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Preparation of 1,3-Thiazolidine-2-thiones by Using Potassium Ethylxanthate as a Carbon Disulfide Surrogate

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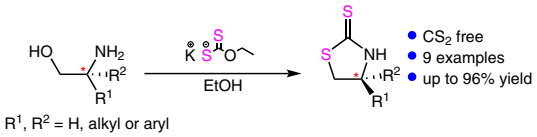

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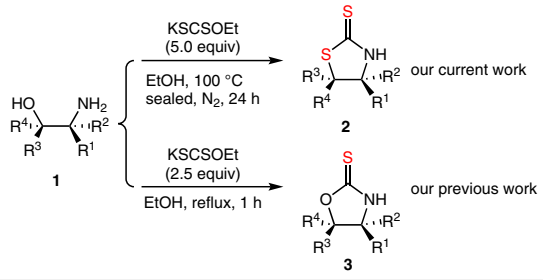
Abstract A simple procedure is presented for preparing 1,3-thiazolidine-2-thiones by using potassium ethylxanthate and the corresponding β-amino alcohols as the starting materials in the presence of ethanol.

Key words thiazolidinethiones, chiral auxiliaries, potassium ethylxanthate, green chemistry, heterocycles, amino alcohols

1,3-Thiazolidine-2-thiones are a class of compounds that are extensively studied in organic chemistry. They are used as chiral auxiliaries in asymmetric aldol addition in modern asymmetric syntheses,[1] and they can be used as precursors to β-lactams (through oxidation and extrusion of SO_2)[2] or alkenes (induced by benzyne).[3] They can also be used as twisted amides to induce asymmetric acylation of secondary alcohols,[4] or as sulfur donor in the preparation of heterotricyclic compounds[5a,b] or 2-methylthiiranes.[5c] Among these applications, their use as chiral auxiliaries is the most familiar. In the formation of two adjacent chiral carbon centers by asymmetric aldol condensation, 1,3-thiazolidine-2-thiones can act as powerful chiral auxiliaries that can be readily removed at a later stage.[6] Furthermore, they can be easily removed after their use in asymmetric aldol reactions, and they can provide high diastereoselectivities in acetate-type aldol reactions.[7] However, the use of 1,3-thiazolidine-2-thiones has been limited by difficulties in their preparation. Carbon disulfide (CS_2) is an essential reagent for building these heterocycles from vicinal amino alcohols[1g,6a,8] or aziridines;[9] however, because it is volatile and highly flammable, CS_2 is classified as a highly hazardous solvent according to the solvent-selection guides of pharmaceutical companies.[10]

In our previous researches, we found that potassium ethylxanthate [KSC(S)OEt] can be employed to form chiral 1,3-oxazolidine-2-thiones **3** from vicinal amino alcohols in good to excellent yields (Scheme 1).[11] On a further detailed study of this reaction, we found that the major byproducts generated for some substrates were the 1,3-thiazolidine-2-thiones **2**. This eventually became a good starting point for the development of a new approach for the synthesis of 1,3-thiazolidine-2-thiones **2**, as reported below.

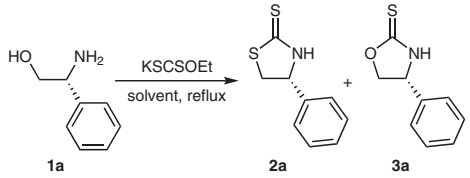


Scheme 1 Formation of 1,3-thiazolidine-2-thiones **2** and 1,3-oxazolidine-2-thiones **3** from vicinal amino acids **1** and potassium ethylxanthate

Using (2*R*)-2-amino-2-phenylethanol (**1a**) as a standard substrate, we investigated the reaction conditions for the synthesis of (4*R*)-4-phenyl-1,3-thiazolidine-2-thione (**2a**) to (4*R*)-4-phenyl-1,3-oxazolidine-2-thione (**3a**) in various ratios by mixing **1a** with KSC(S)OEt in EtOH and refluxing in an oil bath heated to 100 °C.

As shown in Table 1, when 2.5 equivalents of KSC(S)OEt were employed and the mixture was refluxed for one hour, **3a** was isolated exclusively in 88% yield (Table 1, entry 1). However, when the reaction period was extended to eight hours, the yield of **3a** fell significantly and **2a** was isolated in 29% yield (entry 2). On extending the reaction time to 18

Table 1 Optimization of the Conditions for the CS_2-Free Conversion of (*R*)-2-phenylglycinol (**1a**) into the 1,3-Thiazolidine-2-thione **2a** and the 1,3-Oxadiazoline-2-thione **3a** in the Presence of Potassium Ethylxanthate



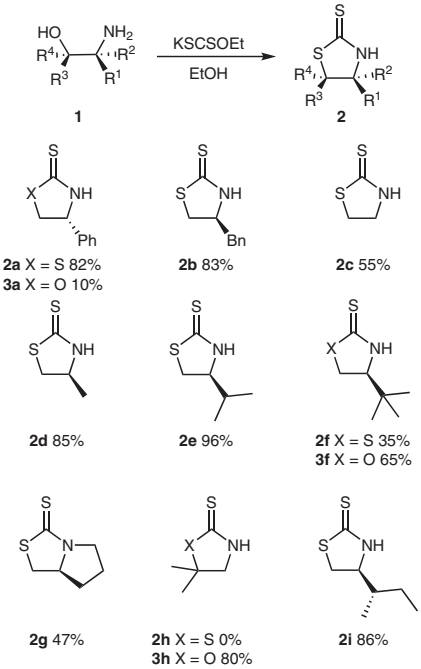
1a **2a** **3a**

Entry	KSC(S)OEt (equiv)	Solvent	Time (h)	Yield (%) of **2a**	Yield (%) of **3a**
1[a]	2.5	EtOH	1	0	88
2[a]	2.5	EtOH	8	29	52
3[a]	1.5	EtOH	8	11	58
4[a]	2.5	EtOH	18	45	7
5[ab]	5.0	EtOH	18	51	24
6[c]	5.0	EtOH	18	26	37
7[d]	5.0	–	18	37	0
8[abe]	5.0	EtOH	24	82	10
9[abe]	5.0	*i*-PrOH	24	74	3
10[abe]	5.0	PrOH	24	78	2
11[abe]	5.0	BuOH	24	80	6
12[abe]	5.0	DMF	24	48	3
13[abe]	5.0	DMSO	24	7	12
14[bef]	5.0	EtOH	24	82	7

[a] The reaction was carried out on a 1.0 mmol scale of amino alcohol **1a** (concentration 0.5 mol/L).
[b] Under N_2.
[c] The reaction was carried out on a 1.0 mmol scale of amino alcohol **1a** (concentration 0.1 mol/L)..
[d] No solvent.
[e] The reaction was carried out in an autoclave.
[f] The reaction was carried out on a 15.0 mmol scale of amino alcohol **1a** (concentration 0.5 mol/L).

hours, the yield of **2a** improved further to 45% (entry 4). Increasing the amount of KSC(S)OEt to 5.0 equivalents resulted in a slightly increase in the yield of **2a** (entry 5). When the reaction was carried out in more-dilute solution, **3a** was formed in preference to **2a** (entry 6). With no solvent, no **3a** was detected and **2a** was isolated in poor yield (entry 7). Then the reaction was carried out in an autoclave under N_2, **2a** was obtained in 82% yield, although **3a** was also isolated in 10% yield (entry 8). To examine the effect of the solvent, several polar solvents were screened. The reaction proceeded fairly well in the protic solvents *i*-PrOH, PrOH, and BuOH (entries 9–11), although the yields were not as good as that in ethanol. On the other hand, yields in the aprotic solvent DMF or DMSO were poor (entries 12 and 13). Because **2a** is a useful chiral auxiliary in stereoselective synthesis, the ability to prepare this compound on a multigram scale is pivotal for the practicability of our method. Under the optimized conditions, a multigram-scale preparation was found to be feasible and gave an equally good outcome in terms of the yield and selectivity to that of the small-scale preparation (entry 14).

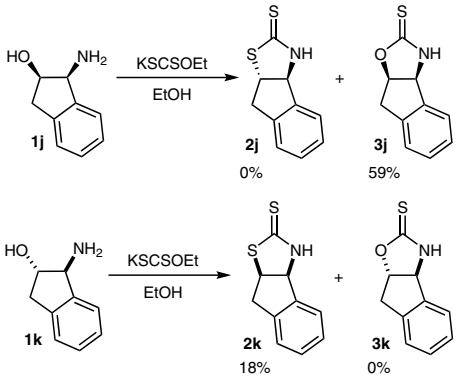
Having identified the optimal conditions, we next examined the scope of the reaction with respect to the use of various vicinal amino alcohols **1** for the synthesis of 1,3-thiazolidine-2-thiones **2** (Scheme 2). Nine amino alcohols with different substituents **1a–i** generally provided the corresponding products **2** in good to excellent yields, except for **1f** and **1h**. The chiral centers of amino alcohols **1a–g** and **1i** were retained in the corresponding 1,3-thiazolidine-2-thiones. It was clear that the substituents had significant impact on this reaction. Appropriate substituent on the carbon adjacent to nitrogen in the amino acid increased the yield of the 1,3-thiazolidine-2-thiones (compare **2c** with **2a**, **2b**, **2d**, **2e**, and **2i**). However, when R^1 (or R^2) was a tertiary alkyl group rather than a methyl group or a primary or secondary alkyl group, the oxazolidine-2-thione was formed in preference to the 1,3-thiazolidine-2-thione **2f**. The strain induced by a fused ring also increased the difficulty of forming the five-membered heterocyclic ring (**2g**). When $R^3 = R^4 = Me$, no 1,3-thiazolidine-2-thione was formed at all, and the oxazolidine-2-thione **3h** was isolated exclusively.



Scheme 2 Screening of the scope of formation of 1,3-thiazolidine-2-thiones **2**. An autoclave was charged with the amino alcohol **1** (1.0 mmol, 0.5 mol L^{-1}) and potassium ethylxanthate (5.0 equiv) then flushed with N_2 for 5 min and heated at 100 °C in an oil bath for 24 h.

To explore the mechanism of our CS_2-free synthesis of 1,3-thiazolidine-2-thiones (**2**), we used two isomers with different geometries as substrates (Scheme 3). When

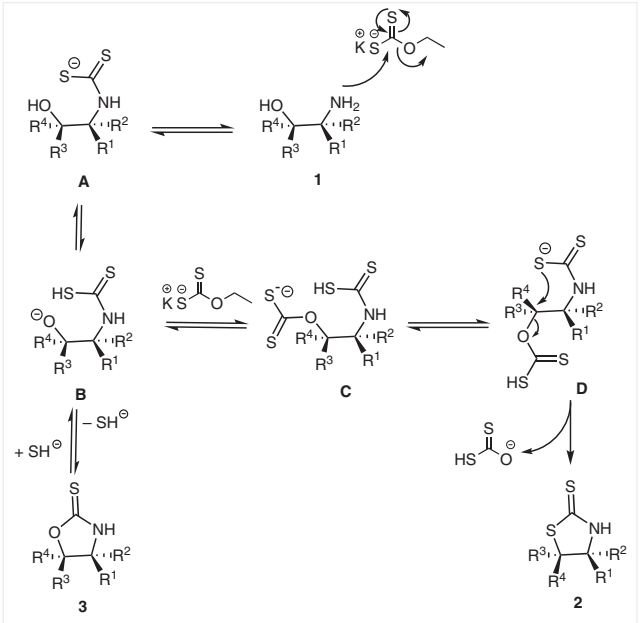
(1*S*,2*R*)-1-aminoindan-2-ol (**1j**) was used under the standard conditions, (3a*S*,8a*R*)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazole-2-thione[12] (**3j**) was isolated in 59% yield and none of the corresponding 1,3-thiazolidine-2-thione **2j** was detected. However, *trans*-1-amino-2-indanol (**1k**) gave *cis*-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]-oxazole-2-thione[7c] (**2k**) in 18% yield, and none of the corresponding 1,3-oxazolidine-2-thione **3k** was isolated. These results clearly show that the geometry of the vicinal amino alcohol is intimately involved in the formation of the heterocycle, which provided strong proof for our proposed mechanism (see below).



Scheme 3 The effect of the geometry, as demonstrated by 1-amino-2-indanols

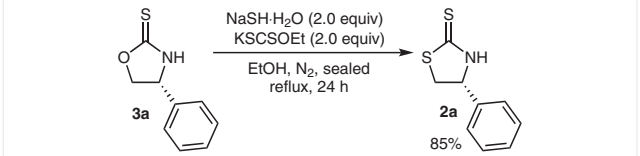
We therefore proposed the plausible mechanism shown in Scheme 4; this was inspired by Le Corre and co-workers' mechanism[8b] for the formation of 1,3-thiazolidine-2-thiones from amino alcohols and CS_2 under basic conditions.

Initially, the ethylxanthate reacts with the amine group to give dithiocarbamate **A** in equilibrium with **B**. If $R^3 \neq H$ and $R^4 \neq H$, a subsequent nucleophilic attack on the thiocarbonyl group affords the oxazolidine-2-thione **3** (see Scheme 2, 2h), for the following reasons. First, steric hindrance on carbon adjacent to the oxygen atom prevent further xanthation. Secondly the *gem*-dialkyl effect, known as the Thorpe–Ingold effect,[13] favors the formation of a five-membered ring.[14] However, if $R^3 = R^4 = H$, another ethylxanthate ion can react with the oxyanion to form the xanthate dithiocarbamate **C** in equilibrium with intermediate **D**. Nucleophilic attack on the thiocarbonyl group then affords the 1,3-thiazolidine-2-thione **2**. The order of yields of the 1,3-thiazolidine-2-thiones from the corresponding amino alcohol is as follows: R^1 (or R^2) = 2° C > Me > 1° C ≈ Ph > 3° C (Scheme 2, 1a–f, 1i). Steric hindrance generated by R^1 or R^2 favors the formation of a five-membered ring. However, when R^1 = *tert*-Bu (**1i**), product **3** is favored over product **2**. This might be because the bulky substituent pushes the thiocarbamate group away, causing it to lean toward the oxyanion in intermediate **B**, thereby favoring ring closure to



Scheme 4 Plausible mechanism for the formation of 1,3-thiazolidine-2-thiones **2** and 1,3-oxazolidine-2-thiones **3** from vicinal amino alcohols and KSC(S)OEt

form products **3** and disfavoring the intermolecular nucleophilic attack on ethylxanthate to form intermediate **C**. The fact that **3a** can be converted into **2a** in excellent yield in the presence of an excess of hydrosulfide and KSC(S)OEt (Scheme 5) supports this mechanism and indicates that the transformation of **2** into intermediate **B** is reversible. (This step is irreversible in Le Corre's mechanism.[8b]) As is shown in our mechanism, both the amount of potassium ethylxanthate and the steric hindrance around the hydroxy group control the chemoselectivity of the reaction. Smaller amounts of KSC(S)OEt and more steric hindrance of the hydroxy group favor products **3**; otherwise, products **2** are the major products.



Scheme 5 Transformation of (**3a**) into (4*R*)-4-phenyl-1,3-oxazolidine-2-thione (**2a**)

In summary, we have developed a CS_2-free approach to the preparation of 1,3-thiazolidine-2-thiones from vicinal amino alcohols in the presence of potassium ethylxanthate as a CS_2 surrogate.[15] Common chiral 1,3-thiazolidine-2-thiones were conveniently prepared in this manner, which should permit a broadening of their use in modern organic synthesis. Meanwhile, we found that 1,3-oxazolidine-2-thiones can be converted into 1,3-thiazolidine-2-thiones in

the presence of hydrosulfide and KSC(S)OEt, thereby providing a deeper understanding of the formation of chiral auxiliaries from vicinal amino alcohols.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612124.

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(15) **(4*R*)-4-Phenyl-1,3-thiazolidine-2-thione (2a) and (4*R*)-4-Phenyl-1,3-oxazolidine-2-thione; Typical Procedure**

Potassium ethylxanthate (802 mg, 5.0 mmol) was rapidly added to a suspension of (2*R*)-2-amino-2-phenylethanol (**1a**; 137 mg, 1.0 mmol) in absolute EtOH (2.0 mL) in a 20 mL autoclave. The autoclave was flushed with N_2 for 5 min, then sealed and heated in an oil bath at 100 °C for 24 h. It was then cooled to r.t. and the mixture was transferred to a 50 mL round-bottomed flask and concentrated under reduced pressure to remove the alcohol. H_2O (10 mL) was added to the slurry, and the mixture was extracted with EtOAc (3 × 30 mL). The organic phases were combined, washed with brine (30 mL), dried (Na_2SO_4), and concentrated to give a crude product that was purified by flash chromatography [silica gel, EtOAc–PE (1:3)] to afford **2a** and **3a**.

2a[8b]

Off-white solid; yield: 160 mg (0.82 mmol, 82%); mp 123–125 °C [Lit.[8b] 124–125 °C (aq EtOH)]; R_f = 0.3 (EtOAc–PE, 1:3), $[\alpha]_D^{22}$ –205.8 (*c* 1.03, $CHCl_3$) [Lit. –209.32 (*c* 0.35, $CHCl_3$)]. IR (KBr): 3132, 2923, 1489, 1452, 1258, 1050, 941, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (br s, 1 H), 7.46–7.36 (m, 5 H), 5.32 (t, *J* = 8.0 Hz, 1 H), 3.86 (dd, *J* = 11.2, 8.0 Hz, 1 H), 3.52 (dd, *J* = 11.2, 8.0 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.6, 138.0, 129.4, 129.2, 126.3, 67.5, 41.6. ESI-MS: *m/z* = 196.0 $[M + H]^+$.

3a[8b,11]

White solid; yield: 18 mg (0.10 mmol, 10%); mp 120.0–120.4 °C (Lit.[8b] 121–122 °C); R_f = 0.3 (EtOAc–PE, 1:3); $[\alpha]_D^{20}$ –78.5 (*c* 0.20, $CHCl_3$) [Lit.[8b] –79.3 (*c* 0.21, $CHCl_3$)]. IR (KBr): 3436, 1525, 1170, 969, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.50 (br s, 1 H), 7.45–7.36 (m, 3 H), 7.34–7.30 (m, 2 H), 5.12 (dd, *J* = 8.8, 7.6 Hz, 1 H), 5.00 (t, *J* = 8.8 Hz, 1 H), 4.49 (dd, *J* = 9.2, 7.2 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.6, 137.9, 129.2, 129.0, 126.2, 77.6, 60.1. ESI-MS: *m/z* = 178.0 $[M–H]^-$.