New Water Soluble 1,3-Dithiolium Salts

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The synthesis of new 1,3-dithiolium chlorides as water soluble compounds has been accomplished through the interconversion of mesoionic 2-(1,3-dithiol-2-ylium)phenolates with the corresponding salts. These salts have been obtained by acid catalyzed cyclocondensation of various substituted 2-(5-bromo-2-hydroxyphenyl)-2-oxoethyldithiocarbamates.

Keywords: dithiocarbamates, 1,3-dithiolium salts, mesoionic compounds

Heterocyclic compounds are of immense importance, biologically and industrially. One of the most important structural features of heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substitutes around a core scaffold in defined three dimensional representations [1, 2]. Synthetic and biosynthetic heterocycles have widespread therapeutic uses, such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antitubercular, antimalarial, herbicidal, analgesic, antiinflammatory, muscle relaxants, anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, and antitumoral agents [3-9]. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the continuous interest of researchers [10-17].

All these natural and synthetic heterocyclic compounds can and do interact with the human body. The way a drug is administered will affect how the body absorbs the substance. Each method of administering the drug will change distribution rates. Excluding intravenous methods, a drug must usually pass through at least one body membrane before reaching the circulatory system. Soluble drugs are more rapidly absorbed, because most membranes are lipid-based. The absorption rate is affected by a variety of factors [18]. Drugs taken in a water solution are absorbed more rapidly than drugs taken in an oily solution or a solid form. For this reason, the synthesis of water soluble heterocyclic compounds with potentially biological activities is of general interest. A 1, 3-dithiolium derivative has been reported to exhibit biological activity against gram-positive and gram-negative bacteria [19].

In view of these facts, we decided to investigate the synthesis of a series of 1, 3-dithiolium chlorides as water soluble compounds.

Experimental part

Analysis methods

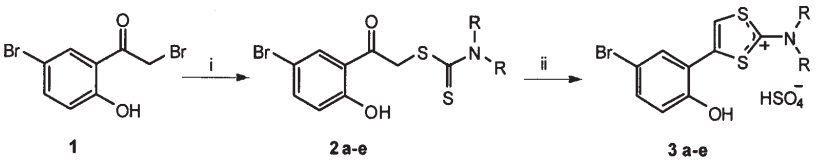
Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. Elemental analyses (C, H, N, S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement (±0.25%) with the calculated values.

Synthesis

w-Bromo-2-hydroxyacetophenone (**1**) [20] has been treated with various salts of dialkylaminodithiocarbamic acids in order to provide aminocarbodithioates (**2a-e**), in good isolated yields (fig. 1).

1-(5-Bromo-2-hydroxyphenyl)-1-oxaethan-2-yl-pyrrolidine-1-carbodithioate (**2c**)*;*

To a 2.94 g solution of 2-bromo-1-(5-bromo-2-hydroxyphenyl)ethan-1-one (0.01mol) in 30mL acetone, a solution of 2.18g pyrrolidinium pyrrolidine-1-carbodithioate (0.01mol) in 30mL acetone-water (1:1 v/v) was added.



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

2, 3, 4, 5	R	R
a	CH_3	CH_3
b	CH_2CH_3	CH_2CH_3
c	$(CH_2)_4$	
d	$(CH_2)_5$	
e	$(CH_2)_2$-O-$(CH_2)_2$	

Fig. 1. Synthesis of dithiocarbamates **2** and 1,3-dithiolium salts **3**.

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	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR ($CDCl_3$)
2a	184-185	89	2944, 1637, 1462, 1278, 1109, 990, 748, 622, 538	*^1H NMR* δ : 3.48 (6H, s, $2CH_3$); 4.90 (2H, s, CH_2); 6.97 (1H, d, H-3); 7.62 (1H, dd, H-4; J_{H3-H4}=7.2 Hz); 7.92 (1H, d, H-6; J_{H4-H6}=2.4 Hz); 11.05 (1H, s, OH). *^{13}C NMR* δ : 41.7, 44.4, 46.0, 110.8, 120.4, 120.6, 132.4, 139.5, 161.3, 194.7, 198.1
2b	123-124	79	2973, 1643, 1472, 1415, 1257, 1205, 1171, 976, 857, 750, 676, 625, 503	*^1H NMR* δ : 1.30 (3H, t, CH_3); 1.38 (3H, t, CH_3); 3.84 (2H, q, CH_2); 4.03 (2H, q, CH_2); 4.89 (2H, s, CH_2); 6.90 (1H, d, H-3); 7.56 (1H, dd, H-4; J_{H3-H4}=7.1 Hz); 8.11 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 11.69 (1H, s, OH). *^{13}C NMR* δ : 11.5, 12.7, 43.5, 47.1, 49.5, 110.4, 120.7, 120.9, 132.8, 139.9, 161.0, 194.1, 197.8
2c	156-157	71	2823, 1645, 1436, 1178, 991, 950, 833, 756, 624, 511	*^1H NMR* δ : 2.06 (4H, m, $2CH_2$); 3.79 (2H, t, CH_2-N); 3.87 (2H, t, CH_2-N); 4.91 (2H, s, CH_2); 6.90 (1H, d, H-3); 7.57 (1H, dd, H-4; J_{H3-H4}=7.2 Hz); 8.11 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 11.68 (1H, s, OH). *^{13}C NMR* δ : 24.4, 26.2, 43.5, 50.9, 55.7, 110.8, 120.3, 120.6, 132.4, 139.5, 161.3, 190.1, 198.2
2d	141-142	86	2951, 1639, 1451, 1280, 1110, 990, 748, 621, 530	*^1H NMR* δ : 1.75 (6H, m, $3CH_2$); 4.10 (4H, m, $2CH_2$-N); 4.89 (2H, s, CH_2); 6.89 (1H, d, H-3); 7.56 (1H, dd, H-4; J_{H3-H4}=7 Hz); 8.09 (1H, d, H-6; J_{H4-H6}=2.1 Hz); 11.68 (1H, s, OH). *^{13}C NMR* δ : 23.5, 24.9, 25.5, 43.1, 50.8, 52.5, 110.5, 120.1, 120.6, 132.8, 139.9, 161.8, 190.4, 198.0
2e	145-146	78	3532, 2900, 1632, 1471, 1285, 1115, 992, 750, 625, 535	*^1H NMR* δ : 3.76 (4H, m, CH_2-O-CH_2); 4.14 (4H, m, CH_2-N-CH_2); 4.86 (2H, s, CH_2); 6.87 (1H, d, H-3); 7.57 (1H, dd, H-4; J_{H3-H4}=7 Hz); 8.06 (1H, d, H-6; J_{H4-H6}=2.1 Hz); 11.65 (1H, s, OH). *^{13}C NMR* δ : 43.5, 50.9, 51.4, 65.8, 110.7, 120.2, 120.5, 132.6, 139.8, 161.5, 189.9, 198.1

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

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*)
3a	230-231 dec.	95	3020, 1566, 1484, 1408, 1297, 1119, 835, 647, 594	*^1H NMR* δ : 3.60 (3H, s, CH_3); 3.63 (3H, s, CH_3); 5.28 (1H, s, HSO_4); 7.05 (1H, d, H-3); 7.43 (1H, dd, H-4; J_{H3-H4}=7.4 Hz); 7.75 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 8.18 (1H, s, H-5); 11.10 (1H, s, OH). *^{13}C NMR* δ : 47.3, 47.8, 111.6, 119.0, 119.6, 121.3, 130.8, 134.4, 134.5, 153.5, 187.6
3b	184-185	64	3267, 3085, 1558, 1465, 1408, 1285, 1101, 1043, 830, 619	*^1H NMR* δ : 1.44 (6H, t, $2CH_3$); 3.90 (2H, q, CH_2); 3.94 (2H, q, CH_2); 5.30 (1H, s, HSO_4); 6.99 (1H, d, H-3); 7.40 (1H, dd, H-4; J_{H3-H4}=7.9 Hz); 7.70 (1H, d, H-6; J_{H4-H6}=2.1 Hz); 8.08 (1H, s, H-5); 11.12 (1H, s, OH). *^{13}C NMR* δ : 17.2, 53.2, 54.4, 111.1, 118.8, 119.4, 121.0, 130.5, 134.2, 134.5, 153.1, 187.1
3c	227-228 dec.	86	2933, 1550, 1448, 1405, 1219, 1150, 1052, 848, 634, 570	*^1H NMR* δ : 2.27 (4H, m, $2CH_2$); 3.76 (4H, m, $2CH_2$); 5.53 (2H, s, OH + HSO_4); 7.05 (1H, d, H-3); 7.47 (1H, dd, H-4; J_{H3-H4}=7.4 Hz); 7.77 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 8.17 (1H, s, H-5). *^{13}C NMR* δ : 26.0, 26.2, 56.5, 56.9, 111.1, 118.5, 119.2, 120.6, 130.5, 133.6, 134.0, 153.0, 181.6
3d	212-213 dec.	87	3382, 2947, 1561, 1443, 1409, 1222, 1155, 1065, 855, 760, 577	*^1H NMR* δ : 1.80 (6H, m, $3CH_2$); 3.88 (4H, m, $2CH_2$); 5.41 (1H, s, HSO_4); 7.09 (1H, d, H-3); 7.55 (1H, dd, H-4; J_{H3-H4}=7.9 Hz); 7.79 (1H, d, H-6; J_{H4-H6}=2.4 Hz); 8.07 (1H, s, H-5); 11.48 (1H, s, OH). *^{13}C NMR* δ : 21.6, 24.8, 24.9, 56.5, 57.5, 111.5, 118.4, 119.5, 120.8, 130.3, 133.8, 134.1, 152.9, 182.3
3e	201-202 dec.	70	2942, 1548, 1454, 1401, 1233, 1148, 1039, 851, 640, 568	*^1H NMR* δ : 3.92 (8H, m, $4CH_2$); 5.50 (2H, s, OH + HSO_4); 7.00 (1H, d, H-3); 7.50 (1H, dd, H-4; J_{H3-H4}=7.7 Hz); 7.78 (1H, d, H-6; J_{H4-H6}=2.0 Hz); 8.13 (1H, s, H-5). *^{13}C NMR* δ : 53.9, 54.5, 64.7, 111.3, 118.6, 119.3, 120.9, 130.4, 133.7, 134.3, 153.1, 181.9

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

The reaction mixture was heated under reflux for 10 min, cooled to room temperature and then poured in water. The precipitate was filtered, washed with water and dried off. Recrystallization from 50mL *i*-PrOH gave 2.55g colorless crystals, with a yield of 71%. Analytical and spectral data of carbodithioates (**2**) are presented in table 1.

4-(5-Bromo-2-hydroxyphenyl)-2-(pyrrolidin-1-yl)-1,3-dithiol-2-ylium hydrogensulfate (**3c**);

To a mixture of 2mL concentrated sulfuric acid and 6mL glacial acetic acid 2g of 1-(5-bromo-2-hydroxyphenyl)-1-oxaethan-2-yl-pyrrolidine-1-carbodithioate (**2c**) (5.55mmol) was added in small portions. The reaction mixture was heated at 80°C for 10 min, cooled and diluted with 50mL methyl acetate. After 24h at -18°C the precipitate was filtered and dried off. Recrystallization from 3mL of DMF gave 2.1g colorless crystals at a yield of 86%. Analytical and spectral data of 1,3-dithiolium hydrogensulfates (**3**) are presented in table 2.

5-Bromo-2-[2-(pyrrolidin-1-yl)-1,3-dithiol-2-ylium-4-yl]phenolate (**4c**);

To 20mL saturated sodium hydrogencarbonate solution 1g of hydrogensulfate (**3c**) (2.27mmol) was added. Carbon dioxide evolved and the reaction mixture became yellow. After 2h under vigorous stirring at room temperature, the yellow solid was filtered off, washed with water, and dried. Recrystallization from DMF-AcOMe gave 0.77g yellow crystals at a 100% yield. Analytical and spectral data of 1,3-dithiolium phenolates (**4**) are presented in table 3.

4-(5-Bromo-2-hydroxyphenyl)-2-(pyrrolidin-1-yl)-1,3-dithiol-2-ylium chloride (**5c**);

To 1 g suspension of mesoionic phenolate (**4c**) (2.9 mmol) in 10mL acetone a solution of 1.22mL HCl (37%, 14mmol) was added. The reaction mixture was vigorously stirred at rt for 2h, then filtered and washed with acetone. Recrystallization from ethanol gave colorless crystals; yield

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*)
4a	235-236 dec.	100	2972, 1541, 1452, 1339, 1168, 874, 819, 619	*^1H NMR* δ : 3.62 (3H, s, CH_3); 3.65 (3H, s, CH_3); 6.95 (1H, d, H-3); 7.23 (1H, dd, H-4; J_{H3-H4}=7.6 Hz); 7.73 (1H, d, H-6, J_{H4-H6}=2.4 Hz); 7.99 (1H, s, H-5). *^{13}C NMR* δ : 46.9, 47.1, 109.9, 118.8, 119.3, 119.6, 130.0, 133.9, 134.6, 154.5, 187.4
4b	209-210 dec.	100	2977, 1548, 1464, 1341, 1170, 884, 821, 620	*^1H NMR* δ : 1.38 (6H, t, $2CH_3$); 3.85 (2H, q, CH_2); 3.88 (2H, q, CH_2); 6.76 (1H, d, H-3); 7.21 (1H, dd, H-4; J_{H3-H4}=8.5 Hz); 7.70 (1H, d, H-6, J_{H4-H6}=3 Hz); 7.94 (1H, s, H-5). *^{13}C NMR* δ : 10.3, 10.6, 51.6, 52.7, 100.9, 109.0, 119.7, 120.8, 126.7, 133.3, 138.5, 154.2, 188.0
4c	199-200 dec.	100	2967, 1550, 1471, 1344, 1171, 880, 820, 620	*^1H NMR* δ : 2.26 (4H, m, $2CH_2$); 3.77 (4H, m, $2CH_2$); 6.84 (1H, d, H-3); 7.26 (1H, dd, H-4; J_{H3-H4}=7.7 Hz); 7.71 (1H, d, H-6, J_{H4-H6}=2.5 Hz); 7.97 (1H, s, H-5). *^{13}C NMR* δ : 26.5, 26.7, 57.0, 57.3, 111.2, 119.1, 119.7, 120.7, 125.6, 130.8, 134.5, 153.9, 182.1
4d	221-222 dec.	100	2948, 1479, 1441, 1257, 817, 620	*^1H NMR* δ : 1.80 (6H, m, $3CH_2$); 3.89 (4H, m, $2CH_2$); 6.88 (1H, d, H-3); 7.25 (1H, dd, H-4; J_{H3-H4}=8.0 Hz); 7.74 (1H, d, H-6, J_{H4-H6}=2.7 Hz); 7.92 (1H, s, H-5). *^{13}C NMR* δ : 21.5, 24.9, 25.0, 56.7, 57.8, 111.7, 118.3, 119.6, 120.7, 130.4, 133.9, 134.0, 152.8, 182.8
4e	216-217 dec.	100	2982, 1569, 1502, 1458, 1335, 1154, 822, 619	*^1H NMR* δ : 3.98 (8H, m, $4CH_2$); 6.89 (1H, d, H-3); 7.28 (1H, dd, H-4; J_{H3-H4}=7.9 Hz); 7.75 (1H, d, H-6, J_{H4-H6}=2.4 Hz); 7.91 (1H, s, H-5). *^{13}C NMR* δ : 53.8, 54.5, 64.9, 111.4, 118.5, 119.5, 120.7, 130.2, 133.5, 134.8, 152.9, 181.5

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

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*)
5a	238-239 dec.	98	3199, 1574, 1411, 1290, 1255, 1185, 1121, 852, 828, 779, 620, 576	*^1H NMR* δ : 3.60 (3H, s, CH_3); 3.64 (3H, s, CH_3); 7.04 (1H, d, H-3); 7.45 (1H, dd, H-4; J_{H3-H4}=7.5 Hz); 7.95 (1H, d, H-6; J_{H4-H6}=2.4 Hz); 8.18 (1H, s, H-5); 11.67 (1H, s, OH). *^{13}C NMR* δ : 46.8, 47.0, 110.1, 119.0, 119.5, 119.8, 129.8, 133.8, 134.5, 154.4, 187.3
5b	226-227 dec.	98	3314, 3019, 1554, 1415, 1290, 1186, 1081, 829, 619	*^1H NMR* δ : 1.42 (6H, t, $2CH_3$); 3.90 (2H, q, CH_2); 3.93 (2H, q, CH_2); 7.01 (1H, d, H-3); 7.49 (1H, dd, H-4; J_{H3-H4}=7.8 Hz); 7.99 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 8.19 (1H, s, H-5); 11.78 (1H, s, OH). *^{13}C NMR* δ : 10.2, 10.7, 51.7, 52.8, 101.0, 109.2, 119.8, 120.7, 126.6, 133.2, 138.6, 154.1, 187.8
5c	229-230 dec.	98	2873, 1561, 1480, 1285, 1121, 1083, 825, 621	*^1H NMR* δ : 2.26 (4H, m, $2CH_2$); 3.77 (4H, m, $2CH_2$); 7.08 (1H, d, H-3); 7.56 (1H, dd, H-4; J_{H3-H4}=7.5 Hz); 7.97 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 8.09 (1H, s, H-5); 11.48 (1H, s, OH). *^{13}C NMR* δ : 26.4, 26.7, 56.9, 57.4, 111.1, 119.2, 119.8, 120.5, 125.7, 130.9, 134.6, 154.1, 182.5
5d	201-202	95	2928, 1539, 1487, 1393, 1254, 1096, 1067, 822, 620, 529	*^1H NMR* δ : 1.81 (6H, m, $3CH_2$); 3.87 (4H, m, $2CH_2$); 7.10 (1H, d, H-3); 7.65 (1H, dd, H-4; J_{H3-H4}=8.0 Hz); 7.75 (1H, d, H-6; J_{H4-H6}=2.5 Hz); 8.11 (1H, s, H-5); 11.68 (1H, s, OH). *^{13}C NMR* δ : 21.3, 24.8, 25.0, 56.5, 57.7, 111.5, 118.1, 119.5, 120.8, 130.3, 133.8, 134.1, 152.7, 181.9
5e	226-227 dec.	96	3257, 2963, 1548, 1484, 1413, 1259, 1116, 1035, 891, 833, 646, 541	*^1H NMR* δ : 3.93 (8H, m, $4CH_2$); 7.19 (1H, d, H-3); 7.42 (1H, dd, H-4; J_{H3-H4}=7.5 Hz); 7.73 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 8.18 (1H, s, H-5); 11.97 (1H, s, OH). *^{13}C NMR* δ : 53.5, 54.3, 64.4, 111.3, 118.4, 119.7, 120.2, 130.4, 133.3, 134.7, 153.1, 181.7

Table 4
ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOLIUM CHLORIDES **5**

1.08g (98%). Analytical and spectral data of 1,3-dithiolium chlorides (**5**) are presented in table 4.

Results and discussions

The synthetic strategy for the target 1,3-dithiolium chlorides involves two major steps: the synthesis of the 1,3-dithiolium ring, followed by the exploitation of interconversion properties of the corresponding mesoionic 1,3-dithiolium phenolates. The first step can be accomplished following two consecutive reactions as described in figure 1. *w*-Bromo-2-hydroxyacetophenone (**1**) [20] has been treated with various salts of dialkylaminodithiocarbamic acids in order to provide aminocarbodithioates (**2a-e**), in good isolated yields (fig. 1). The structure of dithiocarbamates (**2**) has been proved by analytical and spectral data (table 1).

The main synthetic application of phenacyl carbodithioates consists in their conversion to various substituted 1,3-dithiol-2-ylium cations under acidic conditions. Using a concentrated sulfuric acid-glacial acetic acid (1:3 v/v) mixture [21, 22] the cyclization of dithiocarbamates (**2a-e**) takes place under mild reaction conditions. After 10min at 80°C the homogeneous reaction mixture was cooled to room temperature and poured into water. Filtration and recrystallization of the precipitate gives hydrogensulfates as colorless crystals, in good to excellent yields (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. 1630-1640cm^{-1}) and the presence of a new, strong and broad absorption band at ca. 1100cm^{-1}, corresponding to the hydrogen sulfate anion.

The NMR spectra also confirm the heterocyclization of dithiocarbamates **2**. Thus, the ^1H NMR spectra of 1,3-dithiol-2-ylium hydrogen sulfates indicate the absence of the methylene hydrogens from compounds (**2**) (ca. 4.9 ppm) and appearance of a new signal at a low field (>8ppm) corresponding to the hydrogen atom from the 5-position of the heterocycle. ^{13}C NMR spectra also support the synthesis of 1,3-dithiolium salts (**3**) by the disappearance of the carbonyl and thiocarbonyl carbon atoms present in the dithiocarbamates spectra and the appearance of a new

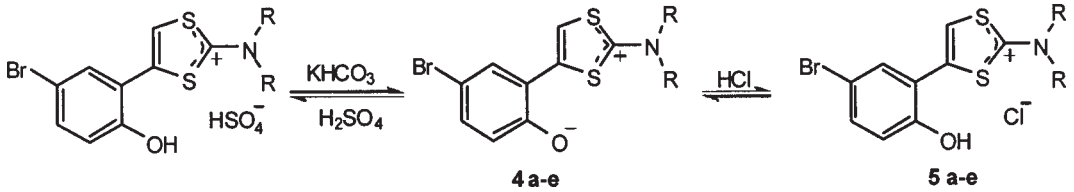

Fig. 2. Synthesis of mesoionic phenolates (**4**) and 1,3-dithiolim chlorides (**5**)

signal at a very low field (ca. 180 ppm) which correspond to the electron deficient C-2 atom. Treatment of hydrogen sulfates (**3a-e**), under heterogeneous conditions, with saturated aqueous potassium hydrogencarbonate solution affords[2-(dialkylamino)-1,3-dithiol-2-ylium-4-yl]phenolates (**4a-e**), in quantitative yields (fig. 2). These compounds were isolated as yellow crystalline products that present the features of mesoionic compounds [23, 24]. 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 concentrated sulfuric acid regenerates the 1,3-dithiolium hydrogensulfates (**3**) in quantitative yields (fig. 2).

Using the interconversion possibilities between the mesoionic phenolates and their salts, we have been able to isolate the 1,3-dithiolium chlorides (**5a-e**). Thus, 4-(5-bromo-2-hydroxyphenyl)-1,3-dithiol-2-ylium chlorides have been isolated as colorless crystalline products by the treatment of an acetone suspension of mesoionic phenolates (**4**) with 37% hydrochloric acid (fig. 2). This is the first class of isolable 1,3-dithiolium chlorides known up to date in the literature; usually, the organic chlorides exhibit a good solubility even in organic solvents. The structure of these water soluble 1,3-dithiolium salts was proved by analytical and spectral data (table 4).

Conclusions

The synthesis of water soluble 4-(5-bromo-2-hydroxyphenyl)-2-dialkylamino-1,3-dithiol-2-ylium chlorides has been accomplished from the corresponding mesoionic phenolates. The latter compounds have been synthesized by heterocondensation of 1-(5-bromo-2-hydroxyphenyl)-2-(*N*,*N*-dialkylaminocarboditioate)-1-ethanones, followed by base treatment of 1,3-dithiolium hydrogensulfates. The biological activity of 1,3-dithiolium chlorides is under investigation.

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