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DESIGN AND SYNTHESIS OF THIAZOLE AND THIAZOLIDINE METALLO-SUPRAMOLECULAR NETWORKS

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Abstract *A mild and selective procedure for the synthesis of 4-carboxy thiazoles and thiazolidines starting from naturally occurring cysteine by condensation with aldehydes is described. The optimized procedure, taking advantage of the positive effect of microwave irradiation on the MnO_2-mediated oxidation step, is suitable for multigram scale. Coordination of these ligands towards a variety of transition metal ions gave new interesting metallorganic supramolecular architectures in which an extensive 3D network is created through hydrogen bonding.*

Keywords Amino acid; coordination complexes; thiazoles; thiazolidines

INTRODUCTION

Nitrogen-containing heterocycles have been widely used as ligands as they may easily support, *via* chelation or multimetallic coordination, the assembly of polymeric, polydimensional architectures. In particular they are able to establish a variety of noncovalent interactions, such as dipole–dipole and hydrogen-bonding.[1] Mixed N,S-heterocycles such as thiazolidines or thiazoles have received much attention in this area and, for instance, nicotinate and isonicotinate derivatives were recently chosen as promising organic connectors in crystal engineering, because they are able to provide both highly directional coordinative metal-to-ligand bonds and flexible complex-to-complex hydrogen bonds.[2] In consideration of that, we decided to screen some new carboxy thiazole–based ligands in order to obtain a better insight on the substituent effects to direct the 3D self-assembly of coordination complexes with transition metals. Thus we we turned our attention to the optimization of synthetic methodologies for the large-scale preparation of thiazole-based carboxylates.[3] In this article we report our results in this area, together with the first studies on the coordination chemistry of such ligands with Co(II) and Zn(II), which lead to the

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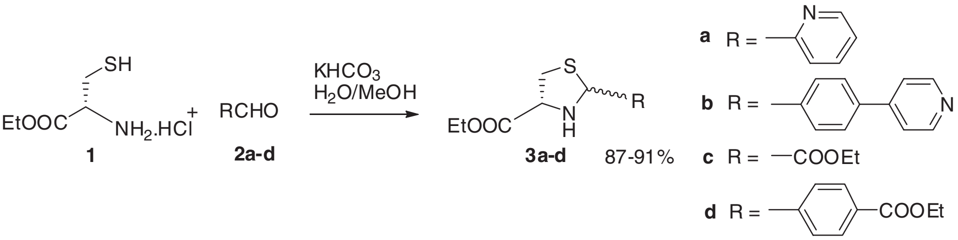
synthesis of a new family of complexes with interesting supramolecular assemblies in the solid state, mainly due to extensive 3D hydrogen-bonded networks.

RESULTS AND DISCUSSIONS

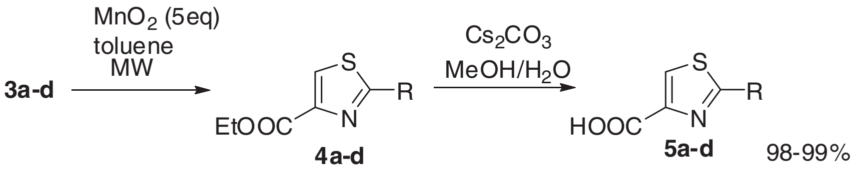
Cyclization of cysteine side-chains onto carbonyl groups yielding thiazole five-membered heterocycles is a well established procedure[4] that has found many applications.[5] Following this approach, L-cysteine ethyl ester **1** was reacted with different pyridyl- or carboxaldehydes **2a–d** to afford the corresponding thiazolidine derivative **3a–d** as shown in Scheme 1.



Scheme 1

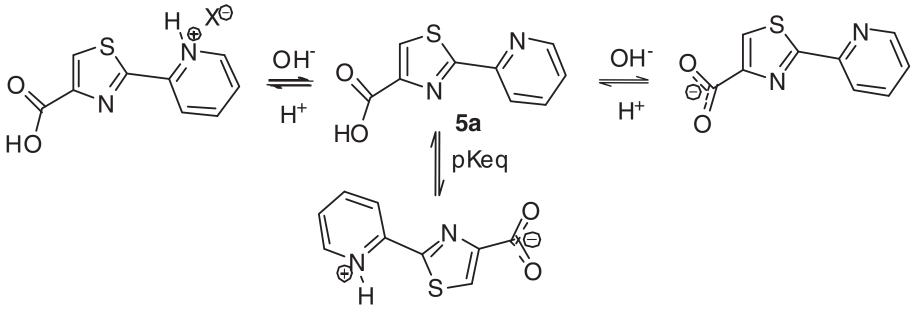
Thus thiazolidines **3a–d** were converted into the corresponding thiazoles **4a–d** *via* oxidative dehydrogenation. Several methods are described to perform this transformation ($CBrCl_3$/DBU,[6] DDQ,[7] NiO_2[5a,8]), albeit drawbacks such as low yields and harsh and hazardous reaction conditions often hamper large scale synthesis. In our case, oxidation was conveniently performed using the commercially available activated MnO_2,[4a,9] which provided the desired thiazoles in very good yields, although under rather harsh conditions, namely benzene as solvent in the presence of pyridine for 24 h at 55°C, using a 25-fold excess of oxidant.

In order to find milder and more general reaction conditions, we decided to investigate the effect of microwave irradiation[10] on this oxidation and, in keeping with our expectations, the use of this technique shortened the reaction time significantly, leading to the quantitative formation of thiazoles **4a–d.** Although an excess of MnO_2 was still necessary under optimized conditions (30 s, 300 W MW, 100°C), this was reduced to 5 eq., toluene was used instead of benzene, and the use of pyridine was not necessary (Scheme 2). Ester saponification with Cs_2CO_3 in aqueous methanol afforded the corresponding carboxythiazoles **5a–d**, which were isolated after crystallization from acid water.[3]



Scheme 2

Complexation ability of **5a** towards different transition metals was studied. The simultaneous presence of an acid and a basic site within the same molecule makes this ligand very interesting from a supramolecular point of view, engaging in multiple coordination modes that are related to its pH-dependent protonation–deprotonation equilibria in water (Scheme 3).



Scheme 3

The regio-isomer of **5a** containing a *para-* or *meta*-pyridyl substituent in the 2-position is known to be capable of generating 3D coordination polymers with silver(I), zinc(II), and copper(II).[11] In our case, discrete complexes are formed, where the *o*-pyridyl substituent (either protonated or deprotonated) is involved in intramolecular hydrogen bonding. This is shown in Figure 1, where the crystal structures of Zn(II) and Co(II) complexes are reported.

In acid medium, a protonated nitrogen atom on the pyridyl substituent is present and complex **A** is formed. The zinc atom is six-coordinated, with the ligand occupying the equatorial plane and two water molecules *trans* to each other complete the octahedral coordination geometry. The "pyridinium-like" ring is involved in a N(2)-H(2)···O(2)#

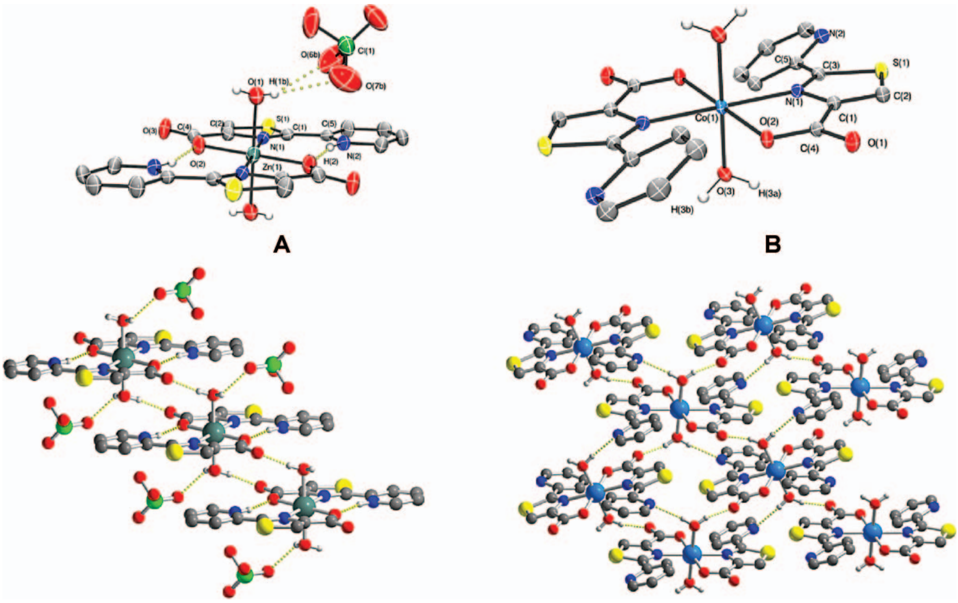


Figure 1 Crystal structure of Zn(II) complex **A** and Co(II) complex **B** with **5a** and their solid state packing evidencing the hydrogen bonding network. H atoms on the organic ligands are omitted for clarity. Weak interactions are shown in dotted lines. The crystallographic data files (CIFs) for complexes **A** and **B** have been deposited (CCDC Numbers 781930-781932). (Color figure is available online.)

hydrogen bonding. Additional interactions between the *aquo* ligands, C=O groups of neighboring molecules, and the disordered perchlorate ions are present, leading to a complex network of embedded H-bonds that holds all the components together in a compact assembly (Figure 1).

The reaction of cobalt(II) acetate tetrahydrate with **5a** at pH = 5 produces purple crystals of complex **B**. The coordination geometry around Co(II) is octahedral (Figure 1), with the same ligand disposition seen in complex **A.** The O(3)-H(3B)···O(1)# hydrogen bond between the aquo ligands and the carboxylic groups of neighboring molecules in the lattice is still present. The not protonated N(pyridyl) engages a *trans*-(N,N) disposition, which is the most energetically stable, and an additional O(3)-H(3A)···N(2)# hydrogen bond with the other proton on the aquo ligands. In both cases, the presence of an extended hydrogen bonding network due to the presence of several polar groups in the asymmetric unit confers a "pseudo-polymeric" nature to these solids, being insoluble in all solvents.

CONCLUSIONS

We have reported a selective and general procedure for the synthesis of 4-carboxythiazoles, showing that both reaction time and the need of polluting reagents can be dramatically reduced by MW irradiation during the oxidation step. The coordination ability of **5a** in aqueous environment has been analyzed, leading to new complexes in which an extensive 3D network is created through hydrogen bonding. Under this perspective, this study can to be considered as the first step towards the synthesis of thiazole-based metal-organic frameworks (MOFs) for potential applications in the field of gas storage.

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