Synthesis of Novel 1,3-Dithiol-2-ylidene Derivatives from the Corresponding Mesoionic Compound

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The synthesis of some new 1,3-dithiol-2-ylidene derivatives has been achieved by the nucleophilic attack of in-situ generated nucleophiles at the C(2) position of the 1,3-dithiolium ring, using mesoionic compounds as starting materials. The newly obtained derivatives were characterized by NMR spectrometry and IR spectroscopy.

Keywords: 1,3-dithiolium salts, mesoionic compounds, 1,3-dithiol-2-ylidene derivatives

Vital to organic synthesis, the formation of carbon-carbon bonds continues to receive a great deal of attention from the scientific community. Recent advances employ the use of ruthenium [1,2], palladium [3], gold [4], and nickel [5] as catalysts, as well as improvements of classical reactions like the Michael addition [6].

Heterocycles are an important resource for the drug industry. Amongst these, sulphur and nitrogen-containing heterocycles receive a great deal of attention [7-20]. 1,3-Dithiolium salts contain a positive charge located at the C(2) position and for this reason these systems are well known for the reactivity of the C(2)-position towards nucleophiles [21]. If the 1,3-dithiolium ring is bound to a hydroxyphenyl moiety, then the salts can be converted into mesoionic compounds using non-nucleophilic bases.

This paper presents the synthesis of some new 1,3-dithiol-2-ylidene derivatives from the corresponding mesoionic compound, via a nucleophilic attack at the C(2) position of the 1,3-dithiolium ring.

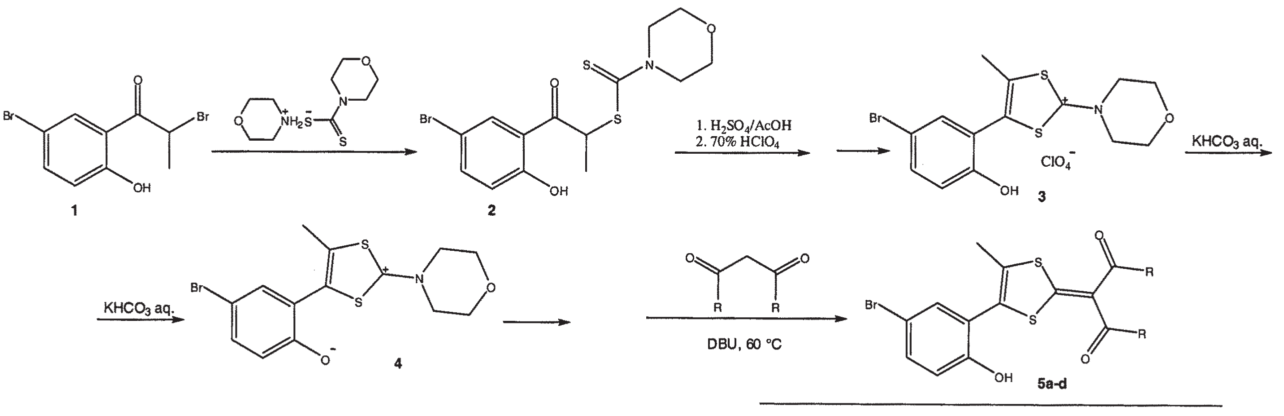
Experimental part

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.

Synthesis

The synthetic pathway used to obtain the new 1,3-dithiol-2-ylidene derivatives is presented in figure 1.



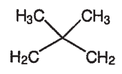
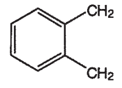
5	R	R
a	CH_3	CH_3
b	OEt	OEt
c		
d		

Fig. 1. Synthesis of 1,3-dithiol-2-ylidene derivatives **5a-d**

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

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR ($CDCl_3$), ppm
2	135-137	85	2853, 1643, 1467, 1259, 1228, 1178, 1112, 999, 786, 625, 543	*^{1}H NMR* δ : 1.64 (3H, d, CH_3); 3.70-3.86 (4H, m, $2CH_2$); 3.86-4.12 (2H, m, CH_2); 4.12-4.50 (2H, m, CH_2); 5.80 (1H, q, CH); 6.92 (1H, d, H-3; J_{H3-H4}=8.9 Hz); 7.57 (1H, dd, H-4); 8.11 (1H, d, H-6; J_{H4-H6}=2.2 Hz); 11.91 (1H, s, OH). *^{13}C NMR* δ : 16.9, 50.8, 110.8, 119.2, 120.7, 132.4, 139.4, 161.9, 194.3, 202.6

Table 2
ANALYTICAL AND SPECTRAL DATA OF PERCHLORATE **3**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
3	192-195	73	1504, 1410, 1266, 1079, 828, 621, 543	*^{1}H NMR* δ : 2.32 (3H, s, CH_3); 3.79-3.86 (4H, m, $2CH_2$); 3.86-3.93 (4H, m, $2CH_2$); 7.00 (1H, d, H-3; J_{H3-H4}=8.4 Hz); 7.52-7.58 (2H, m); 10.85 (1H, s, OH). *^{13}C NMR* δ : 15.4, 54.2, 54.3, 64.8, 64.9, 110.7, 117.7, 118.9, 127.1, 132.4, 133.9, 135.1, 155.5, 185.9

ω,5-Dibromo-2-hydroxypropiophenone (**1**) was synthesized using previously described methods [22, 23].

1-(5-Bromo-2-hydroxyphenyl)-1-oxopropan-2-yl-morpholine-4-carbodithioate (**2**);

To a solution of *ω*,5-dibromo-2-hydroxypropiophenone (3.08 g, 10 mmol) in acetone (50 mL), a solution of morpholinium morpholine-4-carbodithioate (2.5 g, 10 mmol) in water/acetone (40 mL, 1:1) was added and the resulting mixture heated to 50 °C. After 10 min, the resulting solution was brought to room temperature and poured in water (500 mL). Concentrated hydrochloric acid was then added (5 mL) and the resulting precipitate was vacuum filtered, washed with water and then recrystalyzed from ethanol; yield 3.32 g (85%). The spectral data for carbodithioate **2** is presented in table 1.

4-(5-Bromo-2-hydroxyphenyl)-5-methyl-2-(morpholin-4-yl)-1,3-dithiol-2-ylium perchlorate (**3**);

To a mixture of concentrated sulfuric acid (4 mL) and acetic acid (12 mL), 1-(5-bromo-2-hydroxyphenyl)-1-oxopropan-2-yl-morpholine-4-carbodithioate **2** (3.90 g, 10 mmol) was added. The resulting solution was heated to 80 °C and stirred for 10 minutes, then it was allowed to cool down to room temperature, after which it was poured into a solution of perchloric acid (5 mL) in water (500 mL). The precipitate thus formed was vacuum filtered, washed with water and recrystalized from ethanol; yield 3.46 g (73%). The spectral data for perchlorate **3** is presented in table 2.

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

4-(5-Bromo-2-hydroxyphenyl)-5-methyl-2-(morpholin-4-yl)-1,3-dithiol-2-ylium perchlorate **3** (0.472 g, 1 mmol) was suspended in a saturated aqueous solution of sodium bicarbonate (200 mL). After 24 h of vigorous stirring, the yellow precipitate was vacuum filtered, washed with water and allowed to dry; yield 0.372 g (100%). The spectral data for mesoionic **4** is presented in table 3.

1,3-Dithiol-2-ylidene derivative **5c**
General Procedure

To a solution of mesoionic phenolate **4** (0.744 g, 2 mmol) in acetonitrile (20 mL) under nitrogen atmosphere, dimedone (0.281 g, 2 mmol) was added and the reaction mixture was brought to 60 °C. DBU (0.35 mL, 2.3 mmol) was then added and the reaction was left over night under stirring. The solution was then poured into water (300 mL) and concentrated hydrochloric acid was added (5 mL). After stirring for 10 min, the precipitate that formed was filtered under vacuum and recrystalized from ethanol (100 mL); yield 0.494 g (55%). The spectral data for the 1,3-dithiol-2-ylidene derivatives **5a-d** are presented in table 4.

Table 3
ANALYTICAL AND SPECTRAL DATA OF MESOIONIC PHENOLATE **4**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
4	208-211	100	1506, 1436, 1260, 824, 620, 545	*^{1}H NMR* δ : 2.37 (3H, s, CH_3); 3.78-3.85 (4H, m, $2CH_2$); 3.85-3.93 (4H, m, $2CH_2$); 6.80-6.90 (1H, m); 7.40-7.47 (1H, m), 7.47-7.52 (1H, m). *^{13}C NMR* δ : 15.6, 54.0, 64.8, 66.3, 118.2, 119.4, 133.1, 134.7, 186.15

Table 4
ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOL-2-YLIDENE DERIVATIVES **5a-d**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR, ppm
5a	194-196	65	1540, 1410, 1366, 1309, 973, 810, 617, 512	*^{1}H NMR* (DMSO-*d6*) δ : 2.22 (3H, s, CH_3); 2.60 (3H, s, CH_3); 2.61 (3H, s, CH_3); 6.96 (1H, d, H-3; J_{H3-H4}=8.7 Hz); 7.42(1H, d, H-6; J_{H4-H6}=2.4 Hz); 7.46 (1H, dd, H-4); 10.37 (1H, bs, OH). *^{13}C NMR* (DMSO-*d6*) δ : 14.1, 31.2, 31.3, 110.5, 118.8, 120.1, 122.7, 131.6, 133.7, 133.8, 135.4, 155.3, 175.8, 192.3, 192.4
5b	148-150	48	1636, 1608, 1583, 1400, 1381, 1277, 1028, 811, 496	*^{1}H NMR (*$CDCl_3$) δ : 1.36 (3H, t, CH_3); 1.38 (3H, t, CH_3); 2.18 (3H, s, CH_3); 4.29 (2H, q, CH_2); 4.32 (2H, q, CH_2); 6.28 (1H, bs, OH); 6.93 (1H, d, H-3; J_{H3-H4}=8.7 Hz); 7.36 (1H, d, H-6; J_{H4-H6}=2.3 Hz); 7.40 (1H, dd, H-4). *^{13}C NMR (*$CDCl_3$) δ : 14.0, 14.3, 61.0, 61.1, 102.2, 112.4, 118.4, 119.2, 128.2, 133.6, 133.8, 134.4, 153.2, 166.1, 166.2, 176.8
5c	271-273	55	1560, 1363, 1337, 1280, 809, 569, 468	*^{1}H NMR* (DMSO-*d6*) δ : 1.00 (6H, s, 2 CH_3); 2.27 (3H, s, CH_3); 2.50 (2H, s, CH_2); 2.51 (2H, s, CH_2); 6.97 (1H, d, H-3; J_{H3-H4}=8.4 Hz); 7.44-7.51 (2H, m); 10.40 (1H, bs, OH). *^{13}C NMR* (DMSO-*d6*) δ : 14.2, 28.4, 30.9, 50.4, 50.5, 110.6, 116.7, 118.8, 119.7, 131.4, 133.9, 134.0, 135.6, 155.3, 173.1, 192.6, 192.7
5d	228-230	72	1641, 1586, 1471, 1335, 726, 650, 521	*^{1}H NMR* (DMSO-*d6*) δ : 2.32 (3H, s, CH_3); 6.83 (1H, d, H-3; J_{H3-H4}=8.7 Hz); 7.34 (1H, d, H-4); 7.38 (1H, s, H-6); 7.69 (4H, m). *^{13}C NMR* (DMSO-*d6*) δ : 14.8, 106.8, 112.8, 119.4, 119.9, 122.1, 122.2, 131.5, 132.7, 133.2, 133.9, 134.3, 134.3, 140.1, 140.1, 159.6, 165.8, 167.5, 186.9

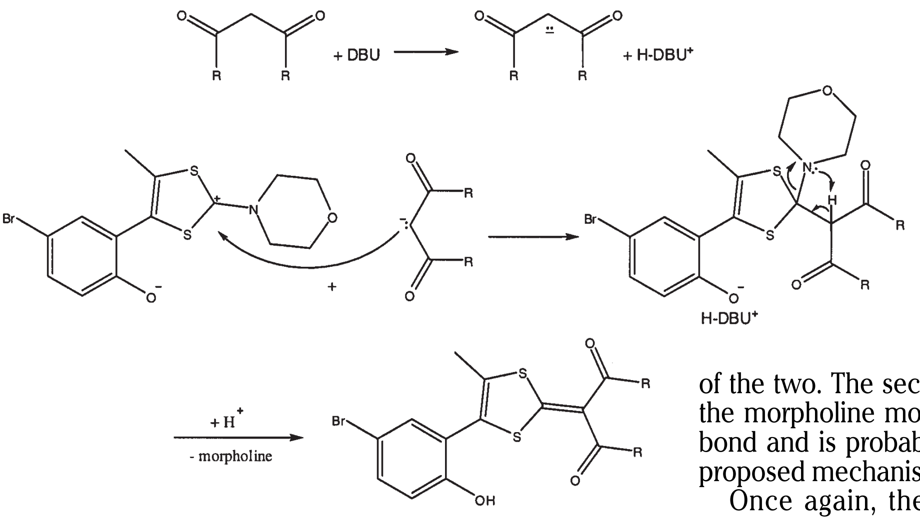

Fig. 2. Proposed reaction mechanism for the formation of the 1,3-dithiol-2-ylidene derivatives **5a-d**

Results and discussions

The synthesis of all compounds presented in figure 1 is supported by spectral data. The ^1H NMR spectra of carbodithioate **2** displays three new aliphatic signals, between 3.70 and 4.50 ppm, corresponding to the morpholine moiety protons, while the ^{13}C NMR spectra shows the appearance of a new signal at around 194 ppm, belonging to the thiocarbonyl group.

Acid catalyzed cyclization of carbodithioate **2** leads to the formation of the 1,3-dithiolium perchlorate **3**. The IR spectra shows the disappearance of the carbonyl and thiocarbonyl signals and the appearance of a new, strong band at 1079 cm^{-1}, corresponding to the perchlorate anion. ^1H NMR spectra indicates the disappearance of the methyne signal at 5.80 ppm, while ^{13}C NMR spectrometry displays the disappearance of the carbonyl (202.6 ppm) and thiocarbonyl (194.3 ppm) signal and the appearance of a new signal at 185.9 ppm, corresponding to the positively charged C(2) atom of the newly formed 1,3-dithiolium ring.

The most important spectral change displayed by the mesoionic derivative **4** is the disappearance of the phenolic proton signal from the ^1H NMR spectra and the disappearance of the perchlorate band at 1079 cm^{-1} from the IR spectra.

The C(2) position of the 1,3-dithiolium ring is prone to nucleophilic attack due to the positive charge located there. The nucleophiles were generated using active methylene compounds and a base. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is a strong enough base to extract a proton from the active methylene moiety, yet it is sterically hindered, therefore a weak nucleophile, which means it does not interact with the 1,3-dithiolium ring. The reaction is performed under a nitrogen atmosphere because water can interfere with the DBU, hindering the formation of the desired products.

In principle, one can use 1,3-dithiolium salts instead of the corresponding mesoionic compounds for this kind of reaction. In that case, one extra equivalent of base is needed and the salt is converted into the mesoionic compound first, followed by the nucleophilic attack of the active methylene on the C(2) position of the 1,3-dithiolium ring. However, DBU is much more expensive than sodium bicarbonate, therefore it is economically more feasible to use the latter to first convert the 1,3-dithiolium perchlorates into mesoionic phenolates.

The reaction mechanism involves two separate stages. The first one is represented by the nucleophilic attack on the 1,3-dithiolium ring, when the C(2) carbon atom changes its hybridization from *sp^2* to *sp^3*, and is probably the fastest of the two. The second stage involves the elimination of the morpholine moiety and the formation of the double bond and is probably the slower of the two stages. The proposed mechanism is presented in figure 2.

Once again, the formation of 1,3-dithiol-2-ylidene derivatives **5a-d** is supported by spectral data. IR spectroscopy indicates the presence of new carbonyl bands, which come from the active methylene moieties. ^1H NMR spectrometry reveals the presence of new methyl/methylene aliphatic signals for derivatives **5a-c**. In the case of compound **5d**, a new aromatic signal can be found at 7.69 ppm, corresponding to the 1,3-indandione moiety. Moreover, the regeneration of the phenolic group is indicated by the presence of a broad singlet at around 10.4 ppm (**5a** and **5c**) and 6.3 ppm in the case of **5b**. ^{13}C NMR spectrometry indicates the disappearance of the positively charged C atom and the appearance of a new signal at around 175 ppm (**5a-c**) or 186 ppm (**5d**), corresponding to the C(2) position of the 1,3-dithiole ring. Also, new signals at around 165-167 ppm (**5b** and **5d**) and 192 ppm (**5a** and **5c**), corresponding to the carbonyl groups, can be observed.

Conclusions

The synthesis of new 1,3-dithiole-2-ylidene derivatives was achieved by reacting the corresponding mesoionic substrate with various active methylene compounds. The latter were converted into nucleophiles *in situ*, using DBU, a non-nucleophilic base. The structures of all new compounds was proven by IR spectroscopy and NMR spectrometry.

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