret through a reflux condenser through a reflux condenser and a dry ice vapor trap. The flask was immersed in a temperature-controlled water bath, the stirred solution was maintained at 25°, and 2.40 g of hexanal (24.0 mmol) in 12 mL of THF and dodecane as an internal standard were injected. No hydrogen evolution was apparent. 3.0-mL aliquot of the reaction mixture was removed and injected into a glycerol-water solution to measure residual hydride. The hydrogen evolved amounted to 0.33 mmol, which indicates that 0.67 mmol of hydride was used for reduction per mmol of compound. At the same time, another aliquot of the reaction mixture was also removed and treated with 3 mL of 3 N NaOH and 1.5 mL of 30% H_2O_2. After stirring for 2 h at 25°, the mixture was saturated with K_2CO_3. The organic layer was separated, dried with anhydrous $MgSO_4$, and subjected to GC analysis, showing the presence of 1-hexanol in a yield of 65%. Aliquots were also removed and analyzed at specific time intervals listed in Table 2. After 72 h, there was not observed any active hydride remaining in the reaction mixture and the GC analysis also showed 100 % 1-hexanol.

Reduction of Carboxylic Acids.- The following procedure for the reduction of hexanoic acid is illustrative. An oven-dried, 50-mL flask, fitted with a side-arm and a reflux condenser connected to a gas buret, was charged with 20.0 mL of a 0.8 M solution of ThxBHO^{s}Bu (16.0 mmol) in THF and immersed in a water bath at 25°, and followed by the dropwise addition, with stirring, of 4 mL of a 2.0 M solution of hexanoic acid (8.0 mmol). One equivalent of hydrogen gas was evolved instantly. The rate of reaction was monitored by measuring periodically the hydride content in a measured aliquot. After 96 h at 25°, the consumption of hydride was complete (Table 3). An aliquot of the reaction mixture (9 mL, 3 mmol) was then withdrawn and subjected to analysis with 2,4-dinitrophenylhydrazine, showing a yield of 90%: mp. of the hydrazone 103-105, lit.[8] mp. 104°.

Reduction of Acid Chlorides.- The reduction of hexanoyl chloride is described as representative. In the usual setup, 1.62 g of hexanoyl chloride (12.0 mmol) was reduced with 30.0 mL of ThxBHO^{s}Bu (0.8 M, 24.0 mmol) at 25°. The rate of reaction was monitored by measuring the hydride content. After 96 h, there was no significant difference in hydride consumption. Obviously, the reaction was

complete in 96 h to indicate the corresponding aldehyde being formed in the reaction mixture. To determine the aldehyde product, an aliquot of the reaction mixture was removed and subjected to analysis with 2,4-dinitrophenylhydrazine, showing a yield of 83%, mp. of the hydrazone 104-105°.

General Procedure for Stereoselectivity Studies.- The reduction of 2-*t*-butylcyclohexanone is described as representative. In the usual assembly, 0.62 g of 2-*t*-butylcyclohexanone (4.0 mmol) was reduced with 10.0 mL of ThxBHO^{t}Bu (0.8 M, 8.0 mmol) at 25°. The rate of reaction was monitored as described above. After 7 d, the reaction mixture was treated with 1 mL of 3 N NaOH and 0.5 mL of 30% H_2O_2. The aqueous layer was saturated with anhydrous K_2CO_3, and the organic layer was subjected to GC analysis using a Carbowax 20 M capillary column, showing the presence of of 2-*t*-butylcyclohexanol in a yield of 92% (a 1:99 ratio of *cis*- and *trans*-epimers).

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