Synthesis of New 1,3-Dithiolium Derivatives from 4-Hydroxyacetophenones

LUCIAN MIHAIL BIRSA[1]*, ANDREI VICTOR SANDU[2], ADRIANA BALAN[3]*

[1] Alexandru Ioan Cuza University of Iasi, Department of Chemistry, 11 Carol I Blvd., 700506, Iasi, Romania

[2] Gheorghe Asachi Techical University of Iasi, Faculty of Science & Engineering Materials, Iasi 700050, Romania

[3] „Grigore T. Popa" University of Medicine and Pharmacy of Iasi, Faculty of Dental Medicine, 16 Universitatii Str., 700115, Iaşi, Romania

Several 4-(3,5-dibromo-4-hydroxyphenyl)-2-(N,N-dialkylamino)-1,3-dithiol-2-ylium salts have been synthesized by the heterocondensation of some 1-(3,5-dibromo-4-hydroxyphenyl)-1-oxaethan-2-yl dithiocarbamates. The latter compounds have been obtained from the reaction of the corresponding substituted ω-bromoacetophenone with various salts of dithiocarbamic acids. UV- Vis investigations proved the intramolecular charge transfer for the mesoionic 1,3-dithiolium phenolates.

Keywords: acetophenones, dithiocarbamates, 1,3-dithiolium salts, mesoionic compounds, UV-Vis

Organic π-donors and their cation radical salts have been studied extensively because of their potential as molecular conductors and superconductors [1-4]. The high electrical conductivity reported for the tetrathiafulvalene (TTF) complex with tetracyanoquinodimethane initiated important efforts aimed at discovering a variety of electron π-donors of the tetrathiafulvalene series [5-7]. The 1,3-dithiol ring is of special interest for organic materials due to its reactivity [8]. The sulfur atoms exhibit a stabilizing effect on neighboring positive as well as negative charges, a very important feature for organic synthesis purposes. The reactivity of 1,3-dithiolium salts has been widely studied and used in the synthesis of the tetrathiafulvalene and dithiafulvene derivatives [9]. Recent reports highlighted the TTFs ability to act as donor groups in intramolecular charge-transfer complexes [10, 11]. A variety of acceptor units has been investigated, nitrogen and sulfur containing cations receiving a great deal of attention [12-20]. Of special interest are systems where the donor moiety is linked through a π- or σ-bonded bridge to the acceptor moiety [21-25]. Recent studies on (1,3-dithiolium-2-yl)phenolates systems revealed that 1,3-dithiolium cations can act as acceptor groups in intramolecular charge-transfer processes [26, 27].

Along with the applications in material chemistry, 1,3-dithiolium cations are interesting systems for medicinal chemistry. Their reactivity at the C(2)-position towards nucleophiles is well known [28]. Moreover, the 1,3-dithiolium core has been found to exhibit biological activities against gram-positive and gram-negative bacteria [29-31].

Following our previous investigation on the synthesis of some 4-(hydroxyaryl)-2-(*N*,*N*-dialkylamino)-1,3-dithiolium salts from the corresponding α-haloketones [12-14], we wish to extend these studies by presenting a new class of 4-(3,5-dibromo-4-hydroxyphenyl)-2-(*N*,*N*-dialkylamino)-1,3-dithiolium salts and the corresponding mesoionic 2,6-dibromo-4-(1,3-dithiolim-2-yl)phenolates.

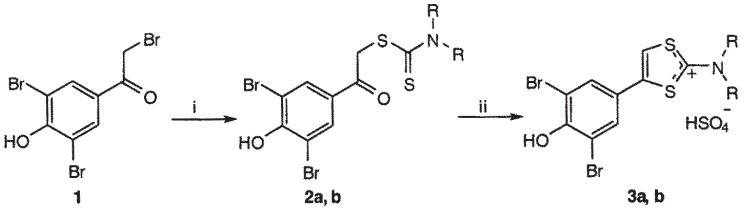
Experimental part

Analysis methods

Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. UV-Vis spectra were recorded on a Varian BioCarry 100 Spectrophotometer. NMR spectra were recorded on a Bruker DPX-300 Spectrometer. Chemical shifts are reported in ppm downfield from TMS. Elemental analyses (C, H, N and S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement (±0.32%) with the calculated values.

Synthesis

The synthetic pathway for the synthesis of carbodithioates **2a** and **2b** and 1,3-dithiolium derivatives **3a** and **3b** is described in scheme 1.



i. $R_2NC(S)S^-$, acetone, reflux; ii. H_2SO_4/AcOH 1:3 (v/v), 80 °C

2, 3, 4	R	R
a	-(CH$_2$)$_5$-	
b	-(CH$_2$)$_4$-	

Scheme 1. Synthesis of dithiocarbamates **2** and 1,3-dithiolium hydrogen sulphates **3**

* *email: lbirsa@uaic.ro; balan.gheo@yahoo.com*

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
2a	202 - 203	81	2951, 1647, 1447, 1352, 1247, 1201, 1137, 849, 774, 697, 551	*^1H NMR* δ : 1.66 (6H, m, $3CH_2$); 4.07 (4H, m, $2CH_2$-N); 4.77 (2H, s, CH_2); 8.12 (2H, d, H-2 + H-6; J_{H2-H6}=2.1Hz); 10.17 (1H, s, OH). *^{13}C NMR* δ : 23.9, 25.6, 26.4, 43.6, 51.7, 53.4, 112.1, 130.8, 133.0, 155.6, 190.27, 193.3 .
2b	181 - 182	71	2958, 1649, 1441, 1345, 1241, 1210, 1121, 850, 755, 674, 540	*^1H NMR* δ : 2.01 (4H, m, $2CH_2$); 3.73 (2H, m, CH_2-N); 3.81 (2H, m, CH_2-N); 4.79 (2H, s, CH_2); 8.15 (2H, d, H-4 + H-6; J_{H2-H6}=2.1 Hz); 11.14 (1H, s, OH). *^{13}C NMR* δ : 24.3, 26.2, 43.3, 51.2, 55.8, 112.1, 130.7, 133.0, 155.7, 190.2, 190.4 .

Table 1
ANALYTICAL AND SPECTRAL DATA OF DITHIOCARBAMATES **2**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
3a	232-233 Dec.	77	3041, 2967, 1547, 1435, 1100, 1010, 858, 772, 569	*^1H NMR* δ : 1.80 (6H, m, $3CH_2$); 3.88 (4H, m, $2CH_2$); 6.29 (2H, s, OH + HSO_4); 7.85 (2H, d, H-2 + H-6; J_{H2-H6}=2.2 Hz); 7.94 (1H, s, H-5). *^{13}C NMR* δ : 23.4, 24.9, 25.4, 43.2, 50.7, 52.4, 112.8, 119.4, 124.1, 130.6, 135.7, 152.9, 181.1 .
3b	238-239 dec.	60	3048, 1550, 1430, 1244, 1079, 885, 614, 542	*^1H NMR* δ : 2.23 (4H, m, $2CH_2$); 3.70 (4H, m, $2CH_2$); 6.27 (2H, s, OH + HSO_4); 7.86 (2H, d, H-2 + H-6; J_{H2-H6}=2.0 Hz); 7.99 (1H, s, H-5). *^{13}C NMR* δ : 26.64, 26.69, 57.1, 58.0, 113.0, 119.3, 124.3, 130.8, 135.8, 153.0, 180.9 .

Table 2
ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOLIUM HYDROGEN SULPHATES **3**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
4a	224-225 dec.	100	2958, 1544, 1447, 1261, 1222, 1125, 845, 760, 648, 551	*^1H NMR* δ : 1.79 (6H, m, $3CH_2$); 3.86 (4H, m, $2CH_2$); 7.84 (2H, d, H-2 + H-6; J_{H2-H6}=2.1 Hz); 7.96 (1H, s, H-5). *^{13}C NMR* δ : 23.1, 25.0, 25.5, 43.1, 50.8, 52.1, 112.7, 119.4, 124.0, 130.4, 135.9, 153.0, 181.0 .
4b	253-254 dec.	100	2948, 1555, 1457, 1441, 1241, 1131, 841, 755, 658	*^1H NMR* δ : 2.24 (4H, m, $2CH_2$); 3.71 (4H, m, $2CH_2$); 7.84 (2H, d, H-2 + H-6; J_{H2-H6}=2.1 Hz); 7.96 (1H, s, H-5). *^{13}C NMR* δ : 26.6, 57.2, 57.9, 113.1, 119.2, 124.2, 130.9, 135.6, 153.2, 181.1 .

Table 3
ANALYTICAL AND SPECTRAL DATA OF MESOIONIC 1,3-DITHIOLIUM PHENOLATES **4**

1-(3,5-Dibromo-4-hydroxyphenyl)-1-oxaethan-2-yl-piperidine-1-carbodithioate (**2a**)

General Procedure

To a solution of 2-bromo-1-(3,5-dibromo-4-hydroxyphenyl)ethan-1-one (**1**, 3g, 8mmol) in acetone (30mL), a solution of piperidinium piperidine-1-carbodithioate (2g, 8mmol) in acetone-water (1:1, 30mL) was added. The reaction mixture was refluxed for 10min, cooled to room temperature and then poured in water. The precipitate was filtered, washed with water and dried off. Recrystallization from dioxane (20mL) gave colorless crystals; yield 2.9g (81%). Analytical and spectral data of carbodithioates **2a** and **2b** are presented in table 1.

4-(3,5-Dibromo-4-hydroxyphenyl)-2-(piperidin-1-yl)-1,3-dithiol-2-ylium hydrogen sulphate (**3a**)

General Procedure

To a mixture of sulfuric acid (98%, 2mL) and glacial acetic acid (6mL), 1-(3,5-dibromo-4-hydroxyphenyl)-1-oxaethan-2-yl-piperidine-1-carbodithioate (**2a** - 2g, 4.4mmol) was added in small portions. The reaction mixture was heated at 80°C for 10 min. After cooling, water (100mL) was added and the precipitate was filtered and dried off. Recrystallization from EtOH (500mL) gave colorless crystals; yield 1.8g (77%). Analytical and spectral data of 1,3-dithiolium hydrogen sulphates **3a** and **3b** are presented in table 2.

2,6-Dibromo-4-[2-(piperidin-1-yl)-1,3-dithiol-2-ylium-4-yl]phenolate (**4a**);

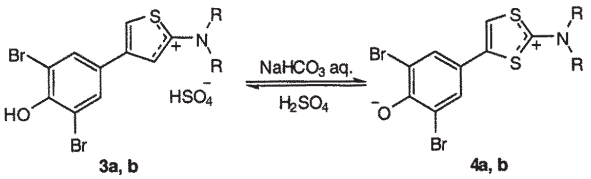
General Procedure

To a saturated sodium hydrogen carbonate solution (20mL), hydrogen sulphate **3a** (1.0g, 1.8mmol) was added. Carbon dioxide evolved and the reaction mixture became yellow. After 2 h under vigorous stirring at room temperature, the yellow solid was filtered off, washed with water, and dried. Recrystallization from ethanol gave yellow crystals; yield 0.8g (100%). Analytical and spectral data of 1,3-dithiolium phenolates **4a** and **4b** are presented in table 3.

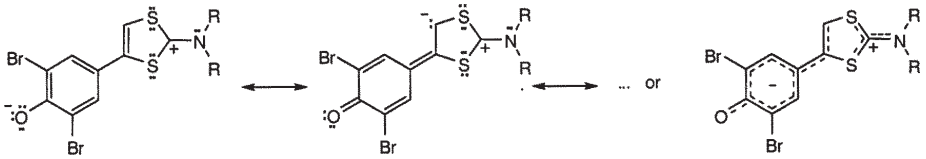
Results and discussions

A convenient method for the synthesis of 4-(3,5-dibromo-4-hydroxyphenyl)-2-(*N*,*N*-dialkylamino)-1,3-dithiolium salts is represented by the cyclization of the corresponding *N*,*N*-dialkylamino carbodithioates. The latter compounds are easily available from 4-hydroxyacetophenone, following a three step synthetic procedure. The synthesis of 2-bromo-1-(3,5-dibromo-4-hydroxyphenyl)ethan-1-one (**1**) has been accomplished by the regioselective double bromination of the aromatic core [32], followed by the selective monobromination of the side chain [33]. Phenacyl dithiocarbamates **2a** and **2b** have been obtained by reacting ω-bromoacetophenone **1** with piperidinium piperidine-1-carbodithioate and pyrrolidinium pyrrolidine-1-carbodithioate, respectively (scheme 1). The structure of dithiocarbamates **2** has been proved by analytical and spectral data (table 1). The ^1H NMR spectra indicate a shift in value for the signal belonging to the α-carbonyl proton to ca. 4.7ppm. Also, new signals appear at high fields corresponding to the signals belonging to the rest of the protons in the piperidine and pyrrolidine moieties. ^{13}C NMR spectra indicate the appearance of additional signals above the 190ppm, attributed to the thiocarbonyl group.

Using a concentrated sulfuric acid-glacial acetic acid (1:3 v/v) mixture [34-37] the cyclization of dithiocarbamates **2a** and **3b** takes place under mild reaction conditions (scheme 1). After 10min at 80°C the homogeneous reaction mixture was cooled to room temperature and water was added. Filtration and recrystallization of the precipitate gives hydrogen sulphates **3** as colorless crystals, in good yields (table 2). The cyclization of dithiocarbamates **2** was accompanied by important spectral changes. The IR spectra revealed the disappearance of the absorption band corresponding to the carbonyl group (1647-1649cm^{-1}) and the presence of new, strong and broad absorption bands at 1000 - 1100 cm^{-1}, corresponding to the hydrogen sulphate anion. Heterocyclization of dithiocarbamates **2** is also supported by the NMR spectra. Thus, the ^1H NMR spectra of 1,3-dithiol-2-ylium hydrogen sulphates indicate the absence of the α-carbonyl hydrogens from compounds **2** (ca. 4.7ppm). ^{13}C NMR spectra also support the synthesis of 1,3-dithiolium



Scheme 2. Synthesis of mesoionic phenolates **4** and their interconversion with the corresponding 1,3-dithiolium hydrogen sulphates **3**



Scheme 3. Extended delocalization charge in mesoionic phenolates **4**

salts **3** by the disappearance of the carbonyl and thiocarbonyl carbon atoms present in the dithiocarbamates spectra and the appearance of a new signal at a very low field (181ppm) which correspond to the electron deficient C(2) atom.

Treatment of hydrogen sulphates **3a** and **3b**, under heterogeneous conditions, with saturated aqueous sodium hydrogen carbonate solution provides 2,6-dibromo-4-[2-(dialkylamino)-1,3-dithiol-2-ylium-4-yl]phenolates **4a** and **4b**, in quantitative yields as yellow compounds (scheme 2). The molecular structure of the new compounds was proved by analytical and spectral data (table 3) and by the following chemical transformation: treatment of an acetone suspension of the mesoionic compounds **4** with sulfuric acid regenerates the 1,3-dithiolium hydrogen sulphates **3** in quantitative yields (scheme 2).

As mentioned before, phenolates **4** have been isolated as yellow products that present the features of mesoionic compounds [38]. The presence of a hydroxy substituent in the *para*-position induces an extended delocalization of the negative charge up to the C(4)-C(5) bond of the dithiolium ring (scheme 3).

In a previous paper [26], the comparative study of UV-Vis absorption spectra of 2-, 3-, and 4-[2-(pyrrolidin-1-yl)-1,3-dithiol-2-ylium-4-yl]phenolates has shown that the yellow color of the above zwitterionic compounds is due to a charge transfer between electron-rich and electron-deficient regions of the molecules and not to the contribution of quinoid structures in the ground states. The intramolecular nature of the charge-transfer band was proved by measurements at different concentrations.

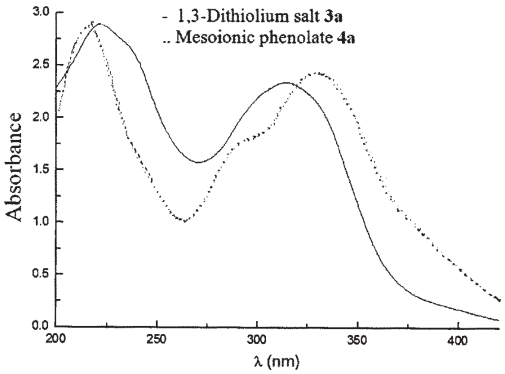


Fig. 1. UV/Vis absorption spectra of 1,3-dithiolium salt **3a** and mesoionic phenolate **4a** in ethanol

Investigations of UV-Vis absorption spectra of mesoionic phenolates **4** confirm the previous findings (fig. 1).

While the intramolecular charge-transfer UV-Vis absorption of such chromophores results from a charge transfer from the HOMO of the donor part to the LUMO of the acceptor part, the electronic effects of the substituents on the extended delocalization of the negative charge should result on a HOMO orbital of lower energy. Thus, the presence of phenolic substituent at the *para* position to the 1,3-dithiolium ring results in an extended conjugation that prompted an enhancement of all absorption bands and the appearance of a new absorption band at 290nm. In comparison with the result reported for the unsubstituted 4-hydroxyphenyl derivatives, the spectrum of 1,3-dithiolium hydrogen sulphate **3a** indicates a bathochromic shift induced by the bromine substituents on the absorption band at 290 nm that overlaps the band corresponding to the $n \rightarrow \pi^*$ transitions. The charge transfer absorption band of mesoionic phenolates **4** (380nm) is overlapped by the large absorption band centered at 330nm. As a result of the extended conjugation, the spectrum of mesoionic phenolate **4a** indicates a new absorption band at 285nm that belongs to the contribution of the *para*-quinoid structure to the real state of the molecule.

Conclusions

A series of 4-(3,5-dibromo-4-hydroxyphenyl)-2-(N,N-dialkylamino)-1,3-dithiol-2-ylium salts has been synthesized by the heterocondensation of the 1-(3,5-dibromo-4-hydroxyphenyl)-1-oxaethan-2-yl dithiocarbamates. The latter compounds have been obtained from the reaction of the corresponding substituted ω-bromoacetophenone with various salts of dithiocarbamic acids. UV- Vis investigations proved the intramolecular charge transfer for the mesoionic 1,3-dithiolium phenolates and revealed a *para*-quinoid structure for mesoionic phenolates **4**.

Acknowledgments: This work was supported by a grant of the Romanian National Authority for Scientific Research, CNDI– UEFISCDI, project number 51/2012.

References

1.HANSEN, T.K., JORGENSEN, T., JENSEN, F., THYGESEN, P.H., CHRISTIANSEN, K.,HURSTHOUSE, M.B.,HARMAN, M.E.,MALIK, M.A.,GIRMAY, B., UNDERHILL A.E., BERGTRUP, M., KILBURN J.D., BELMORE, K., ROEPSTORFF, P., BECHER, J., J. Org. Chem., **58**, 1993, p. 1359.
2.SCHUKAT, G., RICHTER, A. M., FANGHANEL, E., Sulfur Rep., **7**, 1987, p. 155.
3.SCHUKAT, G., FANGANEL, E., Sulfur Rep., **14**, 1993, p. 245.
4.NARITA, M., PITTMAN, C. U. Jr., Synthesis, **1976**, p. 489.
5.SUDMALE, I.V., TORMOS, G.V., KHODORKOVSKY, V.Yu., EDZINA, A.S., NEILANDS, O.J., CAVA, M.P., J. Org. Chem., **58**, 1993, p. 1355.
6.YAMADA, J., NISHIKAWA, H., KIKUCHI, K., J. Mater. Chem., **9**, 1999, p. 617.
7. BRYCE, M. R., J. Mater. Chem., **10**, 2000, p. 589.
8.MARIN, L., ARVINTE, A., Mat. Plast., **50**, no. 1, 2013, p. 23.
9. LORCY, D., PAILLARD, M.-P. Le, ROBERT, A., Tetrahedron Lett., **34**, 1993, p. 5289.

10.PEREPICHKA, D.F., BRYCE, M.R., BATSANOV, A.S., HOWARD, J.A.K., CUELLO, A. O., GRAY, M., ROTELLO, V. M., J. Org. Chem., **66**, 2001, p. 4517.
11. BRYCE, M.R., GREEN, A., MOORE, A.J., PEREPICHKA, D.F., BATSANOV, A.S., HOWARD, J.A.K., LEDOUX-RAK, I., GONZALES, M., MARTIN, N., SEGURA, J.L., GARIN, J., ORDUNA, J., ALCALA, R., VILLACAMPA, B., Eur. J. Org. Chem., 2001, p. 1927.
12.SARBU, L.G., BIRSA, M.L., Acta Chem. Iasi, **19**, 2011, p. 125.
13.BAHRIN, L.G., LUNGU, N.C., FORNA, N.C., SANDU, I., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no. 11, 2013, p. 1343.
14.SARBU, L.G., LUNGU, N.C., FORNA, N.C., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no.12, 2013, p. 1404.
15.CHIRITA, P., SCHLEGEL, M.L., Chem. Geol., **334**, 2012, p. 131.
16.LUNGU, N.C., BAHRIN, L.G., ASAFTEI, I.V., FORNA, N.C., SANDU, I., BIRSA, M.L., Rev. Chim. (Bucharest), **65**, no. 2, 2014, p. 181.
17.SARBU, L.G., LUNGU, N.C., ASAFTEI, I.V., SANDU, I., BIRSA, M.L., Rev. Chim. (Bucharest), **65**, no. 3, 2014, p. 325.
18.CHIRITA, P., Surf. Interface Anal., **41**, 2009, p. 405.
19.SARBU, L.G., BICU, E., HOPF, H., BIRSA, M.L., Rev. Chim. (Bucharest), **65**, no. 4, 2014, p. 398.
20.BAHRIN, L.G., CRACIUN, B.F., SANDU, I., BIRSA, M.L., Rev. Chim. (Bucharest), **65,** no. 5, 2014, p. 525.
21.BRYCE, M. R., Adv. Mater., **11**, 1999, p. 11.
22.SARBU, L.G., BIRSA, A., HOPF, H., BIRSA, M.L., Phosphorus, Sulfur, Silicon, (2011) **186**, 2011, p. 1246.
23.SARAVANAKUMARA, R., MARKOPOULOS, G., BAHRIN, L.G., HOPF, H., Synlett, **24**, 2013, p. 453.
24.SARBU, L.G., BIRSA, A., HOPF, H., BIRSA, M.L., Acta Chem. Iasi, **18**, 2010, p. 186.
25.SARBU, L.G., BIRSA, A., IGNAT, L., HOPF, H., BIRSA, M.L., Acta Chem. Iasi, **18**, 2010, p. 69.
26.BIRSA, M.L., GANJU, D., J. Phys. Org. Chem., **16**, 2003, p. 207.
27.BIRSA, M.L., ASAFTEI, I.V., Monat. Chem., **139**, 2008, p. 1433.
28.BIRSA, M.L., Synth. Commun., **33**, 2003, p. 3071.
29.BAHRIN, L.G., JONES, P.G., HOPF, H., Beilstein J. Org. Chem., **8**, 2012, p. 1999.
30.BIRSA, M.L., SANDU, I., BAHRIN, L.G., Rev. Chim. (Bucharest), **65**, no. 2, 2014, p. 174.
31.BAHRIN, L.G., APOSTU, M.O., BIRSA, M.L., STEFAN, M., Bioorg. Med. Chem. Lett., **24**, 2014, p. 2315.
32.BUU-HOI, Ng. Ph., LAVIT, D., J. Chem. Soc., 1954, p. 1034.
33.PRIESTLEY, H.M., MONESS, E., J. Org. Chem., **5**, 1940, p. 355.
34.SARBU, L. G., BAHRIN, L. G., Acta Chem. Iasi, **21**, 2013, p. 47.
35.LUNGU, N.C., SANDU, I., CHIRITA, P., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no.7, 2013, p. 697.
36.BUHACEANU, R., LUNGU, N.C., FORNA, N.C., ASAFTEI, I.V., CHIRITA, P., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no. 8, 2013, p. 802.
37.BUHACEANU, R., LUNGU, N.C., FORNA, N.C., ASAFTEI, I.V., CHIRITA, P., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no. 9, 2013, p. 960.
38.ATHAYDE FILHO, P. F., MILLER, J., SIMAS, A. M., Synthesis, 2000, p. 1565.

Manuscript received: 23.06.2014