Inorganica Chimica Acta, 68 (1983) 107–109

Formation of the Esters of N-(1,3-dioxa-5-azacyclohexyl)acetic Acid *via* the Demetallation Reaction of the Copper(II) Complex of the Acid

SOON-BENG TEO and SIANG-GUAN TEOH

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

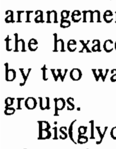
Received May 10, 1982

The copper(II) complex formed by the reaction of bis(glycinato)copper(II) with formaldehyde in the absence of base was treated with sodium borohydride to give the sodium salt of N-(1,3-dioxa-5-azacyclohexyl)acetic acid. The reaction does not cause appreciable cleavage of the saturated heterocyclic ring of the acid.

The methyl and ethyl esters of the acid were subsequently prepared and characterized by gas-chromatography/mass spectrometry (GC/MS).

Introduction

A recent investigation [1] has shown that the product of the reaction of bis(glycinato)zinc(II) monohydrate with formaldehyde is the bis(amino acidato)zinc(II) complex of N-(1,3-dioxa-5-azacyclohexyl)acetic acid, *1* [2].



1

The zinc(II) complex has an essentially octahedral arrangement of donor atoms around the metal ion, the hexacoordination for the zinc being completed by two water molecules and the amino- and carboxy groups.

Bis(glycinato)copper(II) undergoes the same type of condensation reaction with formaldehyde to give the copper(II) complex of *1* which, when treated with H_2S, yields glycine and formaldehyde [3]. However, a previous paper [4] has reported a method for removing the coordinated copper(II) ion from the copper(II) complex of dihydro-1H,3H,5H-oxazolo[3,4-c]oxazole-7a-carboxylic acid without cleavage of the oxazole ring systems.

The present paper gives details of the preparation of the bis(chelate)copper(II) complex of *1* and its reaction with sodium borohydride which leads to the removal of the copper(II) ion with the retention of the ring system in *1*. The methyl and ethyl esters of *1* were then prepared and characterized by gas chromatography-mass spectrometry.

Experimental

Reagents

Methanol and ethanol were dried by formation of Grignard reagent with magnesium turnings, followed by refluxing and distillation of the alcohols. Chloroform was dried by refluxing over and distilling from phosphorus pentoxide. Gaseous hydrogen chloride was generated by the reaction of concentrated sulphuric acid with sodium chloride. Commerical ammonia was dried with calcium oxide.

All other reagents were reagent grade chemicals.

Synthesis

(a) Bis[N-(1,3-dioxa-5-azacyclohexyl)acetato]-copper(II)

A reaction mixture consisting of bis(glycinato)-copper(II) (2.2 g, 0.01 mol) and formaldehyde (30 cm^3 of a 40% w/v solution) was mixed thoroughly and its pH adjusted to 4.5 by dilution with distilled water. The deep blue reaction mixture was filtered and the filtrate was allowed to stand for three days at room temperature.

The deep blue crystals which formed were filtered and washed successively with distilled water, ethanol and acetone and dried under vacuum for 6 hours. Yield 3.0 g (86%). *Anal.* Found: C, 33.6; H, 4.5; N, 7.6. Calcd. for $C_{10}H_{16}N_2O_8Cu$: C, 33.8; H, 4.2; N, 7.4%.

(b) Preparation of the Methyl and Ethyl Esters 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 of 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 hours.

The dried white solid was slurried with the appropriate dry alcohol and esterification was effected by bubbling dry gaseous hydrogen chloride into the stirred slurry, which was cooled to 0 ℃ (to prevent appreciable breakdown of the ring system to give glycine). The precipitated sodium chloride was removed by filtration under nitrogen.

Excess alcohol was removed from the filtrate under vacuum to give a viscous pale-yellow oil. The oil was slurried with dry chloroform and dry gaseous ammonia was bubbled into the rapidly stirred slurry which was cooled to 0 ℃. The precipitated ammonium chloride was removed by filtration (under nitrogen). Excess chloroform was removed from the filtrate under vacuum to give an almost colourless, viscous oil. Both the esters were found to decompose readily on exposure to air and moisture; hence they were stored in the dark at 0 ℃. Mass spectrum of the methyl ester: m/z 161 (M, 5%), 102(38), 88(12), 58(64), 42(100), 31(55). Mass spectrum of the ethyl ester: m/z 175 (M, 27%), 102(30), 88(27), 58(100), 42(57), 31(82).

Instrumentation

Gas-Chromatograph-Mass Spectral Analysis

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

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

For the analysis of the product from the methyl ester preparation the oven was maintained at 100 ℃ and the sample was injected into the column as a solution in diethyl ether.

In the analysis of the product from the ethyl ester preparation the oven was maintained at 180 ℃ and dry chloroform was used as the solvent.

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

Results and Discussion

Analysis of Gas Chromatograms

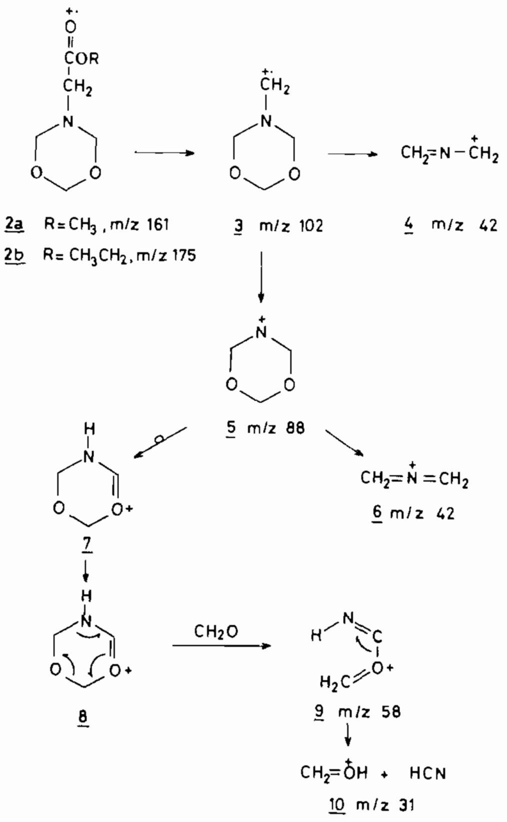
The gas chromatogram of the product from the methyl ester preparation reveals two components.

Assuming that the ionization cross-sections are the same for each component, estimation of the peak areas from the total ion monitor record indicates that the major component constitutes 98% whereas the minor component constitutes the rest of the sample.

For the ethyl ester preparation, there is a major component (97%), a minor component (2%), and a trace of a third component in the sample of the product.

Analysis of the Mass Spectra of the Esters

The proposed breakdown patterns in the mass spectra of the esters are depicted schematically (Scheme 1).



Scheme 1

Molecular ion peaks, $M^{+\bullet}$, are observed in both cases with significant intensity: m/z 161 for the methyl ester, m/z 175 for the ethyl ester.

Intense peaks at m/z 102 (observed for both the compounds) may be attributed to the cleavage of the carboxylalkyl group of the ester, and this behaviour is characteristic of the fragmentation of esters of amino acids [5]. The spectra of both the esters show daughter ion peaks at m/z 88, presumably corresponding to *5* and arising from loss of the group attached to the nitrogen atom of the saturated cyclic system [4–6]. The rearrangement reaction $5 \rightarrow 7$ involves the transfer of a proton from the adjacent methylene group to the nitrogen atom of *5* and this is then followed by the loss of a formaldehyde molecule to give *9*, which gives rise to a prominent peak at m/z 58 in the mass spectrum of the methyl ester. This peak forms the base peak in the spectrum of the ethyl ester. A similar fragmentation pattern is observed in the mass spectra of hexahydro-1,3,5-triazines [6]. Elimination of a molecule of HCN from *9* results in the formation of *10* which is indicated by a strong peak at m/z *31*.

The spectrum of the methyl ester has a base peak at m/z 42 which also shows up prominently in the spectrum of the ethyl ester. This peak (which may be due to the amine fragments *4* (derived from *3*) or *6* (derived from *5*)) suggests that there are competing pathways in the fragmentation of the saturated ring system [7].

As the minor products are in such small quantity, they are not considered important in the reaction and have not been studied in any detail. It is possible that they arise from decomposition in the injector port of the GC oven which is maintained at a somewhat higher temperature than the oven itself. Furthermore, it was extremely difficult to carry out further characterization of the esters because of the low yield obtained (~7%) and the unstable nature of the products.

The Removal of Coordinated Copper(II) by Means of Sodium Borohydride

In aqueous solution, sodium borohydride has been shown to reduce various metal salts to the metallic element [8]. The reaction of sodium borohydride with copper(II) salts yields the black copper(I) hydride. The mass spectral results reported in the present paper, as well as the infrared spectrum of the white solid obtained (ν_{CO} 1630 cm^{-1}) after the sodium borohydride treatment, indicate that the reduction of the carboxylato group has not occurred. The white solid, although not further characterized, is almost certainly the sodium salt of *1*.

The present report shows that esterification of the sodium salt has been successfully applied to the synthesis of the 1,3-dioxa-5-azacyclohexane heterocyclic system which hitherto has been achieved by using organic reagents [9–11].

References

1 S. B. Teo, S. G. Teoh, J. R. Rodgers and M. R. Snow, *J. Chem. Soc., Chem. Commun.*, 141 (1982).
2 It is also known as (perhydro-1,3,5-dioxazin-5-yl)acetic acid.
3 S. B. Teo and S. G. Teoh, unpublished data.
4 M. J. O'Connor, J. F. Smith and S. B. Teo, *Aust. J. Chem., 29,* 375 (1976).
5 K. Biemann, 'Mass Spectrometry', McGraw Hill, New York, 1962, p. 260.
6 R. A. Corral and O. O. Orfeo, *Org. Mass. Spectrom., 11,* 1221 (1976).
7 J. Monstrey, C. Van de Sande and M. Vandewalle, *ibid., 9,* 726 (1974).
8 G. W. Schaeffer, M. C. Walter and L. F. Johnstedt, *Anal. Chem., 33,* 1719 (1961).
9 W. J. Kauffman, *J. Heterocyclic Chem., 12,* 409 (1975).
10 O. O. Orazi and R. A. Corral, *J. Chem. Soc, Perkin Trans. I,* 772 (1974).
11 V. J. Baker, I. J. Ferguson, A. R. Katritzky, R. Patel and S. Rahimi-Rastgoo, *J. Chem. Soc, Perkin Trans. II,* 377 (1978).