A NEW METHOD FOR THE SYNTHESIS OF 5- AND 6-MEMBERED 2-THIOXO-1,3-O,N-HETEROCYCLES

Ge Li* and Takahito Ohtani

Fukui Research Laboratory, Rengo Co., Ltd., 10-8-1 Jiyugaoka Kanazu-Cho, Sakai-Gun, Fukui 919-06, Japan

Abstract — Various 1,3-oxazolidine-2-thiones and tetrahydro-1,3-oxazine-2-thiones are prepared by reacting hydrogen peroxide with a mixture of amino alcohols, carbon disulfide and base in a water-miscible organic solvent. The yields of the heterocyclic products are in the range of 80–100%, considerably higher than those reported in literatures.

2-Thioxo-1,3-O,N-heterocycles have found many applications in biology, pharmacology and chemical synthesis. These cyclic compounds are generally prepared by reacting amino alcohols, usually in the presence of base, with carbon disulfide, and a dehydrosulfurization reagent that is traditionally employed in the synthesis of isothiocyanates, for instance, ethyl chloroformate and lead nitrate. The yields of the cyclic products are often in the range of 30–80%. Apart from the uneconomical aspects, these reactions involve some toxic substances either as the initial raw materials or as the by-products, which cause great environmental concerns nowadays.

In our early work of synthesizing isothiocyanates from primary amines, we found that hydrogen peroxide was an efficient, economical and safe dehydrosulfurization reagent. Since it is a common knowledge that both 1,3-oxazolidine-2-thiones and tetrahydro-1,3-oxazine-2-thiones can be readily made from 2- and 3-hydroxyl isothiocyanates respectively through either spontaneous or base-induced self-condensation, we anticipate that hydrogen peroxide, in a similar manner to the preparation of isothiocyanates, can be applied well to the synthesis of those 5- and 6-membered 2-thioxo-1,3-O,N-heterocycles (scheme 1).

\[
\begin{align*}
R\text{OH} & \xrightarrow{\text{CS}_2, H_2O_2, \text{base}} \xrightarrow{\text{cyclization}} R\text{NCS} \\
R & = -(CR^1R^2)_n^+; \ n = 2, 3.
\end{align*}
\]

Scheme 1

In this paper we report a general method for the preparation of 1,3-oxazolidine-2-thiones and tetrahydro-
1,3-oxazine-2-thiones. This method essentially consists of the reaction of hydrogen peroxide with a mixture of amino alcohol, carbon disulfide and base in a water-miscible organic solvent such as methanol, ethanol and tetrahydrofuran. Unlike in the synthesis of isothiocyanates described in our early work,\textsuperscript{8-11} it is unnecessary to maintain the reaction at below room temperature. Actually, we can run the reactions in a wide range of temperatures from 10 to 70°C without observing obvious differences in respect to the yield. The yields of the cyclic products are in the range of 80-100\%, considerably higher than those reported in literatures (table 1).

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<th>Table 1. Yields of 2-thioxo-1,3-O,N-heterocycles.</th>
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\textsuperscript{a} (2R)-(\textdagger)-2-Amino-1-butanol was used. \textsuperscript{b} (1R,2S)-(\textdagger)-Norephedrine was used. \textsuperscript{c} liquid at rt.

**EXPERIMENTAL**

All the chemical reagents and solvents obtained from commercial sources were used as received. Melting points were determined on a BÜCHI 535 melting point apparatus without temperature correction. \textsuperscript{1}H and \textsuperscript{13}C NMR were recorded on either a JEOL EX90A or a JEOL EX270 spectrometer. Fuji Silysia BW-200 silica gel was used for the liquid chromatography.

**General procedure:** To a stirred solution of amino alcohol (0.05 mol) and triethylamine (5.06 g, 0.05 mol) in methanol (50 mL) was added carbon disulfide (3.81 g, 0.075 mol) with ice cooling. The mixture was stirred at rt for 0.5 h, after which hydrogen peroxide (30\%, 8-10 mL, 0.075-0.1 mol) was added at such a rate that reflux of the solvent was observed until the upper solution of the reaction mixture no longer became cloudy by addition of extra hydrogen peroxide. The reaction mixture was then cooled...
down to rt, filtered and concentrated under reduced pressure. To this residue sufficient amount of an aqueous sodium hydroxide solution (1 M) was added to free the triethylamine that was subsequently removed in vacuo. The mixture was finally neutralized with hydrochloric acid (5 M), filtered and evaporated under reduced pressure to dryness. Purification was carried out either by recrystallization or liquid chromatography on a silica gel.

1,3-Oxazolidine-2-thione (a): This compound was obtained as a colorless crystal after recrystallization from benzene-hexane in 90% yield, mp 97.1-97.9°C; \(^1\)H NMR (90 MHz, CDCl\(_3\)) \(\delta\): 3.84 (t, 2H, \(J = 8.8\) Hz), 4.74 (t, 2H, \(J = 8.7\) Hz), 8.33 (br s, 1H, NH); \(^13\)C NMR (22.4 MHz, CDCl\(_3\)) \(\delta\): 44.2, 70.5, 190.3.

5-Hydroxymethyl-1,3-oxazolidine-2-thione (b): This compound was obtained as a colorless liquid that crystallized slowly on standing after liquid chromatography, using acetonitrile/chloroform (4:6) mixed solvent as the eluant, in 100% yield, mp 57.6-59.6°C; \(^1\)H NMR (270 MHz, D\(_2\)O) \(\delta\): 2.24 (s, 1H, OH), 3.64 (dd, 1H, \(J = 7.2, 10.4\) Hz), 3.74 (dd, 1H, \(J = 4.7, 12.8\) Hz), 3.87-3.95 (m, 2H), 5.08-5.17 (m, 1H); \(^13\)C NMR (67.8 MHz, D\(_2\)O) \(\delta\): 46.3, 62.7, 84.6, 189.4.

(4R)-4-Ethyl-1,3-oxazolidine-2-thione (c): This compound was obtained as a colorless liquid that became semi-crystal on standing after liquid chromatography, using chloroform/acetone (9:1) mixed solvent as the eluant, in 89% yield; \(^1\)H NMR (90 MHz, CDCl\(_3\)) \(\delta\): 0.99 (t, 3H, \(J = 7.3\) Hz), 1.54-1.86 (m, 2H), 3.90-4.30 (m, 1H), 4.76 (t, 1H, \(J = 8.9\) Hz), 8.70 (br s, 1H, NH); \(^13\)C NMR (22.4 MHz, CDCl\(_3\)) \(\delta\): 9.5, 27.5, 58.1, 75.1, 189.5.

(4S, 5R)-4-Methyl-5-phenyl-1,3-oxazolidine-2-thione (d): This compound was obtained as a colorless liquid that crystallized on standing after liquid chromatography, using chloroform/acetone (9:1) mixed solvent as the eluant, in 100% yield, mp 83.4-83.9°C; \(^1\)H NMR (90 MHz, CDCl\(_3\)) \(\delta\): 0.86 (d, 3H, \(J = 6.6\) Hz), 4.31-4.63 (m, 1H), 5.96 (d, 1H, \(J = 8.8\) Hz), 7.20-7.46 (m, 5H), 8.87 (br s, 1H, NH); \(^13\)C NMR (22.4 MHz, CDCl\(_3\)) \(\delta\): 16.3, 55.8, 86.4, 126.0, 128.4, 128.7, 133.5, 188.8.

Tetrahydro-1,3-oxazine-2-thione (e): The concentrated crude product was dispersed in ethanol (100 mL) and filtered. To this ethanol solution was added sodium hydroxide (solid, 4 g, 0.1 mol), after which it was stirred at rt for 2 h. After the solvent and the free triethylamine were removed by evaporation, the remaining residue was dissolved in water (50 mL), neutralized with hydrochloric acid (5 M), decolorized with active carbon powder and finally evaporated under reduced pressure to dryness. Recrystallization from benzene-cyclohexane resulted in 4.93 g (84%) of colorless crystal, mp 126.5-127.3°C; \(^1\)H NMR (90 MHz, CDCl\(_3\)) \(\delta\): 1.97-2.23 (m, 2H), 3.32-3.49 (m, 2H), 4.40 (t, 2H, \(J = 5.4\) Hz), 8.71 (br s, 1H, NH); \(^13\)C NMR (22.4 MHz, CDCl\(_3\)) \(\delta\): 19.8, 40.5, 68.1, 187.0.

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REFERENCES


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