An Efficient, One-Pot Synthesis of 3-Methyl-1,3-thiazolidines

Wataru ANDO*, Toshikazu TAKATA, Liren HUANG, Yoshiharu TAMURA

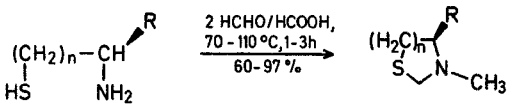
Department of Chemistry, The University of Tsukuba, Sakura, Ibaraki 305, Japan

3-Methyl 1,3-thiazolidines **3a–c** can be prepared easily in good yields by the reaction of β-mercaptoamine derivatives **1a–c** with formalin and formic acid in a one-pot operation. The same procedure is also suitable for the construction of the 3-methyl-tetrahydro-1,3-thiazine skeleton from γ-mercaptoamines as exemplified in the synthesis of **3d**.

Selective *N*-methylation of amines is still a significant problem in organic synthesis, as encountered in the preparation of *N*-thiazolidines **3a–c** from the corresponding thiazolidines **2a–c**. Although the reaction of formaldehyde in conjunction with a suitable reducing agent is applicable, the *N*-methylation of **2** requires a suitable, mild reducing agent, otherwise reductive C—S bond cleavage occurs easily[1,2]. The only known example is the use of sodium cyanoborohydride[3] which results in a much lower yield of the product (**3a**, less than 11 %). Therefore, in the case of **3b** which is used as a photographic silver halide emulsion sensitizer[4], two other synthetic routes have been attempted. One involves reductive ring cleavage of **2b** by means of metallic sodium in liquid ammonia followed by recyclization of *N*-methylcysteine formed with formaldehyde[5,6]. The other is a catalytic reduction of cystine in the presence of formaldehyde, in which reduction, condensation and reductive methylation occur successively[7]. Both routes, however, suffer from either drastic conditions or low efficiency.

Formic acid is a potential mild reducing agent[8], which, however, has never been employed for the preparation of **3**, presumably because of the acid sensitivity of **3**. We have now found that formaldehyde/formic acid system is quite suitable for the direct conversion of **1** to **3** by an one-pot reaction.

The conversion of **1** to **3** consists of two steps. At first **1** condenses with formaldehyde to form the intermediate **2**[9], and in the second step the reductive methylation of **2** with formaldehyde and formic acid occurs. Since formaldehyde is a common reagent in both the steps and the condensation is a fast, acid-catalyzed equilibrium[10], the two steps can be combined in an one-pot reaction, similar to the conversion of 3-amino-propanols to 3-methyl-1,3-oxazines[11,12]. In fact, **3a–c** were obtained in good yields when a solution of **1a** in 35% formaldehyde and 90% formic acid was heated at 110°C for a few hours with evolution of carbon dioxide (Table).



1a-d **3a-d**

2

1–3	n	R
a	1	$COOCH_3$
b	1	COOH
c	1	H
d	2	COOH

The optical rotation of L-**3b** prepared by us is much less than the reported value (Table). To check whether any racemization has occurred, we compared the ^{1}H-N.M.R. spectrum of the methyl ester of L-**3b** recorded in the presence of optically active reagent Eu(hfc)$_3$ with that of DL-**3b** prepared similarly from DL-cysteine. As a result, the protons of the methoxy group of the former did not split to two peaks while the latter did, indicating that the racemization did not occur at all.

When *o*-mercaptoaniline and 2-amino-1-ethanol were used as substrates no reaction to form *N*-methylbenzothiazolidine and 3-methyl-1,3-oxazolidine, respectively was noted.

The method described is of advantage for both easy performance and economy and therefore, can be applied for large-scale preparation (0.2 mol). Furthermore, this method functioned also in the preparation of 3-methyl-tetrahydro-1,3-thiazine (**3d**) from homocysteine (**1d**) under the same reaction conditions (Table).

^{1}H-N.M.R. and IR spectra were recorded by Varian EM 360M NMR spectrometer and HITACHI 260-50 infrared spectrophoto-

Table. Compounds **3a–d** prepared

Substrate	Product[a]	Reaction conditions: Temp. [°C]/ Time [h]	Yield[b] [%]	m.p. [°C] or b.p. [°C]/torr	$[\alpha]_D^{24}$	Molecular Formula[c] or Lit. data	^{1}H-N.M.R. (solvent/std) δ [ppm]
L-**1a**	L-**3a**	110°/3	60	b.p. 104–106°/5	−42.7° (*c* 2.2, $CHCl_3$)	$C_6H_{11}NO_2S$ (161.2)	$CDCl_3$/TMS: 4.35 (d, J = 9 Hz, 1H); 4.00 (d, J = 9 Hz, 1H); 3.96 (t, J = 5 Hz, 1H); 3.82 (s, 3H); 3.35 (s, 1H); 3.25 (d, J = 3 Hz, 1H); 2.50 (s, 3H)
L-**1b**	L-**3b**	80°/1.25	97[d]	m.p. 113–114°[e]	−47.5°[e] (*c* 1.2, H_2O)	m.p. 102–104°[7] $[\alpha]_D^{27}$: −152°[5] (*c* 0.566, H_2O)	D_2O/DSS[f]: 4.70 (d, J = 9 Hz, 1H); 4.30 (d, J = 9 Hz, 1H); 4.20 (t, J = 5 Hz, 1H); 3.78–3.20 (m, 2H); 3.10 (s, 3H)
DL-**1b** · HCl	DL-**3b** · HCl	80°/1.25	89	m.p. 188°	–	m.p. 180–181°[5]	D_2O/DSS: 4.75 (d, J = 11 Hz, 1H); 4.55 (d, J = 2 Hz, 1H); 4.34 (d, J = 11 Hz, 1H); 3.90–3.25 (m, 2H); 3.10 (s, 3H)
1c	**3c**	80°/1	71	b.p. 63–65°/10	–	b.p. 39–41°/4[13]	$CDCl_3$/TMS: 4.10 (s, 1H); 3.00 (m, 4H); 2.35 (s, 3H)
L-**1d**	L-**3d**	70°/1.1	84	m.p. 175° (decomp.)	−311° (*c* 1.3, H_2O)	$C_6H_{11}NO_2S$ (161.2)	D_2O/DSS: 4.45 (s, 1H); 4.40 (s, 1H); 3.75 (dd, J = 5.10 Hz, 1H); 3.00 (s, 3H); 2.85 (t, J = 5 Hz, 2H); 2.50–2.00 (m, 2H)

[a] All the products gave I.R. spectra consistent with the proposed structure.
[b] Isolated yield based on **1** used.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.28, N ±0.31.
[d] Crude yield.
[e] Value obtained for the solid product (see experimental)
[f] Sodium 4,4-dimethyl-4-silapentanesulfonate.

meter respectively. Specific rotations were calculated from optical rotations which were measured by a JASCO DIP-140 polarimeter using 5 cm length quartz cell.

3-Methyl-1,3-Thiazolidines 3a–c and 3-Methyltetrahydro-1,3-thiazine (3d); General Procedure:

A mixture of formic acid (90%, 12 ml), formaldehyde (35%, 7.80 g 90 mmol) and **1** (30 mmol) is heated at 70–110°C until the evolution of carbon dioxide ceases (1–3 h). Excess formic acid is evaporated on a water bath and the residue is made alkaline with aqueous sodium hydrogen carbonate solution. The free base is extracted with ether (3 × 30 ml), and the ethereal solution is dried with magnesium sulfate, filtered and evaporated. The residue is purified by distillation under reduced pressure.

In the case of **3b**, the crude product obtained after the removal of formic acid is a gum or resin which gave spectroscopies satisfactory to the proposed structure, but could only be partially recrystallized from methanol/ether (ca. 40%). As a further identification, the gum is refluxed in saturated methanolic hydrogen chloride (50 ml) to give the ester **3a** in high yield.

In the case of **3b**·HCl and **3d**, the residue obtained after the removal of excess formic acid is dissolved in methanol (30 ml) and the solution is evaporated. The crude product obtained by repeating the same operation three times, is purified by precipitating from methanol-ether.

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