ORIGINAL RESEARCH



Thionation of a cyanoxime derivative to form the sulphur-containing derivative, a novel ligand for complexation with transitional metal ions

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Abstract 2-Cyano-2-(hydroxyimino)dithioacetic acid was prepared starting from cyanoacetic acid methylester via 2-cyano-2-(hydroxyimino)acetic acid methylester. Before thionation, the ester had to be hydrolyzed. The optimum conditions for each reaction were identified. P_4S_{10} was found to be the efficient thionation reactant resulting in the formation of the dithionated product. Its structure was verified with IR, NMR and mass spectrometric measurements.

Keywords Cyanoxime derivative \cdot Thionation $\cdot P_4S_{10}$ \cdot Dithionated product

Introduction

Cyanoximes represent a recently synthesized novel subclass of oximes. They have the general formula of NCC(=NOH)-R, where R is an electron-withdrawing group such as CN, amide/ thioamide, keto, carboxylic ester, and a variety of aryls and heterocycles. They were prepared (40 representatives) with the aim of investigating their ability to form coordination compounds useful in various fields like proteomic research, crystal

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engineering, medicine, agriculture, etc. They form a large variety of mononuclear (with Na, K, Rb, Cs, Ba, Sn(IV), Te(IV), Sb(V), Cu, Ni, Co, Fe, Pd, Pt, lanthanoids) as well as polynuclear (with Ni(II), organotin(IV), Ag(I), Th(I)) complexes, in which the cyanoximes exhibit a large scale of coordination modes. For a recent review describing these structural features and many more in detail by their principle investigator, please see ref. [1].

If sulphur derivatives of the cyanoximes can be made, one may expect even better coordination ability and a larger variety of coordination modes being the sulphur atom larger and thus having a more polarizable electron cloud. Surprisingly, sulphur-containing derivatives except the thioamide derivatives are not known. Possibly, the replacement of one or more oxygens for sulphur atom(s) in these compounds is not an easy exercise, even if there is a number of thionating agents that are in the hands of chemists.

The most often used and best known thionation agents are S_8 [2], P_4S_{10} **1** (Berzelius reagent [3–5]) and the Lawesson's reagent **2** [6–10]. (It is to be noted that the Lawesson's reagent is prepared from the reaction of methylphenyl ether and P_4S_{10} .) (Fig. 1).

Other not so frequently applied thionation reagents have also been developed like hexamethyldisilathiane together with $CoCl_2 \cdot 6H_2O$ co-catalyst [11], the combination of P_4S_{10} and hexamethyldisiloxane [12], P_4S_{10} -pyridyne complex [13] and many others reviewed by Polshettiwar and Kaushik [14]. Interestingly, in many of them, P_4S_{10} is the major component.

Most of the thionation agents, especially P_4S_{10} and the Lawesson's reagent, are used most often for C=O to C=S exchange in compounds containing carbonyl group (ketones, carboxylic acids, esters amides, etc.). P_4S_{10} and the Lawesson's reagent dissociate during the reaction, and the formation of the strong P=O bond drives the reaction (for details, see ref. [10] and any other reviews cited). These



Fig. 1 The Berzelius $(P_4S_{10} \ 1)$ and the Lawesson's (2,4-bis(p-methoxyphenyl)-1,3-dithiadi-phosphetane-2,4-disulfide 2) reagents

reactants are able to replace both oxygens in esters or carboxylic acids [8]. However, the replacement of oxygen to sulphfur in oximes under ambient conditions is not feasible, because the corresponding thio-oxime is only stable at -70 °C or below [15].

In this contribution, we intend to show a convenient way of preparing 2-cyano-2-(hydroxyimino)dithioacetic acid starting from the easily accessible cyanoacetic acid methylester via 2-cyano-2-(hydroxyimino)acetic acid methylester. The ester could be thionated at the carboxylic end leaving the =N–OH group intact.

Experimental

The reactants were either the products of Aldrich Chemical Co. $(P_4S_{10}, cyanoacetic acid methylester, NaNO_2, KOH, NaOH)$ or VWR (HCl, H₃PO₄, glacial acetic acid). The solvents (toluene, methanol, ethanol, hexane, ethyl acetate and DMSO-d₆) were purchased from VWR. They had over 98 % purity and were used without further purification.

The thionation reactions were performed in Ar atmosphere.

The reactions were followed by thin-layer chromatography (TLC, silica gel, Aldrich; eluent: n-hexane:ethyl acetate =1:1). The products were purified with column chromatography with the eluent used in TLC in solution or recrystallization when solid. TLC was performed on a plastic sheet precoated with silica gel 60 F_{254} . Silica gel (pore size 60 Å, 60–100 mesh particle size, Sigma-Aldrich) was used for column chromatography.

Infrared (IR) measurements were carried out on a Bio-Rad FTS-40 FT-IR spectrometer, working in the reflection mode, using 1 % of the sample in KBr (spectroscopic grade, Aldrich Chem. Co.). Two hundred fifty-six scans were collected for the spectra at 4-cm⁻¹ resolution.

NMR measurements were performed in 0.5 mL DMSO-d6 or acetone-d6 (99.96 atom% D, from Sigma-Aldrich Chemical Co.) using Bruker Avance 500, 500-MHz NMR spectrometer with 5-mm glass NMR tubes from Wilmad.

Electrospray ionization mass spectrometric (ESI-MS) measurements were performed using a Micromass Q-TOF Premier (Waters MS Technologies) mass spectrometer equipped with electrospray ion source. The sample was introduced into the MS by applying direct injection method: the built-in syringe pump of the instrument with a 25-mL Hamilton syringe was used. The electrospray needle was adjusted to 3 kV and N_2 was used as nebulizer gas. The computer program used to simulate the theoretical isotope distributions is included in the Masslynx software package.

The syntheses of the intermediates and the final product were prepared by the following recipes:

2-Cyano-2-(hydroxyimino)acetic acid methylester Phosphoric acid (4 mL) was added drop-wise to a 0 °C suspension of methyl cyanoacetate (10 g) and sodium nitrite (6 g) in H₂O (80 mL). The reaction was allowed to warm up to 40 °C in 1 h. The mixture was then cooled and cc. HCl (8 mL) was added gradually. The solution was extracted with ethyl acetate, and the organic phase was collected, dried over Na₂SO₄ and concentrated in *vacou* to give the product, which was purified by recrystallization from toluene. White crystals were obtained with a yield of 91 %.

2-Cyano-2-(hydroxyimino)acetic acid Method 1: A mixture of 3 g of 2-cyano-2-(hydroxyimino)acetic acid methylester and 12 mL of methanol was stirred and maintained at 35 °C in a 50-mL two-neck round-bottom flask; 2.65 g of KOH was added and the contents were stirred for 2 h and then were concentrated in vacou. Twenty-five millilitres of water was added. The mixture was acidified to pH = 2 with 6 M HCl extracted with ethyl acetate. After drying over Na₂SO₄, the solvent was evaporated and the crude 2-cyano-2-(hydroxyimino)acetic acid was obtained. It was purified by column chromatography (eluent: n-hexane: ethylacetate =1:1). White crystals were obtained with a yield of 76 %. Method 2: A mixture of 4.3 g of 2-cyano-2-(hydroxyimino)acetic acid methylester in 40 mL of ethanol was added to a solution of 8 g of NaOH in 80 mL of H₂O. The mixture was refluxed for 4 h, then cooled to room temperature and diluted with 40 mL of THF and acidified to pH = 2 with 6 M HCl. The mixture was then extracted with ethyl acetate. The organic fraction was separated, dried over Na₂SO₄, and the solvent was removed under reduced pressure to give the crude of 2-cyano-2-(hydroxyimino)acetic acid, which was refined the same way as in Method 1. White crystals were obtained with a yield of 74 %.



Fig. 2 The reaction used for the synthesis of the cyanoxime derivative (2-cyano-2-(hydroxyimino)-acetic acid methylester)

Fig. 3 The ¹H (**a**) and the ¹³C (**b**) NMR spectra of the purified 2cyano-2-(hydroxyimino)acetic acid methylester



2-Cyano-2-(hydroxyimino)dithioacetic acid A mixture of 0.34 g of 2-cyano-2-(hydroxyimino)acetic acid and 0.4 g of phosphorus pentasulfide in 20 mL of anhydrous toluene was refluxed for 2 h. After cooling to room temperature, the reaction mixture was placed on silica gel column and the toluene was eluted with n-hexane. The product 2-cyano-2-(hydroxyimino)dithioacetic acid formed was then eluted with n-hexane:ethylacetate =2:1. Orange-coloured crystal with a yield of 39 % was obtained.

Results and discussion

The intermediate cyanoxime could be prepared from cyanoacetic acid methyl ester with in situ formed HNO_2 at or near room temperature [16] (Fig. 2). When glacial acetic acid was used, a 4-h reaction time was needed to gain acceptable yield of the product, and care had to be taken of avoiding excess acid. Using a mixture of concentrated H_3PO_4 and HCl afforded high yield in 2 h at somewhat higher reaction temperature (35 °C).



The structure of the purified product was verified by ¹H and ¹³C NMR spectroscopies (Fig. 3). All lines in the spectra could be assigned to the functional groups of the cyanoxime.

As it seen in the figure, the oxime (C=N) and the cyanide carbons (C=N) are well separated from each other in the ¹³C NMR spectrum. The C=O carbon, as it is expected, appears at the deshielded end, while the methoxy carbon, being the most shielded, is seen at relatively low chemical shifts. Due to fast exchange, the oxime proton is not observed in the ¹H NMR spectrum; however, the methoxy protons are easily identified.

The hydrolysis of the ester was performed by two similar methods. Method 2, hydrolysis in methanolic KOH at 35 °C in 2 h, proved to be better, since there was no by-product formation. To achieve similar yield, the reaction with ethanolic NaOH required higher temperature (100 °C) and longer reaction time (4 h).

Structural identification was performed by IR as well as ¹³C NMR spectroscopies (Fig. 4).

Again, the functional groups could be easily identified. The hydrogen-bonded OH groups gave the typical wide absorption band in the 3400-2400-cm⁻¹ region.



Fig. 5 The IR spectrum of the crude product after thionation (**a**) and the ¹H NMR spectrum of the purified thionated product (**b**)



Then, the thionation reactions were performed with the 2cyano-2-(hydroxyimino)acetic acid intermediate. ESI-MS mass spectroscopic result indicated that there were two sulphur atoms in the product, since the molecular ion was found at M/z = 146. The IR spectra (Fig. 5a) of the crude product indicated the presence of diminished C=O vibration at 1750 cm⁻¹, increased C=S vibration at 863 cm⁻¹, an S-H vibration at 2613 cm^{-1} and a broad band in the 3500–2500cm⁻¹ range indicating H-bonded OH groups from the residual acid reactant and the unchanged =N-OH. The ¹H NMR spectrum of the recrystallized product verified the presence of the -SH and the unchanged =N-OH functional groups (Fig. 5b). These observations mean that both oxygens of the carboxylic group were replaced by sulphur, while, as expected, the oxygen in the =N-OH group was not. The product was 2-cyano-2-(hydroxyimino)dithioacetic acid.

Conclusions

A convenient reaction sequence was elaborated for the synthesis of a novel thionated cyanoxime derivative. The cyanoxime carboxylic acid prepared from cyano acetic acid could be thionated with P_4S_{10} by replacing both oxygens in the carboxylic group. At the same time, the oxygen in the =N–OH functional group was preserved. The sulphur-containing novel compound is a promising ligand in future complexation studies.

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