A Simple Synthesis of the Ripening Agent 1-Aminocyclopropane-1-carboxylic Acid

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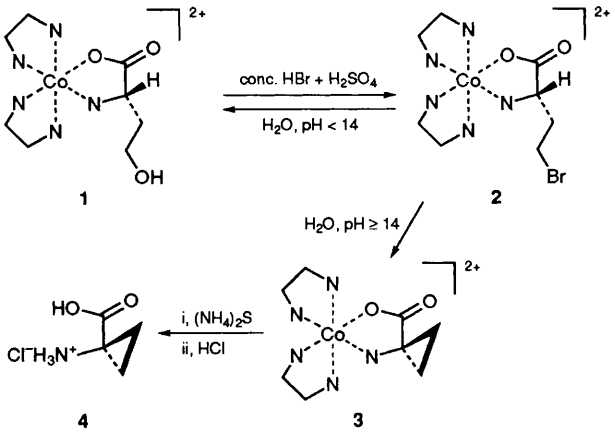
Conversion of chelated homoserine to 2-amino-4-bromobutyrate and treatment with aqueous base leads directly to chelated 1-aminocyclopropane-1-carboxylate.

1-Aminocyclopropane-1-carboxylic acid (acc) is a naturally occurring amino acid which is one of the intermediates in the biosynthesis of ethylene produced during the ripening of fruit.[1,2] While the structures of acc and its homologues are quite simple, the organic syntheses often devised to produce them are not.[3]

We now report that the cyclopropane amino acid may be synthesized from homoserine simply by using the cobalt(III) bis(ethane-1,2-diamine) [$Co(en)_2$] moiety as a protecting and activating group for the amino acids used throughout the synthesis. Firstly, *N*,*O*-chelated homoserine **1**[4] is treated with concentrated hydrobromic and sulfuric acids (3 : 1 v : v) for one hour at 90 °C. The products are added to ethanol, by-products filtered off, and *N*,*O*-chelated 2-amino-4-bromobutyrate complex **2** (60%) is precipitated by addition of ether. The ^1H NMR spectrum of this substance† is similar to that published for the free acid.[5] In this reaction the metal ion functions as a protecting group, preventing the formation of α-aminobutyrolactone which is the usual product in acid solution[6] and allows the homoserine to be brominated directly, a process which has not been achieved by regular organic routes.[7] Chelation of the amino acid also activates the methine group to proton exchange in basic conditions.[8] Coordination of both the carboxy and the amino groups is required for this activation, a combination of ester character and ammonium ion character.

† ^1H NMR spectrum (δ, D_2O): 2.36 (m, β-CH_2) 2.78–2.85 (m, en–CH_2–) 3.80 (m, γ-CH_2) and 3.90 (m, α-CH).



Scheme 1

In 2 mol dm^{-3} NaOH solution the *N*,*O*-chelated 2-amino-4-bromobutyrate complex is deprotonated and the resulting carbanion undergoes intramolecular cyclization to form the corresponding complex **3** of acc as the major product (*ca.* 70%). This is readily isolated by ion-exchange chromatography on Dowex (50W × 2). Intermolecular substitution of the bromide is competitive with cyclization and some chelated homoserine is formed. The complete synthesis is summarized in Scheme 1 but only the Λ isomers are displayed. The acc complex was recrystallized as the dithionate hemihydrate salt and characterized by NMR spectroscopy and microanalysis.‡ The NMR spectra display the characteristic cyclopropyl resonances for ^{13}C at δ *ca.* 19 and for ^{1}H at δ *ca.* 1.5.‡ The spectra show that the product is consistent with an enantiomeric mixture not a pair of diastereoisomers as is the starting material. The homoserine complex has stereogenic centres at cobalt and carbon and exists as a mixture of Λ- and Δ-diastereoisomers but the 1-aminocyclopropane-1-carboxylate complex only has cobalt as the stereogenic centre so the ^{13}C diastereotopicity of the cyclopropyl ring arises from coordination of acc to the chiral metal complex.

When an aqueous solution of the acc complex was treated with ammonium sulfide solution the metal ion was reduced and precipitated as cobalt(II) sulfide and the solution filtered. The filtrate was acidified and chromatographed on Dowex 50W × 2 ion exchange resin (to remove the ethanediamine) and a white solid was isolated from the eluate by rotary evaporation of most of the solvent. The NMR spectra of this substance are in accord with published data from authentic 1-aminocyclopropane-1-carboxylic acid **4**.[5]

The activating and protecting chemistry described here not only allows a simple synthesis of the cyclopropane ripening agent but would promote the synthesis of more complex derivatives from substituted homoserine or appropriate-2-oxo and hydroxy amino acids. Without this activation intermolecular substitution predominates to regenerate the parent homoserine.[9]

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‡ Elemental analyses were satisfactory. ^{1}H NMR (δ, D_2O): 1.3–1.5 (br m, cyclopropyl-$[CH_2]_2$), 2.70, 2.87 (m, en-$[CH_2]_2$); ^{13}C NMR (δ, D_2O): 18.9, 19.4 (cyclopropyl-$[CH_2]_2$-), 39.4 (quat. C), 44.5, 45.7, 45.8, 46.4, (en-$[CH_2]_2$-) 187.0 (CO_2). The cyclopropyl ring methylene groups contain two diastereotopic carbon atoms and four diastereotopic protons.

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