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Synthesis of pentadentate mixed *N/S* dithiolate chelating ligands derived from heterocycles and 2-mercaptoethylamines

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Abstract

Condensation of 2,6-pyridinedialdehyde with 2-mercaptoethylamines or 2-alkylthioethylamines yielded 2,6-bis(substituted-2-thiazolidinyl)pyridine or 2,6-bis-((2-alkyl-thio)ethylimino)methylpyridine. The thiazolidines can be reductively opened to give 2,6-bis-((substituted-2-thioethyl)aminomethyl)pyridines. Alternatively, the latter may be synthesized by reductive amination of 2,6-pyridinedialdehyde with 2-mercaptoethylamines. Reaction of 2,5-thiophenedicarbonyl chloride with 2-mercaptoethylamines led to *N,N'*-bis(substituted-2-thioethyl)-2,5-thiophenedicarboxamides. 2,6-Bis-((substituted-2-thioethyl)aminomethyl)pyridines and *N,N'*-bis(substituted-2-thioethyl)-2,5-thiophenedicarboxamides are novel pentadentate mixed *N/S* dithiolate chelating reagents which can form ferric complexes of biomimetic importance.

Keywords: pyridines; thiophenes; chelation; thiazolidine.

Pentadentate mixed *N/S* dithiolate ligands are expected to form octahedral ferric complexes of biomimetic importance with an auxiliary replaceable ligand. As an example, the metal center of nitrile hydratase (NHase) has been shown to be a ferric ion coordinated with two nitrogens, three thiolates and a water molecule in octahedral geometry.[1] The enzyme catalyzes the hydration of nitriles to give the corresponding amides. Nitrile hydratase has been used in the multi-kiloton production of acrylamide[2] and the asymmetric synthesis of amides.[3] However, due to the facile oxidation of thiols or thiolates to disulfide (Scheme 1),[4] well characterized ferric complexes of pentadentate mixed *N/S* dithiolate ligands are relatively rare.[5] The oxidation is so dominant that, in many cases, isolation of such ligands from reaction mixtures leads to mixtures of product and oxidized products, even in an inert atmosphere. Further purification leads to further oxidation due to contamination by air.

Conventionally, in synthesizing thiol or thiolate compounds, thiol groups need to be protected. However, deprotection under harsh reaction conditions often promotes oxidation and thus makes it difficult to isolate the final product in pure form. 2-Aminoethanethiols (**1**)[6] have been shown to react with aldehydes to give thiazolidines.[7] Vahrenkamp used this method to synthesize **6d** and opened the

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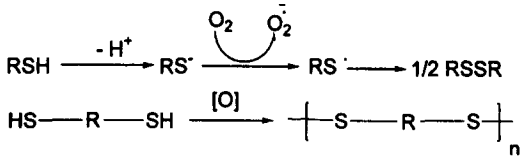
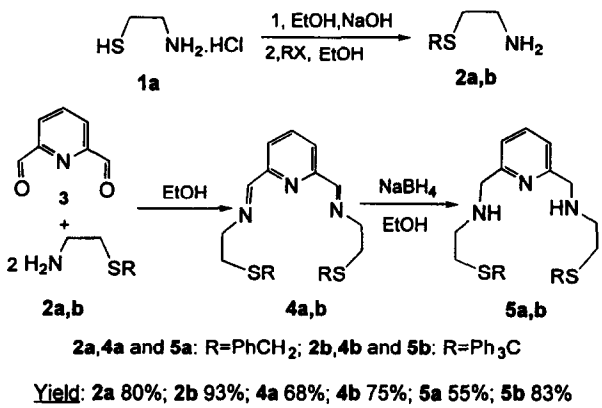


Scheme 1.

thiazolidine rings by a large amount of $NaBH_4$ to afford **7d**.[8] Our attempts to synthesize **7d** showed that it is very easily oxidized, while the intermediate thioazolidine **6d** is much easier to isolate and is quite stable. This seems to be a general method for the synthesis of heterocyclic N_3S_2 dithiolate ligands, and further investigation will probably lead to some novel N_xS_y dithiolate ligands as precursors to models of metalloproteins such as nitrile hydratase.

The reaction of 2-aminoethanethiol hydrochloride (**1a**) with benzyl chloride or trityl bromide gave 2-alkylthioethylamines (**2**). 2-Alkylthioethylamines (**2**) reacted with 2,6-pyridinedialdehyde (**3**), obtained in 97% yield from oxidation of 2,6-pyridinedimethanol,[9] in a 2:1 ratio yielded 2,6-bis((2-alkylthio)ethylimino)methylpyridine (**4**). These Schiff bases (**4**) can be reduced to 2,6-bis((2-alkylthio)ethylamino)methylpyridines (**5**) by $NaBH_4$ (Scheme 2). Attempts to deprotect **5** to form **7a** with Na/NH_3 or Hg^{2+}/H_2S led exclusively to polymerized products (Scheme 1).



2a,4a and **5a**: R=$PhCH_2$; **2b,4b** and **5b**: R=Ph_3C

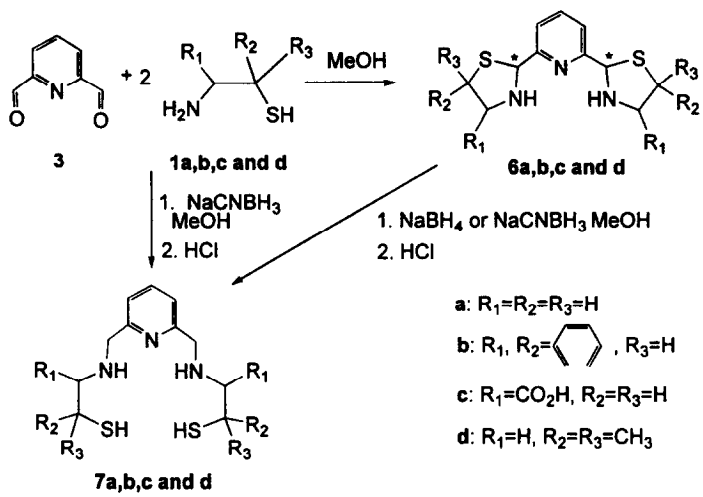
Yield: **2a** 80%; **2b** 93%; **4a** 68%; **4b** 75%; **5a** 55%; **5b** 83%

Scheme 2.

2,6-Pyridinedialdehyde (**3**) reacted with 2-aminoethanethiol hydrochloride (**1a**),[10] 2-aminothiophenol (**1b**) and L-cysteine hydrochloride (**1c**) in a 1:2 ratio to give **6a**, **b** and **c** (Scheme 3). These reactions proceeded well in alcoholic solvents and the products precipitated out of the reaction mixtures, after stirring for 30 min–2 h. In the case of 1-amino-2-methylpropane-2-thiol or its hydrochloride salt (**1d**),[11] the expected product **6d** was not obtained under similar reaction conditions. This may be due to steric hindrance presented in **1d**.

Compounds **6a** and **6b** have two chiral centers and a C_2 axis. They are thus expected to yield three stereoisomers. ^1H NMR showed that the products are 1:1 mixtures of two of the three possible stereoisomers in both cases. Although **6c** has four chiral centers, with two from L-cysteine, it is still expected to have three stereoisomeric products. A 1:1:1 product mixture was found in this case.

The stereoisomeric mixtures of **6a**, **b** and **c** can be reductively opened to give **7a**, **b** and **c** as the only products, respectively (Scheme 3). This has been achieved by using $NaCNBH_3$ under acidic conditions for **6a**, or $NaBH_4$ for **6b** and **6c**. Products have been isolated as colorless crystals of their hydrochloride salt in the case of **7a**, as the free form in the case of **7b**, or as a white precipitate of their sodium salt in the case of **7c**. Alternatively, compounds **7** have been synthesized by reductive amination of **3** with **1** using



Yield: **6a** 97% (HCl salt); **6b** 74%; **6c** 85%;

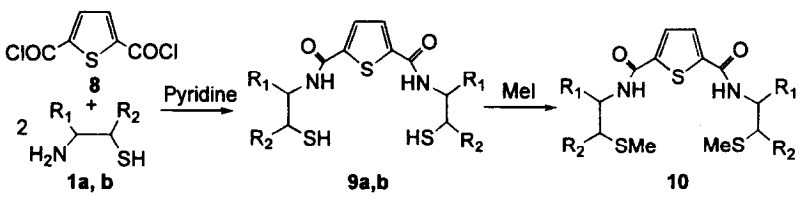
7a 90% (HCl salt); **7b** 88%; **7c** 62% (Na salt); **7d** 46% (HCl salt)

Scheme 3.

$NaCNBH_3$ (Scheme 3). This is especially convenient for **7c** and **7d** where either the product is easy to isolate as in the case of **7c** or the condensation product is difficult to synthesize, as with **6d**.

As an example,[12] to a stirred methanol solution of **6a**, excess $NaCNBH_3$ was added portionwise over a period of 1 h. Meanwhile HCl gas saturated methanol was added dropwise to keep the solution acidic. Stirring was continued for 1 h and the solvent was removed under reduced pressure. Then a mixed solvent of methanol and ethyl acetate was added to dissolve the organic product. Solution was then passed through a silica gel mini-column and the solvent was removed in a controlled manner via a water aspirator, leading to **7a** as colorless crystals.

2,5-Thiophenedicarbonyl chloride (**8**)[13] reacted with **1a** and **1b** to form *N,N′*-bis(substituted-2-thioethyl)-2,5-thiophenedicarboxamides (**9**). Product **9a** was isolated in crystalline form from its alcoholic solution under an inert atmosphere. Product **9b** was difficult to isolate in pure form for the reason given in Scheme 1, but was trapped by adding CH_3I and isolated as *N,N′*-bis(2-methylthiophenyl)-2,5-thiophenedicarboxamide (**10** (Scheme 4)).



1a and **9a**: $R_1=R_2=H$; **1b**,**9b** and **10**: R_1, R_2= 

Yield: **9a** 62%; **10** 66%

Scheme 4.

The synthesis of **9a** may serve as an example.[12] Into a flask containing 2-mercaptoethylamine hydrochloride (**1a**), pyridine was added to dissolve **1a**. Then a half molar ratio of 2,5-thiophenedicarbonyl chloride (**8**) was added as the crystalline solid. The mixture was stirred for 2 h and neutralized with a degassed alcoholic NaOH solution. Solvents were removed by an oil pump and the residue was treated

with methanol. The solid was filtered off, and the clear solution was subjected to quick evaporation under reduced pressure via a water aspirator leading to the formation of **9a** as colorless crystals.

Compounds **7a**, **7b**, **9a** and **9b**[14] formed green ferric complexes. MS characterization of the single crystals of the ferric complex of **7a** showed the presence of a chloride ion at the sixth coordination site. EPR and UV–vis showed that the complex is low spin, with a ligand to metal charge transfer band at 645 nm, similar to that of nitrile hydratase. Further studies on the metal complexes of **7a**, **7b**, **9a** and **9b** are currently under investigation.

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