JOC*Note*

A Facile Access to Chiral 4-Isopropyl-, 4-Benzyl-, and 4-Phenyloxazolidine-2-thione

Yikang Wu,* Yong-Qing Yang, and Qi Hu

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

yikangwu@mail.sioc.ac.cn

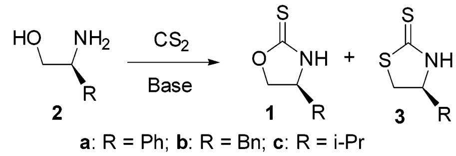
Received February 4, 2004

Abstract: A highly practical procedure for preparing the chiral oxazolidine-2-thione auxiliaries using carbon disulfide and the corresponding chiral amino alcohols as the starting materials in the presence of potassium carbonate and hydrogen peroxide is presented.

Chiral 4-monosubstituted oxazolidine-2-thiones are very useful auxiliaries in enantioselective organic synthesis.[1,2] Among them, the 4-isopropyl, 4-benzyl-, or 4-phenyloxazolidine-2-thione (**1a**−**c**, and the enantiomer of **1a**) are particularly valuable, because they can be prepared from the corresponding amino acids that are commercially available at low prices. These auxiliaries can function equally well as the classical oxazolidinone[3] (Evans) auxiliaries but enjoy a remarkable advantage of easier[2] removal after completion of the chiral induction. Such a feature has great merits in the synthesis of complicated "fragile" molecules containing many different functionalities.

However, the synthesis of the oxazolidinethione auxiliaries themselves remains a substantial barrier to their broad application in asymmetric synthesis. Unlike their oxazolidinones counterparts,[4] **1a**−**c** are still not so readily accessible. They are usually prepared[5] (Scheme 1) from

SCHEME 1



carbon disulfide and amino alcohols either with NEt_3 in CH_2Cl_2 or with an aqueous solution of NaOH or Na_2CO_3 in a biphasic mixture. A cosolvent such as THF or ethanol was sometimes added to facilitate the reaction.

In general, the CH_2Cl_2/NEt_3 conditions require many hours of refluxing to drive the reaction to any synthetically useful extents. As carbon disulfide has a low flash point (−30 °C) and a low boiling point (46 °C), extended (and hence likely to be unattended) periods of refluxing would inevitably create potential danger. Use of aqueous base can remarkably shorten the reaction time and consequently improve the safety of the procedure. However, a thermodynamically favored side product, the corresponding thiazolidine-2-thione (**3**, Scheme 1), is often formed[5e,g] in substantial quantities regardless of the amount of the carbon disulfide present in the reaction system. As a consequence, a tedious chromatographic separation is unavoidable. To get around these problems, Crimmins[6] and co-workers recently introduced a novel time-efficient and high-yielding protocol, which used thiophosgene to replace the CS_2. However, because thiophosgene is highly toxic and expensive, the need for a facile practical access to **1** still remains.

In an exhaustive literature search we found that in 1997 Li and Ohtani reported[7] a unique route to oxazolidine-2-thiones (not related to auxiliaries chemistry), which utilized H_2O_2 to convert the intermediate SH anions into S−S bonds and thus turned the otherwise sluggish ring-closure into a rapid and irreversible process. However, to our knowledge, the potential of this route in the synthesis of chiral auxiliaries such as **1** has never been realized.[8]

Application of Li and Ohtani's procedure on **2a** led to the expected **1a** smoothly. However, as a potential industrial synthesis this procedure suffered from at least two shortcomings: (1) the cost of the base (NEt_3) was too high (compared with inorganic bases) and (2) both the base and the solvent (MeOH) were remarkably toxic and thus would raise safety and environment concerns. Besides, involvement of NEt_3 in the reaction also complicated the workup and product isolation. To circumvent these problems, we conducted the investigation summarized in Table 1.

(1) See, e.g.: (a) Fujita, E.; Nagao, Y. *Adv. Heterocyl. Chem.* **1989**, *45*, 1−36. (b) Garcia-Fernandez, J. M.; Ortiz-Mellet, C.; Fuentes, J. *J. Org. Chem.* **1993**, *58*, 5192−5199. (c) Nagao, Y.; Kumagai, T.; Nagase, Y.; Tamai, S.; Inoue, Y.; Shiro, M. *J. Org. Chem.* **1992**, *57*, 4232−4237.

(2) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884.

(3) See, e.g.: (a) Evans, D. A. *Scinece* **1988**, *240*, 420−426. (b) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921−5942. (d) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453. (e) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660. (f) Nicolaou, K. C.; Gaulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910−7912.

(4) For a high-yielding low-cost access to chiral 4-monosubstituted oxazolidinones auxiliaries, see: Wu, Y.-K.; Shen, X. *Tetrahedron: Asymmetry* **2000**, *11*, 4359−4363.

(5) (a) Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2361−2367. (b) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.* **2001**, *66*, 2382−2393. (c) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989−6992. (d) Moreno-Manas, M.; Padros, I. *J. Heterocycl. Chem.* **1993**, *30*, 1235−1239. (e) Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604−6607. (f) Holmes, A. B.; Nadin, A.; O'Hanlon, P. J.; Pearson, N. D. *Tetrahedron: Asymmetry* **1992**, *3*, 1289−1302. (g) Aitken, R. A.; Armstrong, D. P.; Galt, R. H.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2139−2145. (h) Roth, H. J.; Schlump, H. *Arch. Pharm. (Weinheim)* **1963**, *296*, 213−217. (i) Kitoh, S.-i.; Kunimoto, K.-K.; Funaki, N.; Senda, H.; Kuwae, A.; Hanai, K. *J. Chem. Crystallogr.* **2002**, *32*, 547−553.

(6) Crimmins, M. T.; King, B. W.; Tabet, E. A. Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902. However, it should be noted that chromatographic separation is still needed if one wishes to isolate the pure auxiliary (although the crude product often can be used directly).

(7) (a) Li, G.; Ohtani, T. *Heterocycles* **1997**, *45*, 2471−2474. (b) Li, G.; Tajima, H.; Ohtani, T. *J. Org. Chem.* **1997**, *62*, 4539−4540.

(8) That work of Li's has already been cited several times in the literature, including those papers reporting on the synthesis of other oxazolidinethione auxiliaries. See, e.g.: (a) Ortiz, A.; Quintero, J.; Hernandez, H.; Maldoado, S.; Mendoza, G.; Bernes, S. *Tetrahedron Lett.* **2003**, *44*, 1129−1132. (b) Ortiz, A.; Quintero, L.; Mendoza, G.; Bernes, S. *Tetrahedron Lett.* **2003**, *44*, 5053−5055.

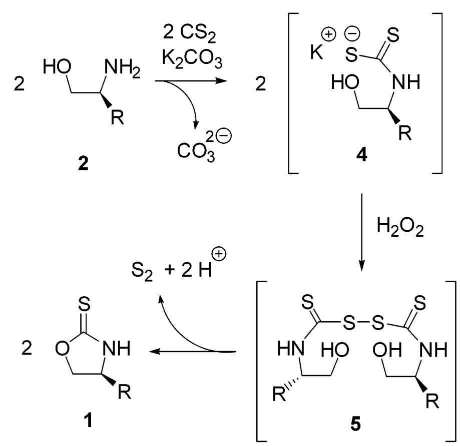
10.1021/jo049799d CCC: $27.50
Published on Web 04/30/2004

TABLE 1. Representative Results of Synthesis of 1 from the Corresponding Aminol 2

entry	solvent	base (quantity)[a]	CS_2[a]	H_2O_2[a]	T 1[b] (°C)	tim[c]e (min)	T 2[d] (°C)	product (yield %)
1	MeOH	$NaHCO_3$ (1.0)	1.5	1.5	10	30	60	**1a** (57)
2	MeOH	K_2CO_3 (1.0)	1.5	1.5	10	30	25	**1a** (67)
3	EtOH	K_2CO_3 (1.0)	1.5	1.5	10	4	80	**1a** (78)
4	EtOH	K_2CO_3 (1.0)	1.5	1.5	10	30	80	**1a** (84)
5	EtOH	K_2CO_3 (1.0)	1.5	2.0	10	30	80	**1a** (90)
6	EtOH	K_2CO_3 (1.0)	1.5	1.5	10	10	10	**1a** (43)
7	EtOH	K_2CO_3 (1.0)	1.5	1.5	10	30	10	**1a** (71)
8[e]	EtOH	K_2CO_3 (1.0)	1.5	1.5	10	30	80	**1a** (55)
9[e]	EtOH	K_2CO_3 (0.5)	1.5	1.5	10	30	80	**1a** (82)
10[f]	EtOH	Na_2CO_3 (0.5)	1.5	1.5	10	30	80	**1a** (70)
11	EtOH	$NaHCO_3$ (2.0)	1.5	1.7	80	0	80	**1a** (40)
12	EtOH	K_2CO_3 (0.2)	1.5	1.5	8	30	80	**1a** (69)
13	EtOH	K_2CO_3 (0.5)	2.0	1.5	50	0	50	**1a** (>99)
14	EtOH	K_2CO_3 (0.5)	2.0	1.5	50	0	50	**1b** (>99)
15	EtOH	K_2CO_3 (0.5)	2.0	1.5	50	0	50	**1c** (93)

[a] All the quantities of the reactants are given in molar equiv with respect to **2**. [b] Bath temperature before addition of H_2O_2. [c] Reaction time before addition of H_2O_2. [d] Bath temperature when introducing H_2O_2. [e] EtOH/H_2O = 3:1. [f] EtOH/H_2O = 95:5.

SCHEME 2



Most of our experiments were performed with **2a** as the starting aminol because of its potential advantages.[9] For economic and safety reasons, EtOH (probably the cheapest and safest organic solvent in industry) was chosen as the solvent after a few preliminary testing runs. Efforts were then made in seeking an inexpensive nontoxic substitute for the NEt_3. Several common inorganic bases were thus examined.

A "problem" we encountered immediately was that the inorganic bases were not very soluble in anhydrous EtOH. Addition of water to the EtOH apparently facilitated the dissolution (giving clear solutions as observed when using NEt_3), but did not seem to improve the yield of **1** so much as expected. However, the preliminary results did show that K_2CO_3 was superior to, e.g., $NaHCO_3$ or Na_2CO_3 (entry 1, and also entries 10 and 11). Therefore, in most of the subsequent experiments, K_2CO_3 was utilized.

Formation of **1** from **2** are believed to involve two intermediates (**4** and **5**, Scheme 2).[7] Addition of the amino group of **2** to CS_2 generates the first intermediate **4**. Then, the thiol anion is oxidized by H_2O_2, affording the second intermediate **5**. Finally, **5** loses two protons and S_2 to yield two molecules of **1**. Our results suggested that the first step of the reaction was pretty fast at temperatures around 50 °C or above, because shortening the reaction time before introduction of H_2O_2 did not seem to have much influence on the yield of **1** (entries 3 and 4). However, if the H_2O_2 was added at lower temperatures, a longer reaction time before introduction of H_2O_2 was beneficial (entries 6 and 7).

Although only an equal molar amount of CS_2 was needed according to the stoichiometry of the reaction, the presence of a slight excess of CS_2 (2 molar equiv) led to higher yields, perhaps because some of the CS_2 escaped from the system during the reaction. Further increasing the amount of the added CS_2, however, was not rewarding. As for the H_2O_2 (commercially available as 30% solution), 1.5 molar equiv appeared to suffice (entries 13–15). The oxidation and the subsequent ring-closure proceeded very fast at 50 °C because sulfur precipitated out immediately after introduction of H_2O_2. On completion of the addition,[10] the reaction was finished. Further stirring was not necessary.

On the basis of a great many experiments, we finally established that the reaction was most satisfactorily run in anhydrous EtOH at temperatures around 50 °C with the molar ratios between the reactants being 1:0.5:2:1.5 for **2**/K_2CO_3/CS_2/H_2O_2. Under such conditions, the aforementioned incomplete dissolution of K_2CO_3 did not cause any discernible problem.[11] As a result of elimination of NEt_3 in the synthesis, the workup became very simple. After completion of the reaction, the solids were filtered off and the product in the filtrate was recovered by conventional aqueous workup in excellent yields and high purity. In particular, **1a** was easily isolated as essentially white crystals in >99% yield[12] after removal of the solvent. Finally, it should be mentioned that the proce-

(9) Compared with **1b** and **1c**, **1a** (and some of its derivatives) is easier to crystallize. Besides, both the (*S*)- and (*R*)-isomer of phenylglycine (the precursor of **2a** and its (*R*)-enantiomer, respectively) are commercially available at rather low prices.

(10) In the presence of excess CS_2 and base, very slow addition of H_2O_2 at high temperatures sometimes may lead to formation of traces of **3**. However, the product **1a** itself appears to be reasonably stable to H_2O_2, because treatment of isolated pure **1a** with H_2O_2 (1.5 molar equiv)/K_2CO_3 (0.5 molar equiv) in EtOH at 50 °C for 1 h did not lead to any discernible reactions at all.

(11) It is interesting to note that reducing the amount of the added K_2CO_3 from 0.5 to 0.2 molar equiv still led to **1a** in 69% yield instead of the "theoretical" 40% (entry 12).

(12) The **1a** was obtained in 78% yield (column chromatography was needed) using Li and Ohtani's NEt_3/MeOH procedure (ref 7a) on the same scale.

dure worked very well not only for the synthesis of **1a**, but also for that of **1b** and **1c**.

Experimental Section.

Representative Procedure (1a). H_2O_2 (30% solution, 1.70 mL, ca. 15 mmol) was added (CAUTION: EXOTHERM!) dropwise to a mixture of (*S*)-2-phenylglycinol[13] (**2a**, 1.371 g, 10 mmol), powdered anhydrous K_2CO_3 (0.690 g, 5 mmol), and CS_2 (1.21 mL, 20 mmol) in commercially available anhydrous ethanol (10 mL) stirred at ca. 50 °C (bath temperature). A yellow-brown color was soon generated and then gradually faded. After completion of the addition (usually taking only a few minutes), the insoluble materials were filtered off with suction. The filtrate was diluted with EtOAc (ca. 70 mL), washed with water (ca. 15 mL × 3) and brine, and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was concentrated to dryness on a rotary evaporator to give **1a**[14] as an essentially white solid (1.779 g, 99.4% yield): mp 120−121 °C; $[\alpha]^{19}_D$ +82.7 (*c* 0.21, $CHCl_3$) (lit.[5e] mp 121−122 °C; $[\alpha]^{22}_D$ −79.3 (*c* 0.21, $CHCl_3$) for the (*R*)-isomer); ^1H NMR (300 MHz, $CDCl_3$) 7.72 (br s, 1H, NH), 7.46−7.27 (m, 5H), 5.13 (dd, *J* = 7.1, 9.4 Hz, 1H), 5.00 (t, *J* = 9.0 Hz, 1H), 4.48 (dd, *J* = 6.9, 8.9 Hz, 1H). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found:[15] C, 60.25; H, 5.11; N, 7.60.

Acknowledgment. Financial support was provided by the National Natural Science Foundation of China (20025207, 20272071, 20372075, 20321202), the Chinese Academy of Sciences ("knowledge innovation" project, KGCX2-SW-209), and the Major State Basic Research Development Program (G2000077502).

JO049799D

(13) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517−5518.

(14) (*S*)-4-Phenyloxazolidine-2-thione was previously obtained as a byproduct (without full characterization) in 17% yield in the preparation of the corresponding thiazolidine-2-thione. See: Yamada, S.; Misono, T.; Ichikawa, M.; Morita, C. *Tetrahedron* **2001**, *57*, 8939−8949.

(15) The elemental analysis and the melting point measuring were performed on the "crude" product without any purification.