DOI: 10.1002/asia.201000063

A Selective Chromogenic Probe for Mercury(II) and Cyanide in Aqueous Buffered Solution from a Cycloaddition Reaction of an Ynamine to Polycyclic Dithiolethiones

Pedro Fuertes, Daniel Moreno, José V. Cuevas, María García-Valverde, and Tomás Torroba*[a]

We dedicate this paper to the memory of Carlos Sáenz de Tejada "Panucci" who passed away July 30th 2009

Abstract: The synthesis of some new polysulfur-nitrogen heterocycles by cycloaddition of an ynamine to bisdithiolothiazine ketothiones or dithiones is described and the interconversion between regioisomers is studied by DFT calculations, showing that the double bond isomerizes at room temperature. This series is a new selective and sensitive chromogenic probe for the naked-eye detection of mercury(II) cation and cyanide anion in buffered (HEPES 0.05 M, pH 7.14) water/acetonitrile 1:1 mixture, with sub-micromolar sensitivity, and constitutes the first example of a new class of colorimetric chemical probes for Hg^{2+} and CN^-.

Keywords: chromogenic probes · cyanides · environmental chemistry · heterocycles · mercury

Introduction

Environmental mercury contamination is a major concern because of the huge amount of mercury released to the environment by human activities and because of the persistence of mercury in the environment.[1] Thus, the volatile metal and the water soluble cations, mercury(II) and methylmercury(II), are interconnected in the environment through the natural cycle of mercury. Therefore, water and food products, especially fish, from contaminated regions need to be monitored for safety.[2] Chemical probes are useful for fast optical detection of mercury(II) cations,[3] usually acting by complexation or reaction of Hg^{2+} with colorimetric[4] or fluorogenic[5] reactive dyes. Several specific dosimeters of Hg^{2+} are sulfur-containing reagents that take advantage of the thiophilicity of Hg^{2+}, undergoing a color[6] or a fluorescence[7] change. We have prepared several polysulfur-nitrogen heterocycles by sequential cycloadditions to polycyclic dithiolethiones of electron-poor acetylenes.[8] Ideal probes for Hg^{2+} should come from electron-rich acetylene starting materials that would improve the complexing ability of cycloadducts. Ynamines are good electron-rich acetylenes, their cycloadditions to monocyclic dithiolethiones have been reported once.[9] In our hands, unsubstituted morpholinoacetylene did not react with our polycyclic dithiolethiones, but 1-morpholino-2-trimethylsilylacetylene, in the presence of scandium triflate, gave clean reactions with ketothiones and dithiones to afford mono- and bis-adducts, respectively, which were tested for their suitability as chemical probes. Therefore, in this paper, we want to report the synthesis of new polysulfur-nitrogen heterocyclic compounds and the results of the best suited from them as a new colorimetric probe for the selective detection of Hg^{2+} and CN^- in buffered water/acetonitrile 1:1 mixture.

Results and Discussion

The synthesis was performed by simply mixing 1-morpholino-2-trimethylsilylacetylene, bis[1,2]dithiolo[1,4]thiazine ketothiones **1a**–**c** or dithiones **2a**–**c**, at room temperature in CH_2Cl_2 for 10 (for **3a**–**c**) to 20 min (for **4a**–**c**) in the presence of $Sc(OTf)_3$ to afford mono- and bis-adducts **3a**–**c** and **4a**–**c**, respectively. Shown in Scheme 1 is the preparation of the cycloadducts **3a**–**c** and **4a**–**c**. Compounds **3a**–**c** and **4a**–**c**

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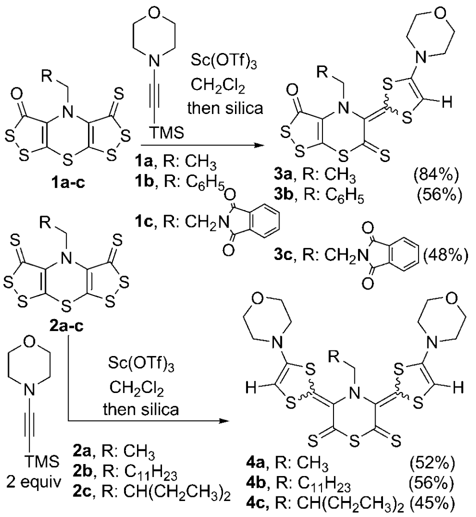
[a] Dr. P. Fuertes, D. Moreno, Dr. J. V. Cuevas, Dr. M. García-Valverde,
Prof. Dr. T. Torroba
Department of Chemistry
University of Burgos
Faculty of Science, 09001 Burgos (Spain)
Fax: (+34) 947258831
E-mail: ttorroba@ubu.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000063.



Scheme 1. Synthesis of chemical probes **3a**–**c** and **4a**–**c**.

were obtained in 48–86 % yields as mixtures of desilylated *Z*/*E* regioisomers after column chromatography protodesilylation in silica gel,[10]and were characterized by using the usual spectroscopic and analytical techniques. The evolution of the cycloaddition-protodesilylation process was followed by using ^{1}H NMR spectroscopy. The TMS group was present in the cycloadduct in the initial reaction mixture, but was not observed before the column chromatography (see the Supporting Information). For such cycloaddition between polar reagents, we expected a high degree of regioselectivity, but the NMR spectra of **3a**–**c** showed equimolecular mixtures of both regioisomers, complicated by the presence of conformational isomers because of the folded structure of the 1,4-thiazine nucleus and the slow nitrogen-inversion process. Although the products were obtained as amorphous solids, the original folded structure was easily confirmed by single crystal X-ray diffraction of one of the starting materials, **2b**, which is shown in Figure 1. The packing of **2b** is dominated by thione-dithiole S–S polar interactions and London dispersion forces of the hydrocarbon chains, giving rise to the well-ordered material shown in Figure 1 B.

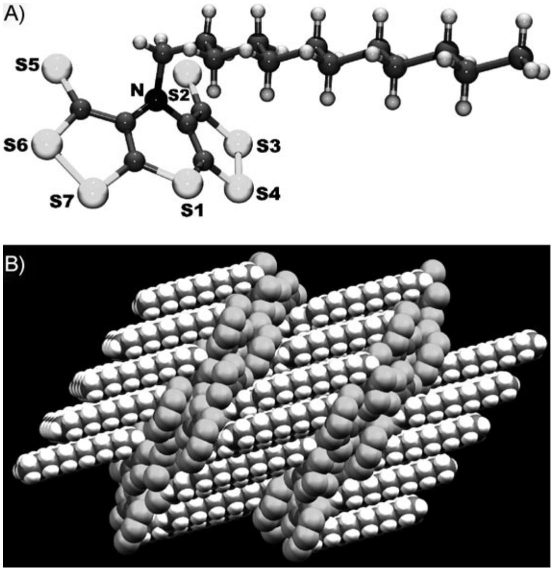


Figure 1. A) Single crystal X-ray diffraction of **2b**. B) Crystal packing of **2b**.

The lack of regioselectivity found in products **3a**–**c** and **4a**–**c** may be a result of exocyclic double bond isomerization after cycloaddition,[8b] a process that we have studied using DFT calculations with Gaussian 03,[11] using the functional B3LYP and the bases 6-311G+(d,p) and 6-311G+(2df,2pd). First, a geometric optimization of the two isomers ***Z*/*E*-3a** was performed and then interconversion between them was studied, from which a transition state was localized (Figure 2). These DFT theoretical calculations were performed at the B3LYP/6-311G+(d,p) level of theory. DFT calculations predict that the interconversion process of **Z-3a** into ***E*-3a** is exergonic by 0.9 kcal mol^{-1}, requiring a free energy of activation of 27.4 kcal mol^{-1}. Single point DFT theoretical calculations performed at the B3LYP/6-311G+-(2df,2pd) level of theory afforded comparable results. In this case, the interconversion process of **Z-3a** into ***E*-3a** is exergonic by 2.1 kcal mol^{-1}, requiring a free energy of activation of 27.7 kcal mol^{-1}. In agreement, variable temperature NMR experiments of **3a** did not show coalescence of the two methyne signals at around 100 °C.

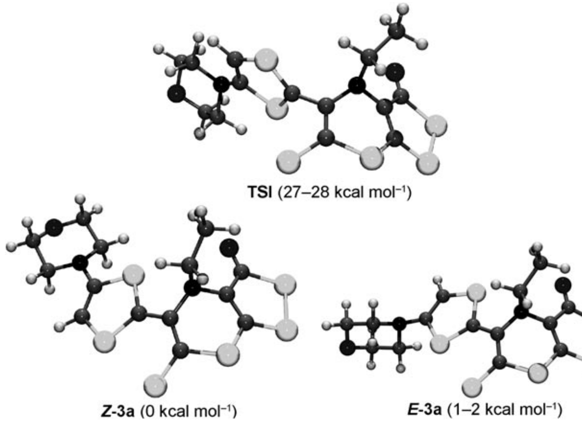


Figure 2. Calculated structures for ***Z*/*E*-3a** and the transition state (**TS1**).

Abstract in Spanish: Se describe la síntesis de nuevos heterociclos poliazufre-nitrógeno mediante la cicloadición de una inamina a bisditiolotiazina cetotionas o ditionas; la interconversión entre regioisómeros se estudia mediante cálculos DFT, mostrando que el doble enlace isomeriza a temperatura ambiente. Se describe el mejor término de estas series como una nueva sonda cromogénica selectiva para la detección a simple vista de catión mercurio(II) y de anión cianuro en mezcla tamponada de agua-acetonitrilo 1:1 (HEPES 0.05 M, pH 7.14), con sensibilidad sub-micromolar, que constituye el primer ejemplo de una nueva clase de sondas químicas colorimétricas para Hg^{2+} y CN^{-}.

Compounds **3a–c** display a deep purple color in solution, which changed in the presence of the most common cations or anions. All of them behave similarly when tested with the same cations or anions, independently of the *N*-alkyl group, therefore the behavior of the most representative example, **3a**, is reported. Addition of 3 equivalents of Hg^{2+} to 5×10^{-4} M solutions of **3a** ($\lambda_{max}=545$ nm, $\varepsilon=6424$ M^{-1}cm^{-1}, 10^{-4} M, MeCN) in MeCN/HEPES (0.05 M in water, pH 7.14), 1:1, resulted in a dramatic change of color from purple to blue-violet. This response was selective for Hg^{2+} under these conditions and addition of 3 equiv of the other cations: Ag^+, Ni^{2+}, Sn^{2+}, Cd^{2+}, Zn^{2+}, Pb^{2+}, Cu^{2+}, Fe^{3+}, Sc^{3+}, and Al^{3+}, as their perchlorate or triflate salts, resulted in no appreciable changes (Figure 3).

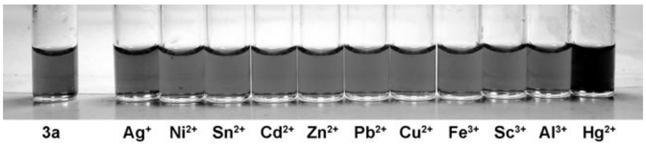


Figure 3. Colour changes of 5×10^{-4} M microsamples of 500 μL solution of **3a** in MeCN//HEPES (0.05 M, pH 7.14), 1:1, in the presence of 3 equiv of every cation.

The sensing action of **3a** and Hg^{2+} was equally effective in a mixture of a 5×10^{-4} M solution of **3a** and 2 equiv of every cation: Ag^+, Ni^{2+}, Sn^{2+}, Cd^{2+}, Zn^{2+}, Pb^{2+}, Cu^{2+}, Fe^{3+}, Sc^{3+}, and Al^{3+} in MeCN/HEPES (0.05 M in water, pH 7.14), 1:1, as solvent. A partial visual loss of color was observed after addition of one equiv of Cu^{2+} or three equiv Fe^{3+}, added as perchlorate salts, to 5×10^{-4} M solutions of **3a** in MeCN or MeCN/H_2O 9:1, owing to acid-catalyzed hydrolysis of the enamine moiety of **3a** (see the Supporting Information). A partial visual loss of color was also observed after addition of three equiv of Cu^{2+} to 5×10^{-4} M solutions of **3a** in MeCN/H_2O 7:3 or 1:1. In these solutions a distinct blue-violet color appeared after addition of three equiv of Ag^+. Therefore, the buffer used for the experiments was important for the selectivity of the response to Hg^{2+}, although the response of **3a** to Hg^{2+} was similar in all solvents studied. Quantitative UV/Vis titration of a 10^{-4} M solution of **3a** in MeCN/H_2O 1:1 and Hg^{2+}, added as perchlorate salt, showed that the original absorption maximum centered at $\lambda=550$ nm expanded as Hg^{2+} was added (Figure 4), generating one isosbestic point at $\lambda=470$ nm. The titration profile fitted nicely to a 1:1 binding model, and the association constant was calculated: $\log K=5.23\pm0.08$. The UV/Vis titration of a 10^{-4} M solution of **3a** in MeCN gave an association constant: $\log K=5.82\pm0.28$.

Job's plot analysis of the UV/Vis titrations carried out in MeCN revealed a maximum at a 50% mole fraction, in accord with the proposed 1:1 binding stoichiometry (Figure 5). The detection limit of a 10^{-4} M solution of **3a** in MeCN, calculated from the UV/Vis absorption spectrum using the blank variability method,[12] was 3.28×10^{-7} M.

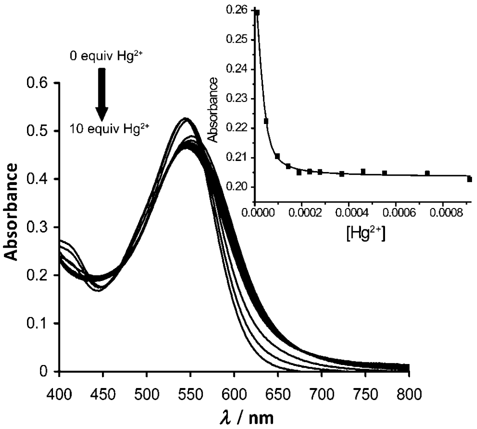


Figure 4. UV/Vis titration curves and titration profile of a 10^{-4} M solution of **3a** in MeCN/H_2O 1:1 with Hg^{2+}.

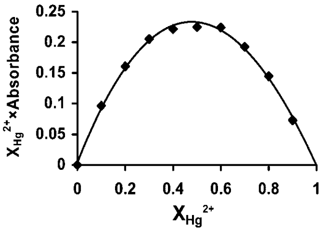


Figure 5. Job's plot analysis of **3a** (10^{-4} M in MeCN) with Hg^{2+}.

We also carried out ^{1}H NMR titration experiments of a 10^{-1} M solution of **3a** in CD_3CN with Hg^{2+} (Figure 6). By addition of increasing amounts of Hg^{2+} in CD_3CN, the two methyne signals at $\delta=5.9$ and 6.1 ppm, corresponding to both geometric isomers of **3a**, merge to one single signal at $\delta=7.1$ ppm, corresponding to complex **3a**[Hg^{2+}]. The methylene protons close to morpholine oxygen are almost unaffected, but the signal corresponding to the methylene protons, close to morpholine nitrogen, move to lower field, indicating that complexation by Hg^{2+} extracted charge from the 1,3-dithiole ring. In addition, the initially diastereotopic methylene protons of the *N*-ethyl group, seen as multiplets at $\delta=3.3$ and 3.4 ppm, are transformed into a well defined quartet signal at $\delta=3.4$ ppm after complexation. Therefore

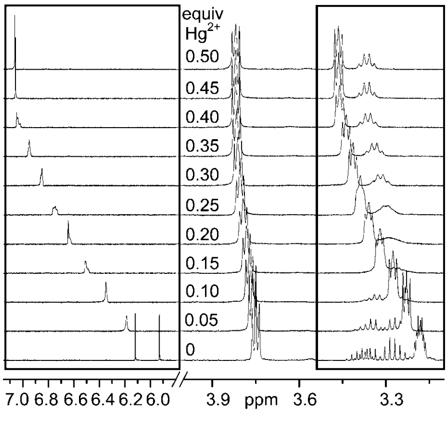
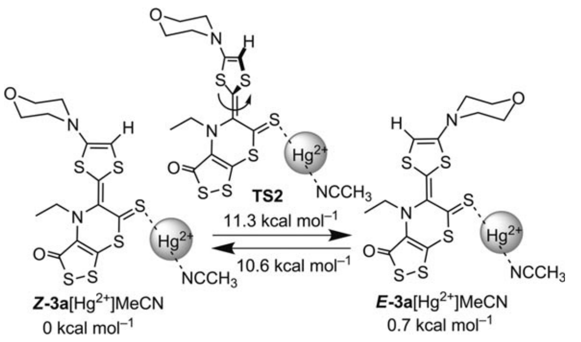


Figure 6. ^{1}H NMR titration of a 10^{-1} M solution of **2a** in CD_3CN with Hg^{2+}.

NMR titration indicated that complexation was probably effected through the thione group by forming a complex in which Hg^{2+} extends the conjugation between amine and thione groups, causing a bathochromic shift of the main absorption band in the UV/Vis spectrum. The structure of the complex was calculated with Gaussian 03[11] DFT using the functional B3LYP and the bases Lanl2DZ for Hg and 6-311G+(d,p) for the other elements.

Shown in Scheme 2 and Figure 7 are the models and calculated structures of both regioisomers ***Z*/*E*-3a**-[Hg^{2+}]·MeCN. The conversion of ***Z*-3a**[Hg^{2+}]·MeCN into ***E*-3a**[Hg^{2+}]·MeCN is an exergonic process of 0.7 kcal mol^{-1}. This little difference in energy is very similar to the one found for the non-coordinated isomers. Notwithstanding, a difference is found in the C=C double bond length between the six-membered and the five-membered heterocycles which enlarged to 1.43 Å in the models of complexes. The coordination of the metal does not change the thermodynamic stability of the geometric isomers. The transition state **TS2** that connects both structures through the rotation of the double bond between heterocycles was found. It shows a single imaginary frequency that is consistent to the rotation around the C=C double bond between both heterocycles. With these values, the obtained free energies of activation are 11.3 and 10.6 kcal mol^{-1}, respectively. The lowering in the values of these activation energies with respect to the non-coordinated models is consistent to the enlargement of the rotating C=C double bond that gives rise to a lowering in the bond order, therefore facilitating the rotation around the now enlarged bond. This fact permits a fast interconversion at room temp, therefore giving a single signal in the ^{1}H NMR profile.



Scheme 2. Calculated models and energies for ***Z*/*E*-3a**[Hg^{2+}]·MeCN and the transition state (**TS2**).

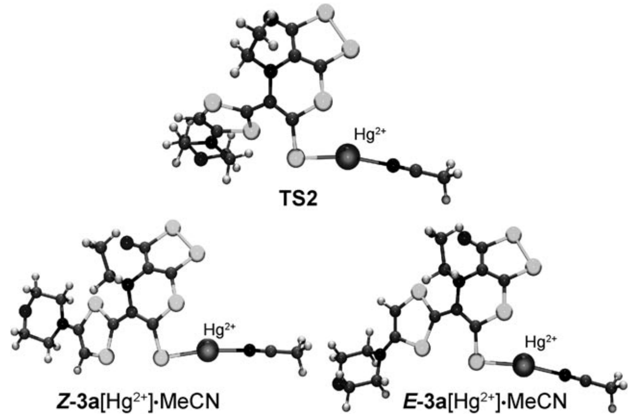


Figure 7. Calculated structures for ***Z*/*E*-3a**[Hg^{2+}]·MeCN and the transition state (**TS2**).

We have also optimized the structures of some possible cationic complexes having two ligands coordinated to a mercury(II) cation, [Hg**3a**$_2$]$^{2+}$, that should be possible in concentrated solutions. The previous models found with a ligand **3a** and a mercury(II) cation have shown a preference for the coordination of the mercury atom to the thione sulfur and a preferred orientation through the sulfur atom of the thiomorfoline moiety, so we used structures built with these premises. We used, as examples for the study, two models, one of them having two ligands with the same geometry, ***E*-3a**[Hg^{2+}]***E*-3a** and another one with two ligands with mixed geometry, ***E*-3a**[Hg^{2+}]***Z*-3a** and optimized both of them. As in previous cases, the differences in energy are small (0.9 kcal mol^{-1}) and account for the difference in energy between the geometric isomer which is different in every case (see the Supporting Information).

The sensing of Hg^{2+} by **3a** also worked supported on silica (Figure 8). Thus, a solution of **3a** in MeCN (5 mL, 10^{-4} M) was added to silica 60 (0.04–0.06 mm, 0.07 g, colorless), stirred for one minute, and the solvent evaporated to get the purple silica (Figure 8, left). Then, a solution of Hg^{2+} (2 equiv) was added and the solvent evaporated to get the blue-violet silica (Figure 8, centre). To test the reversibility of the silica test probe, a solution of 3,6-dioxa-1,8-octanedithiol **5** (2 equiv) was added and the solvent evaporated to get again the purple silica (Figure 8, right). The reversibility in the detection of Hg^{2+} by **3a** (10^{-4} M in MeCN/HEPES 0.05 M in water, pH 7.14, 1:1), in the presence of **5** (1 equiv) was also effective in solution (see the Supporting Information). The color changes were fast and clearly detected, therefore suitable for practical applications.

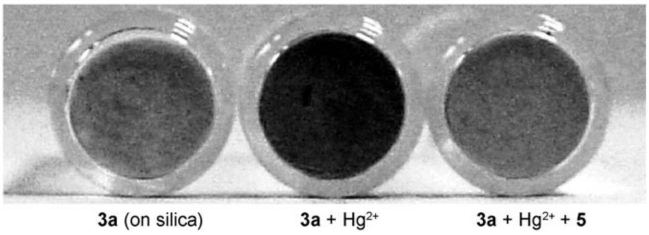


Figure 8. Colour changes of **3a** on silica before and after addition of Hg^{2+} and then **5**.

We also checked the suitability of compounds **4a–c** as chemical probes for Hg^{2+}. Their behavior was similar to that reported for **3a–c**, but **4a–c** were less colored and the selectivity for Hg^{2+} was lower, showing interferences with Ag^{+}, Cu^{2+}, and Fe^{3+} in all solvents studied.

Cyanide is one of the most toxic anions yet it is widely used industrially,[13] therefore development of chemical probes for cyanide anion is an area of interest.[14] Chemical probes based on nucleophilicity have proven successful.[15] As our systems could undergo nucleophilic additions, we decided to explore the interactions of derivatives **3a–c** with anions. Addition of 3 equiv of different anions added as their tetrabutylammonium salts to a 5×10^{-4} M solution of **3a** in MeCN/HEPES (0.05 M in water, pH 7.14), 1:1, resulted in a selective change of color from purple to red in the presence of CN^- (Figure 9). The same behavior was observed for the rest of compounds **3b–c**, but the selectivity of **4a–c** was again much lower, showing interferences with F^- in all solvents studied.

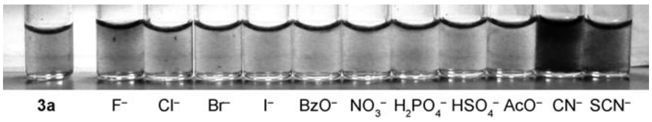


Figure 9. Colour changes of 5×10^{-4} M microsamples of 500 μL solution of **3a** in MeCN//HEPES (0.05 M, pH 7.14), 1:1, in the presence of 3 equiv of every anion.

The sensing action of **3a** and CN^- was equally effective in a mixture of a 5×10^{-4} M solution of **3a** and 2 equiv of the rest of the anions in MeCN/HEPES (0.05 M in water, pH 7.14), 1:1 and the sensing action of **3a** (10^{-4} M in MeCN/HEPES 0.05 M in water, pH 7.14, 1:1) and cyanide anion (1 equiv) was reversed to the original color by addition of trifluoroacetic acid (1 equiv) (see the Supporting Information). Quantitative UV/Vis titration of a 10^{-4} M solution of **3a** in MeCN/H_2O 1:1 and CN^-, added as Bu_4N^+ CN^- salt, showed that the original absorption maximum centered at $\lambda = 550$ nm underwent a hypsochromic shift, as CN^- was added (Figure 10), generating one isosbestic point at $\lambda = 396$ nm. The changes in absorbance as a function of $[CN^-]$ were fitted to a 1:1 binding equilibrium model, giving an association constant of $\log K = 4.74 \pm 0.06$ in MeCN/H_2O 1:1. The UV/Vis titration of a 10^{-4} M solution of **3a** in MeCN gave an association constant: $\log K = 5.21 \pm 0.07$.

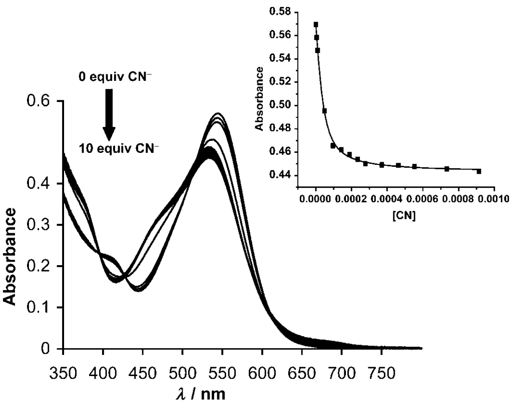


Figure 10. UV/vis titration curves and titration profile of a 10^{-4} M solution of **3a** in MeCN/H_2O 1:1 with CN^-.

Job's plot analysis of the UV/Vis titrations carried out in MeCN revealed a maximum at a 50% mole fraction, in accord with the proposed 1:1 binding stoichiometry (Figure 11). The detection limit of a 10^{-4} M solution of **3a** in MeCN and CN^-, calculated by UV/Vis absorption using the blank variability method,[12] was 3.46×10^{-7} M.

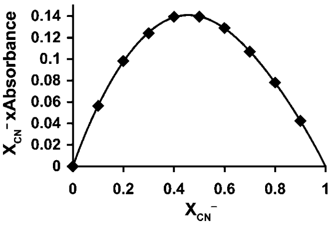


Figure 11. Job's plot analysis of **3a** (10^{-4} M in MeCN) with CN^-.

We also carried out ^{1}H NMR titration experiments of a 10^{-1} M solution of **3a** in CD_3CN with CN^- (Figure 12). By addition of increasing amounts of CN^- in CD_3CN, the two methyne signals (H_b) decrease in intensity as two new signals grow at higher field ($H_b{}^1$) and, at the same time, the protons of the ethyl group ($CH_{3a}CH_{2a}$) also decrease in intensity as new signals grow at higher field, indicating that the newly formed species undergoes a shielding in these protons with respect to previous one. This is in agreement to the break of conjugation of the α,β-unsaturated system and may give clues about whether the process is a 1,2- or 1,4-addition.

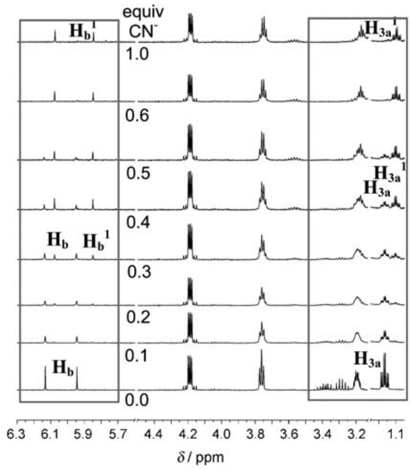
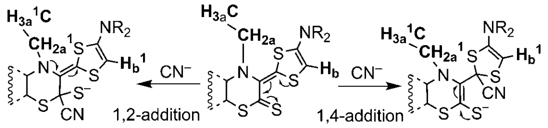


Figure 12. ^{1}H NMR titration (400 MHz, 0.1 M CD_3CN, 20 °C) of **3a** and CN^-.

The 1,2- and 1,4- addition processes of cyanide anion to **3a** should give different NMR results. The 1,2-addition should not show much effect on the chemical shift of the ethyl protons because of the cross conjugation. The 1,4-addition should show some shielding effect on the ethyl protons because of the conjugated thioenolate moiety, in addition of the shielding effect on the chemical shift of the vinylic proton because of disruption of the conjugation between sulfur atoms (Scheme 3). Therefore, from the results in Figure 12, a reversible 1,4-addition looks more plausible as the mechanism of cyanide detection by **3a**.



Scheme 3. The 1,2- and 1,4- addition processes of cyanide anion to **3a**. The curved arrows indicate in each case the main direction of electronic delocalization.

^{13}C NMR titration experiments of **3a** and Bu_4N^+ CN^- (1 equiv) in CD_3CN show the appearance of a CN signal at $\delta = 110$ ppm, the CS signal is seen at $\delta = 95$ ppm and the ethyl CH_2 signal at $\delta = 25$ ppm, all supporting the 1,4-addition (see the Supporting Information).

Conclusions

In conclusion, we have described the synthesis of some new polysulfur-nitrogen heterocycles by a rare cycloaddition reaction of an ynamine to bisdithiolothiazine ketothiones or dithiones, in turn obtained in one pot from tertiary amines. The double bond isomerization between regioisomers of the products was studied by DFT calculations of the most representative example. The best suited term of this series was described as a deeply colored selective and sensitive chromogenic probe for the naked-eye detection of Hg^{2+} in buffered water/acetonitrile 1:1 mixture, by a reversible change of color from purple to blue-violet, which is selective for Hg^{2+} even in the presence of several equivalents of other common cations. From the combined NMR titrations and DFT calculations, the complex between Hg^{2+} and the thione group of the probe was studied, constituting the first example of a new class of chemical probes for Hg^{2+} with sub-micromolar sensitivity. The probe showed also a selective change of color from purple to red in the presence of CN^- in buffered water/acetonitrile 1:1 mixture, even in the presence of several equivalents of other common anions, by means of a reversible nucleophilic 1,4-addition, with sub-micromolar sensitivity. Because of the easy synthesis and the selectivity in mixed organic-aqueous solvents, the probe can be useful for fast protocols of detection of Hg^{2+} or CN^-, with different response for every analyte, from environmental samples in the range of trace amounts ($\mu g L^{-1}$), where their presence poses toxic risks.

Experimental Section

Techniques

The reactions performed with air sensitive reagents were conducted under dry nitrogen. The solvents were distilled under nitrogen over calcium hydride or sodium filaments. Melting points were determined in a Gallenkamp apparatus and are not corrected. Infrared spectra were registered by using a Nicolet Impact 410 spectrometer using potassium bromide tablets. NMR spectra were recorded by using Varian Mercury-300 and Varian Unity Inova-400 machines, in [D$_6$]DMSO, $CDCl_3$, CD_3CN, CD_3OD. Chemical shifts are reported in ppm with respect to residual solvent protons, coupling constants ($J_{X\text{-}X'}$) are reported in Hz. Elemental analyses of C, H, and N were taken by using a Leco CHNS-932. Mass spectra were taken by using a Micromass AutoSpec machine, by electronic impact at 70 eV. Quantitative UV/Vis measurements were performed by using a Varian, Cary 300 Bio UV spectrophotometer, in 1 cm UV cells at 25 °C.

Synthesis

Bis[1,2]dithiolo[1,4]thiazine ketothiones **1a–c** and bis[1,2]dithiolo-[1,4]thiazine dithiones **2a–c** were prepared following the reported methodology.[16]

4-Ethyl-5-(4-morpholino-1,3-dithiol-2-ylidene)-6-thioxo-5,6-dihydro[1,2]dithiolo[3,4-b][1,4]thiazin-3(4H)-one, ***3a***

4-[(Trimethylsilyl)ethynyl]morpholine (20 μL, 19 mg, 0.10 mmol) and Sc-(OTf)$_3$ (11 mg, 0.02 mmol) were successively added to a solution of 4-ethyl-5-thioxo-4,5-dihydro-3*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazin-3-one **1a** (30 mg, 0.093 mmol) in dichloromethane (10 mL) at room temperature and the mixture was stirred for ten minutes. Then the solvent was evaporated and the crude product was purified by flash column chromatography (silica, dichloromethane to dichloromethane/ethyl acetate, 95:5 v/v), to give **3a** (*Z*/*E*, 1/1, 34 mg, 84 %) as a dark purple solid, m.p.: 74–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.84$ (s, $\frac{1}{2}$H, =CH), 5.67 (s, $\frac{1}{2}$H, =CH), 3.84–3.81 (m, 4H, 2×CH_2), 3.50–3.39 (m, 1H, $\frac{1}{2}CH_2$), 3.29–3.22 (m, 1H, $\frac{1}{2}CH_2$), 3.20–3.18 (m, 4H, 2×CH_2), 1.22 ppm (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.1$ and 184.6 (C=S), 183.7 (C=O), 153.0, 152.3, 132.4, 132.3, 131.7, 131.0, 94.1, 93.9, 66.0, 66.0, 50.9, 48.1, 47.8, 13.4 ppm; IR (KBr): $\tilde{\nu} = 2923$, 2853, 1638 (C=O), 1536 (C=S), 1445, 1352, 1111 cm^{-1}; MS (EI): *m*/*z* (%): 434 (M^+, 35), 405 (100), 323 (15), 290 (55); HRMS: calcd for $C_{14}H_{14}N_2O_2S_6$: 433.9380; found: 433.9402; elemental analysis calcd (%) for $C_{14}H_{14}N_2O_2S_6$: C 38.69, H 3.25, N 6.44; found: C 38.47, H 3.35, N 6.29.

4-Benzyl-5-(4-morpholino-1,3-dithiol-2-ylidene)-6-thioxo-5,6-dihydro[1,2]dithiolo[3,4-b][1,4]thiazin-3(4H)-one, ***3b***

4-[(Trimethylsilyl)ethynyl]morpholine (26 μL, 24 mg, 0.13 mmol) and Sc-(OTf)$_3$ (16 mg, 0.03 mmol) were successively added to a solution of 4-benzyl-5-thioxo-4,5-dihydro-3*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazin-3-one **1b** (50 mg, 0.13 mmol) in dichloromethane (10 mL) at room temperature and the mixture was stirred for ten minutes. Then the solvent was evaporated and the crude product was purified by flash column chromatography (silica, dichloromethane to dichloromethane/ethyl acetate, 95:5 v/v), to give **3b** (*Z*/*E*, 1/1, 36 mg, 56 %) as a dark purple solid, mp 65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$–7.22 (m, 4H, C_6H_5), 7.09–7.07 (m, 1H, C_6H_5), 5.87 (s, $\frac{1}{2}$H, =CH), 5.69 (s, $\frac{1}{2}$H, =CH), 4.43 (dd, $J =$ 14.25 Hz, $J = 4.5$ Hz, 1H, $\frac{1}{2}CH_2Ph$), 4.16 (d, $J = 14.25$ Hz, 1H, $\frac{1}{2}CH_2Ph$), 3.86–3.83 (m, 4H, 2×CH_2), 3.25–3.22 ppm (m, 4H, 2×CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 185.6$ (C=S), 184.8 (C=O), 152.9, 152.3, 135.7, 135.6, 131.4, 131.3, 131.1, 129.8, 128.4, 128.3, 94.3, 93.6, 66.1, 66.0, 56.5, 56.1, 50.9 ppm; IR (KBr): $\tilde{\nu} = 2923$, 2853, 1652 (C=O), 1539 (C=S), 1455, 1357, 1261, 1111 cm^{-1}; MS (EI): *m*/*z* (%): 496 (M^+, 10), 494 (20), 464 ($M-$S, 100); HRMS: calcd for $C_{19}H_{16}N_2O_2S_6$ 495.9536; found: 495.9523; elemental analysis calcd (%) for $C_{19}H_{16}N_2O_2S_6$: C 45.94, H 3.25, N 5.64; found: C 45.79, H 3.33, N 5.52.

4-[2-(N-Phthalimidoyl)ethyl]-5-(4-morpholino-1,3-dithiol-2-ylidene)-6-thioxo-5,6-dihydro[1,2]dithiolo[3,4-b][1,4]thiazin-3(4H)-one, ***3c***

4-[(Trimethylsilyl)ethynyl]morpholine (32 μL, 29 mg, 0.16 mmol) and Sc-(OTf)$_3$ (26 mg, 0.05 mmol) were successively added to a solution of 4-[2-(*N*-phthalimidoyl)ethyl]-5-thioxo-4,5-dihydro-3*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazin-3-one 1c (50 mg, 0.11 mmol) in dichloromethane (10 mL) at room temperature and the mixture was stirred for ten minutes. Then the solvent was evaporated and the crude product was purified by flash column chromatography (silica, dichloromethane to dichloromethane/ethyl acetate, 95:5 v/v), to give **3c** (*Z*/*E*, 1/1, 30 mg, 48%) as a dark purple solid, m.p.: 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.79 (m, 2 H, C_6H_4), 7.71–7.69 (m, 2 H, C_6H_4), 5.86 (s, $\frac{1}{2}$H, =CH), 5.68 (s, $\frac{1}{2}$H, =CH), 4.00–3.95 (m, 2 H, CH_2), 3.85–3.81 (m, 4 H, 2×CH_2), 3.74–3.64 (m, 2 H, CH_2), 3.23–3.20 ppm (m, 4 H, 2×CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.7 and 184.2 (C=S), 183.2 (C=O), 167.9 (C=O), 152.9, 152.4, 134.0, 131.9, 130.7, 125.0, 123.3, 123.1, 94.2, 93.6, 66.2, 66.0, 50.9, 49.4, 49.1 ppm; IR (KBr): $\tilde{\nu}$ = 2924, 2855, 1710 and 1635 (C=O), 1538 (C=S), 1358, 1112, 1069 cm^{-1}; MS (EI): *m*/*z* (%): 579 (M^+, 36), 405 (100); HRMS: calcd for $C_{22}H_{17}N_3O_4S_6$: 578.9543; found: 578.9542; elemental analysis calcd (%) for $C_{22}H_{17}N_3O_4S_6$: C 45.58, H 2.96, N 7.25; found: C 45.69, H 3.13, N 7.34.

4-Ethyl-3,5-bis(4-morpholino-1,3-dithiol-2-ylidene)thiomorpholine-2,6-dithione, ***4a***

4-[(Trimethylsilyl)ethynyl]morpholine (80 µL, 75 mg, 0.40 mmol) and Sc(OTf)$_3$ (40 mg, 0.08 mmol) were successively added to a solution of 4-ethyl-3*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazine-3,5(4*H*)-dithione **2a** (50 mg, 0.15 mmol) in dichloromethane (10 mL) at room temperature and the mixture was stirred for twenty minutes. Then the solvent was evaporated and the crude product was purified by flash column chromatography (silica, petroleum ether (40–60 °C) to dichloromethane/ethyl acetate, 80:20 v/v), to give **4a** (43 mg, 52%) as a dark reddish purple solid, m.p.: 100–101 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (s, 0.4 H, =CH), 5.82 (s, 0.6 H, =CH), 5.57 (s, 0.6 H, =CH), 5.54 (s, 0.4 H, =CH), 3.87–3.81 (m, 8 H, 4×CH_2), 3.34–3.28 (m, 2 H, CH_{2ethyl}), 3.22–3.18 (m, 8 H, 4×CH_2), 1.23–1.19 ppm (m, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 190.0 and 189.4 (C=S), 164.6, 164.2, 151.9, 151.4, 151.3, 133.4, 132.5, 94.4, 92.9, 66.1, 51.1, 50.8, 49.3, 49.2, 14.2 ppm; IR (KBr): $\tilde{\nu}$ = 2926, 2854, 1652 (C=O), 1575 and 1539 (C=S), 1455, 1261, 1112, 1023 cm^{-1}; MS (EI) *m*/*z* (%): 561 ($M^{+\cdot}$, 90), 532 (64); HRMS: calcd for $C_{20}H_{23}N_3O_2S_7$: 560.9835; found: 560.9824; elemental analysis calcd (%) for $C_{20}H_{23}N_3O_2S_7$: C 42.75, H 4.13, N 7.48; found: C 42.64, H 4.25, N 7.36.

4-Dodecyl-3,5-bis(4-morpholino-1,3-dithiol-2-ylidene)thiomorpholine-2,6-dithione, ***4b***

4-[(Trimethylsilyl)ethynyl]morpholine (51 µL, 49 mg, 0.26 mmol) and Sc(OTf)$_3$ (26 mg, 0.05 mmol) were successively added to a solution of 4-dodecyl-3*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazine-3,5(4*H*)-dithione **2b** (50 mg, 0.10 mmol) in dichloromethane (10 mL) at room temperature and the mixture was stirred for twenty minutes. Then the solvent was evaporated and the crude product was purified by flash column chromatography (silica, petroleum ether (40–60 °C) to dichloromethane/ethyl acetate, 80:20 v/v), to give **4b** (41 mg, 56%) as a dark reddish purple solid, m.p.: 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (s, 0.4 H, =CH), 5.82 (s, 0.6 H, =CH), 5.55 (s, 0.6 H, =CH), 5.51 (s, 0.4 H, =CH), 3.86–3.80 (m, 8 H, 4×CH_2), 3.21–3.16 (m, 10 H, 5×CH_2), 1.67–1.64 (m, 2 H, CH_2), 1.25–1.19 (m, 18 H, 9×CH_2), 0.87 ppm (t, *J* = 6.6 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.6, 190.0, 189.3, 164.3, 163.8, 151.9, 151.2, 133.8, 132.8, 94.4, 92.8, 66.1, 55.1, 55.1, 51.1, 50.9, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.3, 27.5, 22.7, 14.1 ppm; IR (KBr): $\tilde{\nu}$ = 2920, 2850, 1637, 1543 (C=S), 1410, 1370, 1267, 1200, 1112, 1024 cm^{-1}; MS (FAB$^+$); *m*/*z* (%): 702 (M^++ 1, 90), 532 (85), 188 (100); HRMS (FAB$^+$): calcd for M^++1, $C_{30}H_{44}N_3O_2S_7^+$: 702.1473; found: 702.1464; elemental analysis calcd (%) for $C_{30}H_{43}N_3O_2S_7$: C 51.32, H 6.17, N 5.98; found: C 51.39, H 6.11, N 5.90.

4-(2-Ethylbutyl)-3,5-bis(4-morpholino-1,3-dithiol-2-ylidene)thiomorpholine-2,6-dithione, ***4c***

4-[(Trimethylsilyl)ethynyl]morpholine (50 µL, 46 mg, 0.25 mmol) and Sc(OTf)$_3$ (31 mg, 0.06 mmol) were successively added to a solution of 4-(2-ethylbutyl)-3*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazine-3,5(4*H*)-dithione **2c** (50 mg, 0.13 mmol) in dichloromethane (10 mL) at room temperature and the mixture was stirred for twenty minutes. Then the solvent was evaporated and the crude product was purified by flash column chromatography (silica, petroleum ether (40–60 °C) to dichloromethane/ethyl acetate, 80:20 v/v), to give **4c** (35 mg, 45%) as a dark reddish purple solid, m.p.: 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (s, 0.4 H, =CH), 5.82 (s, 0.6 H, =CH), 5.56 (s, 0.6 H, =CH), 5.53 (s, 0.4 H, =CH), 3.88–3.77 (m, 8 H, 4×CH_2), 3.20–3.17 (m, 8 H, 4×CH_2), 3.10–3.08 (m, 2 H, CH_2), 1.67–1.59 (m, 1 H, CH), 1.38–1.28 (m, 4 H, 2×CH_2), 0.78 ppm (t, *J* = 6.75 Hz, 6 H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.43, 189.96 and 189.50 (C=S), 164.14, 163.69, 151.84, 151.03, 134.28, 133.22, 94.41, 92.72, 66.07, 58.55, 51.12, 50.84, 39.02, 25.49, 25.34, 11.12 ppm; IR (KBr): $\tilde{\nu}$ = 2956, 2921, 2852, 1644, 1544 (C=S), 1415, 1372, 1272, 1201, 1114 cm^{-1}; EM (FAB$^+$): *m*/*z* (%): 618 ($M^{+\cdot}$+1, 100), 532 (70); HRMS (FAB$^+$): calcd for M^++1, $C_{24}H_{32}N_3O_2S_7^+$: 618.0534; found: 618.0543; elemental analysis calcd (%) for $C_{24}H_{31}N_3O_2S_7$: C 46.65, H 5.06, N 6.80; found: C 46.79, H 5.14, N 6.67.

Titration Techniques

Perchlorate salts were used for cations: Ag^+, Ni^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Fe^{3+}, Al^{3+}, and Hg^{2+}, and triflate salts for the rest of cations: Sn^{2+}, Zn^{2+}, and Sc^{3+}. 5×10^{-2} M, 5×10^{-3} M, 5×10^{-4} M solutions of every salt were prepared, and then a 10^{-4} M solution of the compound under study was prepared. For qualitative experiments, 2 mL solutions of the compound under study were measured and the corresponding amount of salt was added by micropipette, but for microsamples of 500 µL volume, 5×10^{-4} M solutions were used to get a deeper color. Quantitative measures were performed with a Varian, Cary 300 Bio UV spectrophotometer. As a general procedure, to a 5000 µL solution of complex, the corresponding amount (µL) of solution of the corresponding salt (5×10^{-2} M, 5×10^{-3} M, 5×10^{-4} M solutions) was added, using the minor amount of solvent.

Calculations

DFT calculations were performed with the hybrid method known as B3LYP, in which the Becke three-parameter exchange functional[17] and the Lee–Yang–Parr correlation functional were used,[18] implemented in the Gaussian 03 (Revision C.02) program suite.[11] The effective core potentials (ECPs) of Hay and Wadt with a double-ζ valence basis set (Lanl2DZ)[19] were used in describing Hg. The basis set for the main group elements was split-valence and included polarization and diffuse functions in all atoms [C, N, O, S, and H, abbreviated as 6-311G+(d,p)].[20] The structures were optimized and the energies of the structures were calculated at the level described above and transition states were confirmed by a vibrational analysis (one imaginary frequency) and IRC calculations.[21]

Crystal Structure Determination for Compound ***2b***

A single crystal of **2b** was coated in glue and mounted on a glass fiber. X-ray measurements were made using a Bruker SMART CCD area-detector diffractometer with $Mo_{K\alpha}$ radiation (λ = 0.71073 Å).[22] Intensities were integrated[23] from several series of exposures, each exposure covering 0.3° in ω, and the total data set being a sphere. Absorption corrections were applied, based on multiple and symmetry-equivalent measurements.[24] The structure was solved by direct methods and refined by least squares on weighted F^2 values for all reflections.[25] All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. All hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters. Refinement proceeded smoothly to give the residuals. Complex neutral-atom scattering factors were used.[26] Crystal data for **2b**, $C_{18}H_{25}NS_7$, M = 479.81, monoclinic, $P21/c$, a = 18.472(2) Å, b = 9.2865(11) Å, c = 13.0854(15) Å, α = 90°, β = 90.027(2)°, γ = 90°; V = 2244.7(4) Å^3, Z = 4, ρ_{calcd} = 1.420 gcm^{-3}, $\mu(Mo_{K\alpha})$ = 0.707 mm^{-1}. Dark red needle, 0.60×0.30×0.02 mm, 22729 measured reflections, 4405 independent (R_{int} = 0.0494), 3534 observed ($I > 2\sigma(I)$). R_1 = 0.0589, wR_2 = 0.1220 (all data). CCDC 762858 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif

Acknowledgements

We gratefully acknowledge financial support from the Ministerio de Ciencia e Innovación, Spain (Projects CTQ2006-15456-C04-04BQU and CTQ2009-12631-BQU), Junta de Castilla y León, Consejería de Educación y Cultura y Fondo Social Europeo (Projects BU023A09 and GR170). We thank SCAI of the University of Burgos for solving structure **2a** by single-crystal X-ray diffraction.

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Received: January 22, 2010