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An improved synthesis of the antithyroid factor DL-goitrin≠

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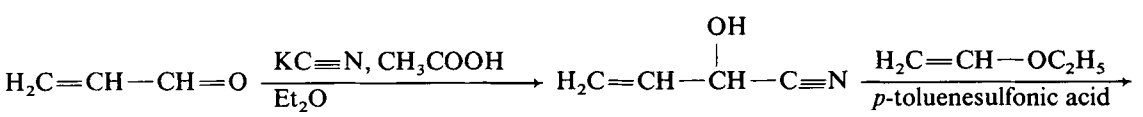
Abstract. DL-1-Amino-3-buten-2-ol $H_2C=CH-CH(OH)-CH_2NH_2$ has been synthesized in a satisfactory overall yield by reduction of the protected cyanohydrin $H_2C=CH-CH(OR)-C\equiv N$ [R = $-CH(CH_3)OC_2H_5$] with aluminum hydride, followed by removal of the protecting group with aqueous hydrochloric acid and treatment with potassium hydroxide. The amino alcohol is a key intermediate in a synthesis of the antithyroid factor goitrin reported previously.

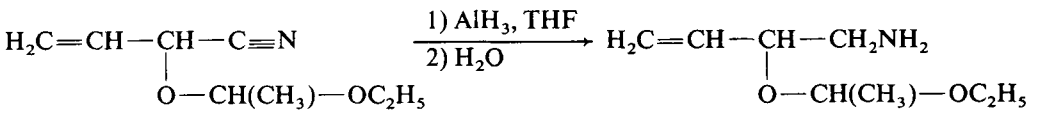
Goitrin[1] is the trivial name for 5-vinyloxazolidine-2-thion (**6**), a compound showing antithyroid activity[2] in several species of *Brassicae* and *Cruciferae*, including turnip, cabbage and rape. Both the racemic mixture of **6** and the naturally occurring L-isomer may cause simple goiter upon ingestion. The compound **6** has been obtained in a good yield by converting 1-amino-3-buten-2-ol (**5**) with aqueous alkali and carbon disulfide and subsequently treating the dithiocarbamate $H_2C=CH-CH(OH)-CH_2NH(CS)SK$ with lead nitrate[3]. Reaction of butadiene 1,2-epoxide with aqueous ammonia gave **5** in 45% yield, in addition to its isomer, 2-amino-3-buten-1-ol. The 1-isomer **5** was obtained from the mixture via fractional crystallization of the oxalates. The most serious draw-back of this synthesis, however, is the difficult accessibility of butadiene 1,2--epoxide. It is commercially available but the price is very high.

Since, for toxicity studies, a large quantity of DL-goitrin was required, we developed an alternative synthesis for the key intermediate DL-1-amino-3-buten-2-ol (**5**). In view of the good yield (~70%) of DL-goitrin, obtained from this amino alcohol, our synthesis, depicted in the scheme below, may be considered as a formal synthesis of DL-goitrin.

In our first attempts to prepare the hydroxy nitrile **2** we followed the original procedure[4], which gave an impure product in a moderate yield. Distillative purification gave rise to extensive decomposition. Particularly the water, still present in the undistilled product, caused serious difficulties (sluggish and incomplete reaction, formation of intractable brown by-products) during the acid-catalysed protection of the OH function with ethyl vinyl ether. For these reasons, we developed a modified procedure for the hydroxy nitrile **2**, consisting of addition of glacial acetic acid (excess) to a



(1) (2)



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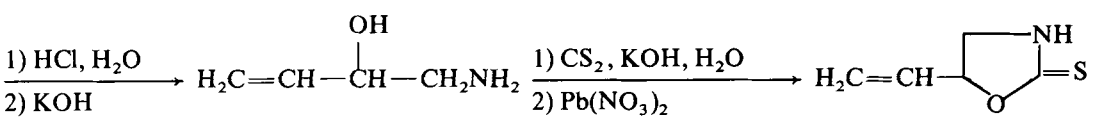

(5) (6)

≠ Dedicated to Prof. *G. J. M. van der Kerk* on the occasion of his 75th birthday.

mixture of dry potassium cyanide (corresponding excess), freshly distilled acrolein and dry diethyl ether, initially cooled below 0°C. The reaction with ethyl vinyl ether of the undistilled product, obtained by filtration and evaporative removal of the solvent, proceeded smoothly and afforded pure **3** in 64–70% yields. The latter compound turned out to be very base-sensitive: dilute aqueous potassium hydroxide, for example, caused a fast and complete isomerization to $CH_3CH=C(C\equiv N)-O-CH(CH_3)OC_2H_5$. This base sensitivity explains why attempts to reduce the nitrile function in **3** with $LiAlH_4$ failed completely. Application of *Browns'* method[5], using aluminum hydride, however, gave the protected aminobutenol **4**, in a good yield. Deprotection of **4** with aqueous hydrochloric acid, followed by addition of an excess of potassium hydroxide, afforded 1-amino-3-buten-2-ol (**5**) in overall yields of 35 to 40%.

Experimental

1. Preparation of the cyanohydrin **2** *and its addition to ethyl vinyl ether*

A mixture of 3.0 mol (148 g) of dry, powdered potassium cyanide and 3 l of dry diethyl ether was cooled to −10°C and freshly distilled acrolein (2.0 mol, 106 g) was added. 100% Acetic acid (3.0 mol, 180 g) was added portionwise over 30 min while maintaining the temperature between −10 and 0°C. A very thick suspension was gradually formed (requiring the use of an efficient stirrer). After the addition, the cooling bath was removed and the temperature allowed to rise to 15°C. Stirring at this temperature was continued for an additional 1½ h, after which the reaction mixture was subjected to suction filtration through sintered glass (G-2 filter). The solid was rinsed well with dry ether. The almost colourless solution was then concentrated under reduced pressure (in view of the presence of HC≡N in the solution, all operations should be carried out in a well-ventilated hood!). To 3.5 mol (excess) of freshly distilled ethyl vinyl ether was added, with efficient stirring at −5°C, 500 mg of *p*-toluenesulfonic acid (monohydrate or anhydrous). Subsequently, the crude cyanohydrin **2** was added in 5-g portions over ~30 min, while maintaining the temperature between 0 and +5°C (a bath with dry ice and acetone is indispensable!). After an additional 30 min (at +5°C), the mixture was cooled again to −5°C and a solution of 5 g of potassium carbonate in 50 ml of water was added in one portion with very vigorous stirring (for 1–2 min). The layers were then separated and the aqueous layer extracted twice with ether. After drying over anhydrous potassium carbonate, the organic solution was filtered and the filtrate concentrated under reduced pressure. The almost colourless liquid remaining after removal of the ether reduced pressure was carefully distilled through a 40-cm Vigreux column: prior to distillation, 1 g of triethylamine was added to prevent decomposition of **2** by traces of acid which might adhere to the glass of the distillation flask and column. The fraction collected between 75 and 95°C/15 mm Hg, n_D^{20} 1.421, appeared to be sufficiently pure (almost 95% **3** according to ^{1}H NMR). The yields were 64 to 70%. There was a considerable, somewhat viscous, residue, The ^{1}H NMR spectrum* ($CDCl_3$) of **3** showed the following groups of signals: 1.0–1.4 (m, 6H); 3.2–3.8 (m, 2H); 4.7–5.1 (m, 2H); 5.2–6.1 (m, 3H).

2. Reduction of the protected cyanohydrin **3** *with aluminum hydride*

Lithium aluminum hydride (1.2 mol, 46 g) was dissolved in 1.5 l of dry tetrahydrofuran (THF). A cold (0°C) mixture of 100% sulfuric acid (0.6 mol, 59 g) and 300 ml of THF was added dropwise over 1 h with efficient stirring (the drops should fall directly into the solution), while maintaining the temperature between 0 and 5°C. After an additional 1½ h, during which period the temperature was allowed to rise to 20°C, the suspension was cooled to 0°C and 150 ml of water was added dropwise over 45 min with vigorous stirring and cooling between 10 and 20°C. The suspension was then filtered through a sintered glass funnel and the solid rinsed well with THF. The light-yellow filtrate was successively dried over 100 g of anhydrous K_2CO_3 (stirring for 1 h, then filtration and rinsing with THF) and 50 g of machine-powdered KOH (shaking or stirring for 15 min, then filtration). The greater part of the THF was then distilled off at atmospheric pressure through a 40-cm Vigreux column and the remaining liquid carefully distilled. The protected aminobutenol **4**, b.p. ~80°C/15 mm Hg, n_D^{20} 1.441, was obtained in 72–78% yield. The small first fraction contained a small amount of water. The ^{1}H NMR spectrum* ($CDCl_3$) of (**4**) showed the following groups of signals: 1.0–1.3 (m, 8H); 2.7 (d, *J* 5 Hz, 2H); 3.2–4.1 (m, 3H); 4.6 (q, *J* 5 Hz, 1H); 4.9–6.0 (m, 3H).

3. Deprotection of **4** *and isolation of 1-amino-3-buten-2-ol* (**5**)

Concentrated aqueous hydrochloric acid (37%, corresponding to 0.53 mol, slight excess) was added in small portions to a stirred mixture of 0.50 mol (79.5 g) of **4** and 30 ml of water, while maintaining the temperature between 0 and +5°C. The acidic solution was then warmed to 30°C and the volatile products (acetaldehyde and ethanol) removed *in vacuo* on the rotary evaporator (the bath temperature was gradually raised to 80°C). KOH pellets (50 g) were subsequently added in portions with vigorous swirling and cooling in ice water. The water was then thoroughly removed under reduced pressure (rotary evaporator) and the aminobutenol extracted from the resulting mixture with small portions of diethyl ether (several extractions had to be carried out). The ethereal solution was dried by shaking with a sufficient amount of machine powdered KOH and subsequently concentrated *in vacuo*. Distillation of the remaining syrup through a short Vigreux column gave 1-amino-3-buten-2-ol, b.p. ~45°C/0.5 mm Hg. The distillate solidified in the receiver or in the condensor. The ^{1}H NMR spectrum* ($CDCl_3$) of **5** showed the following groups of signals: 2.6 (d, *J* 6 Hz, 2H); 3.4 (s, 3H); 3.9–4.3 (m, 1H); 5.0–5.4 (m, 1H); 5.5–6.1 (m, 2H).

Acknowledgement

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* All ^{1}H NMR spectra were recorded on a Varian EM 360 spectrometer.