

## Facile Synthesis of *trans*-S-1-Propenyl-L-Cysteine Sulfoxide (Isoalliin) in Onions (*Allium cepa*)

Sangku Lee,\* Jae Nyounng Kim,<sup>†</sup> Dong-Ho Choung, and Hyeong Kyu Lee\*

Immune Modulator Research Center, KRIBB, Daejeon 305-806, Korea

\*E-mail: sangku@kribb.re.kr (S.L.), hykylee@kribb.re.kr (H.K.L.)

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea

Received October 12, 2010, Accepted November 2, 2010

**Key Words:** Natural product, Amino acid, Isoalliin, Sulfoxide, Onion

*Allium* species such as onions (*Allium cepa*) and garlic (*Allium sativum*) contain a variety of sulfur compounds which exhibit significant biological activities including anticarcinogenic,<sup>1</sup> anti-tumorigenic,<sup>2</sup> antimutagenic,<sup>3</sup> antimicrobial,<sup>4</sup> immunomodulatory,<sup>2a</sup> cardiovascular-protective,<sup>5</sup> and antioxidant effects.<sup>6</sup> Several S-alk(en)yl-L-cystein sulfoxides have been reported to be present in genus *Allium* in the form of nonprotein sulfur amino acids.<sup>7</sup> *Trans*-S-1-propenyl-L-cystein sulfoxide (isoalliin, **1**) has been isolated from onions,<sup>7a,8</sup> and it has been shown to be the precursor of the lachrymatory properties of *Allium cepa* by the action of the enzyme alliinase on the conversion of odorless *trans*-S-1-propenyl-L-cystein sulfoxide into the corresponding volatile thiosulfinate.<sup>9</sup>

Quantification of S-alk(en)yl-L-cystein sulfoxides is an important issue in *Allium* research. The unusual amino acid *trans*-S-1-propenyl-L-cystein sulfoxide (**1**) is in demand in the field of *Allium* chemistry including metabolism and biological studies,<sup>9a</sup> and serves as a standard for determination of S-alk(en)yl-L-cystein sulfoxides. Herein, we describe the facile synthesis of *trans*-S-1-propenyl-L-cystein sulfoxide in three steps.

The synthesis of *trans*-S-1-propenyl-L-cystein sulfoxide (**1**) was reported by three research groups. Nishimura and co-workers<sup>10</sup> performed the isomerization of a terminal triple bond (ethyl prop-2-ynyl sulfide) to ethyl prop-1-ynyl sulfide and the subsequent reductive coupling with alkyl chloride as key reaction steps. Parry and Sood<sup>11</sup> reported the synthesis of compound **1** in five steps without presenting a detail experimental description. They also used the isomerization of a terminal triple bond (benzyl prop-2-ynyl sulfide) to benzyl prop-1-ynyl sulfide in the scheme of synthesis of **1**. Namyslo and Stanitzek<sup>12</sup> utilized palladium-catalyzed coupling of a thiol with alkenyl bromide and completed the synthesis of compound **1** in five steps.

Our synthesis started with the formation of vinylsulfide **3**

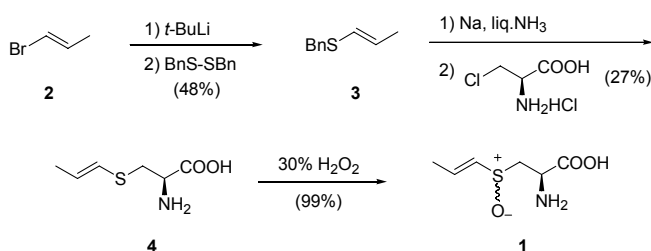
from the commercially available (*E*)-1-bromo-1-propene (**2**), which by treatment with *t*-BuLi and the successive addition of dibenzyl disulfide afforded (*E*)-1-(benzylthio)-1-propen (**3**) (Scheme 1).<sup>13</sup> The isomerically pure *trans*-(1-propen) compound **3** was obtained providing the characteristic large NMR coupling of the *trans*-olefinic protons ( $J = 15.0$  Hz). Reductive cleavage of a C-S bond in compound **3** by Na in liquid NH<sub>3</sub> followed by addition of 3-chloro-L-alanine hydrochloride gave *trans*-S-1-propenyl-L-cystein (**4**).<sup>14</sup> Finally, the oxidation of sulfide **4** by aqueous hydrogen peroxide provided sulfoxide **1** in a quantitative yield. Compound **1** was obtained as a mixture of two diastereomers with a new formed sulfur chiral center. The structure of **1** was confirmed by a comparison with those in the literature.<sup>9b,12</sup>

In summary, a natural amino acid, *trans*-S-1-propenyl-L-cystein sulfoxide (**1**) was synthesized from (*E*)-1-bromo-1-propene in a concise way, via the sequential (i) the formation of vinylsulfide from lithiated propene and disulfide, (ii) reductive cleavage/alkylation of vinylsulfide, (iii) sulfide oxidation to sulfoxide. This compound is widely used as a reference for studies on *Allium* chemistry including biosynthesis of S-alkenyl-L-cystein sulfoxides, metabolism studies and biological investigations.

### Experimental

**Compound 3.** To a solution of *t*-BuLi (35.6 mL of a 1.7 M solution in pentane, 60.5 mmol) in THF (80 mL) at  $-78$  °C was added (*E*)-1-bromo-1-propene (**2**) (2.4 mL, 27.9 mmol). After 30 min, dibenzyl disulfide (6.56 g, 26.6 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of propylene oxide (20 mL) and the mixture was stirred for 30 min. The reaction mixture was poured into a 15% NaOH solution, extracted with hexane, washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane as an eluent) to give 2.1 g (48%) of compound **3**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.24 (m, 5H), 5.93 (br.dd,  $J = 15.0, 1.2$  Hz, 1H), 5.71 (dq,  $J = 15.0, 6.9$  Hz, 1H), 3.85 (s, 2H), 1.73 (dd,  $J = 6.9, 1.2$  Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  137.8, 128.7, 128.4, 127.1, 126.9, 122.8, 37.5, 18.4; HRMS (EI)  $m/z$  164.0658 [(M)<sup>+</sup>, calcd for C<sub>10</sub>H<sub>12</sub>S 164.0660].

**Compound 4.** Ammonia was condensed into a two-necked flask fitted with a dry ice-isopropyl alcohol condenser, which



Scheme 1

contained a solution of compound **3** (2.0 g, 12.2 mmol) in ethyl ether (4 mL). The mixture was cooled to  $-42\text{ }^{\circ}\text{C}$  in a dry ice- $\text{CH}_3\text{CN}$  bath and small pieces of sodium (0.82 g, 35.6 mmol) were added until the blue color was persisted for 20 min. Solid ammonium chloride was added to destroy the excess of sodium until the blue color disappeared. The ammonia was evaporated by a stream of argon, and the residue was dissolved in THF and cooled to  $0\text{ }^{\circ}\text{C}$ . 3-Chloro-L-alanine hydrochloride (1.9 g, 12.0 mmol) was added, and the reaction mixture was stirred for 18 h at room temperature and poured into water. The mixture was adjusted to be pH 5 - 6 using acetic acid, added to strongly acidic Amberlite and stirred for 10 min. The ion exchanger was filtered by washing with water and MeOH. The filtered ion exchanger was washed with 4N- $\text{NH}_4\text{OH}$  solution and the collected solution was concentrated in vacuo to yield 0.53 g (27%) of compound **4**:  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ )  $\delta$  5.91-5.83 (m, 2H), 3.82 (m, 1H), 3.17 (dd,  $J=14.7, 3.6$  Hz, 1H), 2.99 (dd,  $J=14.7, 8.1$  Hz, 1H), 1.67 (d,  $J=4.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{D}_2\text{O}$ )  $\delta$  172.1, 131.8, 120.1, 53.9, 33.2, 17.6.

**Compound 1 (isoalliin).** To a solution of compound **4** (0.4 g, 2.5 mmol) in  $\text{H}_2\text{O}$  (35 mL) at  $0\text{ }^{\circ}\text{C}$  was added 30%  $\text{H}_2\text{O}_2$  (0.29 mL, 2.6 mmol). The mixture was stirred at room temperature for 16 h and concentrated in vacuo to give 0.43 g (99%) of compound **1**:  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ )  $\delta$  6.69-6.54 (m, 2H), 6.47-6.39 (m, 2H), 4.11-4.01 (m, 2H), 3.57-3.15 (m, 4H), 1.91 (d,  $J=6.9$  Hz, 3H), 1.87 (d,  $J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{D}_2\text{O}$ )  $\delta$  171.6, 171.5, 143.6, 142.8, 130.4, 129.1, 52.5, 51.1, 50.5, 49.9, 17.4, 17.3.

**Acknowledgments.** This research was supported by a grant from KRIBB Research Initiative Program.

## References

- (a) Lau, B. H. S.; Tadi, P. P.; Tosk, J. M. *Nutr. Res.* **1990**, *10*, 937. (b) Singh, S. V.; Pan, S. S.; Srivastava, S. K.; Xia, H.; Hu, X.; Zaren, H. A.; Orchard, J. L. *Biochem. Biophys. Res. Commun.* **1998**, *244*, 917.
- (a) Kyo, E.; Uda, N.; Suzuki, A.; Kakimoto, M.; Ushujima, M.; Kasuga, S.; Itakura, Y. *Phytomedicine* **1998**, *5*, 259. (b) Siegers, C.-P.; Robke, A.; Pentz, R. *Phytomedicine* **1999**, *6*, 13.
- Ishikawa, K.; Naganawa, R.; Yoshida, H.; Iwata, N.; Fukuda, H.; Fujino, T.; Suzuki, A. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 2086.
- Weber, N. D.; Anderson, D. O.; North, J. A.; Murray, B. K.; Lawson, L. D.; Hughes, B. G. *Planta Med.* **1992**, *58*, 417.
- (a) Mirhadi, S. A.; Singh, S. *Ind. J. Exp. Biol.* **1991**, *29*, 162. (b) Morimitsu, Y.; Morioka, Y.; Kawakishi, S. *J. Agric. Food Chem.* **1992**, *40*, 368.
- (a) Prasad, K.; Laxdal, V. A.; Yu, M.; Raney, B. L. *Mol. Cell. Biochem.* **1995**, *148*, 183. (b) Yin, M.-C.; Cheng, W.-S. *J. Agric. Food Chem.* **1998**, *46*, 4097.
- (a) Spare, G.; Virtanen, I. *Acta Chem. Scand.* **1963**, *17*, 641. (b) Stoll, A.; Seebeck, E. *J. Experientia* **1947**, *3*, 114. (c) Virtanen, I.; Matikkala, J. *Acta Chem. Scand.* **1959**, *13*, 1898. (d) Thomas, J.; Parkin, L. *J. Agric. Food Chem.* **1994**, *42*, 1632.
- (a) Carson, J. F.; Lundin, R. E.; Lukes, T. M. *J. Org. Chem.* **1966**, *31*, 1634. (b) Krest, I.; Glodek, J.; Keusgen, M. *J. Agric. Food Chem.* **2000**, *48*, 3753.
- (a) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135. (b) Breu, W. *Phytomedicine* **1996**, *3*, 293.
- Nishimura, H.; Mizuguchi, A.; Mizutani, J. *Tetrahedron Lett.* **1975**, 3201.
- Parry, R. J.; Sood, G. R. *J. Am. Chem. Soc.* **1989**, *111*, 4514.
- Namyslo, J. C.; Stanitzek, C. *Synthesis* **2006**, 3367.
- Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503.
- Ford, P. W.; Narbut, M. R.; Belli, J.; Davidson, B. S. *J. Org. Chem.* **1994**, *59*, 5955.