The Partial Reduction of Carboxylic Acids to Aldehydes *via* 3-Acylthiazolidine-2-thiones with Diisobutylaluminum Hydride and with Lithium Tri-*t*-butoxyaluminum Hydride

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3-Acylthiazolidine-2-thiones, easily prepared from carboxylic acids and readily available thiazolidine-2-thione, were reduced to the corresponding aldehydes either with diisobutylaluminum hydride in toluene at −78—−40 °C in 70—90% yields or with lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran at −20—0 °C in 80—90% yields. The present method appears to be applicable to the synthesis of aldehydes from both aromatic and aliphatic derivatives having chloro, bromo, nitro, and noncojugated double bond, except for the reduction of α,β-unsaturated derivatives with lithium tri-*t*-butoxyaluminum hydride and of cyano derivative with diisobutylaluminum hydride. Completion of the reduction is indicated by disappearance of the original yellow color of the reaction mixture.

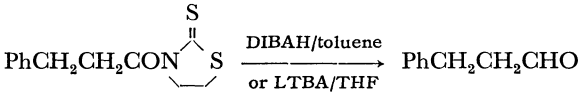
One of the most convenient synthetic routes to aldehydes is the utilization of readily available carboxylic acids. Many methods have been reported for the partial reduction of such acid derivatives to the corresponding aldehydes by catalytic hydrogenation (the Rosenmund reduction) or by use of various hydride reducing agents. For example, carboxylic esters were converted into the corresponding aldehydes with aluminum hydride reagents, such as diisobutylaluminum hydride (DIBAH),[1a] sodium aluminum hydride,[1b] sodium bis(methoxyethoxy)aluminum hydride,[1c] and bis(dialkylamino)aluminum hydride.[1d] The partial reduction of various carboxamides was also carried out with lithium aluminum hydride,[1e] lithium di- and triethoxyaluminum hydride,[1f] or bis(dialkylamino)aluminum hydride.[1g] Moreover, the lithium tri-*t*-butoxyaluminum hydride (LTBA) reductions of acyl halides[1h] and of phenyl esters[1i] provided mild synthesis of aldehydes. The reduction is widely applied to the syntheses of natural products.[2] However, in most cases the desired aldehydes are often contaminated by further reduced products, *i.e.*, alcohol and/or amine.

In the preceding communications,[3,4] we reported preliminary results of the partial reduction of 3-acylthiazolidine-2-thiones **1** to aldehydes **2** with DIBAH or with LTBA. We now wish to describe the reaction in detail.

In order to determine the optimum conditions for the synthesis of 3-phenylpropanal (**2a**) from 3-(3-phenylpropionyl)thiazolidine-2-thione (**1a**), the effect of molar ratio of the reducing agents to **1a** was studied first. The reduction with the hydrides, DIBAH and LTBA, was carried out in toluene at −78——40 °C, and in tetrahydrofuran (THF) at −20—0 °C, respectively. The results are summarized in Table 1.

The table shows that no decrease in the yield of **2a** can be found with change in the molar ratio of DIBAH to **1a** from 1.2 to 2.1 equivalents. **2a** was isolated in 67% yield even when 4.0 equivalents of DIBAH were employed. The results are reasonably ratioalized by considering an aluminum-contained six-membered chelate intermediate **3** produced by the reaction of **1** with DIBAH. The chelate complex of the resulting aluminum alkoxide **3** is inert toward the further reduction under the reaction conditions. Thus, aldehyde **2** is liberated after quenching the reaction mixture with dilute acid. On the other hand, in the case of LTBA, employment of a slight excess amount of reducing agent gave the best results. The yield of **2a** decreased to 57% when 2.4 equivalents of LTBA were introduced. This is explained by assuming that the reduction of **1a** is much faster than that of **2a** generated in the reaction mixture before hydrolysis, in contrast with the case of DIBAH; the employment of excess LTBA causes the overreduction of **2a**. Moreover, longer reaction time and the mode of addition of the reactants did not significantly affect the yields of aldehydes. When a

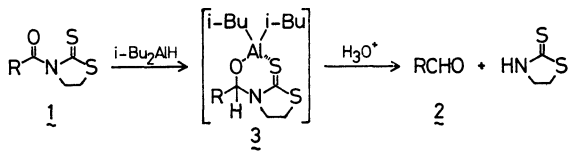
TABLE 1. EFFECTS OF MOLAR RATIO[a] OF REDUCING AGENT TO **1**



1a **2a**

DIBAH[b]			LTBA[c]		
Molar ratio	Mode of addn.[d]	Yield (%)[e]	Molar ratio	Mode of addn.[d]	Yield (%)[e]
1.2	N	91	1.1	N	87
1.2	R	85	1.15	N	89
1.5	N	93	1.2	R	85
2.1	N	90	2.4	N	57
4.0	N	69			

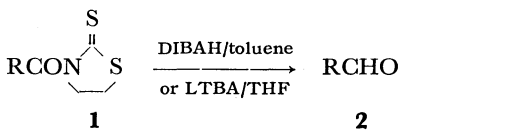
a) Hydride/**1a**. b) Reduction carried out at −78 °C for 0.25—4.5 h and then at −50——40 °C for 1—1.5 h. c) Reduction carried out at −20 °C for 1—1.5 h and then at 0 °C for 1—4 h. d) N: normal addition (addition of **1a** in a solid state to hydride in solution); R: reverse addition (addition of DIBAH in solution or of LTBA in a solid state to **1a** in solution). e) Isolated yield by TLC (silica gel) or by distillation.



stoichiometric amount of reducing agents was employed, the desired aldehyde was always contaminated with a small amount of starting material.

Thus, 3-acylthiazolidine-2-thiones **1** derived from representative carboxylic acids were converted into the corresponding aldehydes **2** with DIBAH by employing the optimum reduction conditions. In the case of DIBAH, when **1** is a solid mass, normal addition generally gave slightly better results than the reverse one (normal addition: **1** in a solid state added to DIBAH in toluene; reverse addition: DIBAH in toluene added to **1** in toluene). And when an oily substance, reverse addition gave better results than the normal one. On the other hand, in the case of LTBA, the mode of addition did not significantly affect the yields of aldehydes **2** (normal addition: **1** in a solid state added to LTBA in THF; reverse addition: LTBA in a solid state added to **1** in THF). The results are summarized in Table 2.

TABLE 2. PREPARATION OF ALDEHYDEES **2** IN THE REDUCTION OF 3-ACYLTHIAZOLIDINE-2-THIONES **1** WITH DIBAH AND WITH LTBA



1 **2**

	R	DIBAH Mode of addn.	DIBAH Yield[a] (%)	LTBA Mode of addn.	LTBA Yield[a] (%)
a	$PhCH_2CH_2$	N[b]	93	N	89
		R[c]	85	R	(85)
b	$PhCH_2$	N	64	R	(69)[d]
c	CH_3CH_2PhCH	R	75	R	(86)
d	$PhCH_2CH_2CH_2$	N	90	N	86
e	$CH_3(CH_2)_{15}CH_2$	N	82	N	85[e]
f	$CH_2=CH(CH_2)_7CH_2$	R	74	R	(78)
g	$CH_3(CH_2)_3$-$(PhCH_2O)CH$	R	80	R	(91)[f]
h	$Br(CH_2)_9CH_2$	N	88	R	80
i	$NC(CH_2)_9CH_2$	N	—[g]	R	71
j	Ph	N	(49)	R	(83)
k	*p*-ClC_6H_4	N	84	N	86
l	*p*-$O_2NC_6H_4$	N	89	R	88
m	PhCH=CH	R	74	R	—[g]
n	*p*-$ClC_6H_4CH=CH$	N	70	R	—[g]

a) Isolated yield by TLC (silica gel). Numbers in parentheses indicate the yield by distillation. Bp (bath temp) °C/mmHg; **2a**: 120—140/20, **2b**: 105—135/24, **2c**: 110—130/21, **2f**: 130—140/30, and **2j**: 120—140/95. Bp of **2g**: 101—105 °C/0.9 mmHg. b) N: normal addition. c) R: reverse addition. d) Reaction carried out at −20 °C for 5 h. e) Reaction carried out at 0 °C for 4 h and then at room temp for 4 h. f) Reaction carried out at −40 °C for 2 h. g) Isolation of aldehydes not tried.

The yields of the reduction of 3-acylthiazolidine-2-thiones **1** to aldehydes **2** with DIBAH and with LTBA are generally good to high, *i.e.*, 70—90 and 80—90%, respectively, both in the cases of aliphatic and aromatic derivatives with a few exceptions. When the reduction of 3-(phenylacetyl)thiazolidine-2-thione (**1b**) with LTBA was carried out under similar conditions, only a polymerized product was obtained. Phenylacetaldehyde (**2b**) was isolated in 69% yield by keeping the reaction temperature −20 °C throughout the reduction. The α-benzyloxy derivative **1g** was very susceptible to the reduction with LTBA even at −40 °C to give 2-benzyloxyhexanal (**2g**) in 91% yield. The reduction of 3-(11-cyanoundecanoyl)thiazodine-2-thione (**1i**) with LTBA proceeded smoothly to afford 11-cyanoundecanal (**2i**) in 71% yield, but the same reaction was not observed with use of 1.2 equivalents of DIBAH and, when 2.2 equivalents of DIBAH were employed, 51% yield of dodecanedial was isolated. In the case of α,β-unsaturated derivatives, **1m** and **1n**, the reduction with LTBA gave no satisfactory results.

Various aldehydes possessing other substituents in the same molecules, such as bromo, chloro, nitro, and nonconjugated double bond, were easily obtained in good yields.

It is concluded that the present method is widely applicable to the partial reduction of various carboxylic acids *via* 3-acylthiazolidine-2-thiones, and the yields of the corresponding aldehydes are comparable or preferable to those of the conventional methods.[1] Further advantages of the present procedure is simplicity of the reaction, 3-acylthiazolidine-2-thione **1** being simply added to the reducing agent or *vice versa*, and that the completion of the reaction is clearly indicated by disappearance of the original yellow color of the reaction mixture.

Experimental

General. Melting and boiling points are uncorrected. ^1H NMR spectra were recorded on a Hitachi R-24 spectrometer with Me_4Si as an internal standard. IR spectra were taken on a Hitachi EPI-G2 spectrophotometer. MS data were obtained on a Hitachi RMU-6L at 70 eV. CH_2Cl_2 was dried over P_2O_5, distilled over CaH_2, and stored over molecular sieves 4A. Toluene was distilled over Na and then stored over molecular sieves 4A. THF was distilled over Na, followed by redistillation over $LiAlH_4$ before use.

DIBAH was synthesized by the pyrolysis of *i*-Bu_3Al according to the procedure of Ziegler *et al.*[5] LTBA was prepared from $LiAlH_4$ and *t*-BuOH according to a similar method of Brown and McFarlin.[6]

Reduction was carried out under argon atmosphere, all the apparatus being dried before use.

Materials. Acyl chlorides were either obtained commercially or synthesized from carboxylic acids and $SOCl_2$ according to standard methods.

*Preparation of 3-Acylthiazolidine-2-thiones **1a—1n**.* **A**: A CH_2Cl_2 (5 ml) solution of acyl chloride (20 mmol) was added dropwise to an ice-cooled, stirred CH_2Cl_2 (20 ml) suspension of thiazolidine-2-thione (2.38 g, 20 mmol) and Et_3N (2.12 g, 21 mmol) over the period of 1 h. The resulting mixture was stirred at room temperature for 1 h, and then washed with H_2O and brine, the organic layer being dried (Na_2SO_4) and concentrated. Purification of the products **1a—n** was accomplished by recrystallization or by column chromatography on silica gel using PhH as an eluent: yields 80—95%. The physical data for **1a—n** are given in Table 3.

Table 3. Physical data of 3-acylthiazolidine-2-thiones **1**

1	Mp °C	Found (Calcd), % C	H	N	S	X	IR ν_{CO} cm^{-1}	NMR δ($CDCl_3$)
1a	66.0—67.5 (CH_2Cl_2–Et_2O)[a]	57.59 (57.34	5.21 5.21	5.51 5.57	25.22 25.48)		1685	3.0 (t, J=7 Hz, 2H), 3.2 (t, J=7 Hz, 2H), 3.6 (t, J=7 Hz, 2H), 4.5 (t, J=7 Hz, 2H), 7.25 (s, 5H)
1b	84.5—85.5 (CH_2Cl_2–Et_2O)	55.38 (55.67	4.60 4.67	5.71 5.90	26.93 26.98)		1700	3.1 (t, J=7.5 Hz, 2H), 4.45 (t, J=7.5 Hz, 2H), 4.6 (s, 2H), 7.25 (s, 5H)
1c	oil	59.00 (58.88	5.77 5.70	5.39 5.28	23.94 24.13)		1700	0.85 (t, J=8 Hz, 3H), 1.5—2.5 (m, 2H), 3.05 (t, J=7.5 Hz, 2H), 4.4 (t, J=7.5 Hz, 2H), 5.75 (t, J=7.5 Hz, 1H), 7.3 (s, 5H)
1d	85.5 (CH_2Cl_2–Et_2O)	59.05 (58.88	5.76 5.70	5.09 5.28	23.97 24.13)		1690	1.95 (m, 2H), 2.65 (m, 2H), 2.9—3.4 (m, 4H), 4.45 (t, J=7.5 Hz, 2H), 7.15 (s, 5H)
1e	54—63 (hexane)	65.94 (65.40	10.34 10.19	3.76 3.63	16.26 16.60)		1705	0.8 (t, 3H), 1.25 (m, 30H), 3.2 (m, 2H), 3.25 (t, J=7 Hz, 2H), 4.55 (t, J=7 Hz, 2H)
1f	oil	59.08 (58.91	8.35 8.12	4.90 4.91	22.03 22.43)		1705	1.2—2.5 (m, 14H), 3.25 (t, J=7 Hz, 2H), 3.3 (t, J=8 Hz, 2H), 4.6 (t, J=8 Hz, 2H), 4.8 (m, 1H), 5.05 (m, 1H), 5.5—6.2 (m, 1H)
1g	oil	59.22 (59.41	6.71 6.54	4.54 4.33	20.09 19.80)		1705	0.9 (t, 3H), 0.9—2.1 (m, 6H), 3.15 (t, J=8 Hz, 2H), 4.4 (t, J=8 Hz, 2H), 4.5 (s, 2H), 5.75 (m, 1H), 7.3 (s, 5H)
1h[b]	66.0—66.5 (Et_2O–hexane)	45.03 (45.89	6.92 6.60	3.71 3.82	17.15 17.48	20.77 21.81)	1695	1.2—2.1 (m, 16 H), 3.1—3.6 (m, 6 H), 4.6 (t, J=7 Hz, 2H)
1i	75.5—76.5 (CH_2Cl_2–Et_2O)	57.88 (57.67	8.04 7.74	8.90 8.96	20.84 20.49)		1690	1.1—2.05 (m, 16 H), 2.35 (t, J=7 Hz, 2H), 3.25 (t, J=7 Hz, 2H), 3.3 (t, J=7 Hz, 2H) 4.6 (t, J=7 Hz, 2H)
1j	112.5—113.5 (CH_2Cl_2–Et_2O)	53.63 (53.79	4.09 4.06	6.26 6.27	28.30 28.68)		1675	3.4 (t, J=7 Hz, 2H), 4.5 (t, J=7 Hz, 2H), 7.2—8.0 (m, 5H)
1k	118.0—119.0 (CH_2Cl_2–Et_2O)	46.47 (46.60	2.97 3.13	5.40 5.43	24.56 24.88	13.86 13.75)	1680	3.4 (t, J=7 Hz, 2H), 4.5 (t, J=7 Hz, 2H), 7.3 (d, J=8 Hz, 2H), 7.7 (d, J=8 Hz, 2H)
1l	168.5—170.0 (THF–Et_2O)	45.00 (44.78	2.86 3.01	10.67 10.44	23.79 23.87)		1670	3.5 (t, J=7 Hz 2H), 4.55 (t, J=7 Hz, 2H), 7.75 (d, J=18 Hz, 2H), 8.25 (d, J=18 Hz, 2H)
1m	84.5—85.5 (CH_2Cl_2–Et_2O)	57.56 (57.81	4.30 4.45	5.60 5.62	25.56 25.68)		1670	3.3 (t, J=7 Hz, 2H), 4.55 (t, J=7 Hz, 2H), 7.4 (m, 5H), 7.65 (d, J=15.5 Hz, 1H), 7.95 (d, J=15.5 Hz, 1H)
1n	132.0—132.5 (CH_2Cl_2–Et_2O)	50.73 (50.79	3.41 3.55	5.13 4.94	22.57 22.57	12.98 12.49)	1670	3.4 (t, J=7 Hz, 2H), 4.6 (t, J=7 Hz, 2H), 7.45 (m, 5H), 7.55 (d, J=15 Hz, 2H), 7.9 (d, J=15 Hz, 1H)

a) Recrystallization solvents. b) MS, *m/e*, 367 and 365 (M^+), 249 and 247, 120, and 119.

Table 4. Spectrum data of aldehydes **2**

Aldehyde	IR ν_{CO} cm^{-1}	NMR δ(CCl_4)
2a	1730	2.5—3.0 (m, 4H), 7.15 (s, 5H), 9.7 (t, J=1.5 Hz, 1H)
2b	1730	3.5 (d, J=2.5 Hz, 2H), 7.2 (m, 5H), 9.6 (t, J=2.5 Hz, 1H)
2c	1730	0.85 (t, J=8 Hz, 3H), 1.85 (m, 2H), 3.3 (dt, J=2, 8 Hz 1H), 7.2 (m, 5H), 9.55 (d, J=2 Hz, 1H)
2d	1730	1.9 (m, 2H), 2.1—2.8 (m, 4H), 7.2 (s, 5H), 9.55 (t, J=1.5 Hz, 1H)
2e	1730	0.9 (t, J=6 Hz, 3H), 1.3 (m, 30H), 2.4 (m, 2H), 9.8 (t, J=1.5 Hz, 1H)
2f	1730	1.2—2.6 (m, 16H), 4.75 (br s, 1H), 5.0 (br d, 1H), 5.7 (m, 1H), 9.7 (br s, 1H)
2g	1730	0.9 (t, 3H), 0.9—1.9 (m, 6H), 3.6 (m, 1H), 4.4 (d, J=12 Hz, 1H), 4.65 (d, J=12 Hz, 1H), 7.25 (s, 5H), 9.55 (br s, 1H)
2h	1710	1.1—2.1 (m, 14 H), 2.35 (m, 2 H), 3.35 (d, J=6.5 Hz, 2H), 9.7 (t, J= 1.5 Hz, 1H)
2i	1720	1.1—2.1 (m, 14H), 2.1—2.6 (m, 4H), 9.75 (t, J=1.5 Hz, 1H)
2j	1700	7.2—7.6 (m, 3H), 7.6—8.0 (m, 2H), 9.5 (s, 1H)
2k	1690	7.5 (d, J=8.5 Hz, 2H), 7.75 (d, J= 8.5 Hz, 2H), 9.5 (s, 1H)
2l	1705	8.15 (d, J=8.5 Hz, 2H), 8.45 (d, J= 8.5 Hz, 2H), 10.2 (s, 1H)[a]
2m	1680	6.45 (dd, J=16, 7.5 Hz, 1H), 7.4 (d, J=16 Hz, 1H), 7.4 (m, 4H), 9.7 (d, J=7.5 Hz, 1H)
2n	1690	6.6 (dd, J=16, 7.5 Hz, 1H), 7.4 (d, J=16 Hz, 1H), 7.4 (m, 4H), 9.7 (d, J=7.5 Hz, 1H)

a) $CDCl_3$ used as a sovent.

B: A CH_2Cl_2 (1 ml) solution of Et_3N (2.23 g, 22 mmol) was added at −20 °C to a stirred CH_2Cl_2 (20 ml) suspension of carboxylic acid (10 mmol), thiazolidine-2-thione (1.19 g, 10 mmol), and 2-chloro-1-methylpyridinium iodide (2.81 g, 11 mmol), and the mixture was stirred at room temperature for 1.5 h—overnight. The resulting mixture was washed with

H_2O, 1M HCl and brine, dried (Na_2SO_4), and evaporated. Purification of the products was performed by the method described above.

General Procedure for the Reduction with DIBAH. Normal Addition: 3-Acylthiazolidine-2-thione **1** (1.0 mmol) in a solid state was added in one portion to a stirred toluene (2 ml) solution of DIBAH (171 mg, 1.2 mmol) at −78 °C. The mixture was stirred for 0.25—2 h at this temperature, and then at −50——40 °C till the yellow color of the reaction mixture disappeared (0.5—3 h). To the mixture were successively added 1M H_2SO_4 (*ca.* 0.5 ml), petroleum ether (*ca.* 20 ml) (or CH_2Cl_2 (*ca.* 20 ml) in the cases of **1i, 1k, 1l,** and **1n**), and Na_2SO_4 (*ca.* 1 g), and the resulting white precipitate was filtered off. The organic filtrate was dried (Na_2SO_4) and concentrated *in vacuo*, and the desired aldehyde **2** was purified by thin layer chromatography on silica gel using PhH and/or CH_2Cl_2 as a developing solvent.

Reverse Addition: A toluene solution (0.5 ml) of DIBAH (171 mg, 1.2 mmol) was injected to a stirred toluene (2 ml) suspension or solution of **3** at −78 °C, and the mixture was stirred at this temperature until completion of the reaction (1—2 h), followed by repetition of *Normal Addition* to give product **2**. The results and physical data for **2a—n** are given in Tables 2 and 3, respectively.

General Procedure for the Reduction with LTBA. Normal Addition: Crystalline **3** (1.0 mmol) was added at once to a stirred THF (2 ml) solution of LTBA (305 mg, 1.2 mmol) at −20 °C. The mixture was stirred for 0.5—5 h at this temperature and then at 0 °C until the orginal yellow color of the reaction mixture disappeared (0.5—7 h). After successive addition of 1M H_2SO_4 (*ca.* 0.5 ml), petroleum ether (*ca.* 20 ml) (or CH_2Cl_2 (*ca.* 20 ml) in the case of **1i, 1k, 1l,** and **1n**), and saturated Na_2SO_4 solution (*ca.* 0.5 ml), the organic layer was separated from the white pasty mass by decantation, dried (Na_2SO_4), and evaporated *in vacuo*. Thin layer chromatography of the residue on silica gel developed with PhH and/or CH_2Cl_2 gave aldehyde **2**.

Reverse Addition-A: Powdered LTBA (305 mg, 1.2 mmol) was added in one portion to a stirred THF (2 ml) solution or suspension of **3** (1.0 mmol) at −20 °C, followed by repetition of the procedure described above to afford compound **2**.

Reverse Addition-B: The preceding reaction was repeated with use of LTBA (1.53 g, 6.0 mmol), **3** (5.0 mmol), and THF (10 ml). After completion of the reaction, 1 M H_2SO_4 (*ca.* 2 ml), petroleum ether (*ca.* 80 ml), and saturated Na_2SO_4 solution (*ca.* 4 ml) were successively added to the resulting mixture, and the organic layer was decanted, washed with H_2O and brine, and dried (Na_2SO_4). Removal of the solvent *in vacuo*, followed by short-path distillation of the residual oil afforded aldehyde **2**. The results are given in Table 2, the physical data being identical with those of **2** prepared by the reduction with DIBAH.

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