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Benzoylamido-substituted thiazoles and thiazolidines and their rhenium complexes

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ABSTRACT

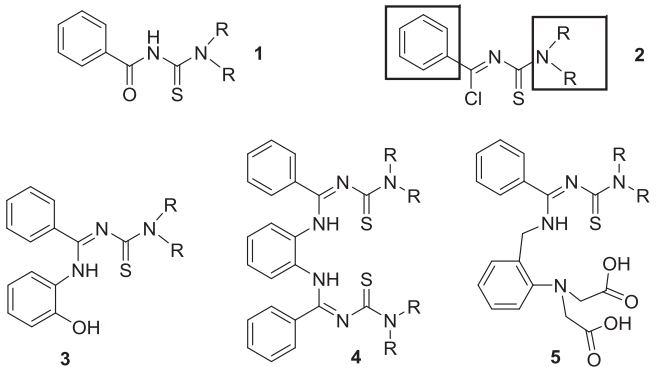
Cyclization reactions dominated attempts to synthesize *N*-alkyl- or *N*-dialkyl-*N*′-benzoylthiourea ligands having an alkyne group at the amine residue. While exclusively thiazolidine or thiazole derivatives could be isolated during reactions of benzoyl chloride, $(NH_4)SCN$ and *N*-methypropargylamine, an open-chain benzoylthiourea was obtained with unsubstituted propargylamin. But also the latter product isomerized under the influence of a strong base and heat to the corresponding cyclic derivatives.

The resulting heterocycles, a 5-methylenthiazolidine (HL4) and a 5-methylthiazole (HL5), react with $(NBu_4)[ReOCl_4]/PPh_3$ mixtures or $[ReOCl_3(PPh_3)_2]$ under formation of the neutral Re(III) complex $[ReCl_2(PPh_3)_2(L4)]$ and the cationic Re(V) compound $[ReO_2(PPh_3)_2(HL5)]$, respectively. The products have been isolated in crystalline form and studied spectroscopically and by X-ray diffraction.

1. Introduction

N,*N*-Dialkyl-*N*′-benzoylthioureas (**1**) are potentially bidentate ligands and form stable complexes with a large variety of metal ions including the $\{Re{=}O\}^{3+}$ and $\{Tc{=}O\}^{3+}$ cores [1–7]. Corresponding nickel(II) complexes have been used for the synthesis of thiocarbamoylbenzimide chlorides (**2**) [8], which are versatile building blocks for the synthesis of chelating ligands of variable denticity. Some tri-, tetra- and pentadentate ligands of this class have been prepared recently by reactions with appropriate amines (**3**–**5**), and their rhenium(V) and technetium(V) complexes have been introduced recently [9–11]. Since such stable metal complexes possess considerable potential for applications in diagnostic and therapeutic nuclear medicine, the search for appropriate anchor groups for orthogonal bioconjugation becomes interesting. Possible positions for such modifications in the thiocarbamoyl part of the final multidentate ligands are the phenyl ring and the peripheral amino group of the benzamidine as is indicated in the formula of compound **2**.

In the present paper, we describe our attempts of the synthesis of an *N*,*N*-dialkyl-*N*′-benzoylthiourea with a side-chain containing an alkyne residue for prospective coupling reactions with azide-containing biomolecules following a standard 'Click' protocol [12].



2. Results and discussion

2.1. Formation and isomerization of the methylenethiazolidin *L1*

The synthesis of benzoylthioureas is usually made by one pot reactions of benzoyl chloride with thiocyanate salts and amines using dry acetone as solvent and triethylamine as a supporting base [13]. Keeping in mind that such reactions work best with secondary amines, we attempted the introduction of a terminal alkyne by the use of *N*-methylpropargyl amine in refluxing acetone. In the case of this reaction, however, cyclization was

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observed and finally an imidothiazolidine derivative (**L1**) was obtained. The formation of heterocycles during reactions of thiocyanates with propargyl derivatives is not without precedent and the formation of thiazoles has been reported before for a number of similar reactions [14–16]. The product of the present reaction could be isolated with high yields as a pure colorless solid. All our attempts to reduce the reaction time and reactions at lower temperatures did not result in the formation the open-chain benzoylthiourea, but only reduced the yields. Prolonged heating in ethanol, however, causes isomerization and the thiazole derivative **L2** is formed (Scheme 1). The identities of both compounds have been proven by spectroscopic methods and by X-ray diffraction.

First evidence of cyclization and formation of the methylenethiazolidine **L1** is given with the ^{1}H NMR spectrum of the compound, in which the typical signal of a propargyl group (a triplet between 2.0 and 2.5 ppm, caused by long range couplings between the alkyne hydrogen and the methylene group) is missing. Instead of this signal, a multiplet at 5.30 ppm was found, which could be assigned to the terminal hydrogen atoms of the formed exo-double bond. Another signal at 4.37 ppm has the same intensity and is caused by the methylene group of the thiazolidine ring. The resonance of the methyl group causes a singlet at 3.33 ppm. The IR-spectrum of **L1** shows the band of the $\nu_{C=O}$ stretch at 1614 cm^{-1}. The absence of sharp absorption bands in the ranges between 2300 and 2100 cm^{-1} and between 3400 and 3500 cm^{-1}, which should be observed in the presence of a propargyl residue, is another proof for the cyclic nature of the product.

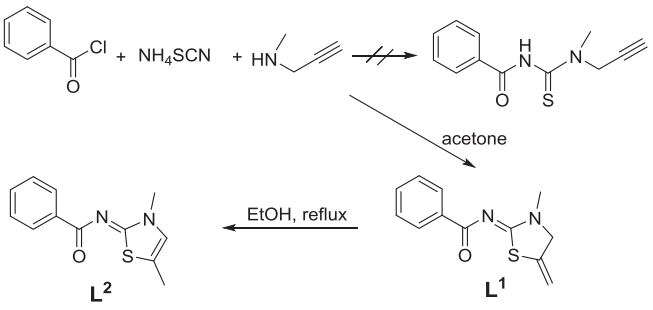
The isomerization of **L1** in boiling ethanol is clearly reflected by the spectroscopic data. The ^{1}H NMR signals of the methylenethiazolidine at 4.37 ppm disappear in the spectrum of **L2**. All further signals remain almost unchanged.

The results of the crystal structure analyses confirm the findings of the spectroscopic data. Fig. 1 shows a comparison of the molecular structures of the methylenethiazolidin **L1** and the thiazole **L2**. While the heterocycle in **L1** shows marked deviations from planarity (0.028 (1) Å for C23), the thiazole ring is almost perfectly planar with maximum deviation of 0.001(2) Å. The isomerization of **L1** in boiling ethanol is also supported by the detected bond lengths and angles (Table 1) and the fact that the positions of all hydrogen atoms could be derived from the final Fourier maps at the correct positions.

In order to understand the driving force of the unexpected isomerization of **L1**, a DFT calculation was undertaken [17]. The optimized parameters for both compounds are in good agreement with the experimental ones. The bond lengths differ by less than 0.04 Å (with exception of the C2–S1 bond, where the difference is 0.1 Å) and the angles by 4° or less. A comparison of the electric energies of optimized structures of the two structural isomers **L1** and **L2** strongly suggests that the latter compound is more stable by a value of more than 50 kJ/mol. This energetic difference is nearly independent of the employed methods as well as of the basis set combinations (Table 2). These facts together with the slight discrepancy between the experimental and optimized bonding parameters underlines the reliability of performed calculations and identify the thiazole form of the two isomers as the more stable.

2.2. Synthesis and isomerization of H_2L3

Unlike the reaction of benzoyl chloride and $(NH_4)SCN$ with *N*-methylpropargylamine, an analog reaction with unsubstituted propargylamine results in the formation of the open-chain benzoylthiourea **H_2L3** (Scheme 2) as can clearly be derived from the ^{1}H NMR and IR spectra of the product. The ^{1}H NMR spectrum in $CDCl_3$ shows the typical propargylic signals: (i) a triplet with a coupling constant of 2.6 Hz at 2.35 ppm caused by the terminal



Scheme 1. Formation of **L1** and **L2**.

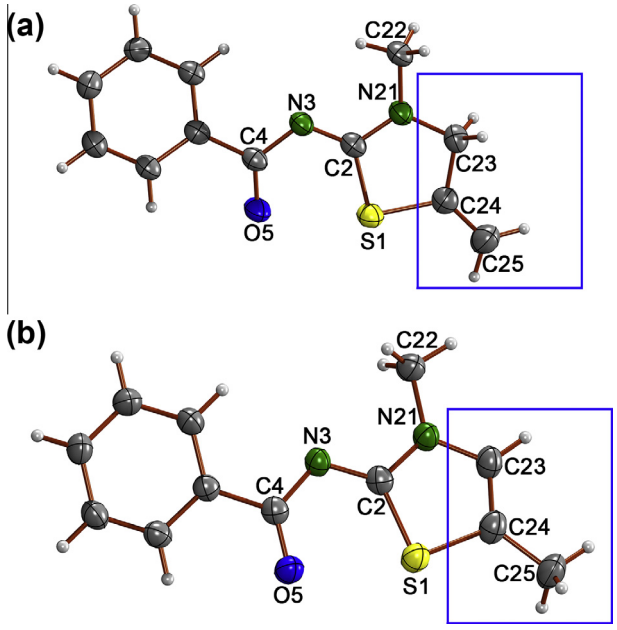


Fig. 1. Molecular structures of **L1** and **L2**. Main structural differences appear in the highlighted rectangles. Thermal ellipsoids represent 50% probability.

Table 1
Selected bond lengths (Å) and angles (°) in **L1** and **L2**.

Bond length	L1/L2	Bond length	L1/L2
O5–C4	1.234(2)/1.242(2)	C2–N21	1.335(2)/1.347(2)
C4–N3	1.375(2)/1.362(2)	N21–C23	1.448(2)/1.390(2)
N3–C2	1.314(2)/1.326(2)	C23–C24	1.496(2)/1.344(2)
C2–S1	1.762(2)/1.743(2)	C24–C25	1.329(2)/1.489(2)
Angle	**L1/L2**	**Angle**	**L1/L2**
O5–C4–N3	125.1(1)/125.1(2)	N21–C23–C24	107.5(1)/113.6(2)
N3–C2–S1	127.0(1)/129.3(2)	S1–C24–C25	123.3(2)/121.3(2)
S1–C2–N21	111.7(1)/109.5(2)	C23–C24–C25	125.8(1)/128.3(2)

Table 2
Energies of optimized geometries of **L1** and **L2** at different levels of theory.

Basis sets	Level of theory	E_{L1} (Hartree)	E_{L2} (Hartree)	$\Delta E_{el} = E_{L2} - E_{L1}$ (kJ/mol)
6-311G	MP2	−1044.062	−1044.082	−52.51
	B3LYP	−1047.373	−1047.394	−55.14
6-311G++	MP2	−1044.100	−1044.119	−52.51
	B3LYP	−1047.385	−1047.406	−55.14
6-311G++(d,p)	MP2	−1045.185	−1045.209	−63.01
	B3LYP	−1047.612	−1047.634	−57.16