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Demetallation and Esterification Reactions of Heterocyclic Amino Acid Complexes

SOON-BENG TEO and SIANG-GUAN TEOH

School of Chemical Sciences, Universiti Sains Malaysia, Penang, Malaysia

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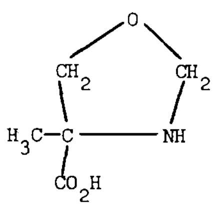
Abstract

The copper(II) complex of 4-methyloxazolidine-4'-carboxylic acid and the nickel(II) complex of 3N,7N-(1,3,5,7-tetraazabicyclo[3.3.1]nonyl)diacetic acid were prepared and then treated with sodium borohydride to form the sodium salts of the respective acids. The saturated heterocyclic rings of the acids are retained in the reactions.

The methyl esters of the acids were subsequently prepared under anhydrous conditions and characterized by gas chromatography/mass spectrometry (GC/MS).

Introduction

As a continuation of our studies on the reactions of bis(α-aminoacidato)metal(II) complexes with aldehydes [1–3] we have investigated the condensation reactions of bis(α-alaninato)copper(II) [4] and bis(glycinato)nickel(II) [5] respectively with formaldehyde. The former reaction (at pH 8.0) results in the formation of the copper(II) complex of 4-methyloxazolidine-4'-carboxylic acid, **1**, while the latter reaction yields the nickel(II) complex of 3N,7N-(1,3,5,7-tetraazabicyclo[3.3.1]nonyl)diacetic acid, **2**. The structures of both these complexes have been established by X-ray crystallography [4, 5].



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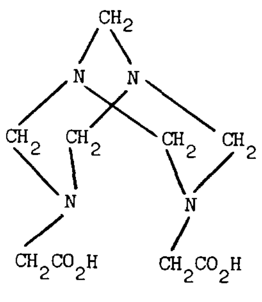

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Treatment of the metal(II) complexes of **1** and **2** with H_2S causes rupture of the heterocylic rings to give the metal-free α-methylserine and glycine respectively [6]. However, recent investigations [7, 8] have shown that removal of the coordinated metal ion from heterocyclic amino acid complexes may be accomplished without cleavage of the heterocyclic ring systems. The demetallating agent utilized in the reactions was sodium borohydride which has been known to reduce various metal salts in aqueous solutions to their metallic elements and their hydrides [7–10].

In this paper, we report the preparation of the copper(II) complex of **1** and the nickel(II) complex of **2** and their reactions with sodium borohydride leading to the removal of their respective metal ions without rupture of their heterocyclic ring systems. The methyl esters of **1** and **2** were subsequently prepared and characterized by gas chromatography mass spectrometry.

Experimental

Reagents

Methanol was dried by formation of Grignard reagent with magnesium turnings followed by refluxing and distillation of the alcohol. Chloroform was dried by refluxing over and distilling from phosphorous pentoxide. Gaseous hydrogen chloride was generated by the reaction of concentrated sulphuric acid with sodium chloride. Commercial ammonia was dried with calcium oxide.

All other reagents were reagent grade chemicals.

Synthesis

(a) Bis(4-methyloxazolidine-4'-carboxylato)copper(II) Dihydrate

30 cm^3 of a 40% w/v solution of formaldehyde (0.4 mol) was added to a 30 cm^3 aqueous solution of bis(α-alaninato)copper(II) (2.4 g, 0.01 mol). The pH of the reaction mixture was adjusted to 8.0 by addition of concentrated ammonia solution after which the whole was left standing for a week when

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deep blue crystals appeared. These were filtered, washed successively with cold distilled water, ethanol and acetone and were finally dried under vacuum at 50 ℃ for 5 h. Yield 2.5 g (69%). *Anal.* Found: C, 33.2; H, 5.7; N, 7.8. Calcd. for $C_{10}H_{20}N_2O_8Cu$: C, 33.4; H, 5.6; N, 7.8%.

(b) [3N,7N-(1,3,5,7-tetraazabicyclo[3.3.1]nonyl)-diacetato]nickel(II)

30 cm^3 of a 40% w/v solution of formaldehyde (0.4 mol) was added to a 30 cm^3 aqueous solution of bis(glycinato)nickel(II) (2.2 g, 0.01 mol). Concentrated ammonia solution was added until the pH of the solution was 8.5 and the reaction mixture was left standing at room temperature. After a week, orange, needle shaped crystals were obtained. These were purified in a manner similar to that for the copper(II) complex in part (a). Yield 2.3 g (75%). *Anal.* Found: C, 36.0; H, 4.4; N, 18.8. Calcd. for $C_9H_{14}N_4O_4Ni$: C, 36.0; H, 4.7; N, 18.6%.

*(c) Methyl Ester of **1***

The copper(II) complex described in part (a) was slurried with distilled water (15 cm^3) and solid sodium borohydride was added slowly to the slurry until all the blue complex was converted into a black solid which was then filtered. The resulting colourless filtrate was evaporated under vacuum (0.1 Torr) to give a white solid which was further dried in a desiccator for 24 h.

The dried white solid was slurried with dry methanol and esterification was carried out by bubbling dry gaseous hydrogen chloride into the stirred slurry which was ice-cooled. The precipitated sodium chloride was removed by filtration under nitrogen.

Excess methanol was removed from the filtrate under vacuum to give a viscous yellow oil. The oil was slurried with dry chloroform and dry gaseous ammonia was bubbled into the rapidly stirred slurry which was cooled by ice. The precipitated ammonium chloride was removed by filtration (under nitrogen). Excess chloroform was removed from the filtrate under vacuum to yield an almost colourless viscous oil. The ester was found to decompose readily on exposure to air and moisture; hence it was stored in the dark at 0 ℃. Mass spectrum of the ester: m/z 145 (M, 30%), 86(40), 85(45), 57(8), 56(100).

*(d) Methyl Ester of **2***

The nickel(II) complex obtained in part (b) was slurried with distilled water (15 cm^3) and the addition of solid sodium borohydride was carried out slowly until all the orange complex was converted into a blackish brown solid. The rest of the esterification procedure is similar to that described in (c). Mass spectrum of the methyl ester: m/z 272 (M, 25%), 154(30), 126(38), 84(55), 56(40), 42(60), 29(100).

Instrumentation

Gas Chromatograph-Mass Spectral Analysis

The mass spectra were recorded on a Hewlett Packard HP 5992B gas chromatograph-mass spectrometer equipped with a total ion monitor and a desk top computer HP 5825 B.

A 16-in., 0.25-in. o.d. glass column packed with 3% OV101 on Chromosorb G (60–80 mesh) was employed for the analysis and the carrier gas was helium (flow rate 15 cm^3 min^{-1}).

The oven was maintained at 160 ℃ for the analysis of both the esters and the samples were injected into the column as solutions in diethyl ether.

In both instances the electron beam energy was 70 eV and the ion source temperature was 250 ℃.

Results and Discussion

Analysis of Gas Chromatograms

The gas chromatogram of the product obtained from the esterification in part (c) shows two components. Assuming that the ionization cross sections are the same for each component, estimation of the peak areas from the total ion monitor (T.I.M.) record indicates that the major component constitutes 99% with the minor component making up the rest of the sample.

The T.I.M. chromatogram of the product from (d) shows that the sample consists almost entirely of one major component with only a trace quantity of a second component.

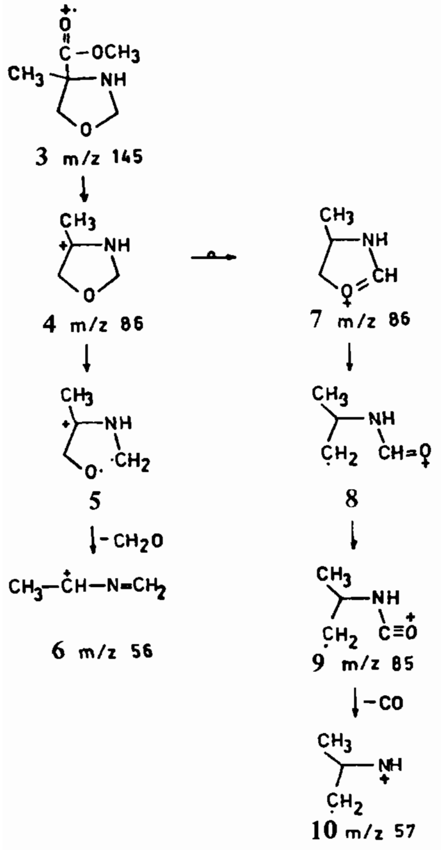
Analysis of the Mass Spectra of the Esters

*(a) Methyl Ester of **1***

The proposed breakdown pattern in the mass spectrum of the ester is depicted in Scheme 1.

The molecular ion peak, $M^{+\bullet}$ is observed with significant intensity (m/z 145). An intense peak at m/z 86 (corresponding to **4**) may be attributable to the cleavage of the carboxymethyl group of the ester, a behaviour which is characteristic of the fragmentation of amino acid esters [11].

The spectrum has a base peak at m/z 56 (corresponding to **6**) which represents the loss of a formaldehyde molecule from **4**. This loss presumably occurs via the initial O–C homolytic cleavage to produce the intermediate **5**. Intense peaks at m/z 85 and m/z 57 correspond to losses of H and CO from **4** respectively. These could arise as a result of the rearrangement reaction **4** $\xrightarrow{a}$ **7** which involves the transfer of a proton from the methylene to the methine group. Cleavage of the O–C bond then occurs giving rise to the intermediate, **8**, which then eliminates a hydrogen atom to give **9**. This step is



Scheme 1.

followed by the expulsion of a CO molecule to produce **10**. A similar fragmentation pattern is observed in the mass spectra of cyclic ethers [12].

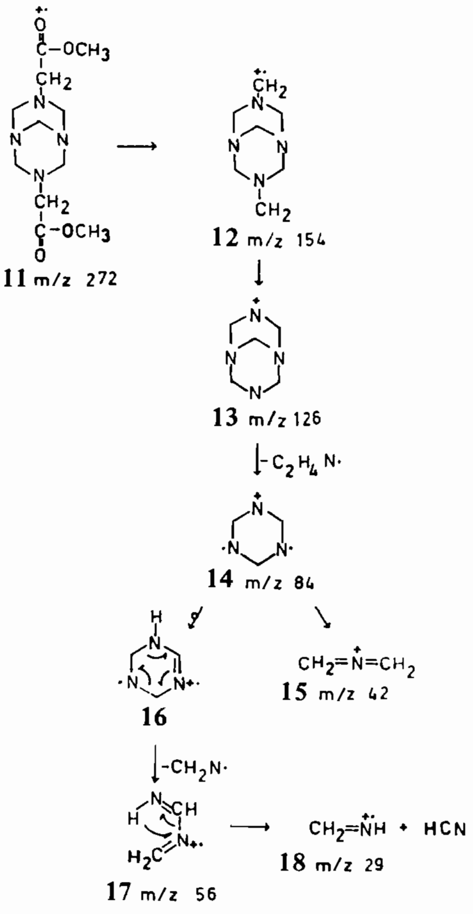
(b) Methyl Ester of 2

The proposed breakdown pattern in the mass spectrum of the ester is shown in Scheme 2.

The molecular ion peak, $M^{+\cdot}$, is observed with significant intensity (m/z 272). Typical of the fragmentation of amino acid esters [11], an intense peak attributable to the cleavage of a carboxyalkyl group is observed at m/z 154. The mass spectrum also shows a daughter ion peak at m/z 126 presumably corresponding to **13** and arising from the loss of methylene groups attached to the nitrogen atoms of the saturated cyclic system [8, 11, 13]. A major ion peak at m/z 84 appears to have been formed by the rupture of two N–C bonds at the bridgehead of **13** [14] and the loss of a C_2H_4N radical. The rearrangement reaction **14** $\xrightarrow{a}$ **16** precedes the expulsion of a CH_2N radical from the latter to give **17** which gives rise to a prominent peak at m/z 56. Similar fragmentation patterns are observed in the mass spectra of hexahydro-1,3,5-triazines [13] and in those of the alkyl esters of N(1,3-dioxa-5-azacyclohexyl)acetic acid [8]. Elimination of a molecule of HCN from **17** leads to the formation of **18** which is indicated by the base peak at m/z 29. The presence of the prominent peak at m/z 42 due to the ammine fragment **15** (derived from **14**) suggests that there are competing pathways in the fragmentation of the saturated ring system [8, 15].

As only trace amounts of the minor products are obtained in both esterification reactions, they are considered unimportant and have not been studied in any detail. They could have arisen from decomposition in the injector part of the GC oven when it is maintained at a somewhat higher temperature than the oven itself. Furthermore, it was extremely difficult to carry out further characterization of the esters owing to their low yield (~6%) and their unstable nature.

Although reduction of the metal(II) complexes has taken place in the reactions with sodium borohydride [7–10], the mass spectral results reported herein as well as the infrared spectra of the white solids obtained (ν_{CO} ~ 1630 cm^{-1}) after treatment with sodium borohydride, indicate that reduction of the carboxylato group of **1** and those of **2** have not occurred. The white solids, although not further



Scheme 2.

characterized, are most probably the sodium salts of **1** and **2** respectively.

The present paper shows that the method of demetallation (using sodium borohydride) and esterification under dry and cold conditions may be applied to the synthesis of the oxazolidine and 1,3,5,7-tetraazabicyclo[3.3.1]nonane heterocyclic systems which previously have been mostly obtained using organic or organometallic reagents [16].

Acknowledgement

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