Utilisation of Sulphur-containing Leaving Groups. Part 2.[1] Monitored Reduction of Carboxylic Acids into Alcohols or Aldehydes *via* 3-Acylthiazolidine-2-thiones by Sodium Borohydride or Di-isobutylaluminium Hydride

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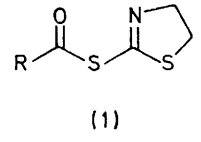
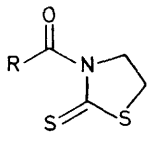
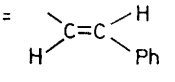
3-Acylthiazolidine-2-thiones (2) have been prepared by three methods, and treated with di-isobutylaluminium hydride or sodium borohydride to give aldehyde or alcohol in high yield, respectively. The original yellow colour disappears when reduction is finished, enabling the reaction to be monitored. The high reactivity of the carbonyl group in amide (2) was briefly discussed.

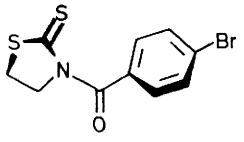
PREVIOUSLY, we have published a communication on a monitored reduction of carboxylic acids into alcohols or aldehydes *via* 2-thiazoline-2-thiol esters (1).[2] At almost the same time, Izawa and Mukaiyama [3] reported a similar reduction of carboxylic acids into aldehydes *via* the amide, 3-acylthiazolidine-2-thione (2). Although their procedure for the preparation of (2) was different from ours for the preparation of (1), we thought that our 'thioester' and their 'amide' might be the same. Thus an *X*-ray crystallographic analysis was carried out [4] on the *p*-bromobenzoyl derivative, prepared by reaction of the thallium(I) salt of thiazolidine-2-thione with *p*-bromobenzoyl chloride (Method A). As the result, the amide structure (3) was proved to be correct, contrary to our original prediction.



(1)



(2) a; R = $(CH_2)_4Me$
b; R = $(CH_2)_8Me$
c; R = $(CH_2)_{14}Me$
d; R = Ph
e; R = 



(3)

Treatment of *p*-bromobenzoyl chloride with thiazolidine-2-thione and triethylamine in hot tetrahydrofuran (Method B) or dehydration of *p*-bromobenzoic acid and thiazolidine-2-thione with dicyclohexyldi-imide (DCC) in ethyl acetate (Method C) also gave the amide (3). We thus revise the thioester structure (1), assigned previously, to the amide structure (2). We have now synthesized several 3-acylthiazolidine-2-thiones (2) in good yields using the foregoing three methods (Table 1). Subsequently, reduction of amides (2) was tried. A 20% solution of di-isobutylaluminium hydride (DIBAH) [5] in hexane was added dropwise into a yellow solution of (2) in hexane–dichloromethane (1 : 1) with stirring under argon or nitrogen at −20 to −50 °C. The disappearance of the original yellow colour was observed at the end of the reaction, and aldehyde (4) was produced in good yield. A solution of sodium borohydride in aqueous tetrahydrofuran (THF) was added dropwise to a yellow solution of (2) in THF with stirring at room temperature.

TABLE 1

Preparation of 3-acylthiazolidine-2-thiones

3-Acylthiazolidine-2-thione	Yield (%) Method A,	B,	C	ν_{CO}*/ cm^{-1}	δ(CDCl$_3$)
(2a)	81,	—,	75	1 695	0.88 (3 H, t-like), 3.23 (2 H, t, *J* 7 Hz), 4.59 (2 H, t, *J* 7 Hz),
(2b)	79,	—,	69	1 695	0.86 (3 H, t-like), 3.24 (2 H, t, *J* 7 Hz), 3.30 (2 H, t, *J* 7 Hz), 4.58 (2 H, t, *J* 7 Hz),
(2c)	83,	99,	89	1 705	0.85 (3 H, t-like), 1.25 (26 H, br m), 3.23 (2 H, t, *J* 7 Hz), 3.30 (2 H, t, *J* 7 Hz), 4.60 (2 H, t, *J* 7 Hz)
(2d)	97,	97,	84	1 690	3.45 (2 H, t, *J* 7 Hz), 4.54 (2 H, t, *J* 7 Hz), 7.25—7.80 (5 H, m)
(2e)	92,	91,	—	1 680	3.30 (2 H, t, *J* 7 Hz), 4.53 (2 H, t, *J* 7 Hz), 7.30—7.68 (5 H, m), 7.53 (1 H, d, *J* 15 Hz), 7.90 (1 H, d, *J* 15 Hz)
(3)	93,	84,	43	1 690	3.45 (2 H, t, *J* 7 Hz), 4.52 (2 H, t, *J* 7 Hz), 7.55 (4 H, s)
(7)	—,	—,	77	1 722 1 708	3.20 (3 H, t, *J* 7 Hz), 3.23 (2 H, t, *J* 7 Hz), 3.62 (3 H, s), 4.54 (2 H, t, *J* 7 Hz)
(10)	—,	—,	79	1 718 1 690	3.42 (2 H, t, *J* 7 Hz), 3.88 (3 H, s), 4.54 (2 H, t, *J* 7 Hz), 7.70 and 8.04 (each 2 H, AB q, *J* 7 Hz)

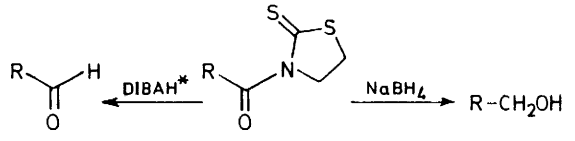
* I.r. spectra were recorded in $CHCl_3$ except for compounds (3) and (7) (KBr disc).

The end-point of the reaction was also judged by the disappearance of the yellow colour in this case; alcohol (5) was obtained in high yield (Table 2). It is noteworthy that the reduction of cinnamic acid amide (2e) affords the desirable αβ-unsaturated aldehyde (4e) or allyl alcohol (5e) without hydrogenation. The reduction of cinnamoyl chloride with $NaBH_4$ in hot dioxan has been reported to give only 3-phenylpropanol in 12% yield.[6]

This method was shown to be useful for the selective reduction of a carboxy-group when the molecule also contains a methoxycarbonyl group. Thus, amides (7) and (10), synthesised from hemi-acids (6) and (9), were

TABLE 2

Reduction of 3-acylthiazolidine-2-thione (2) with DIBAH or $NaBH_4$

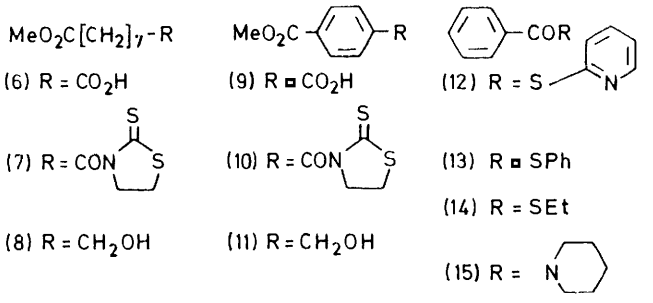


(4)	(2)	(5)
Yield, %		Yield, %
(4a) 54	(2a)	(5a) 96
(4b) 72	(2b)	(5b) 98
(4c) 79	(2c)	(5c) 99
(4d) 93	(2d)	(5d) 92
(4e) 64	(2e)	(5e) 92

* Reaction temperature: −50 °C for (2b) and (2d); −30 °C for (2a) and (2e); −20 °C in (2c).

treated with $NaBH_4$ in aqueous THF to give alcohols (8) and (11), respectively, in high yield.

Finally, the $NaBH_4$ reduction was compared between several benzoic acid derivatives: amide (2d), *S*-2-pyridyl ester (12), *S*-phenyl ester (13), and *S*-ethyl ester (14).



The results are summarised in Table 3; amide (2d) was shown to be most efficiently reduced to benzyl alcohol.

The i.r. spectrum of amide (2d) exhibited an absorption band at 1 690 cm^{-1}, an unusually high value compared with that for ordinany amines [*cf.* $\nu_{max.}$ ($CHCl_3$) 1 615 cm^{-1} for amide (15)]; the *X*-ray analysis of amide (3) has shown that the lone pair on the N-3 atom conjugates more favourably with the π-bond of thione group than with that of the acyl carbonyl group. Thus amide (2) has an independent active carbonyl group and a good leaving group (thiazolidine-2-thione) in the molecule, and shows high reactivity towards the hydride anion.

TABLE 3

Comparison of reduction of amide (2d) with reductions of thioesters (12), (13), and (14) by $NaBH_4$ [a]

Compound	Reaction time/min	Yield of benzyl alcohol (%)	Monitoring	ν_{CO}/cm^{-1} ($CHCl_3$)
(2d)	25	93	Excellent [b]	1 690
(12)	30	86	Not good [c]	1 680
(13)	120	59	Impossible [d]	1 675
(14)	120	0		1 660

[a] At room temperature; 3 mol equiv. of $NaBH_4$ in aqueous THF. [b] Yellow→colourless. [c] Pale yellow→yellow. [d] Colourless→colourless.

EXPERIMENTAL

Melting points were determined with a Yanagimoto microapparatus. I.r. spectra were measured on Jasco A-202 and Hitachi EPI-S2 spectrophotometers. U.v. spectra were recorded on a Hitachi EPS-3 spectrophotometer. ^1H N.m.r. and ^{13}C n.m.r. spectra were taken with a Varian T-60 instrument and with a JEOL JMN-FX100 instrument, respectively, in $CDCl_3$; signals are given in p.p.m. from $SiMe_4$ as internal standard. Mass spectra were determined on a JEOL JMS-OISG double-focusing mass spectrometer. Extracts were dried over anhydrous Na_2SO_4. A mixture of Kieselgel 60 (70—230 mesh) (Merck) and silicic acid (Mallinckrodt) (3 : 1) was used for column chromatography. Diisobutylaluminium hydride [20% in n-hexane, 95% $(C_4H_9)_2AlH$] was purchased from Alfa Division Ventron Corporation, U.S.A. Sodium borohydride was purchased from Merck & Co., Inc., Germany. Thiazolidine-2-thione, pyridine-2-thiol, benzenethiol, ethanethiol, dicyclohexylcarbodi-imide, carboxylic acids, acyl chlorides, aldehydes, and alcohols were purchased from Wako Pure Chemical Ind. Ltd., Osaka, Japan, Nakarai Chemicals Co., Kyoto, Japan, and Tokyo Kasei Kogyo Co., Tokyo, Japan.

General Procedure for Preparation of 3-Acylthiazolidine-2-thiones.—Method A. The thallium(I) salt [7] of thiazolidine-2-thione (1.2 mol equiv.) was added to a solution of the acyl chloride (500 mg) in THF (15 ml). The mixture was stirred at room temperature for 3 h. The solid material (TlCl) was filtered off and washed with CH_2Cl_2. After addition of water, the filtrate was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated *in vacuo* to leave a yellow residue, which was purified on a silica gel column to give the desired 3-acylthiazolidine-2-thione as a yellow crystalline product or a yellow oil. The yield is shown in Table 1.

Method B. Thiazolidine-2-thione (500 mg) and Et_3N (1.5 mol equiv.) were added to a solution of the acyl chloride (1.1 mol equiv.) in THF (50 ml). The mixture was stirred at 50 °C under N_2 for 30 min and a large amount of CH_2Cl_2 was added. The mixture was washed with 10% HCl, then brine, dried, and evaporated *in vacuo* to give a yellow residue, which was purified on a silica gel column to give 3-acylthiazolidine-2-thione.

Method C. Dicyclohexylcarbodi-imide (1.5 mol equiv.) was added to a solution of the carboxylic acid (500 mg) and thiazolidine-2-thione (1 mol equiv.) in AcOEt (50 ml). The mixture was stirred at room temperature for 24 h, then filtered, and the filtrate concentrated *in vacuo* to give a yellow residue, which was chromatographed on a silica gel column to yield 3-acylthiazolidine-2-thione. Spectroscopic and physical data of the 3-acylthiazolidine-2-thiones are in Tables 1 and 4, respectively.

General Procedure for the Reduction of 3-Acylthiazolidine-2-thiones with DIBAH.—A solution of DIBAH in n-hexane was injected dropwise onto a yellow solution of 3-acylthiazolidine-2-thione (100 mg) in dry n-hexane (12.5 ml)–dry CH_2Cl_2 (12.5 ml) at −50 to −20 °C with stirring under N_2 or Argon until the original yellow colour of the reaction medium vanished. The colourless mixture was stirred for a further 5 min at the same temperature and methanol was then added. The mixture was washed with aqueous $NaCO_3$,

water, and brine, and then dried. After evaporation of the solvent, the residue was chromatographed on silica gel to give the pure aldehyde; the spectroscopic data of each aldehyde were identical with those of authentic materials. The yields of aldehydes are in Table 2.

General Procedure for the Reduction of 3-Acylthiazolidine-2-thiones with $NaBH_4$.—A solution of $NaBH_4$ (3 mol equiv.) in THF (4 ml)–H_2O (5 drops) was added to a yellow solution of 3-acylthiazolidine-2-thione (100 mg) in THF (4 ml). The mixture was stirred at room temperature until the original yellow colour of the solution vanished, and then 10% aqueous HCl solution was added to destroy any excess of $NaBH_4$. The acidic solution was extracted with CH_2Cl_2, and the extract washed with aqueous Na_2CO_3, water, and brine. The CH_2Cl_2 extract was dried, and evaporated *in vacuo* to give a residue, which was chromatographed on silica gel (silica gel impregnated with 10% $AgNO_3$ is sometimes more effective for separation of thiazolidine-2-thione from the desired alcohol) to afford the pure alcohol. Spectroscopic data for each alcohol were identical with those of authentic samples. The yields of alcohol are in Table 2.

Reduction of Compound (7) *with* $NaBH_4$.—A solution of $NaBH_4$ (38 mg, 3 mol equiv.) in THF (1 ml)–H_2O (5 drops) was added to a solution of compound (7) (100 mg) in THF (4 ml). The mixture was stirred at room temperature for 30 min and worked up as above to give methyl 9-hydroxynonanoate (8) (45 mg, 73%) as a colourless oil, $\nu_{max.}$ ($CHCl_3$) 3 450 cm^{-1}; δ 3.66 (2 H, t-like, CH_2OH), and 3.72 (3 H, s, CO_2Me).

Benzoylation of Alcohol (8).—Benzoyl chloride (90 mg) and Et_3N (64 mg) were added to a solution of alcohol (8) (100 mg) in CH_2Cl_2 (2 ml). The mixture was stirred at room temperature for 12 h and treated as usual to give the benzoyl derivative of (8) as a colourless *oil* (121 mg, 78%); $\nu_{max.}$ ($CHCl_3$) 1 712 cm^{-1}; δ 3.72 (3 H, s, $-CO_2Me$), 4.38 (2 H, t, *J* 6 Hz, CH_2–O–COPh), and 7.30—8.22 (5 H, m, aromatic protons) (Found: M^+, 292.167. $C_{17}H_2O$ requires *M*, 292.167).

Reduction of Compound (10) *with* $NaBH_4$.—A solution of $NaBH_4$ (57 mg, 3 mol equiv.) in THF (2 ml)–H_2O (5 drops) was added to a solution of compound (10) (140 mg) in THF (6 ml). The mixture was stirred at room temperature for 5 min and worked up as usual to give the *alcohol* (11) (79 mg, 95%) as a colourless powder, m.p. 43—44 °C; $\nu_{max.}$ (KBr) 3 320 and 1 722 cm^{-1}; δ 2.54br (1 H, s, OH), 3.98 (3 H, s, CO_2Me), 4.80 (2 H, s, *p*-MeO_2C–C_6H_4–CH_2OH), and 7.44 and 8.04 (each 2 H, AB type, *J* 8 Hz, aromatic protons) (Found: C, 64.8; H, 6.25%; M^+, 166. $C_9H_{10}O_3$ requires C, 65.05; H, 6.05%; *M*, 166).

Preparation of the Thallium (I) *Salt of Pyridine-2-thiol*.—A solution of pyridine-2-thiol (4.224 g) in EtOH (120 ml) was added dropwise to a solution of thallium(I) acetate (10 g) in EtOH (400 ml) during 10 min with stirring, during which time a yellow precipitate appeared. Stirring was continued for further 3.5 h at room temperature. The precipitate was filtered off and washed with large amounts of EtOH and ether to give a yellow *powder* (8.853 g, 70%), m.p. 201—204 °C (decomp). (Found: C, 19.0; H, 1.35; N, 4.6. C_5H_4NSTl requires C, 19.1; H, 1.3; N, 4.45%).

TABLE 4

Physical constants and elemental analyses of 3-acylthiazolidine-2-thiones

3-Acylthiazolidine 2-thione *		M.p. (°C)	Formula	Analysis (%) Found (Calc.) C	H	N	M^+ Found (Calc.)
(2a)	Oil		$C_9H_{15}NOS_2$				217.055 (217.059)
(2b)	Oil		$C_{13}H_{23}NOS_2$				273.122 (273.122)
(2c)	Needles (from MeOH)	59.5—60	$C_{19}H_{35}NOS_2$	63.5 (63.85)	10.0 (9.85)	3.6 (3.9)	
(2d)	Needles (from MeOH)	167—168	$C_{10}H_9NOS_2$	53.75 (53.8)	4.2 (4.05)	6.15 (6.3)	223 (223)
(2e)	Prisms (from $CHCl_3$–MeOH)	75.5—76.5	$C_{12}H_{11}NOS_2$	57.75 (57.85)	4.35 (4.45)	5.4 (5.6)	249 (249)
(3)	Prisms (from $CHCl_3$)	118.5—119.5	$C_{10}H_8BrNOS_2$	39.6 (39.75)	2.45 (2.65)	4.7 (4.65)	303 and 301 (303 and 301)
(7)	Needles (from Et_2O)	39.5—40	$C_{13}H_{21}NO_3S_2$	51.5 (51.5)	7.1 (7.0)	4.7 (4.6)	303 (303)
(10)	Needles (from MeOH)	145—146	$C_{12}H_{11}NO_3S_2$	51.05 (51.25)	4.05 (3.95)	4.9 (5.0)	281 (281)

* All compounds are yellow.

Preparation of the S-2-*Pyridyl Benzoate* (12).—The thallium(I) salt of pyridine-2-thiol (2.7 g, 1.2 mol equiv.) was added to a solution of benzoyl chloride (1 g) in THF (40 ml). The mixture was stirred at room temperature for 2.5 h and worked up as usual to afford the *thioester* (12) (1.417 g, 92%) as pale yellow plates from ether, m.p. 47—49 °C; $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1}; δ 6.68—8.90 (9 H, m, aromatic and pyridyl protons) (Found: C, 67.0; H, 4.1; N, 6.6%; M^+ 215. $C_{12}H_9ONS$ requires C, 66.95; H, 4.2; N, 6.5%; *M* 215).

Preparation of the S-*Phenyl Benzoate* (13).—Thallium(I) benzenethiolate [7] (1.246 g, 1.2 mol equiv.) was added to a solution of benzoyl chloride (468 mg) in THF (15 ml). The mixture was stirred at room temperature for 4 h and worked up as usual to afford the *thioester* (13) (495 mg, 70%) as colourless needles from $CHCl_3$–MeOH, m.p. 54—55 °C; $\nu_{max.}$ ($CHCl_3$) 1 675 cm^{-1}; δ 7.18—8.10 (10 H, m, aromatic protons) (Found: C, 73.05; H, 4.65%; M^+, 214. $C_{13}H_{10}OS$ requires C, 72.9; H, 4.7%; *M*, 214).

Preparation of the S-*Ethyl Benzoate* (14).—Thallium(I) ethanethiolate [7] (2.255 g, 1.2 mol equiv.) was added to a solution of benzoyl chloride (1 g) in THF (25 ml). The mixture was stirred at room temperature for 4 h and then worked up as usual to give the thiol ester (14) (1.151 g, 98%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 660 cm^{-1}; δ 1.24 (3 H, t, *J* 7 Hz, SCH_2Me), 2.98 (2 H, q, *J* 7 Hz, SCH_2Me), and 7.08—8.00 (5 H, m, aromatic protons).

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