Preparation of Thioacethydrazide from a Nickel Complex

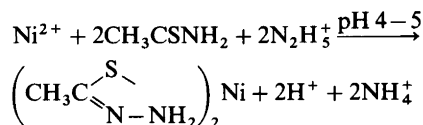K. A. JENSEN[a] and ERIK LARSEN[b]

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Dedicated to Jannik Bjerrum on the occasion of his 70th birthday

Coordination compounds of thioacethydrazide have been obtained in an indirect way from thioacetamide. Free thioacethydrazide, however, has hitherto been considered too unstable to be isolated. It has now been shown that it can be prepared by addition of a base to tris(thioacethydrazide)nickel(II) ions. When pure, the hydrazide is sufficiently stable to be characterized by melting point, UV, IR and NMR spectroscopy. It has also been possible to prepare thioacethydrazide by the conventional method from carboxymethyl dithioacetate and hydrazine. At room temperature it rapidly eliminates hydrogen sulfide with the formation of 1,4-dihydro-3,6-dimethyl-1,2,4,5-tetrazine which may rearrange to 4-amino-3,5-dimethyltriazole.

In a study of potential methods for the preparation of thiocarboxylic hydrazides [1] it was found that the reaction of carboxymethyl dithioates with hydrazine generally represents a convenient method for preparing the corresponding hydrazides. Sometimes, however, a thiadiazole or a dihydrotetrazine is the main product.[2] Although thiopivalic hydrazide and phenylthioacethydrazide could be prepared without difficulty in this manner, attempts to synthesize the hydrazides of thioacetic and thiopropionic acid were unsuccessful. It was therefore concluded that N-unsubstituted aliphatic thiohydrazides with at least one α-hydrogen atom would be unstable. By contrast the N-substituted derivatives are generally quite stable.[3]

Recently, thioacethydrazide was found to be trapped as a ligand [4] when thioacetamide, hydrazinium ions and nickel(II) ions are brought together at pH 4–5:

$$Ni^{2+} + 2CH_3CSNH_2 + 2N_2H_5^+ \xrightarrow{pH\,4-5}$$

$$\left(CH_3C\underset{N-NH_2}{\overset{S}{\diagdown}}\right)_2 Ni + 2H^+ + 2NH_4^+$$

The complex bis(thioacethydrazidato)nickel(II), [Ni(tah)$_2$], is easily obtained from the above reaction and is a convenient starting material for preparing a series of ketonethiohydrazonato complexes with ketones.[5] Other thioamides with α-hydrogen atoms react similarly with Ni^{2+} and N$_2$H$_5^+$, while thiobenzamide and thiourea, for example, do not.

Bis(thioacethydrazidato)nickel(II) resembles bis(thiobenzhydrazidato)nickel(II) and bis(thiosemicarbazidato)nickel(II) formerly studied by one of the authors.[6–8] The compounds, for example, will disproportionate when the ligands are protonated on treatment with acid:[9]

$$3NiL_2 + 6H^+ \rightarrow 2Ni(HL)_3^{2+} + Ni^{2+}$$
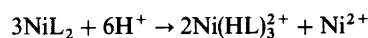
The cationic complex can be isolated in high yield as the chloride. The reaction demonstrates that thioacethydrazide has a certain stability. We speculated that when base is added to a solution of [Ni(Htah)$_3$]Cl$_2$ the free ligand might be liberated in accordance with the following reaction:

$$\underset{1}{[Ni(Htah)_3]^{2+}} + 2HO^- \rightarrow \underset{2}{Ni(tah)_2} + \underset{3}{Htah} + 2H_2O$$
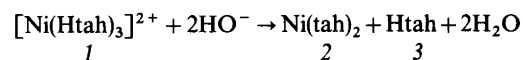
This reaction scheme has been used in the present work to isolate and characterize thioacethydrazide. Once its properties were known, thioacethydrazide

could also be prepared in acceptable yield (~ 50 %) from carboxymethyl dithioacetate and hydrazine in analogy with earlier preparations of thiocarboxylic hydrazides.[1,10]

In accordance with the earlier observations[1,2] thioacethydrazide readily eliminates hydrogen sulfide with the formation of 1,4-dihydro-3,6-dimethyl-1,2,4,5-tetrazine. As a pure, white crystalline substance it can be kept for weeks at -30 °C. At room temperature it is rapidly transformed into the dihydrotetrazine (which is oxidized in air to the red tetrazine) and 4-amino-3,5-dimethyltriazole.

The UV spectrum of thioacethydrazide exhibits a single maximum at 266 nm (ε 15 000). This absorption is caused by the allowed $\pi \rightarrow \pi^*$ transition.

The acidic character of the $-CS-NH-$ grouping of thioacethydrazide has been studied by the standard titrimetric method. The medium was 1 M $NaClO_4$ at 25 °C. The pK_a value was determined graphically to be 8.90. This is somewhat lower than the values found earlier[1,3] for N-unsubstituted thiohydrazides in 50 % aqueous-ethanolic solutions.

The ^{1}H NMR spectrum of thioacethydrazide in methanol-d_4 or dimethyl sulfoxide-d_6 show an unsplit methyl peak and with the same total intensity the three N-bound protons.

The IR spectrum of thioacethydrazide in KBr has no $S-H$ band (at ca. 2600 cm^{-1}) and thus excludes the tautomeric formula $CH_3C(SH)=N-NH_2$. This is also consistent with the NMR results. However, the low values of the NH stretching frequencies and two broad IR bands at $2750-2950$ cm^{-1} and $830-860$ cm^{-1} suggest that the hydrazide in solid state is present as the zwitterion $CH_3C(S^-)=\overset{+}{N}-\overset{\cdot}{N}H_3$ with intramolecular hydrogen bonds.

The difference between the pK_1 values for tris-(thioacethydrazide) cobalt(III) ($pK_1 = 1.4$) and tris-(thiosemicarbazide) cobalt(III) ($pK_1 = 4.8$) may be approximately equal to the difference between the values of pK_a for thioacethydrazide and thiosemicarbazide since they obviously both exist as the $RCSNHNH_2$ tautomer in the complexes and as free ligands. We would, therefore, predict that thiosemicarbazide should have $pK_a \sim 12.3$.

EXPERIMENTAL

Tris(thioacethydrazide)nickel(II) chloride monohydrate, *1*,[9] *bis*(thiohydrazidato)nickel(II), *2*,[4] and

carboxymethyl dithioacetate, *4*,[11] were prepared according to literature specification.

UV spectra were recorded on a Cary 118 spectrophotometer, infrared spectra on a Perkin Elmer 337 grating infrared spectrophotometer and NMR spectra on a Bruker 90 MHz instrument.

Preparation of thioacethydrazide (3). (a) From the nickel compound *1*: 8.0 g of *1* was dissolved in 80 ml of water at 40 °C and stirred with 250 ml of ethyl acetate under addition of ca. 40 ml of 1 M NaOH until pH=6. The brown complex *2* was filtered off, the ethyl acetate layer was separated and the aqueous solution extracted with 5×60 ml of ethyl acetate. The combined ethyl acetate solutions were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The residue was washed with ether to remove an oily by-product. Yield 1.1 g (61 %). The product was purified by dissolving it in ethyl acetate (25 ml) adding pentane until turbidity began and cooling at -20 °C. Ca. 70 % was recovered as colourless needles. Anal. $C_2H_6N_2S$: C, H, N, S. M.p. $95-96$ °C (with decomposition, see below). UV (methanol): λ_{max} 266 nm (ε 15 000). Impure samples also have absorption bands at ca. 220 and 290 nm. These are due to 1,4-dihydro-3,6-dimethyl-1,2,4,5-tetrazine and 3,6-dimethyl-1,2,4,5-tetrazine, respectively.[12] ^{1}H NMR (methanol-d_4): δ 2.38 (3 H, s); 4.9 (3 H, br. s). (DMSO-d_6): δ 2.20 (3 H, s); 5.4 (2 H, br. s); 10.7 (1 H, br. s). IR (KBr): 3230 (vs), 3190 (vs), 3100 (vs), $2750-2950$ (vs), 1590 (vs, br), 1470 (w), 1402 (s), 1375 (m), 1310 (m), 1287 (w), 1200 (m), 1182 (m), 1148 (s), 1130 (m), 1052 (m), 1037 (m), 945 (s), $830-860$ (s), 685 (s), 595 (m), 582 (m), 530 (w), 450 (m) cm^{-1}. A hydrochloride was precipitated from the ethereal solution of the hydrazide by gaseous HCl. Anal. $C_2H_7ClN_2S$: C, H, N, Cl.

On melting, the hydrazide eliminates H_2S and is transformed into 4-amino-3,5-dimethyltriazole. When kept for 1 week over KOH it also eliminates H_2S and is transformed into almost pure 1,4-dihydro-3,6-dimethyl-1,2,4,5-tetrazine. When kept for a longer time over KOH the dihydrotetrazine is gradually transformed into (impure) 4-amino-3,6-dimethyltriazole. The dihydrotetrazine and aminotriazole were identified by comparison with authentic samples of these compounds. The pure dihydrotetrazine was prepared by warming an ethanolic solution of thioacetamide and hydrazine hydrate at 50 °C for 5 min. On prolonged heating it is completely rearranged into the aminotriazole which was the only product isolated by King and Anson[14] from the reaction of thioacetamide and hydrazine in aqueous solution. The infrared spectrum of the dihydrotetrazine accords with that reported by Skorianetz and Kovats[12] for 1,4-dihydro-3,6-dimethyl tetrazine and not with that of the 1,5 isomer.

In our first experiments when ether was used instead of ethyl acetate the yields were lower. The hydrazide is very soluble in water but only slightly soluble in ether and during extraction, evaporation and recrystallization much is lost because of the elimination of H_2S. When the aqueous solution was continuously extracted with ether the only product obtained was 1,4-dihydro-3,6-dimethyl-1,2,4,5-tetrazine. Also, when pH is higher than 7 the elimination of H_2S accelerates and in the presence of air the dihydrotetrazine is oxidized to the red tetrazine. This was extracted with pentane, purified by sublimation and identified by its m.p. and IR spectrum (*cf.* Ref. 13).

(b) From carboxymethyl dithioacetate (*4*): 7.5 g of *4* was stirred with 100 ml of ethyl acetate, and 2.5 g of hydrazine hydrate and a solution of 6.0 g of Na_2S9H_2O in 50 ml of water was added until pH = 6. After complete decolourization of the solution (*ca.* 15 min), the ethyl acetate layer was separated and the aqueous layer washed with 6×80 ml ethyl acetate. The ethyl acetate solution was dried with $MgSO_4$ and evaporated. The residue was dissolved in 10 ml of warm ethyl acetate, and by adding pentane and cooling as above 2.1 g of crystals were obtained (47 %).

The preparation has also been carried out with NaOH instead of Na_2S but the yields were lower, probably because the tendency of *3* to eliminate H_2S is suppressed by the presence of the sulfide.

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