Synthesis of 1,3-Dithiol-2-ylium Salts by Functionalization of Some Toluenols

DANIELA DIRTU[1], IULIEAN VASILE ASAFTEI[1], PAUL CHIRITA[2], IOAN GABRIEL SANDU[3,4], MIHAIL LUCIAN BIRSA[1], KAMEL EARAR[5]*, LAURA GABRIELA SARBU[1]*

[1] Alexandru Ioan Cuza University of Iasi, Department of Chemistry, 11 Carol I Blvd., 700506, Iasi, Romania
[2] University of Craiova, Department of Chemistry, 107I Calea Bucuresti, 200478, Craiova, Romania
[3] Gheorghe Asachi Technical University, Faculty of Materials Science and Engineering, 64 Mangeron Bld., 700050, Iasi, Romania
[4] Romanian Inventors Forum, 3 Sf. Petru Movila St., 700089, Iasi, Romania
[5] Dunãrea de Jos University of Galaþi, Romania, Faculty of Medicine and Farmacy, 47 Domneasca Str., 800008, Galati, Romania

A new class of 2-(dialkylamino)-1,3-dithiol-2-ylium compounds derived from various toluenols has been synthesized by the intramolecular condensation of the corresponding phenacyl carbodithioates. The target compounds have been obtained following a two step procedure that involves the reactions of w-bromo-1-(2-hydroxyaryl)ethan-1-ones with salts of dithiocarbamic acids and heterocyclocondensation under acidic conditions.

Keywords: xylenols, dithiocarbamates, 1,3-dithiolium salts, IR and NMR Spectrometer

Heterocyclic compounds have significant implications in both biological and industrial fields [1-3]. They are used by the drug industry for their antibacterial, anticancer, anticonvulsant, antiinflammatory, antimycobacterial, antitubercular, anti-HIV, antidepressant activities [4-8]. A great interest has nitrogen and sulfur-containing heterocycles [9-22]. Amongst the great variety of this classes of heterocyclic compounds, 1,3-dithiolium derivatives have been found to exhibit an excellent biological activity, especially against gram-positive and gram-negative bacteria [23]. Additionally, 1,3-dithiolium salts can be used as building blocks in the synthesis of tetrathiafulvalenes (TTF), the later being good *p*-electron donors for organic metals [24]. The implication of TTFs as donor groups in intramolecular charge-transfer complexes has been recently reviewed [25]. In this context, different types of acceptor units have been investigated with a special attention paid to the nature of cationic systems. Special interest was devoted to the systems where the donor moiety is linked through a π- or σ-bonded bridge to the acceptor moiety [26-34].

Toluenols are an important class of organic compounds that exhibits good antibacterial properties. In view of the above information, we decided to investigate the synthesis of a new class of 2-(dialkylamino)-1,3-dithiol-2-ylium compounds derived from toluenols.

Experimental part

Analysis methods

Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker DPX-300 Spectrometer. Chemical shifts are reported in ppm downfield from TMS. Elemental analyses (C, H, N, S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement (±0.31%) with the calculated values.

Synthesis

The 1,3-dithiolium salts **3a-e** have been synthesized following the reaction pathway described in scheme 1.

4-(3-Bromo-2-hydroxy-5-methylphenyl)-2-N,N-dimethylamino-1,3-dithiol-2-ylium hydrogen sulphate (**3a**); *General Procedure*

To a mixture of sulfuric acid (98%, 1mL) and glacial acetic acid (3mL), 1-(3-bromo-2-hydroxy-5-methylphenyl)-1-oxaethan-2-yl-*N,N*-dimethyldithiocarbamate (**2a**, 1g, 2.33mmol) was added in small portions. The reaction mixture was heated at 80°C for 10 min. After cooling, methyl acetate (100mL) was added in order to isolate the corresponding hydrogen sulphate. The precipitate was filtered and dried off. Recrystallization from ethanol (100mL) gave colorless crystals; yield 0.95g (77%). Analytical and spectral data of 1,3-dithiolium hydrogen sulphates **3** are presented in table 1.

4-(3,5-Dibromo-2-hydroxy-4-methylphenyl)-2-N,N-dimethylamino-1,3-dithiol-2-ylium bromide (**3e**)

To a mixture of sulfuric acid (98%, 1mL) and glacial acetic acid (3mL), 1-(3,5-dibromo-2-hydroxy-4-methylphenyl)-1-oxaethan-2-yl-*N,N*-dimethylamino-1-carbodithioate (**2e**, 1g, 2mmol) was added in small portions. The reaction mixture was heated at 80 °C for 10 min. After cooling, hydrobromic acid (1mL) and methyl acetate (100mL) was added in order to isolate the corresponding 1,3-dithiolium bromide. The precipitate was filtered and dried off. Recrystallization from ethanol (100mL) gave colorless crystals; yield 0.91g (91%). Analytical and spectral data of 1,3-dithiolium bromide **3e** are presented in table 2.

Results and discussions

The reaction pathway for the synthesis of 1,3-dithiol-2-ylium salts involves two steps, as described in scheme 1: the synthesis of the corresponding phenacyl carbodithioates, followed by their cyclocondensation under acid conditions. The key precursors for phenacyl dithiocarbamates **2a-e** are 2-bromo-1-(3-bromo-2-hydroxy-5-methylphenyl)ethan-1-one [35], 2-bromo-1-(5-bromo-2-hydroxy-3-methylphenyl)ethan-1-one [36], and 2-bromo-1-(3.5-dibromo-2-hydroxy-4-methylphenyl)ethan-1-one [37], compounds that have been synthesized according to

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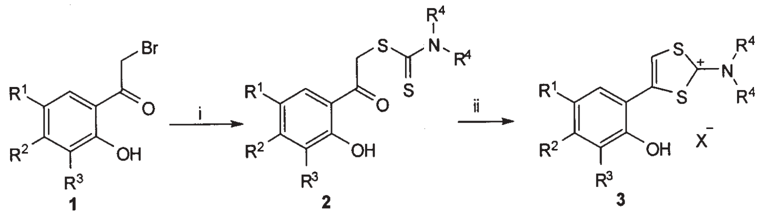
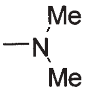
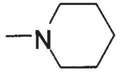
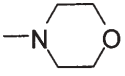
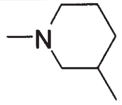
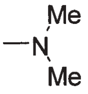
*email: *erar_dr.kamel@yahoo.com*; *laura_gabriela84@yahoo.com*



i. $(R^4)_2NC(S)S^-$, acetone, reflux; ii. H_2SO_4/AcOH 1:3 (v/v), 80 °C

1, 2, 3	R^1	R^2	R^3	$-NR^4_2$	X
a	Me	H	Br	 $-\mathrm{N}(\mathrm{Me})_2$	HSO_4
b	Me	H	Br		HSO_4
c	Me	H	Br		HSO_4
d	Br	H	Me		HSO_4
e	Br	Me	Br	 $-\mathrm{N}(\mathrm{Me})_2$	Br

Scheme 1
Synthesis of 1,3-dithiolium salts **3a-e**

Table 1
ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOLIUM HYDROGEN SULFATES **3a-d**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
3a	224-225 dec.	77	3551, 3107, 1555, 1511, 1404, 1247, 1035, 614	*^{1}H NMR* δ : 2.22 (3H, s, CH_3-5); 3.55 (3H, s, CH_3-N); 3.59 (3H, s, CH_3-N); 6.29 (2H, s, HSO_4 + OH); 7.35 (1H, d, H-4); 7,59 (1H, d, H-6; $J_{H4\text{-}H6}$= 2.4 Hz); 8.15 (1H, s, H-5). *^{13}C NMR* δ : 19.4, 46.5, 46.9, 112.8, 116.5, 117.4, 128.4, 129.5, 130.3, 132.7, 154.2, 187.6.
3b	202-203 dec.	89	3547, 3102, 1548, 1514, 1432, 1248, 1021, 604	*^{1}H NMR* δ : 1.66 (6H, m, $3CH_2$); 2.23 (3H, s, CH_3-5); 3.85 (4H, m, $2CH_2$); 6.20 (2H, s , HSO_4 + OH); 7.30 (1H, d, H-4); 7.53 (1H, d, H-6, $J_{H4\text{-}H6}$= 2.4 Hz); 8.10 (1H, s, H-5). *^{13}C NMR* δ : 19.8, 21.4, 24.5, 56.2, 56.5, 112.0, 116.8, 118.5, 128.7, 130.1, 131.4, 132.8, 154.4, 187.8.
3c	219-220 dec.	85	3558, 3111, 1545, 1425, 1239, 1047, 619	*^{1}H NMR* δ : 2.24 (3H, s, CH_3-5); 3.95 (8H, m, $4CH_2$); 6.22 (2H, s, HSO_4 + OH); 7.45 (1H, d, H-4); 7.61 (1H, d, H-6; $J_{H4\text{-}H6}$= 2.4 Hz); 8.10 (1H, s, H-5). *^{13}C NMR* δ : 19.6, 57.9, 58.3, 68.8, 112.4, 116.9, 118.0, 128.5, 129.7, 130.9, 132.4, 155.2, 187.3 .
3d	222-223 dec.	88	3489, 1458, 1335, 1219, 1135, 1012, 850, 751, 685	*^{1}H NMR* δ : 0.97 (3H, d, CH_3); 1.25 (1H, m, H-3); 1.86 (4H, m, 2 H-4 + 2 H-5); 2.22 (3H, s, CH_3-3); 3.38 (1H, m, H-2); 3.60 (1H, m, H-2); 3.95 (2H, m, H-6); 6.29 (2H, s, HSO_4 + OH); 7.34 (1H, d, H-4); 7.59 (1H, d, H-6; $J_{H4\text{-}H6}$=2.3 Hz); 8.04 (1H, s, H-5). *^{13}C NMR* δ : 11.5, 19.8, 20.1, 21.4, 24.5, 56.2, 56.5, 112.5, 116.9, 118.4, 128.5, 129.7, 131.1, 132.5, 154.1, 187.6.

the reported procedures. The salts of dialkyldithiocarbamic acid are easily available from the reaction of secondary amine with carbon disulfide, under various experimental conditions [38]. The reactions of these compounds with the above mentioned *w*-bromoacetophenones represent a useful method for the synthesis of a large variety of phenacyl carbodithioates [39-41]. Following this synthetic strategy we synthesized dithiocarbamates **2a-e** in good to excellent yields.

The second step for the synthesis of 1,3-dithiol-2-ylium salts **3a-e** consists in the acid catalyzed cyclocondensation of the phenacyl carbodithioates. Several synthetic methods have been previously reported, including those for sensitive starting materials [42-46]. Using a mixture of concentrated sulfuric acid-glacial acetic acid (1:3 v/v) the cyclization of dithiocarbamates **2a-e** takes place under mild reaction conditions. After 10 min at 80 °C a homogeneous reaction mixture was obtained. 1,3-Dithiolium hydrogen sulphates **3a-d** have been isolated as white solids by adding water to the crude reaction products. Filtration and recrystallization of the precipitate provides 1,3-dithiolium sulphates **3a-d** as colorless crystals, in good to excellent yields (scheme 1, table 1). 1,3-Dithiolium bromide **3e** has been obtained by adding hydrobromic acid to aqueous solution of 1,3-dithiolium cation; in this particular case the 1,3-dithioliun hydrogen sulphates proved to be water soluble and a different counter-anion was necessary for isolation of this derivative. The analytical and spectral data of 1,3-dithiolium bromide **3e** are presented in table 2. The cyclization of dithiocarbamates **2** is accompanied by important spectral changes. The IR spectra revealed the disappearance of the absorption band corresponding to the carbonyl group (ca. 1630 cm^{-1}) and the presence of a new, strong and broad, absorption band at ca. 1030-1050 cm^{-1}, corresponding to the hydrogen sulphate anion in salts **3a-d**. ^{1}H NMR spectra of the new synthesized 1,3-dithiol-2-ylium salts indicate the absence of the *a*-carbonyl hydrogen from compounds **2**. ^{13}C NMR spectra also support the cyclization of dithiocarbamates **2** to the corresponding 1,3-dithiolium salts by the disappearance of the carbonyl and

Table 2
ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOLIUM BROMIDE **3e**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
3e	241-242 dec.	91	3377, 2521, 1525, 1443, 1122, 928, 842	^{1}*H NMR* δ : 2.57 (3H, s, CH_3-4); 3.57 (6H, s, $2CH_3$-N); 4.06 (1H, s, OH); 7.97 (1H, s, H-6); 8.16 (1H, s, H-5). ^{13}*C NMR* δ : 19.5, 47.5, 47.9, 112.4, 114.6, 122.2, 122.8, 130.5, 134.5, 136.2, 150.1, 187.8

thiocarbonyl atoms from dithiocarbamates spectra and the appearance of a new signal at a very low field (ca. 187 ppm) which correspond to the electron deficient C(2) atom.

Conclusions

The synthesis of a new class of 2-(dialkylamino)-1,3-dithiol-2-ylium compounds derived from toluenols has been accomplished by the heterocondensation of the corresponding phenacyl carbodithioates. The title compounds have been obtained following a two step procedure that involves the reaction of 2-bromo-1-(2-hydroxyaryl)ethan-1-one with various salts of dithiocarbamic acids and heterocyclocondensation under acidic conditions.

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