Reactions of Vinyloxyboranes.[1] A Convenient Method for the Preparation of β-Hydroxy Thiolesters, Esters and Ketones

Katsuhiko INOMATA, Masayoshi MURAKI, and Teruaki MUKAIYAMA

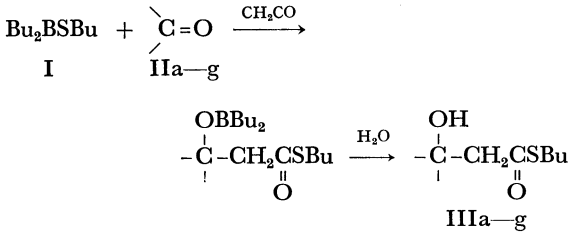
Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

(Received November 27, 1972)

It was found that the reaction of thioboronites with carbonyl compounds and ketene proceeds with the initial formation of vinyloxyboranes (VII). The boranes were found to be important intermediates for the formation of β-hydroxythiolesters by the reaction with various carbonyl compounds. Vinyloxyborane derivatives can be alternatively prepared by the reactions of trialkylboranes and α-diazocarbonyl compounds. The boranes similarly reacted with carbonyl compounds to give β-hydroxyketones and β-hydroxyesters.

In a previous paper,[2] it was reported that the reaction of thioboronite with carbonyl compounds and ketene afforded β-hydroxyalkanethioates in excellent yields. This paper deals with an extention of earlier works.[2,3]

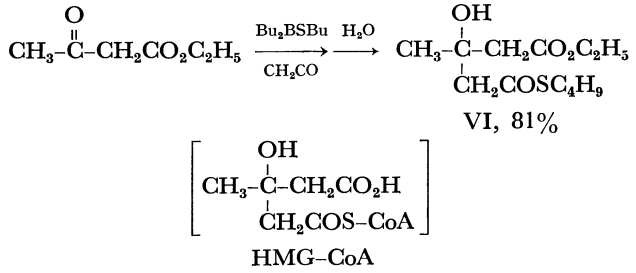
A typical reaction of thioboronite with carbonyl compounds and ketene is shown in the following. When equimolar amounts of *n*-butyl di-*n*-butylthioboronite (I) and various carbonyl compounds (IIa—g) in dry ether were treated with excess gaseous ketene at 0 °C for 2 hr followed by hydrolysis, the corresponding β-hydroxyalkanethioates (IIIa—g) were obtained in excellent yields (Scheme 1). The results are summarized in Table 1.



Scheme 1

In the same way, β-hydroxyalkanethioates (Va—e) were obtained by the treatment of other thioboronites (IVa—e) prepared from tri-*n*-butylborane and thiols with benzaldehyde and ketene, followed by hydrolysis, in excellent yields (Table 2). Thus, it became clear that the reaction of thioboronites with carbonyl compounds and ketene is an excellent method of preparing various β-hydroxyalkanethioates.

By utilizing this reaction, *S*-*n*-butyl ethyl β-hydroxy-β-methyl-thioglutarate (VI), the analog of β-hydroxy-β-methyl-glutaryl coenzyme A (HMG-CoA), was obtained in 81% yield from ethyl acetoacetate by the following procedure (Scheme 2).



Scheme 2

Table 1. Yields and properties of β-hydroxyalkanethioates[a]

IIa—g	Carbonyl compound	Product	Bp °C /mmHg	Isolated yield, %		Elemental analyses, % C	H	S
IIa	$CH_3(CH_2)_2CHO$	IIIa	97—98 /4.5	84	Found	58.51	9.92	15.87
					Calcd	58.80	9.87	15.67
IIb	C_6H_5CHO	IIIb	145—146 /4.5	90	Found	65.47	7.90	13.16
					Calcd	65.53	7.61	13.43
IIc	$C_6H_5CH=CHCHO$	IIIc	163 /0.18	90	Found	68.46	7.76	11.93
					Calcd	68.16	7.63	12.11
IId	$(CH_3)_2CO$	IIId	82—84 /3.0	98	Found	56.61	9.66	16.65
					Calcd	56.82	9.54	16.82
IIe		IIIe	112—113 /1.5	91	Found	62.59	9.69	14.12
					Calcd	62.58	9.63	13.90
IIf	$C_6H_5(C_2H_5)CO$	IIIf	139 /3.0	91	Found	67.58	8.42	12.13
					Calcd	67.64	8.33	12.01
IIg	$(C_6H_5)_2CO$	IIIg	[b]	94	Found	72.39	7.07	10.06
					Calcd	72.59	7.05	10.18

a) In ether at 0°C for 2 hr. b) Mp 75.5—76.5 °C.

1) Presented in part at the 23rd Symposium on Organic Reaction Mechanisms of the Chemical Society of Japan, Kobe, October, 1972. Preliminary communication: T. Mukaiyama, K. Inomata, and M. Muraki, *J. Amer. Chem. Soc.*, **95**, 967 (1973).

2) T. Mukaiyama and K. Inomata, This Bulletin, **44**, 3215 (1971).

3) a) T. Mukaiyama, K. Inomata, and S. Yamamoto, *Tetrahedron Lett.*, **1971**, 1097. b) T. Mukaiyama, S. Yamamoto, and K. Inomata, This Bulletin, **44**, 2807 (1971).

Table 2. Yields and properties of β-hydroxyalkanethioates[a)]

$$Bu_2BSR + PhCHO \xrightarrow[ii)\ H_2O]{i)\ H_2C=C=O} PhCHCH_2CSR \quad (OH,\ O)$$

IVa—e Va—e

IVa—e	R	Product	Bp °C /mmHg (Mp °C)	Isolated yield, %		Elemental analyses, % C	H	S
IVa	$-C_6H_5$	Va	(84.5—85.5)	96	Found	69.57	5.29	12.63
					Calcd	69.74	5.46	12.41
IVb	$-CH_2C_6H_5$	Vb	182—184 /2.0	94	Found	70.93	5.66	12.06
					Calcd	70.56	5.92	11.77
IVc	$-CH_2-$(furyl)	Vc	b)	71	Found	64.21	5.42	12.25
					Calcd	64.09	5.38	12.23
IVd	$-C(CH_3)_3$	Vd	138—139 /2.5	93	Found	65.11	7.54	13.49
					Calcd	65.51	7.61	13.45
IVe	$-CH(CH_3)C_2H_5$	Ve	138 /2.5	97	Found	65.70	7.51	13.33
					Calcd	65.51	7.61	13.45

a) In ether at 0 °C. b) This is an oily substance and decomposed during the course of vacuum distillation.

It was postulated that the above reaction of thioboronites with carbonyl compounds and ketene proceeds with the initial formation of a coordination complex of thioboronite and a carbonyl compound, followed by a nucleophilic attack of the thiolate anion on ketene.[2] However, the present results show that this reaction proceeds through vinyloxyborane (VII), formed from thioboronite and ketene, as sketched in the following scheme.

$$H_2C=C=O + RSBR_2' \longrightarrow H_2C=C(SR)(OBR_2') \xrightarrow{H_2O} CH_3CSR \quad (O)$$

VII VIII

$$VII + >C=O \longrightarrow \left[H_2C=C(SR)-C(O\rightarrow B R_2')-O \right] \xrightarrow{H_2O} -C(OH)-CH_2CSR \quad (O)$$

IX

When nearly one equivalent of gaseous ketene was passed through a solution of phenyl di-*n*-butylthioboronite in carbon tetrachloride at −20——30 °C under argon, formation of VII (R=C_6H_5, R′=*n*-C_4H_9) was confirmed by the PMR spectrum of the reaction mixture which displayed two doublets for the vinyl hydrogens at δ 4.57 and 4.63 (*J*=*ca.* 1.5 Hz). On hydrolysis of this reaction mixture, phenyl thioacetate (VIII, R=C_6H_5) was isolated by preparative tlc.

It was established that the treatment of VII (R=C_6H_5, R′=*n*-C_4H_9) with acetone in ether, followed by hydrolysis, afforded phenyl β-hydroxy-isovalerothioate (IX, R=C_6H_5) in 67% yield.

Excess gaseous ketene was bubbled into a solution of equimolar amounts of thioboronites and carbonyl compounds at 0 °C in dry ether. Completion of the reaction by this procedure took a longer time as compared with the above procedure of treating vinyloxyboranes with carbonyl compounds. This might be attributed to the presence of the coordination complex of thioboronite with carbonyl compound and the necessity of ligand exchange of the carbonyl compound and ketene to proceed further.

The reactions of vinyloxyboranes prepared by other methods were studied with the expectation that these compounds would be important synthetic intermediates.

Hooz and Linke reported that the reaction of trialkylboranes and α-diazo ketones[4] or esters,[5] followed by hydrolysis, gave the corresponding α-alkyl carbonyl compounds, the intermediate being β-ketoborane.[4] Pasto and Wojtkowski[6] proposed vinyloxyborane to be an intermediate by means of NMR and UV spectra. It was found that the vinyloxyboranes (XI, Y=C_6H_5; XI′, Y=OC_2H_5), obtained from α-diazo carbonyl compounds and tri-*n*-butylborane, gave β-hydroxy ketones (XII) and β-hydroxy esters (XII′), respectively, on treatment with carbonyl compounds in THF at room temperature as follows. The results are summarized in Tables 3 and 4.

$$N_2CHCY(O) + Bu_3B \xrightarrow{-N_2} BuCH=C(Y)(OBBu_2)$$

X, Y=C_6H_5; X′, Y=OC_2H_5 XI or XI′

$$XI\ or\ XI' + >C=O \xrightarrow{H_2O} -C(OH)-CH(Bu)CY \quad (O)$$

XII or XII′

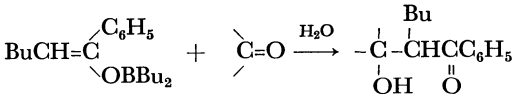
It was found that the vinyloxyborane (XIV) prepared from tri-*n*-butylborane and ethyl α-diazohydrocinnamate (XIII)[7] reacted with benzaldehyde to give ethyl 2-*n*-butyl-2-benzyl-3-hydroxy-hydrocinnamate (XV) in 70% yield under similar conditions.

$$N_2C(CH_2C_6H_5)CO_2C_2H_5 + Bu_3B \xrightarrow{-N_2} C_6H_5CH_2(Bu)C=C(OC_2H_5)(OBBu_2)$$

XIII XIV

4) J. Hooz and S. Linke, *J. Amer. Chem. Soc.*, **90**, 5936 (1968).
5) J. Hooz and S. Linke, *ibid.*, **90**, 6891 (1968).
6) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, **1970**, 215.

Table 3. Yields of β-hydroxyketones[a)]

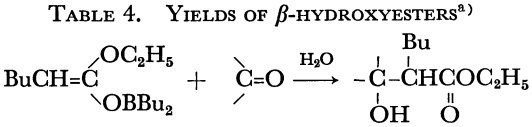


XI XIIa—d

Carbonyl compound	Time	Product	Isolated yield, %
$CH_3(CH_2)_2CHO$	10 min	XIIa	88
C_6H_5CHO	10 min	XIIb	98
	1 day	XIIc	69
$(CH_3)_2CO$	3 days	XIId	42

a) In THF at room temperature.

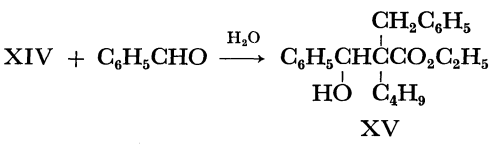
Table 4. Yields of β-hydroxyesters[a)]



XI′ XII′a—e

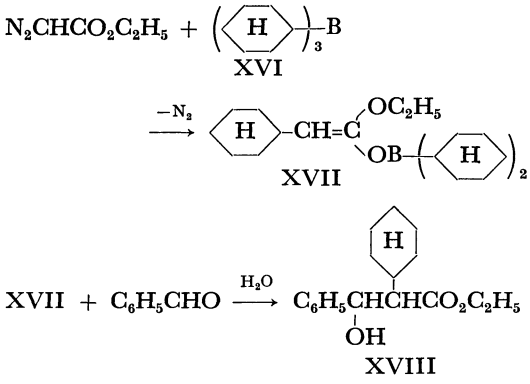
Carbonyl compound	Time	Product	Isolated yield, %
$CH_3(CH_2)_2CHO$	1 day	XII′a	87
C_6H_5CHO	1 day	XII′b	81
	1 day	XII′c	96
$(CH_3)_2CO$	1 day	XII′d	73
$C_6H_5(C_2H_5)CO$	1 day	XII′e	68

a) In THF at room temperature.

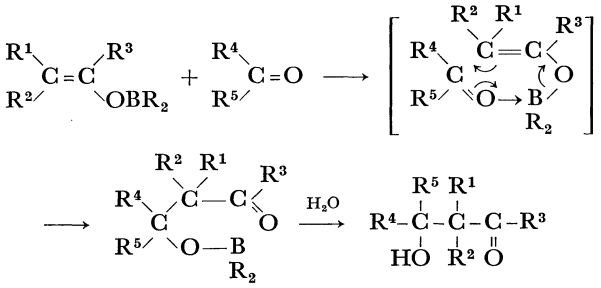


XV

Tricyclohexylborane (XVI) also reacted with ethyl diazoacetate to afford another vinyloxyborane (XVII) which further reacted with benzaldehyde to give ethyl 2-cyclohexyl-3-hydroxyhydrocinnamate (XVIII) in 87% yield.



It is to be noted that vinyloxyboranes, which afford the corresponding β-hydroxycarbonyl derivatives by the reaction with carbonyl compounds according to the following scheme, are useful intermediates in organic synthesis because of their high reactivity with carbonyl compounds and their availability.[6,8,9]



Experimental[10]

Materials. Tri-*n*-butylborane was prepared from boron trifluoride diethyl etherate and *n*-butylmagnesium bromide in dry ether under argon. Tricyclohexylborane was prepared by hydroboration of cyclohexene in THF.

*s-Butyl Di-*n*-butylthioboronite (IVe).*[11] *s*-Butylmercaptan (1.65 g, 18.3 mmol) was added to tri-*n*-butylborane (3.42 g, 18.8 mmol) in the presence of some boiling stone at room temperature under argon. The reaction mixture was then heated at 150 °C for 1 hr and distilled *in vacuo* under argon. Bp 100—103 °C/7 mmHg. 3.19 g (81.5%). PMR ($CDCl_3$) δ 0.7—1.8 (m, 26H), 3.23 (q, J=7 Hz, 1H).

Other thioboronites (IVa—e) were prepared from tri-*n*-butylborane and the corresponding mercaptans in a similar way. The results are listed in Table 5.

Table 5. Yields of thioboronites[a)]

n-Bu_3B + RSH ⟶ n-Bu_2BSR IVa—e

Mercaptan	Conditions	Yield, %	Bp °C/mmHg
C_6H_5SH	180°, 4 hr	IVa, 80	107—108 /2
$C_6H_5CH_2SH$	160°, 3 hr	IVb, 81	157—159 /8.5
-CH_2SH	180°, 4 hr	IVc, 76	130—134 /6
$(CH_3)_3CSH$	160°, 4 hr	IVd, 81	99—102 /7
$C_2H_5(CH_3)CHSH$	150°, 1 hr	IVe, 82	100—103 /7

a) These were confirmed by PMR spectra under argon. IVa; PMR (CCl_4) δ 0.5—2.0 (m 18H), 7.14 (s 5H) IVb; ($CDCl_3$) δ 0.7—1.5 (m 18H), 3.89 (s 2H), 7.17 (s 5H). IVc; ($CDCl_3$) δ 0.7—1.4 (m 18H), 3.94 (s 2H), *ca.* 4.10 (dd, J=3 Hz, J=1 Hz, 1H), *ca.* 4.25 (dd, J=3 Hz, J=2 Hz, 1H), *ca.* 7.25 (dd, J=2 Hz, J=1 Hz, 1H). IVd; ($CDCl_3$) δ 0.7—1.8 (m 18H), 1.45 (s 9H). IVe; ($CDCl_3$) δ 0.7—1.8 (m 26H), 3.23 (sex J=6 Hz, 1H).

Reaction of n-*Butyl Di-*n*-butylthioboronite with Benzaldehyde and Ketene.* Equimolar amounts of *n*-butyl di-*n*-butylthioboronite (1.09 g, 5.1 mmol) and benzaldehyde (0.54 g, 5.1 mmol) in 15 ml dry ether were treated with ketene (prepared by thermal cracking of acetone) at 0 °C for 2 hr with stirring. After removal of the ether, the oily substance was treated with 30% H_2O_2 (4 ml) in MeOH (20 ml) at room temperature. The solution was allowed to stand overnight and water was added. The mixture was concentrated *in vacuo* to remove

7) N. Takamura, T. Mizoguchi, K. Koga, and S. Yamada, *Tetrahedron Lett.*, **1971**, 4495.

8) J. J. Tufariello, L. T. C. Lee, and P. W. Wojtkowski, *J. Amer. Chem. Soc.*, **89**, 6804 (1967).

9) R. Köster and W. Fenzl, *Angew. Chem.*, **80**, 756 (1968).

10) Melting and boiling points are uncorrected.

11) Prepared according to Mikhailov's method. B. M. Mikhailov and Yu. N. Bubrov, *Izv. Akad. Nauk SSSR., Ser. Khim.*, **1964**, 2248; *Chem. Abstr.*, **62**, 9161c (1965).

the methanol and the residue was extracted with three portions of ether. The combined ether layers were washed with 5% solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 1.09 g (90%) of *S-n*-butyl *β*-hydroxyhydrocinnamethioate (IIIb); IR: 3440, 1670cm^{-1}. PMR ($CDCl_3$) δ 1.0—2.2 (m, 7H), 3.17 (t, J=7 Hz, 2H), *ca.* 3.20 (m, 2H), 3.74 (s, 1H), 5.42 (dd, J=8 Hz, J=6 Hz, 1H), 7.58 (s, 5H). Bp 145—146 °C/4.5 mmHg. Found: C, 65.47; H, 7.90; S, 13.16%. Calcd for $C_{13}H_{18}O_2S$: C, 65.53; H, 7.61; S, 13.43%.

Preparation of S-n-*Butyl Ethyl β-Hydroxy-β-methyl-thioglutarate (VI).* Ketene was bubbled into a solution of *n*-butyl di-*n*-butylthioboronite (973 mg, 4.55 mmol) in 15 ml dry ether at 0 °C for 15 min with stirring, and ethyl acetoacetate (545 mg, 4.19 mmol) in 10 ml dry ether was added. After bubbling ketene for 1 hr, the reaction mixture was worked up as in the preparation of IIIb to give a crude oil. The residue was separated by preparative tlc (silica gel) using methylene chloride. Elution of the main band and the evaporation under reduced pressure at *ca.* 50 °C gave 891 mg (81%) of *S-n*-butyl ethyl *β*-hydroxy-*β*-methyl-thioglutarate (VI); IR 3510, 1740, 1720 (shoulder), 1690 cm^{-1}. PMR (CCl_4) δ 0.6—1.8 (m, 13H), 2.54 (s, 2H), 2.6—3.0 (m, 2H), 2.83 (s, 2H), 3.4—3.8 (br s, 1H), 4.14 (q, J=*ca.* 7.5 Hz, 2H). Bp 119 °C/1.5 mmHg. Found: C, 54.87; H, 8.55; S, 12.48%. Calcd for $C_{12}H_{22}O_4S$: C, 54.95; H, 8.45; S, 12.20%.

Reaction of Vinyloxyborane (XI) with Benzaldehyde. To a stirred solution of diazoacetophenone (154 mg, 1.05 mmol) in 5 ml THF (dried $LiAlH_4$) was added tri-*n*-butylborane (216 mg, 1.19 mmol) at room temperature under argon. N_2 was immediately evolved. After being stirred for 45 min, the reaction mixture was treated with a solution of benzaldehyde (92 mg, 0.87 mmol) in 5 ml THF for 10 min at room temperature. The mixture was worked up as in the preparation of IIIb to give a crude oil. It was purified by preparative tlc (silica gel) using methylene chloride to give 240 mg (98%) of 2-hydroxybenzyl-1-phenylhexan-1-one (XIIb, oil); IR 3440, 1660 cm^{-1}. PMR (CCl_4) δ 0.3—2.0 (m, 9H), 3.4—3.9 (m, 2H), 4.6—4.9 (m, 1H), 6.8—7.4 (m, 8H), 7.5—8.0 (m, 2H).

The IR and PMR spectra of other *β*-hydroxyketones (XIIa—d) are consistent with the assigned structure: XIIa; IR 3430, 1660 cm^{-1}. PMR (CCl_4) δ 0.4—2.1 (m, 16H), 3.1—4.1 (m, 3H), 7.1—7.6 (m, 3H), 7.7—8.1 (m, 2H). XIIc; IR 3480, 1650 cm^{-1}. PMR (CCl_4) δ 0.3—2.4 (m, 19H), 3.19 (s, 1H), 3.50 (dd, J_A=6 Hz, J_B=8 Hz, 1H), 7.2—7.6 (m, 3H), 7.7—8.2 (m, 2H). XIId; IR 3460, 1660 cm^{-1}. PMR (CCl_4) δ 0.5—2.1 (m, 15H), 2.98 (s, 1H), 3.47 (dd, J_A=5 Hz, J_B=8 Hz, 1H), 7.1—7.6 (m, 3H), 7.7—8.1 (m, 2H).

Reaction of Vinyloxyborane (XI') with Benzaldehyde. To a solution of tri-*n*-butylborane (346 mg, 1.9 mmol) and benzaldehyde (169 mg, 1.6 mmol) in dry THF (3 ml) was added a solution of ethyl diazoacetate[12] (195 mg, 1.7 mmol, dried over P_2O_5) in THF (1 ml) at room temperature under argon with stirring. N_2 was immediately evolved and the yellow coloration characteristic of ethyl diazoacetate disappeared. The reaction mixture was allowed to stand at room temperature for 1 day. After removal of THF, the residue was treated with 30% H_2O_2 (1 ml) in MeOH (3 ml) for 2 hr and water was added. The mixture was concentrated *in vacuo* to remove most of the methanol and extracted with ether. The ether layer was washed with 5% solution of $NaHCO_3$ and saturated solution of NaCl, dried over Na_2SO_4 and the solvent was removed. The crude oil was purified by preparative tlc (silica gel, CH_2Cl_2) to give the pure oil of ethyl 2-*n*-butyl-3-hydroxyhydrocinnamate (XII'b, 320 mg, 81%); IR 3450, 1710 cm^{-1}. PMR (CCl_4) δ 0.6—1.6 (m, 9H), 1.18 (t, J=7 Hz, 3H), 2.5—2.9 (m, 1H), 3.05 (br s, 1H), 4.15 (q, J=7 Hz, 2H), 4.75 (d, J=7 Hz, 1H), 7.25 (s, 5H). Found: C, 72.02; H, 8.96%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

The IR and PMR spectra of other *β*-hydroxyesters (XII'a—d) are consistent with the assigned structure: XII'a; IR 3430, 1710 cm^{-1}. PMR (CCl_4) δ 0.7—1.6 (m, 16H), 1.25 (t, J=7 Hz, 3H), 2.25 (m, 1H), 2.68 (br s, 1H), 3.55 (m, 1H), 4.16 (q, J=7 Hz, 2H). XII'c; IR 3500, 1710 cm^{-1}. PMR (CCl_4) δ 0.65—1.9 (m, 19H), 1.25 (t, J=7 Hz, 3H), 2.30 (t, J=7 Hz, 1H), 2.79 (s, 1H), 4.15 (q, J=7 Hz, 2H). XII'd; IR 3450, 1710 cm^{-1}. PMR (CCl_4) δ 0.7—1.5 (m, 9H), 1.15 (s, 6H), 1.26 (t, J=7 Hz, 3H), 2.1—2.4 (m, 1H), 2.9 (br s, 1H), 4.14 (q, J=7 Hz, 2H). XII'e; IR 3480, 1700 cm^{-1}. PMR (CCl_4) δ 0.4—1.5 (m, 17H), 2.85 (t, J=9 Hz, 1H), 3.79 (q, J=7 Hz, 2H), 3.8 (s, 1H), 7.25 (s, 5H).

12) N. B. Searle, "Organic Syntheses," Coll. Vol. IV, p. 424 (1963).