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Biochemistry

Synthesis and studies on properties of dibutyltin-(*S*) – (camphorsulfonyl) hydride – a new reagent for stereoselective reduction of ketones and α-bromoesters of carboxylic acids

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Summary:

Synthesis and studies on physicochemical properties of dibutyltin-(*S*)-(camphorsulfonyl) hydride, a new reagent for stereoselective reduction of ketones were carried out.

Key words: mixed organotin hydrides, stereoselective reduction.

The goal of the study was to develop a novel method of stereoselective reduction of ketones and α-bromoesters of carboxylic acids. The reagent used in the reactions was di-*n*-butyl-(S)-(camphorsulfonyl)tin hydride and derivatives thereof.
Organotin hydrides were first obtained by reduction of corresponding organotin chlorides with lithium aluminum hydride. Currently, this method is widely used in laboratory practice.

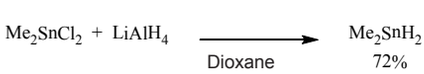

Figure 1.

Due to its properties (lower volatility and toxicity compared to other homologs) and price, the readily available tri-*n*-butyltin hydride found wide use in organic synthesis. In laboratory conditions, tri-*n*-butyltin hydride may be obtained by distillation of tri-*n*-butyltin oxide and poly(methylhydroxysiloxane) (PHMS) under reduced pressure (80 °C and 0.4 mmHg) [1].

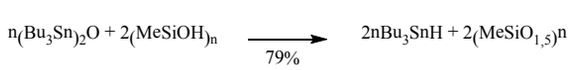

Figure 2.

Organotin dihydrides, R_2SnH_2, following their combination with dialkyltin(IV) compounds, R_2SnX_2 (where X = halide, carboxylate, sulfonate etc), undergo disproportionation to form as part of chemical equilibrium new hydrides of formula R_2SnXH, with properties different from starting dihydrides or the better known trialkyltin hydrides R_3SnH [2, 4]. These new hydrides are decomposed in the presence of amines with decomposition rate depending on the nature of substituent X. Electronegative substituents at the tin atom increase the reactivity of free stannyl radicals. The more electronegative the substituent, the higher its electron density due to the transfer of electrons from the tin atom. Decomposition of mixed organotin hydrides occurs via a free radical-based chain mechanism [5], leading to formation of molecular hydrogen and appropriate tetrakis(organo)ditin XR_2SnSnR_2X [4, 6].

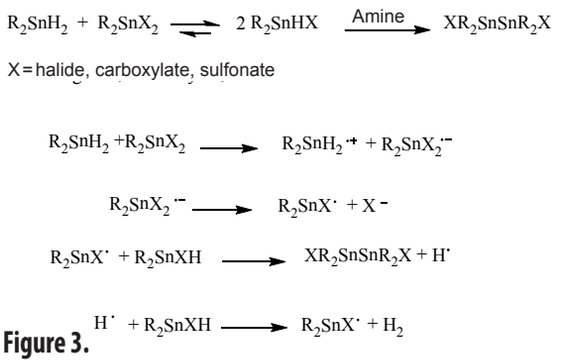

Figure 3.

Since decomposition of compounds of general formula R_2SnHX occurs at temperatures as low as room temperature, they are an attractive alternative to other tin hydrides, which react at higher temperatures or upon UV lamp irradiation. Thus, mixed hydrides may be used e.g. in the presence of substances sensitive to high temperatures [5].

M. Murakata, H. Tsutsui and O. Hoshino were the first to publish examples of efficient free-radical reduction proceeding in an enantioselective manner in the presence of a Lewis acid. Their research focused on α-methoxy-α-iodolactone reduced by tri-n-butyltin hydride conjugated with a chiral amine and magnesium iodide [7].

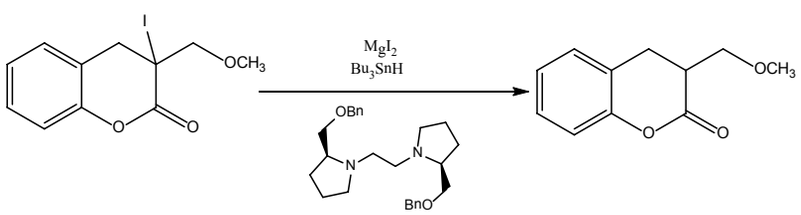

Figure 4. The first stage of our study was the synthesis of starting organotin hydrides.

Dibutyldihydrydotin was obtained by the van der Kerk's method, i.e. by reducing dibutyltin chloride with lithium aluminum hydride $LiAlH_4$. Etherate solution of the hydride was placed in a two-necked flask equipped with a dropping funnel and reflux condenser with calcium chloride tube on top.

Dibutyldichlorotin solution was added slowly from the dropping funnel as the flask content was stirred. After addition of the entire amount of Bu_2SnCl_2, stirring was continued for 1.5 hours. After that time, a small amount of hydroquinone was added to bind the aluminates formed in the reaction, followed by water to quench the reaction.

A 20% aqueous solution of potassium sodium tartrate was used for extraction. Subsequent extractions using Et_2O followed by distillation allowed to obtain Bu_2SnH_2 with a nearly 100% yield.

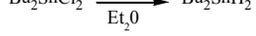

Figure 5.

The ^1H NMR spectrum of di-*n*-butyltin dihydride is characterized by the following chemical shift values:

$\delta_H(C_6D_6)$: 4.58 (2H, m, $^1J^{117}_{Sn} = 1542.8$ Hz; $^1J^{119}_{Sn} = 1614.7$ Hz; SnH_2);

The ^{13}C NMR spectrum of di-*n*-butyltin dihydride is characterized by the following chemical shift values:

δ_C 7.11 ($^1J^{117}_{Sn} = 357.9$ Hz; $^1J^{119}_{Sn} = 374.5$ Hz; C-α); 13.90 (C-δ); 27.16 ($^3J^{117/19}_{Sn} = 64.7$ Hz;C-γ); 30.61($^2J^{117/119}_{Sn} = 23.7$ Hz;C-β);

Di-*n*-butylchlorotin hydride was obtained in the reaction of disproportionation between di-*n*-butyltin hydride and di-*n*-butyltin chloride. Equilibrium was reached as early as 90 minutes after mixing equimolar amounts of both reagents in ethanol, benzene or toluene.

The ^1H-NMR spectrum of the equilibrium mixture showed that under these conditions, the mixture contained 97% of di-*n*-butylchlorotin hydride and 3% of starting di-*n*-butyltin chloride.

The ^1H NMR spectrum of di-*n*-butylchlorotin hydride is characterized by the following chemical shift values:

$\delta_H(C_6D_6)$: 7.42 (1H,s,$^1J^{117}_{Sn} = 1875.8$ Hz,$^1J^{119}_{Sn} = 1963.0$; SnHCl);

The ^{13}C NMR spectrum of di-*n*-butylchlorotin hydride is characterized by the following chemical shift values:

δ_C 13.65 (C-γ); 17.00 ($^1J^{117}_{Sn} = 379.7$ Hz,$^1J^{119}_{Sn} = 397.4$ Hz;C = α);

27,65 ($^3J^{117/119}_{Sn} = 63.37$Hz; C-γ); 28.20($^2J^{117/119}_{Sn} = 40.24$ Hz; C = β);

Acetoxydi-*n*-butyltin hydride was obtained in the reaction of disproportionation between di-*n*-butyltin hydride and di-*n*-butyltin diacetate. In this kind of solution, equilibrium is shifted towards the starting reagents.

The ^{1}H NMR spectrum of acetoxydi-*n*-butyltin hydride is characterized by the following chemical shift values:

$\delta_H(C_6D_6)$: 7.6 (1H, s, SnH);

The ^{13}C NMR spectrum of acetoxydi-*n*-butyltin hydride is characterized by the following chemical shift values:

δ_C 13.71 (C-β); 18.75 ($^{1}J^{117}_{Sn}$ = 415.9 Hz, $^{1}J^{119}_{Sn}$ = 435.2 Hz; C-α); 26.82 ($^{3}J^{117/119}_{Sn}$ = 78.9 Hz; C-γ); 27.85 ($^{2}J^{117/119}_{Sn}$ = 24.8 Hz; C-β)

Dibutyldi(camphorsulfonyl)tin was obtained from dibutyltin oxide and camphorsulfonyl acid by means of aseotropic dehydration conducted in a distillation system equipped with a Dean-Stark apparatus. The initial product of this reaction is dibutyldi(camphorsulfonyl)tin dihydrate, which sheds two molecules of water upon drying, forming dibutyldi(camphorsulfonyl)tin. Dibutyldi(camphorsulfonyl)tin undergoes disproportionation with Bu_2SnH_2 in the solution, forming dibutyl(camphorsulfonyl)tin hydride.

The ^{119}Sn NMR spectrim of freshly prepared dibutyldi(camphorsulfonyl)tin dihydrate is characterized by the following chemical shit values:

δ_{Sn}(DMSO): -378.5 ppm

The next stage of the study was the preparation of equipment for kinetic measurements and preparation of solutions, on which the kinetic studies of decomposition of organotin hydrides in the presence of amines were to be carried out. The equipment consisted of:

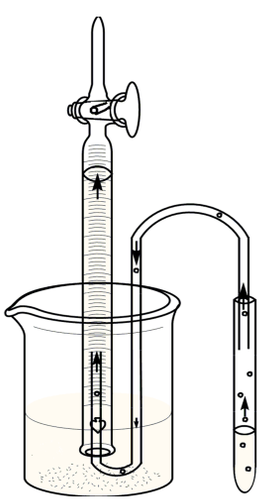

Figure 6.

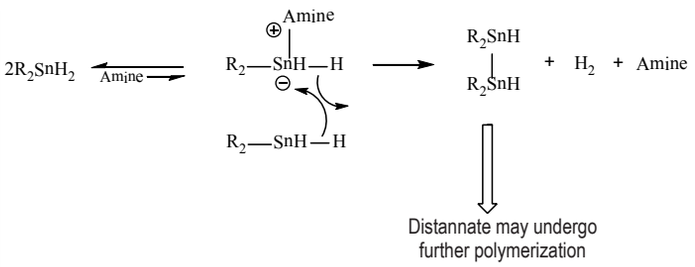

Figure 7.

- A glass tube, in which the reaction mixture was placed.
- A rubber tubing at the end of the glass tube to deliver hydrogen generated in the reaction to an inverted, callibrated burette immersed in a beaker containing water. The gas accumulated in the burette pushed water outside the burette, allowing to measure the volume of hydrogen generated during the reaction.

Observation of the ongoing reactions and the reaction equations showed that all reactions followed the first-order kinetics. For ln[A], the relationship is linear in time t [s], where [A] is the concentration of the organotin hydride in the reaction mixture.

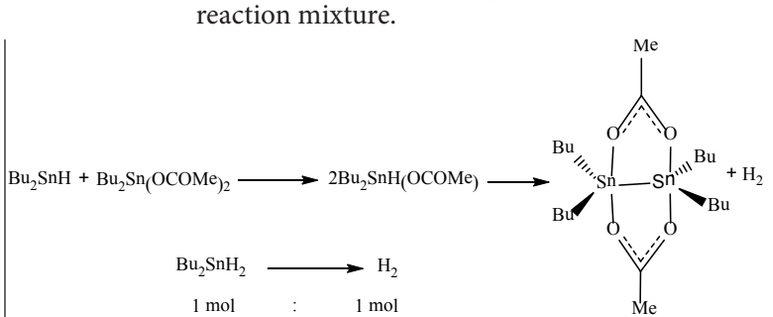

Figure 8.

Spontaneous, amine-free process

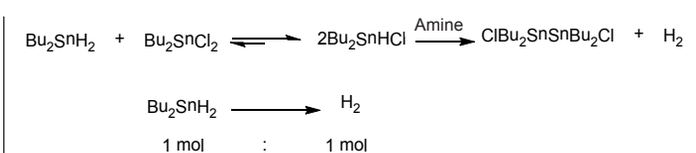

Figure 9.

The values of the reaction rate constant k and the half time $t_{0.5}$ for the 1° reaction were determined in a graphical method using the MS EXCEL spreadsheet {the least squares method – function "*reglinp*" y = -bx-a, where tgα = -k_i, to this end, a graph of the function ln[A] = f(t) was plotted

out} and by substituting the value to the formula for calculating k_i, $t_{0.5}$:

Graphical method:

where tgα $y=-bx-a$, $y=\ln a$, $x=t_{[s]}$

Haf time $t_{0.5}$: $t_{0,5}=\frac{\ln 2}{k_{i(graf)}}$

Table 1: Rate constants for the reaction of decomposition of organotin hydrides in the presence of amines. Values in the table are mean values determined by the graphical method. $Bu_2Sn(OSO_2camphor)H$ stands for di-n-butyl(camphorsulfonyl)tin hydride.

Tin Hydride	Amine	Solvent	mean k_{graf} [s^{-1}]
Bu_2SnHCl	pyridine	$CHCl_3$	1.34E-03
$Bu_2Sn(OCOCH_3)H$	morpholine	$CHCl_3$	1.07E-03
Bu_2SnH_2	Et_3N	$CHCl_3$	8.05E-03
Bu_2SnHCl	Et_3N	$CHCl_3$	1.77E-02
$Bu_2Sn(OCOCH_3)H$	Et_3N	$CHCl_3$	4.22E-02
Bu2SnHCl	pyridine	TOLUENE	2.35E-04
$Bu_2Sn(OCOCH_3)H$	pyridine	TOLUENE	2.52E-04
$Bu_2Sn(OCOCH_3)H$	morpholine	TOLUENE	4.77E-04
Bu2SnHCl	Et_3N	TOLUENE	2.81E-04
$Bu_2Sn(OCOCH_3)H$	Et_3N	TOLUENE	5.84E-03
$Bu_2Sn(OSO_2camphor)H$	pyridine	METHANOL	2.38E-04

Table 2: Percentage yield of acetophenone hydrostannylation using selected organotin hydrides. Omes represents methylsulfonate.

Time [h]	Bu_3SnH [%]	Bu_2SnHX [%]				
		X=H	X=Cl	X=OCOMe	X=Omes	X=camphsulph
1	0	0		46	69	81 (41 after 15 min)
2	0	0	51	68	81	
3	0	0	84			

We have also attempted the assessment of reactivity of a series of studied organotin hydrides in acetophenone reduction process. We observed no reaction between Bu_3SnH or Bu_2SnH_2 and acetophenone at room temperature. Meanwhile, hydrides of the type Bu_2SnHX react within several hours, yielding a dibutyltin derivative of 1-phenylethanol, and the sequence of reactivity is correlated with the rate of homolytic decomposition of these hydrides at room temperature. This shows that the rate of reaction is determined by the initiation stage not involving acetophenone.

By means of theoretical calculations, isotropic absolute nuclear shielding constants $\sigma_{iso}(^{119}Sn)$ and chemical shifts $\delta(^{119}Sn)$ and $\delta(^{1}H)$ were calculated for hydrides of formula Bu_2SnHX with optimized geometry. Calculations were performed by methods based on the B3PW91 hybrid functional, and IGLO-II/III functional databases [107]. IGLO-III database was used for H, C, O, F and Cl atoms, while IGLO-II was used for Br, Sn and I.

Chemical shifts $\delta(^{1}H)$ of the proton directly bound to the tin atom were also studied for molecules of formula n-Bu_2SnHX.

We have conducted studies [8] on the following molecules: Me_4Sn, n-Bu_2SnH_2, n-Bu_2SnCl_2, n-Bu_2SnHCl,n-$Bu_2SnH(O_2CMe)$, n-$Bu_2SnH(OSO_2Me)$ and n-Bu_3SnH.

The *n*-$Bu_2SnH(OSO_2Me)$ molecule was studied instead of di-*n*-butyl(camphorsulfonyl)tin hydride, which proved too complex for quantum calculations. Only basic geometry optimization was performed for each molecule. Conformational analysis was not performed.

Table 3: Calculated energy of tin-hydrogen bond dissociation BDE(0K), entalpy Δ_fH°(298K), entropy Δ_fS°(298K) and free Gibbs energy Δ_fG°(298K) for the reaction of hydrogen dissociation for molecules of n-Bu_2SnH_2, n-Bu_2SnHCl, n-$Bu_2SnH(OSO_2Me)$ and n-Bu_3SnH.

Molecule	BDE(0K)[1,2] [kcal/mol]	Δ_fH°(298K)[3] [kcal/mol]	Δ_fS°(298K) [cal/(mol·K)]	Δ_fG°(298K) [kcal/mol]
n-Bu_2SnH_2	77.30	78.56	25.00	71.11
n-Bu_2SnHCl	75.01	76.34	28.73	67.77
n-$Bu_2SnH(OSO_2Me)$	75.13	76.56	31.99	67.02
n-Bu_3SnH	77.67	77.99	24.27	70.64

[1] values are corrected for zero-point energy (ZPE).
[2] the energy of the hydrogen atom was assumed to be the exact value of $E_0 = -0.5$ au.
[3] corrected for temperature.

Based on the obtained values of standard enthalpy of formation, the energy effect of hydrogen dissociation was determined for the following molecules: *n*-Bu_2SnH2, *n*-Bu_2SnHCl, *n*-$Bu_2SnH(OSO_2Me)$ and *n*-Bu_3SnH. Observation of changes in the Sn–H bond dissociation energy at 0K, BDE (0K), shows that the energy of the Sn–H bond decreases in the following series:

n-Bu_3SnH > n-Bu_2SnH_2 > n-$Bu_2SnH(OSO2Me)$ ≅ Bu_2SnHCl

Table 4: Reduction products of (1*R*)-camphor, optically inactive camphor, (2*S*,5*R*)-(-)-menthone, 3-iodo-3-methyl-3,4-dihydrocoumarin and 2-bromo-2-(6-methoxy-2-naphthyl)propionate using di-*n*-butyl-(S)- (1) and di-n-butyl-(*R*)-(camphorsulfonyl)tin hydride (2).

No.	Reduced ketone	Reducing reagent	Product	Yield [%]	Enantiomeric excess [%]
1	(1*R*)-camphor	(1)	(1*R*,2*R*)-isoborneol	100	100
2	(1*R*)-camphor	(2)	(1*R*,2*R*)-isoborneol	100	100
3	camphor	(1)	(1*S*,2*S*)-isoborneol	100	100
4	camphor	(2)	(1*S*,2*S*)- and (1R,2R)-isoborneol (1*S*,2*R*)- and (1R,2S)-isoborneol	45:30:15:15	
5	(2*S*,5*R*)-(-)-menthone	(1)	(1*R*,2*S*,5*R*)-(–)-menthol (1*S*,2*S*,5*R*)-(+)-neomenthol	40:60	100
6	(2*S*,5*R*)-(-)-menthone	(2)	(1*R*,2*S*,5*R*)-(–)-menthol (1*S*,2*S*,5*R*)-(+)-neomenthol	73:27	100
7	3-iodo-3-methyl-3,4-dihydrocoumarin	(1)	3-methyl-3,4-dihydrocoumarin	100	7
8	methyl 2-bromo-2-(6-methoxy-2-naphthyl) propionate	(1)	methyl 2-(6-methoxy-2-naphthyl) propionate	100	30

Reduction of camphor by di-*n*-butyl-(*S*)-(camphorsulphonyl)tin hydride or its (*S*) enantiomer confirmed a strong impact of sterical effects on the course of the reaction. Steric requirements of camphor determine the preference for the hydride approaching from *endo* side, leading, as a consequence, to formation of exo product in case of (*R*)-camphor. The reaction product was (1*R*,2*R*)-isoborneol. The product of analogous reaction of (*S*)-camphor was (1*S*,2*S*)-isoborneol. In case of reduction of optically inactive camphor using di-*n*-butyl-(*R*)-(camphorsulfonyl)tin hydride, a mixture of following products was formed: (1*R*,2*R*)-isoborneol, (1*S*,2*S*)-isoborneol, (1*R*,2*S*)-borneol and(1*S*,2*R*)-borneol in quantitative ration of 3:2:1.

Reductionof(2*S*,5*R*)-(−)-menthonewitheither (*S*)- or di-*n*-butyl-(*R*)-(camphorsulfonyl) tin hydride led to formation of a mixture of two products: (1*R*,2S,5*R*)-(−)-menthol and (1*S*,2*S*,5*R*)-(+)-neomenthol. The quantitative composition of both mixtures was different. The (*S*) hydride led to preferential formation of neomenthol, formed in 3:2 ratio relative to menthol. The (*R*) hydride led to preferential formation of menthol, which was generated in 73% yield.

Reduction of methyl 2-bromo-2-(6-methoxy-2-naphthyl)propionate led to methyl (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionate. Enantiomeric excess value for this reaction was 30%. The product is a methyl ester of naproxene. Comparing the obtained result with analogous reduction of acetophenone, for which enentiomeric excess on the order of 6% was obtained without the use of a catalyst, one may expect that the ee might reach values close to 100% in the presence of $ZnCl_2$, Bu_2SnCl_2 or $MnCl_2 \cdot 4H_2O$. Confirmation of this hypothesis would require further studies.

The procedure of reduction methyl 2-bromo-2-(6-methoxy-2-naphthyl)propionate consisted

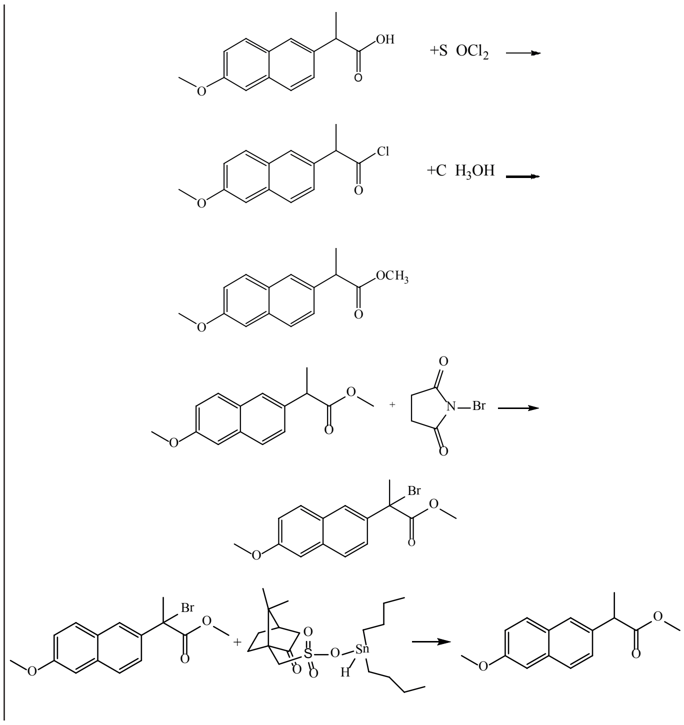

Figure 10.

of three stages. In the first stage, racemic 2-bromo-2-(6-methoxy-2-naphthyl)propionic acid was converted into its methyl esther. Next stages involved bromination followed by reduction consisting in dissolution of 0.001 mol of di-*n*-butyldi-(*S*)-(camphortsulfonyl)tin in 5 mL of benzene. A value of 0.001 mol of di-*n*-butyltin hydride was added to the obtained solution, followed by 0.001 mol of methyl 2-bromo-2-(6-methoxy-2-naphthyl)propionate. The mixture was then stored for 48 hours at room temperature. The reaction product was purified by column chromatography on silica gel using 30% solution of petroleum ether in ethyl acetate as the eluting phase.

Methyl esther of (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionate, which is a derivative of naproxene, was obtained as the product of this reduction reaction with quantitative yield and 30% ee.

The distinctness of each of the studied hydrides compared to other reagents was also manifested in reduction of cyclopropyl(4-methoxyphenyl)methanone. Reduction of this compound with lithium aluminum hydride led to formation of corresponding alcohol. The compound obtained from the mixed organotin products was 1-(cyclopropylmethyl)-4-methoxybenzene. The mechanism of this reaction has not been fully established. In case of reduction with Bu_3SnH, the reaction followed yet another course, as shown in the scheme.

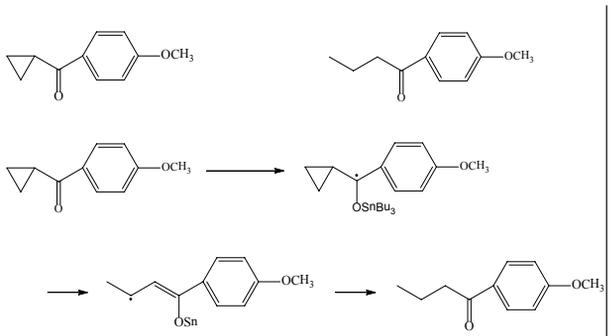

Figure 11.

In our opinion, the difference in the behavior of Bu_3SnH compared to other studied tin hydrides is largely due to different mechanisms of the initiation processes. In case of Bu_3SnH, free radicals that initiate the process are generated by electron transfer. In case of other studied tin hydrides (Bu_2SnHX), undergoing spontaneous free radical-based decomposition at room temperature, the initiation process proceeds largely according to the following mechanism:

We found that reduction of acetophenone with di-*n*-butyl-(1*S*)-(camphorsulfonyl)tin hydride

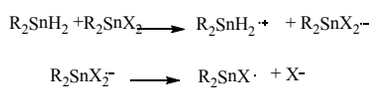

Figure 12.

Table 5: Reduction of acetophenone by di-n-butyl-(*S*)-(camphorsulphinyl)tin hydride (1) and di-n-butyl-(R)-(camphorsulphinyl)tin hydride (2) or diphenyl-(S)-(camphorsulphinyl)tin hydride (3) in the presence of catalysts. The product of acetophenone reduction was 1-phenylethanol, obtained in quantitative yields.

Reducing agent	Catalyst	ee (enantiomeric excess) [%]
(1)	–	6
(2)	–	8
(1)	ZnCl2	37
(1)	MnCl2 · 4H2O (20 molar equivalents)	31
(2)	MnCl2 · 4H2O (10 molar equivalents)	13.5
(1)	SnCl4	10.8
(2)	SnCl4	5.2
(1)	BF3	6
(3)	–	11

(21) leads to formation of 1-phenylethanol with 6% ee. Better selectivity was obtained when using diphenyl-(*S*)-(camphorsulfonyl)tin hydride (23) (11% ee) , with (–)-1-fenyloetanolu being the excess enantiomer. On the other hand, reduction using di-*n*-butyl-(1*R*)-(camphorsulfonyl)tin hydride (22) led to formation of (+)-1-phenylethanol with enantiomeric excess of 8%. Addition of ca. 20 equivalents of $ZnCl_2$ to the reaction mixture including di-*n*-butyl-(*S*)-(camphorsulfonyl)tin hydride led to significant increase in enantioselectivity. The (–)-1-phenylethanol was obtained with 37% ee. Analogous effect in case of $MnCl_2 \cdot 4H_2O$ was 31%. These results confirm a strong impact of Lewis acids on the enantioselectivity of studied reduction reactions.

Conclusions

1) Dibutyldi(camphorsulfonyl)tin was obtained from dibutyltin oxide and camphorsulfonyl acid by means of aseotropic dehydration conducted

in a distillation system equipped with a Dean-Stark apparatus.

2) An initial product of this reaction is dibutyldi(camphorsulfonyl)tin dihydtate, which sheds two molecules of water upon drying, forming dibutyldi(camphorsulfonyl)tin.

3) Dibutyldi(camphorsulfonyl)tin undergoes disproportionation with Bu_2SnH_2 in the solution, forming dibutyl(camphorsulfonyl)tin hydride.

4) As shown by theoretical calculations, kinetic measurements of decomposition of a wide range of organotin hydrides catalyzed by different amines, and studies comparing the rates of acetophenone reduction using these hydrides, dibutyl(camphorsulfonyl)tin hydride is the most reactive of these compounds.

5) The difference in the behavior of dibutylcamphorsulfonyltin hydride compared to the commercially available Bu_3SnH was also observed in case of cyclopropyl 4-methoxyphenyl ketone reduction.

6) We suspect that the particular properties of dibutylcamphorsulfonyltin hydride are determined by the ease of its initiation at room temperature.

7) Optically active dibutyl-(*S*)-camphorsulfonyltin hydride and its derivatives, dibutyl-(*R*)-camphorsulfonyltin hydride, diphenyl-(*S*)-camphorsulfonyltin hydride were successfully used in stereoselective reduction of acetophenone and methyl 2-bromo-2-(6-methoxy-2-naphthyl)-propionate.

Acknowledgements:

The above paper is a translated reprint from the 5-th Polish Conference- Progress in Medical andPharmaceutical Studies, Medical University in Lodz, Department of Pharmacy, November 21-23, 2010.

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