A New Synthesis of DL-5-Vinyloxazolidine-2-thione, a Natural Antithyroid Factor

C. Gardrat* and L. Latxague

Laboratoire Chimie Appliquée, Université Bordeaux I,
351 Cours de la Libération, F-33405 - Talence, France

J. P. Picard

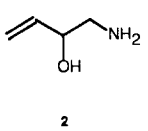
Laboratoire de Chimie Organique et Organométallique, URA 35 du CNRS, Université Bordeaux I,
351 Cours de la Libération, F-33405 - Talence, France

Received December 13, 1989

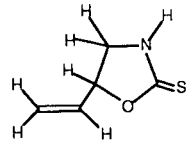
A new procedure for the preparation of DL-5-vinyloxazolidine-2-thione (goitrin) **3** *via* a facile and practical synthesis of the key intermediate DL-1-amino-3-buten-2-ol **2** is described.

J. Heterocyclic Chem., **27**, 811 (1990).

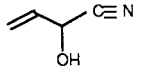
Goitrin **3** is the trivial name for 5-vinyloxazolidine-2-thione, a compound present in several species of *Brassicae* and *Cruciferae* such as rutabaga, turnip, cabbage and rape. When consumed by humans or animals, it presents an antithyroid activity both in its enantiomeric or racemic forms [1,2]. Administration of **3** to rats leads to a depression of brain norepinephrine and to an elevation of heart adrenal dopamine [3].



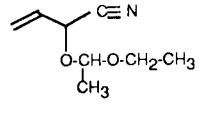
2



3



4



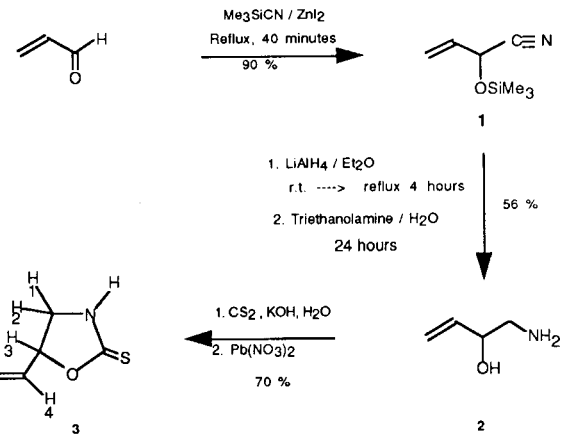
5

Goitrin has been obtained in good yield by converting 1-amino-3-buten-2-ol **2** with aqueous alkali and carbon disulfide into a dithiocarbamate subsequently treated by lead nitrate [4]. However, to our knowledge, two main methods only for preparing **2** have been reported which appear to be quite tedious. Reaction of butadiene monoxide with aqueous ammonia leads to two regioisomers which have to be separated *via* fractional crystallization of their oxalates [3,4]. More recently, a new multistep synthesis of **2** was described [5]: the hydroxynitrile **4** obtained by adding hydrogen cyanide, generated *in situ*, to acrolein was protected as a ketal **5** which was reduced with aluminium hydride in tetrahydrofuran. The aminoalcohol **2** was isolated after removal of the protecting group with aqueous hydrochloric acid, and treatment with potassium hydroxide.

These syntheses suffer from many drawbacks as for instance the use of a very expensive starting material (butadiene monoxide), dangerous reagents (hydrogen cyanide) or, more severely, the difficulty to recover the pure aminobutenol **2** due to its high solubility in water.

These disadvantages were circumvented by developing an alternative synthesis of **2** based on the use of (i) trimethylsilyl cyanide, a readily accessible reagent on large scale [6,7] and of (ii) a new procedure for recovering aminoalcohols from aqueous solutions [8] which has been very efficient in this case (Scheme 1).

Scheme 1



Addition of trimethylsilyl cyanide to acrolein in the presence of a catalytic amount of zinc iodide according to reported procedure [9] gave the adduct **1** in quantitative yield. This protected cyanohydrin was reduced directly into the corresponding aminoalcohol **2** with the aid of lithium aluminium hydride [10]. Then the very soluble aminoalcohol **2** was easily recovered by using the triethanolamine/water hydrolytic system instead of the classical water/sodium hydroxide/water system. Finally, **2** was converted into goitrin **3** in good yield according to a previously reported procedure [4] with slight modifications.

EXPERIMENTAL

Mineral products except zinc iodide and lithium aluminium hydride were purchased from Prolabo (France). All organic reagents, zinc iodide and lithium aluminium hydride purchased from Janssen Chimica or Aldrich Chemical Company were of analytical grade. Trimethylsilyl cyanide was prepared according to the literature [7]. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were performed by "ATX Laboratoires" (Nanterre, France); ir spectra were obtained on a Perkin-Elmer 157 apparatus; high resolution mass spectrum was recorded on a VG model 70/70-F spectrometer; pmr spectra were taken on a Perkin-Elmer Hitachi R-24 spectrometer; the pmr and cmr spectra of goitrin were also obtained using a Bruker AC-250 spectrometer.

2-(Trimethylsilyloxy)-3-butenenitrile (**1**).

A mixture of freshly distilled acrolein (12.7 g, 226 mmoles), trimethylsilyl cyanide (22.5 g, 226 mmoles) and a minute amount of zinc iodide (5 mg) was heated for 40 minutes under reflux. The reaction was followed by infra red; after the disappearence of the carbonyl band, the orange colored solution was distilled under reduced pressure to give **1** (15 g, 90%) as a colorless liquid, bp 72°/10 Torr (lit [11] bp 84°/35 Torr); ir (film): ν 3000, 1650, 1250, 840, 760 cm^{-1}; pmr (carbon tetrachloride/benzene): δ 0.4 (s, 9H, $Si(CH_3)_3$), 4.85-5.15 (m, 1H, CHO), 5.20-6.25 (m, 3H, $CH_2=CH$).

1-Amino-3-buten-2-ol (**2**).

A mixture of **1** (19 g, 120 mmoles) and anhydrous ether (200 ml) was slowly added during 3 hours to a suspension of lithium aluminium hydride (9.5 g, 250 mmoles) in anhydrous ether (400 ml). After refluxing during 75 minutes, the reaction mixture was cooled to room temperature. Triethanolamine (39 g, 261 mmoles) was then added under stirring over a period of 1 hour, followed by distilled water (9.5 g, 527 mmoles) over a period of 25 minutes. A greyish mass was formed and stirring was continued for 24 hours, during which time the solid got a sandy consistency. The mixture was then filtered, the solid washed with ether (6 x 50 ml). The organic phase was dried (magnesium sulfate) and the solvent removed under vacuum. The yellow viscous liquid was distilled under reduced pressure to give **2** (6 g, 56%) as a colorless liquid, bp 46°/0.3 Torr (lit [5] bp 45°/0.5 Torr); solidification as white deliquescent plates occurred in the cold; ir (film): ν 3300, 3100, 1600 cm^{-1}; pmr (carbon tetrachloride/DMSO-d_6): δ 2.4-2.6 (m, 2H, CH_2-NH_2), 2.65 (s, 3H, NH_2, OH), 3.85 (m, 1H, CHO), 4.8-6.0 (m, 3H, $CH_2=CH$).

5-Vinyloxazolidine-2-thione (**3**).

In a flask equipped with a condenser, a cold solution of potassium hydroxide (3.65 g, 65 mmoles) in water (20 ml) and **2** (5.5 g, 63.2 mmoles) in dioxane (50 ml) was magnetically stirred. Carbon disulfide (4.9 g, 64.4 mmoles) was added and the solution turned orange. Five minutes later, potassium hydroxide (3.65 g, 65 mmoles) in water (30 ml) and lead nitrate (21 g, 63.4 mmoles) in water (60 ml) were successively added. The brown solution was stirred and heated at 60° for one hour. The black thin precipitate was discarded by filtration and washed with hot water (100 ml). The yellowish solution was evaporated *in vacuo* and the powdered residue extracted with boiling benzene (300 ml). The solution was then filtered and concentrated to 75 ml. The flask was frozen and goitrin was obtained as a light brown powder, 5.7 g (70%); recrystallization from ether afforded a white solid, mp 63.3° (lit [4] mp 64-65°); pmr (deuteriochloroform): δ 3.51-3.61 (m, 1H, H_1), 3.96-4.00 (m, 1H, H_2), 5.34-5.53 (m, 3H, H_3, H_5, H_6), 5.91-6.05 (m, 1H, H_4), 8.65 (s, 1H, NH); cmr (deuteriochloroform): δ 49.27 (CH_2), 83.51 (CH), 120.69 (=CH), 133.15 (CH_2=), 189.09 (C=S); high resolution ms: mass Calcd. for C_5H_7NOS: m/z 129.02483. Found: 129.02476.

Anal. Calcd. for C_5H_7NOS: C, 46.48; H, 5.46; N, 10.84; S, 24.83. Found: C, 46.65; H, 5.50; N, 10.74; S, 24.67.

REFERENCES AND NOTES

[1] C. H. Van Etten and H. L. Tookey, CRC Handbook of Naturally Occurring Food Toxicants, CRC Series in Nutrition and Food, CRC Press Inc., Boca Raton, Florida, 1983, p 115.

[2] H. L. Tookey, C. H. Van Etten and M. E. Daxenbichler, Toxic Constituents of Plant Foodstuffs, 2nd Ed, I. E. Liener ed, Academic Press, New York, 1980, Chapter 4.

[3] N. Zenker, L. S. Hubbard and J. Wright, *J. Nat. Prod.*, **5**, 862 (1988).

[4] M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950).

[5] L. Brandsma, K. D. Bos, M. A. Keegstra and H. D. Verkruijsse, *Rec. Trav. Chim.*, **107**, 132 (1988).

[6] M. G. Voronkov, J. K. Roman and E. A. Maletina, USSR Patent 596,589 (1978); *Chem. Abstr.*, **89**, 24525 (1978).

[7] J. P. Picard, A. A. Elyusufi, R. Calas, J. Dunoguès and N. Duffaut, *Organometallics*, **3**, 1660 (1984).

[8] J. Powell, N. James and S. J. Smith, *Synthesis*, 338 (1986).

[9] D. A. Evans, L. K. Truesdale and G. L. Carroll, *J. Chem. Soc., Chem. Commun.*, 55 (1973); D. A. Evans, G. L. Carroll and L. K. Truesdale, *J. Org. Chem.*, **39**, 914 (1974).

[10] We should note that the reduction of the non-protected cyanohydrin **1** required the use of aluminium hydride, lithium aluminium hydride leading to an isomerized product.

[11] R. M. Jacobson, G. P. Lahm and J. W. Clader, *J. Org. Chem.*, **45**, 395 (1980).