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# The complex $[ReO\{HNN(CH_3)CS_2CH_3\}_2]Cl$, a suitable precursor for the preparation of bis(dithiocarbamato)nitridorhenium(V) species

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**Abstract**

The rhenium intermediate $[ReO\{HNN(CH_3)CS_2CH_3\}_2]Cl$ **1** reacts in acetone with *N*,*N*-disubstituated dithiocarbamate salts $R_2R_1NCS_2X$ ($R_1 = R_2 =$ Me, Et, $C_6H_5$ or $R_1R_2 = [-CH_2-]_5$, X = Na or Li) to provide a good yield of a characteristic nitrido compound: bisdialkyl(-diaryl)dithiocarbamatonitridorhenium(V), $ReN(S_2CNR_1R_2)_2$. The new preparation of the key species **1** in water is also reported. It allows an original one-pot synthesis of bis(diethyldithiocarbamato)nitridorhenium (V) complex $ReN(S_2CNEt_2)_2$. © 1999 Elsevier Science S.A. All rights reserved.

*Keywords:* Nitrido-rhenium; Dithiocarbamate; N-methyl-S-methyldithiocarbazate; Aqueous chemistry; One-pot synthesis

## 1. Introduction

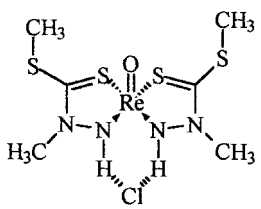
Knowledge and development of the chemistry of new neutral rhenium complexes are of crucial importance for the design and the easy synthesis of future therapeutic radiopharmaceuticals using Re-186/188 [1–6].

Rhenium complexes in the oxidation state + V with ligands such as bulky thiols [7], diphosphines [8], *o*-aminophenyldiphenylphosphine [9] benzamidinates and dithiophosphinates [10,11] have been studied, and the chemistry of the Re≡N core has been widely developed. Several complexes of rhenium V containing dithiocarbamate ligands have been reported [12–14] and have shown at microscopic level a myocardial uptake similarly to analogous compounds prepared with the isostructural radioelement $^{99m}Tc$ [15–17].

Traditionally, at macroscopic level, neutral dithiocarbamate complexes of rhenium V are obtained by substitution reaction in organic medium of the previously prepared nitridorhenium precursor $ReNCl_2(PPh_3)_2$ [18,19].

Recent attempts have been focused on the transformation of the oxorhenium core ($Re^V$=O) into nitrido complexes bearing thiosemicarbazides in hydrochloric acid medium but mechanistic approaches are still necessary to elucidate the N–N bond cleavage step [20,21].

In this paper, we describe the use of the oxo-species $[ReO(HNN(CH_3)CS_2CH_3)_2]Cl$ **1** for the formation of characterized bis(dithiocarbamato)nitridorhenium (V) complexes $ReN(S_2CNR_1R_2)_2$. We report also the original preparation of the key intermediate **1** in water and the one-pot synthesis of the bis(diethyldithiocarbamato)nitridorhenium compound $ReN(S_2CNEt_2)_2$.



Scheme 1.

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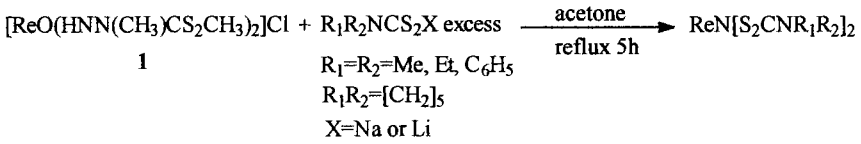



Scheme 2.

## 2. Synthesis of bis(dithiocarbamato)nitridorhenium (V)

Recently, Marchi et al. reported the synthesis of the complex $[ReO(HNN(CH_3)CS_2CH_3)_2]Cl$ **1** (Scheme 1) starting from $ReOCl_3(PPh_3)_2$ and the transformation into the chloro–nitrido compounds $ReNCl_2(PPh_3)_2$ **2** when **1** is treated with an excess of hydrochloric acid and triphenylphosphine [22]. Here, we describe a route for the synthesis of bis(dithiocarbamato)nitridorhenium complexes isostructural to $^{99m}TcN$ radiopharmaceuticals.

On a macroscopic scale, the oxo species **1** reacts in acetone with an excess of sodium or lithium dithiocarbamate salt $R_2R_1NCS_2^-$ ($R_1 = R_2 = Me$, Et, $C_6H_5$ or $R_1R_2 = [-CH_2-]_5$) to form nitrido species $ReN(S_2CNR_1R_2)_2$ (Scheme 2). A suitable excess of dithiocarbamate salts (four equivalents with respect to **1**) is required to give an efficient reaction. The mixture is heated at reflux for five hours. A yellow precipitate is formed which can be recrystallized from a mixture of acetone/$CH_2Cl_2$ to afford crystals of bisdialkyl(-diaryl)dithiocarbamatonitridorhenium (Table 1) with a satisfactory isolated yield (30–55%). All complexes have been characterized by spectroscopic and elemental analysis.

The formation of nitrido compounds of rhenium is the result of the cleavage of the hydrazinic group N–N of **1** by the presence of an excess of ligand. Very poor yields are obtained if the reaction is carried out in stoichiometric amounts and we confirm the easy transformation of the oxo-rhenium core into nitrido-rhenium core. In contradiction with the formation of the known chloro-complex **2**, we have observed that the presence of HCl is not required [22]. It seems that the oxo core $[Re{=}O]^{3+}$ was sufficiently reactive to promote the cleavage of the hydrazine N–N moiety by succesive protonation with the concomitant triple bond Re≡N formation. We think that the proton of the hydrazinic group **H**NN($CH_3$)– is the potential source for the protonation of the oxo group in a concerted process. Further studies towards the mechanism are in progress in our laboratory.

## 3. Original one-pot synthesis of bis(diethyldithiocarbamato)nitridorhenium (V) in water

The main strategy, using exchange reaction from dichlorobistriphenylphosphine nitridorhenium (V) $ReNCl_2(PPh_3)_2$, is limited by the poor solubility of the starting complex in organic solvents. An easy and cheap access to nitridorhenium V species must start with the commercially available potassium perrhenate $KReO_4$ which is water soluble. We have shown that the cationic complex $[ReO(HNN(CH_3)CS_2CH_3)_2]Cl$ **1** obtained by Marchi et al. in an organic medium can be easily and rapidly synthetized in water. In this context, we have developed a new route for the formation of dithiocarbamate-complex in water and shown the feasibility of a one-pot synthesis.

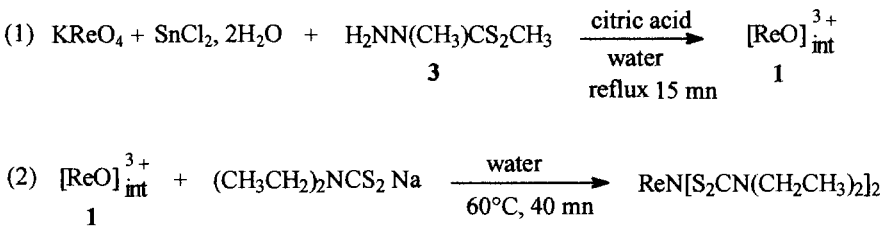
Since a reduction step must occur, we tried several reagents including triphenylphosphine sodium metatrisulfonate (TPPTS–Na) which have proved useful in other circumstances [15]. Finally, best results were obtained with stannous chloride and the N-methyl-S-methyldithiocarbazate ($H_2NN(CH_3)CS_2CH_3$: **3**) as the nitrido donating group [23–25] proved to be the most convenient in comparison to S-methyldithiocarbazate ($H_2NNHCS_2CH_3$) or succinic dihydrazide ($H_2NNHCOCH_2CH_2CONHNH_2$).

All reactions proceed in the same flask in water solution containing citric acid. This complexing reagent brings several advantages: (i) a favorable pH value for the reduction in Re (V), (ii) a convenient efficiency to the complexation of tin derivatives in solution, (iii) a probable participation in the temporary stabilization of the nitrido–rhenium core in the solution before the displacement by **3**.

This one-pot synthesis occurs via successive reactions in water solution: formation after 15 min at 100°C of a yellow solution containing the rhenium intermediate complex **1** then the addition of an excess of $(CH_3CH_2)_2NCS_2$–Na at neutral pH (i.e. pH 7) to give the required complex (Scheme 3).

Table 1
Synthesis of $[ReN(S_2CNR_1R_2)_2]$ from $[ReO(HNN(Me)C(S)SMe)_2]Cl$

| $R_1R_2NCS_2X$ | | | $ReN(R_1R_2NCS_2)$ |
|---|---|---|---|
| $R_1$ | $R_2$ | X | Rdt (%) |
| Me | Me | Na | 37 |
| Et | Et | Na | 31 |
| $C_6H_5$ | $C_6H_5$ | Li | 40 |
| $[-CH_2-]_5$ | | Na | 55 |




Scheme 3.

The nitrido complex is purified by column chromatography over silica gel eluated with diethylether. The yield of the isolated product is 41% based on $KReO_4$. The success of this method is based on the reaction conditions which optimize the formation of the intermediate and allow a one-pot synthesis with the appropriate stabilizing ligands. We have isolated the intermediate compound by extraction into $CH_2Cl_2$ and purification by column chromatography to confirm the structure (see Section 5) and we have verified that the same product $[ReN(S_2CNEt_2)_2]$ is obtained in organic medium with the route described in Scheme 2.

The intermediate complex **1** which is obtained in water shows an efficient ability to form nitrido complexes with an excess of ligand. Recently, we have observed also the same process in the preparation of the neutral radiopharmaceuticals $[^{188}ReN\{Et(EtO)NCS_2\}_2]$ or $[^{188}ReN\{CH_3(CH_2)_8CS_2\}_2]$ for leucocyte labelling [26,27].

## 4. Conclusion

We have reported the feasibility of a one-pot synthesis in water of bis(dithiocarbamato)nitridorhenium complexes. In a first step, an intermediate species $[ReO\{HNN(CH_3)CS_2CH_3\}_2]Cl$ is obtained which reacts with a dithiocarbamate salt to give easily nitrido–rhenium complexes with efficient yield. New macroscopic reactions using the key intermediate with other ligands such as thioamide $[R_1C(=S)NHR_2]$ which were tested with the analogous technetium-99m at microscopic level for white blood cells labelling [28], are underway.

## 5. Experimental

NMR spectra were recorded on a Bruker ARX 400, MS spectra on a Finnigan Mat-Incos 500 EX, IR spectra on a Nicolet 205 and elemental analysis on a Carlo Erba 1106 (ENSCR). All manipulations were carried out in an atmosphere of nitrogen using conventional Schlenk-type apparatus. Distilled water was degassed prior to use. The compounds N-methyl-S-methyldithiocarbazate **3** [23] and dithiocarbamate sodium salts [15] were synthesized as described previously.

### *5.1. Synthesis of bis(N-methyl-S-methyldithiocarbazato)oxorhenium (V) chloride $[ReO(HNN(Me)C(S)SMe)_2]Cl$*

(a) A total of 30 mg (104 μmol) of potassium perrhenate in 5 $cm^3$ water was added in a solution of 60 mg (266 μmol) stannous chloride dihydrate, 2.5 g (13 mmol) of citric acid and 100 mg (819 μmol) of **3** in 95 $cm^3$ of water. After 15 min at 100°C, the solution turned yellow. The organic products were extracted from the yellow aqueous solution by chloroform (3 × 20 $cm^3$). The combined extracts were concentrated and the orange residue was chromatographed on silica gel, using acetone as an eluant. The last orange fraction was concentrated to yield pure compound (19 mg, 35%). m.p. = 180–190°C (dec.) ($CH_2Cl_2$/hexane). $C_6H_{14}ClN_4OS_4Re$: calc.: C, 14.18; H, 2.78; N, 11.03. Found: C, 13.94; H, 2.78; N, 10.68. $^1$H-NMR ($CD_2Cl_2$): 2.89 (s, 6H, $SCH_3$); 4.14 (s, 6H, $NCH_3$); 13.07 (s, 2H, NH). $^{13}C\{^1H\}$-NMR ($CD_2Cl_2$): 18.47 ($SCH_3$); 44.20 ($NCH_3$); 167.90 ($CS_2$). I.R. $\nu(cm^{-1})$ 1600 [$\delta$(N–H)]; 1230 (C=S); 395 (Re–S).

(b) An alternative procedure [22] is as follows: to a suspension of trichlorobis(triphenylphosphino)oxorhenium (V) (0.14 g, 0.18 mmol) in a mixture of $CH_2Cl_2$/$C_6H_6$ (1:1, 50 $cm^3$), N-methyl-S-methyldithiocarbazate **3** (0.054 g, 0.4 mmol) dissolved in the minimum volume of $CH_2Cl_2$ was added . The reaction mixture was refluxed with stirring for 30 min, producing an orange precipitate on partial evaporation of the solvent. The solution was cooled to room temperature and the precipitate was filtered off, and dried with diethylether. The product was crystallized in $CH_2Cl_2$/hexane (60 mg, 66%).

### *5.2. Synthesis of $[ReN(S_2CNR_1R_2)_2]$ from $[ReO(HNN(Me)C(S)SMe)_2]Cl$*

Typical procedure: to a solution of bis(N-methyl-S-methyldithiocarbazato)oxorhenium (V) chloride (100 mg, 0.20 mmol) in acetone (50 $cm^3$) the desired dithiocarbamate (0.80 mmol) dissolved in the minimum volume of acetone was added. The solution was refluxed with stirring for 5 h under a stream of nitrogen. The solution gradually became yellow–brown and was concentrated to a lower volume under reduced pressure.

The reaction mixture was allowed to cool to room temperature, producing a yellow precipitate. This was filtered off and chromatographed on silica gel, using $CH_2Cl_2$ as eluant, the yellow fraction was concentrated to give crystals of the desired product which could be recrystallized in acetone or acetone/$CH_2Cl_2$.

$ReN(S_2CNMe_2)_2$: $^1$H-NMR ($Me_2SO$-$d_6$): 1.85 (t, 12H, $J = 7.1$ Hz, $CH_3$). $^{13}C\{^1H\}$-NMR ($Me_2SO$-$d_6$): 15.34 ($CH_3$); 231.08 ($CS_2$). $C_6H_{12}N_3S_4Re$: Calc.: C, 16.36; H, 2.75; N, 9.54. Found: C, 16.1; H, 2.61; N, 9.4%. IR ($cm^{-1}$): 1020 ($\nu_{Re\equiv N}$).

$ReN(S_2CN(C_6H_5)_2)_2$: $^1$H-NMR ($CDCl_3$): 7.46–7.39 (m, $C_6H_5$ 10H,). $^{13}C\{^1H\}$-NMR ($CDCl_3$): 127.0, 129.2, 129.9 (3CH), 141.4 ($C_q$); 259.6 ($CS_2$).). $C_{26}H_{20}N_3S_4Re$: Calc.: C, 45.33; H, 2.93; N, 6.1. Found: C, 45.91; H, 2.88; N, 6.0%.

$ReN(S_2CN(-CH_2-)_5)_2$: m.p. = 255–260°C (acetone). $C_{12}H_{20}N_3S_4Re$: calc.: C, 27.68; H, 3.87; N, 8.07. Found: C, 27.64; H, 3.84; N, 7.56%. $^1$H-NMR ($CD_2Cl_2$): 1.72–1.77 (m, 6H, $CH_2$); 3.85 and 3.95 (2m, 4H, $NCH_2$). $^{13}C\{^1H\}$-NMR ($CD_2Cl_2$): 24.0 ($CH_2$); 25.8 ($CH_2$); 49.4 ($NCH_2$); 230.9 ($CS_2$).

$ReN(S_2CNEt_2)_2$: m.p. = 245°C (dec). $^1$H-NMR ($Me_2SO$-$d_6$): 3.83 (m, 4H); 3.69 (m, 4H); 1.28 (t, 12H). $^{13}C\{^1H\}$-NMR ($Me_2SO$-$d_6$): 13.22 ($CH_3$); 46.50 ($CH_2$); 230.16 ($CS_2$). MS (CI, $NH_3$) $m/z$ 498 (100) $[M+H]^+$ ($^{187}$Re); 496 (42) $[M+H]^+$ ($^{185}$Re). IR ($cm^{-1}$): 1010 ($\nu_{Re\equiv N}$).

### 5.3. One-pot synthesis of $[ReN(S_2CNEt_2)_2]$ in water

A total of 30 mg (104 μmol) of potassium perrhenate in 5 $cm^3$ water was added to a solution containing 60 mg (266 μmol) of stannous chloride dihydrate, 2.5 g (13 mmol) of citric acid and 100 mg (819 μmol) of 3 in 95 $cm^3$ of water. After 15 min at 100°C, the solution turned yellow. The solution was neutralized with carbonate buffer (pH 10.3, 0.5 mol $l^{-1}$) and 1 g (4.4 mmol) of DEDC–Na in 10 $cm^3$ water was added. After 40 min at 60°C, the organic products were extracted by chloroform ($3 \times 30$ $cm^3$), and the solution dried and concentrated. The resulting mixture was chromatographed over silica gel using diethyl ether as eluant. Concentration of the last yellow fractions gave a yellow powder. $m = 20$ mg (41 μmol, 41%). m.p. = 245°C (dec). $^1$H-NMR (400.13 MHz, DMSO-$d_6$) $\delta$ (ppm): 1.10 (t, 12H, $CH_3$); 3.70 (m, 4H, $CH_2$–Ha); 3.82 (m, 4H, $CH_2$–Hb). $^{13}$C-NMR (100.2 MHz, DMSO-$d_6$) $\delta$ (ppm): 13.2 ($CH_3$); 46.4 ($CH_2$); 230.2 ($CS_2$). MS (CI, $NH_3$) $m/z$ 498 (100) $[M+H]^+$ ($^{187}$Re); 496 (42) $[M+H]^+$ ($^{185}$Re). IR ($cm^{-1}$): 1523 ($\nu_{CN}$); 1077 ($\nu_{CS}$); 1010 ($\nu_{Re\equiv N}$). $C_{10}H_{20}N_2S_4Re$: calc.: C, 24.20; H, 4.06; N, 8.5. Found: C, 24.30; H, 4.00; N, 8.70%.

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