1,3-Dithiol-2-ylium Compounds Derived from Substituted Butyrophenone

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A new class of 2-(dialkylamino)-1,3-dithiol-2-ylium compounds derived from substituted butyrophenone has been synthesized by the heterocondensation of the corresponding phenacyl carbodithioates. The title compounds have been obtained following a three step procedure that involves the reaction of 2-bromo-1-(2-hydroxyaryl)butan-1-one with various salts of dithiocarbamic acids, heterocyclocondensation under acidic conditions and treatment with weak aqueous bases.

Keywords: butyrophenones, dithiocarbamates, 1,3-dithiolium salts, mesoionic compounds, X-ray crystallography

Heterocyclic compounds are of great importance, from both biological and industrial point of view. The versatility presented by a core scaffold, which can be variously substituted within a well defined three dimensional space, represents one of their most important features [1-4]. Heterocycles are extensively used by the drug industry for their antibacterial, anticancer and lipid peroxidation inhibitor, anticonvulsant, antiinflammatory, anti-mycobacterial, antitubercular, anti-HIV, antidepressant, hypnotic, herbicidal activities [5-9]. A great deal of attention is focused on nitrogen and sulfur-containing heterocycles [10-15]. Amongst the great variety of this classes of heterocyclic compounds, 1,3-dithiolium derivatives have also been found to present biological activity, in a particular case, against gram-positive and gram-negative bacteria [16]. Moreover, 1,3-dithiolium systems are known for their reactivity at the C(2)-position towards nucleophiles [17]. Besides the synthetic interest for these reactions, it should be noted that the nucleophilic addition of the purinic bases of DNA to the model compounds was postulated as the Maxam-Gilbert mechanism for the biological activity of electrophilic substrates [18]. Additionally, 1,3-dithiolium salts can be used as building blocks in the synthesis of tetrathiafulvalenes (TTF), the later being good π-electron donors for organic metals [19]. Recent studies focus on TTFs as donor groups in intramolecular charge-transfer complexes [20]. In this context, a variety of acceptor units has been investigated, special attention being devoted to the nature of cationic systems. Thus, of special interest are systems where the donor moiety is linked through a π- or σ-bonded bridge to the acceptor moiety [21-29].

On the other hand, butyrophenones are a class of pharmaceutical drugs derived from butyrophenone, compounds used to treat various psychiatric disorders such as schizophrenia, as well acting as antiemetics. They represent the third class of antipsychotics developed in the late 1950s. The representative members of this class are haloperidol, benperidol, and triperidol [30].

In view of the above presented facts, we decided to investigate the synthesis of a new class of 2-(dialkylamino)-1,3-dithiol-2-ylium compounds derived from substituted butyrophenone.

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, S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement (±0.35%) with the calculated values.

Synthesis

The synthesis of compounds **4**, **5** and **6** is described in scheme 1 and 2.

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-oxabutan-2-yl-pyrrolidine-1-carbodithioate (**4a**)

General Procedure

To a solution of 2-bromo-1-(3-bromo-2-hydroxy-5-methylphenyl)butan-1-one [31] (**3**, 2.01g, 5mmol) in acetone (30mL), a solution of pyrrolidinium pyrrolidine-1-carbodithioate (1.09g, 5mmol) in acetone-water (1:1, 15mL) was added. The reaction mixture was heated at reflux for 15 min, cooled to room temperature and then poured in water. The precipitate was filtered, washed with water and dried off. Recrystallization from EtOH (50mL) gave colorless crystals; yield 1.6g (80%). Analytical and spectral data of carbodithioates **4** are presented in table 1.

4-(3-Bromo-2-hydroxy-5-methylphenyl)-5-ethyl-2-(pyrrolidin-1-yl)-1,3-dithiol-2-ylium perchlorate(**5a**);

General Procedure

To a mixture of sulfuric acid (98%, 1mL) and glacial acetic acid (3mL), 1-(3-bromo-2-hydroxy-5-methylphenyl)-

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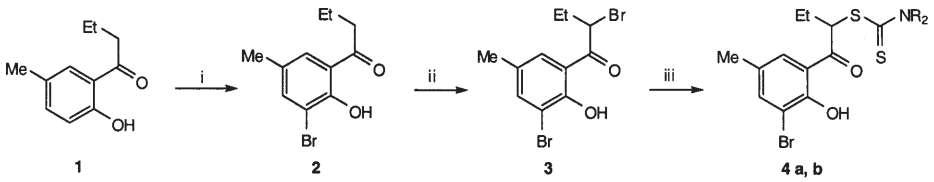
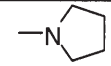
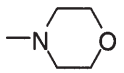


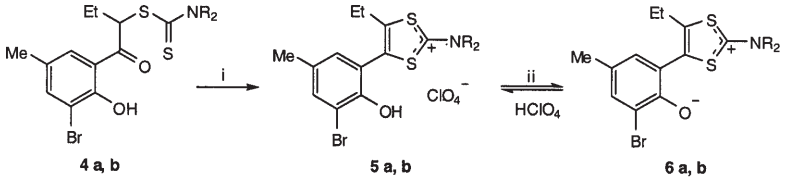
Scheme 1. Synthesis of dithiocarbamates **4 a, b**

i. Br_2, aq. AcOH (66%), reflux; ii. Br_2, gl. AcOH, reflux; iii. $R_2NC(S)S^-$, acetone, reflux

4, 5, 6	-NR_2
a	
b	

	M.p. (°C)	η (%)	IR-ATR (cm^{-1})	NMR (DMSO-d_6) (ppm)
4a	82 - 83	80	2955, 2841, 1638, 1450, 1212, 1133, 967	*^1H NMR* δ : 1.00 (3H, t, CH_3); 1.99 (4H, m, $2CH_2$); 2.03 (2H, m, CH_2); 2.28 (3H, s, CH_3-5); 3.77 (2H, t, CH_2-N); 3.87 (2H, t, CH_2-N); 5.77 (1H, t, CH); 7.54 (1H, d, H-4); 7.83 (1H, d, H-6, J_{H4-H6}= 2.3 Hz); 12.54 (1H, s, OH). *^{13}C NMR* δ : 11.7, 20.8, 25.0, 25.5, 25.9, 51.5, 52.9, 57.4, 111.5, 119.2, 129.3, 129.8, 141.0, 157.4, 194.8, 201.0.
4b	125 - 126	72	2959, 2850, 1634, 1439, 1261, 1187, 939	*^1H NMR* δ : 1.02 (3H, t, CH_3); 2.04 (2H, m, CH_2); 2.25 (3H, s, CH_3-5); 3.79 (4H, m, CH_2OCH_2); 4.13 (4H, m, CH_2-N-CH_2); 5.79 (H, t, CH); 7.58 (1H, d, H-4); 7.83 (1H, d, H-6, J_{H4-H6}= 2.3 Hz); 12.55 (1H, s, OH). 43.9, 51.2, 52.0, 66.0, *^{13}C NMR* δ : 11.5, 20.4, 24.8, 43.8, 51.1, 52.1, 57.8, 111.4, 119.6, 129.1, 129.7, 141.2, 157.1, 194.5, 200.8.

Table 1
ANALYTICAL AND SPECTRAL DATA OF DITHIOCARBAMATES **4**



Scheme 2. Synthesis 1,3-dithiolium perchlorates **5** and mesoionic phenolates **6**

i. H_2SO_4/AcOH 1:3 (v/v), 80 °C, 70% $HClO_4$; ii. $NaHCO_3$ (aq)

1-oxabutan-2-yl-pyrrolidine-1-carbodithioate (**4a**, 1g, 2.4mmol) was added in small portions. The reaction mixture was heated at 80°C for 10min. After cooling, $HClO_4$ (70%, 0.5mL) and water (150mL) were added in this order to isolate the corresponding perchlorate. The precipitate was filtered and dried off. Recrystallization from acetone (50mL) gave colorless crystals; yield 1.1g (92%). Analytical and spectral data of 1,3-dithiolium perchlorates **5** are presented in table 2.

6-Bromo-2-[5-ethyl-2-(pyrrolidin-1-yl)-1,3-dithiol-2-ylium-4-yl]-4-methylphenolate (**6a**)

General Procedure

To a saturated sodium hydrogencarbonate solution (20mL), perchlorate **5a** (1g, 2mmol) 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 dichloromethane gave yellow crystals; yield 0.79g (100%). Analytical and spectral data of 1,3-dithiolium phenolates **6** are presented in table 3.

	M.p. (°C)	η (%)	IR-ATR (cm^{-1})	NMR (DMSO-d_6) (ppm)
5a	202 - 203	92	3350, 2941, 1597, 1481, 1338, 1098 (br), 848	*^1H NMR* δ : 1.19 (3H, t, CH_3); 2.25 (3H, s, CH_3-5); 2.24 (4H, m, $2CH_2$); 2.63 (2H, q, CH_2); 3.65 (2H, t, CH_2); 3.76 (2H, t, CH_2); 7.15 (1H, d, H-4); 7.50 (1H, d, H-6, J_{H4-H6}= 2.1 Hz); 9.72 (1H, s, OH). *^{13}C NMR* δ : 15.1, 19.7, 23.1, 23.4, 56.3, 56.6, 112.4, 118.1, 127.6, 131.5, 131.6, 136.2, 139.7, 150.2, 185.7.
5b	120 - 121 dec.	73	3358, 2939, 1588, 1463, 1310, 1092 (br), 870	*^1H NMR* δ : 1.20 (3H, t, CH_3); 2.27 (3H, s, CH_3-5); 2.66 (2H, q, CH_2); 3.91 (8H, m, $4CH_2$); 7.05 (1H, d, H-4); 7.45 (1H, d, H-6, J_{H4-H6}= 2.1 Hz); 9.40 (1H, s, OH). *^{13}C NMR* δ : 15.3, 19.8, 23.5, 56.4, 56.8, 64.5, 64.6, 112.1, 118.5, 127.3, 131.4, 131.2, 136.5, 139.8, 150.4, 185.8.

Table 2
ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOLIUM PERCHLORATES **5**

	M.p. (°C)	η (%)	IR-ATR (cm^{-1})	NMR (DMSO-d_6) (ppm)
6a	163-164 dec.	100	3383, 2532, 1550, 1488, 1431, 1183, 930, 855	*^1H NMR* δ : 1.18 (3H, t, CH_3); 2.22 (3H, s, CH_3-5); 2.24 (4H, m, $2CH_2$); 2.64 (2H, q, CH_2); 3.64 (2H, t, CH_2); 3.78 (2H, t, CH_2); 7.18 (1H, d, H-4); 7.52 (1H, d, H-6, J_{H4-H6}= 2.0 Hz). *^{13}C NMR* δ : 15.0, 19.7, 23.0, 23.4, 56.4, 56.8, 112.3, 118.0, 127.7, 131.4, 131.8, 136.4, 139.8, 150.1, 185.4.
6b	86-87 dec.	100	3350, 2547, 1564, 1450, 1427, 1184, 990, 859	*^1H NMR* δ : 1.19 (3H, t, CH_3); 2.25 (3H, s, CH_3-5); 2.67 (2H, q, CH_2); 3.90 (8H, m, $4CH_2$); 7.08 (1H, d, H-4); 7.47 (1H, d, H-6, J_{H4-H6}= 2.0 Hz). *^{13}C NMR* δ : 15.1, 19.9, 23.4, 56.5, 56.9, 64.4, 64.7, 112.0, 118.6, 127.4, 131.5, 131.3, 136.4, 140.0, 150.2, 185.5.

Table 3
ANALYTICAL AND SPECTRAL DATA OF MESOIONIC 1,3-DITHIOLIUM PHENOLATES **6**

$C_{16}H_{19}BrNO_2S_2 \cdot ClO_4 \cdot H_2O$	$F(000) = 1056$
$M_r = 518.82$	$D_x = 1.614 Mg \cdot m^{-3}$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, $\lambda = 0.7107 Å$
$a = 8.0190$ (5) Å	Cell parameters from 2471 reflections
$b = 18.3365$ (9) Å	$\theta = 4.1–26.5°$
$c = 14.5821$ (8) Å	$\mu = 2.28 mm^{-1}$
$\beta = 95.227$ (6)°	$T = 294$ K
$V = 2135.2$ (2) $Å^3$	Plate, clear pale yellow
$Z = 4$	0.50×0.35×0.25mm
SuperNova, Dual, Cu at zero, Eos diffractometer	4876 independent reflections
Radiation source: SuperNova (Mo) X-ray Source	3489 reflections with $I > 2\sigma(I)$
mirror	$R_{int} = 0.039$
Detector resolution: 8.0851 pixels mm^{-1}	$\theta_{max} = 29.3°$, $\theta_{min} = 3.2°$
ω scans	$h = -10 \rightarrow 10$
Absorption correction: multi-scan *CrysAlis PRO*, Agilent Technologies, Version 1.171.36.32 (release 02-08-2013 CrysAlis171 .NET) (compiled Aug 2 2013,16:46:58) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	$k = -16 \rightarrow 24$
$T_{min} = 0.658$, $T_{max} = 1.000$	$l = -19 \rightarrow 18$
9958 measured reflections	
Refinement on F^2	Primary atom site location: iterative
Least-squares matrix: full	Hydrogen site location: mixed
$R[F^2 > 2\sigma(F^2)] = 0.059$	H-atom parameters constrained
$wR(F^2) = 0.175$	$w = 1/[\sigma^2(F_o^2) + (0.0918P)^2 + 1.4768P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.04$	$(\Delta/\sigma)_{max} < 0.001$
4876 reflections	$\Delta\rangle_{max} = 1.15 e Å^{-3}$
259 parameters	$\Delta\rangle_{min} = -0.88 e Å^{-3}$
0 restraints	

Table 4
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR **5b**

*X-ray Structure Determination of **5b***

Single crystals of $C_{16}H_{21}BrClNO_7S_2$ (C16 H19 Br1 N1 O2 S2 1+, Cl1 O4 1-, H2 O1) were grown by re-crystallization from methanol. The intensity data of **5b** was collected on a SuperNova, Dual, Cu at zero, Eos diffractometer. The data were collected using Olex2 [32]; the structure was solved with the Superflip [33, 34] structure solution program using Charge Flipping and refined with the ShelXL [35] refinement package using Least Squares minimization. Numerical details are presented in table 4.

CCDC-1003400 contain the supplementary crystallographic data for compound **5b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and discussions

The synthetic strategy for 1,3-dithiol-2-ylium derivatives involves two steps: the synthesis of the corresponding phenacyl carbodithioates, followed by their cyclocondensation under acid conditions. The synthetic pathway required to accomplish the first step is described in Scheme 1. The key intermediate 2-bromo-1-(3-bromo-2-hydroxy-5-methylphenyl)butan-1-one (**3**) has been synthesized according to the literature procedure, through a consecutive bromination sequence of 1-(2-hydroxy-5-methylphenyl)butan-1-one (**1**) and 1-(3-bromo-2-hydroxy-5-methylphenyl)butan-1-one (**2**), respectively [31]. The salts of dialkyldithiocarbamic acid are readily available from the reaction of secondary amine with carbon disulfide, under various experimental conditions [36, 37]. The reactions of these compounds with α-bromophenones represent a useful method for the synthesis of a large variety of phenacyl carbodithioates [38-41]. Following this synthetic strategy, we obtained phenacyl dithiocarbamates **4a, b** by reacting α-bromobutanone **3** with pyrrolidinium pyrrolidine-1-carbodithioate and morpholinium morpholine-4-carbodithioate, respectively. These compounds have been obtained as colorless crystals in good isolated yields. The structure of dithiocarbamates **4** has been proved by analytical and spectral data (table 1). The ^1H NMR spectra indicate a shift in value for the quartet belonging to the α-carbonyl proton from 5.1ppm to ca. 5.7ppm. Also, the presence of new signals belonging to the protons in pyrrolidine and morpholine moieties confirms the structure of the new compounds. ^{13}C NMR spectra indicate the appearance of new aliphatic signals, belonging to the pyrrolidine and morpholine moieties; the new signals appeared at 194ppm was attributed to the thiocarbonyl group.

As mentioned before, the second step for the synthesis of 1,3-dithiol-2-ylium derivatives consist in acid catalyzed cyclocondensation of phenacyl carbodithioates. Several synthetic methods have been previously reported, including

those for sensitive starting materials [42-47]. Using a mixture of concentrated sulfuric acid-glacial acetic acid (1:3 v/v) the cyclization of dithiocarbamates **4a, b** takes place under mild reaction conditions. After 10 min at 80°C, the homogeneous reaction mixture was cooled to room temperature, 70% perchloric acid was added and then poured into water. Filtration and recrystallization of the precipitate provides 1,3-dithiolium perchlorates **5a, b** as colorless crystals, in good to excellent yields (Scheme 2, Table 2). The cyclization of dithiocarbamates **4** is accompanied by important spectral changes. The IR spectra revealed the disappearance of the absorption band corresponding to the carbonyl group (ca. 1630cm^{-1}) and the presence of a new, strong and broad, absorption band at ca. 1090cm^{-1}, corresponding to the perchlorate anion. ^{1}H NMR spectra of 1,3-dithiol-2-ylium perchlorates indicate the absence of the α-carbonyl hydrogen from compounds **4** (ca. 5.7ppm). Is worthy to note the high acidity of phenolic hydrogen, with a chemical shift of 9.7ppm. ^{13}C NMR spectra also support the cyclization of dithiocarbamates **4** to the corresponding of 1,3-dithiolium salts by the disappearance of the carbonyl and thiocarbonyl atoms from dithiocarbamates spectra and the appearance of a new signal at a very low field (ca. 185ppm) which correspond to the electron deficient C(2) atom.

The structure of 4-(3-bromo-2-hydroxy-5-methylphenyl)-5-ethyl-2-(morpholin-4-yl)-1,3-dithiol-2-ylium perchlorate (**5b**) was unambiguously proved by X-ray crystallography (fig. 1). In this salt, the benzene and 1,3-dithiolium planes form a dihedral angle of 106.905°, a significantly higher deviation than that previously reported for a similar compound [48]; this deviation from planarity most likely appears due to the sterical hindrance induced by the ethyl substituent in the 5-position of the 1,3-dithiolium ring. Moreover, no hydrogen bond was found between the phenolic —-O—H group and the sulfur atoms. The recorded data confirms the double bonding character of the C(7)-N(12) bond (numbering from fig. 1); the lenght of N(12)-C(7) bond is 1.294(6)Aº, shorter than N(12)-C(17) and N(12)-C(13) that are essentially σ-bonds (1.46(6)Aº). A molecule of water was also identified to crystallize within the elementary cell.

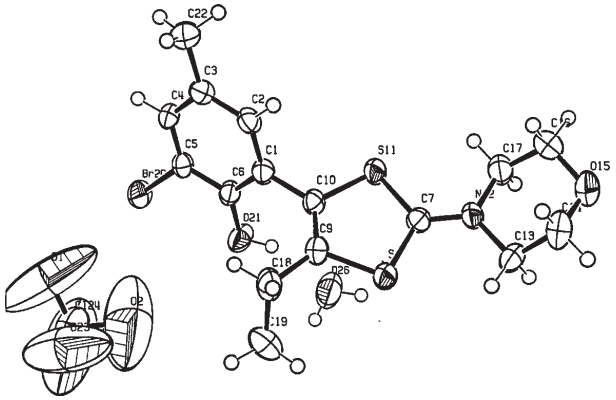


Fig. 1. Molecular structure of compound **5b**. Ellipsoids represent 50% probability levels [49]. Selected molecular dimensions (Å, °): C(1)-C(10) 1.479(6), C(9)-C(10) 1.343(6), C(9)-S(8) 1.747(4), C(10)-S(11) 1.744(4), C(7)-S(8) 1.715(4), C(7)-S(11) 1.723(4), C(7)-N(12) 1.294(6), C(17)-N(12) 1.469(6), C(13)-N(12) 1.455(6), S(11)-C(7)-S(8) 114.6(3), S(11)-C(7)-S(8) 122.9(3).

Treatment of perchlorates **5a, b**, under heterogeneous conditions, with saturated aqueous sodium hydrogencarbonate solution gives 2-[2-(dialkylamino)-1,3-dithiol-2-ylium-4-yl]phenolates **6a, b**, in quantitative yields (scheme 2). The structure of the new compounds has been proved by analytical and spectral data (table 3) and by the following chemical transformation: treatment of an acetone suspension of the mesoionic compounds **6** with 70% perchloric acid regenerates the 1,3-dithiolium perchlorates **5** in quantitative yields (scheme 2).

Conclusions

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

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