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3-Methylpiperidinyl Carbodithioates as Building Blocks for 1,3-Dithiolium Derivatives

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Abstract: New 1,3-dithiolium derivatives have been synthesized by heterocyclocondensation of various 3-methylpiperidinyl carbodithioates derived from 2-hydroxypropiophenones. Thus, 1,3-dithiolium perchlorates have been obtained by the treatment of the corresponding dithiocarbamates with a mixture of acetic and sulfuric acid, followed by the addition of perchloric acid. 1,3-Dithiolium perchlorates have been converted to the corresponding 2-(1,3-dithiolium) phenolates under weak basic conditions. These phenolates exhibit mesoionic character with an internal charge transfer absorption band.

Keywords: Dithiocarbamates; 1,3-Dithiolium salts; Mesoionic phenolates.

Introduction

One of the most important structural features of heterocyclic compounds, 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*

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heterocycles are widely used for therapeutic purposes, 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 antitumor agents.[3-7] Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the continuous interest of researchers.[8-12] 1,3-Dithiolium systems are well known for the reactivity of the C(2)-position towards nucleophiles.[13] 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.[14]

On the other hand, 1,3-dithiolium salts are well-known precursors of tetrathiafulvalenes (TTF), which in turn are notable π-electron donors in organic metals.[15,16] Although tetrathiafulvalenes are well-known electron donor systems, a variety of acceptor units have been investigated, special attention being paid to cationic systems.[17] Of special interest are systems where the donor moiety is linked through a π- or σ-bonded bridge to the acceptor moiety.[18-22] Heteroatoms may act as auxiliary donors or acceptors and improve the overall polarizability of the chromophore. In this context, investigations on a series of (1,3-dithiolium-2-yl)phenolates showed that 1,3-dithiolium ions can also serve as an acceptor moiety in intramolecular charge-transfer systems.[23]

In view of the above facts, we decided to investigate the synthesis of new 1,3-dithiolium systems bearing a 3-methylpiperidinyl moiety at the 2-position using 2-hydroxypropiophenone derivatives as starting materials.

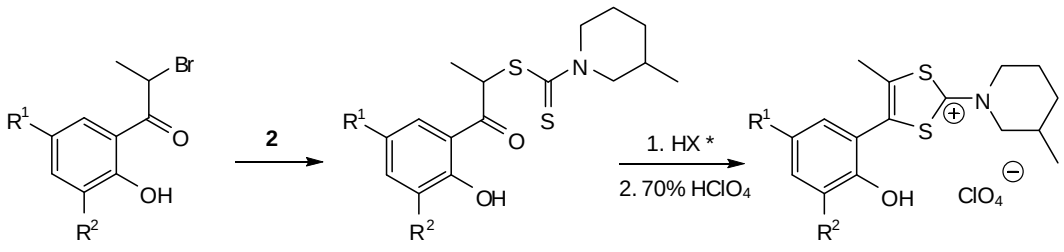
These systems can be of interest from both medicinal and synthetical points of view.

Results and Discussion

The synthesis of 2-dialkylamino-1,3-dithiolium salts is well-known in the literature.[24,25] The most used method consists in the heterocyclocondensation of the corresponding dithiocarbamates.[26-29] The synthetic sequence of the target compounds is described in Scheme 1.

ω-Bromo-2-hydroxypropiophenones **1** were synthesized according to the literature procedures. Thus, compound **1a** was obtained by regioselective double bromination of 2-hydroxypropiophenone in chloroform,[30] while compounds **1b**[31] and **1c**[32] by regioselective side chain bromination of the corresponding substituted 2-hydroxypropiophenones.

Phenacyl *N*,*N*-dialkyldithiocarbamates **3** have been prepared by reaction of the corresponding *ω*-bromo-ketones with 3-methylpiperidinium *N*-(3-methylpiperidinyl)carbodithioate (**2**). Using a mixture of sulfuric acid and glacial acetic acid (1:3 v/v), the cyclization of dithiocarbamates **3a-c** takes place under mild reaction conditions (Scheme 1).



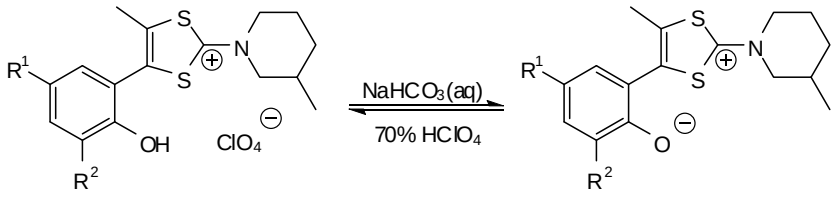
(**1**) (**3**) * HX = H_2SO_4/AcOH 1 : 3 (v/v) (**4**)

1, 3, 4, 5	R^1	R^2
a	Br	H
b	Br	Br
c	Me	Br

Scheme 1

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 gives the corresponding perchlorates **4** as colorless crystals, in good to excellent yields. The cyclization of phenacyl carbodithioates **3** to the corresponding 1,3-dithiolium perchlorates was accompanied by significant changes in the spectral features. The IR spectra revealed the disappearance of the carbonyl absorption band from the region of 1633 - 1636 cm^{-1}. Nuclear magnetic resonance spectra also indicated that the heterocyclocondensation has occurred through the disappearance of the signal for aliphatic hydrogen atoms (5.74-5.84 ppm).

Treatment of salts **4** under heterogeneous conditions, with a saturated aqueous sodium hydrogencarbonate solution affords 2-(1,3-dithiol-2-ylium-4-yl) phenolates (**5a-c**), in quantitative yields. These compounds were isolated as yellow crystalline products that present the features of mesoionic compounds.[33-35] The presence of a hydroxy substituent in an *ortho*-position induces an extended delocalization of the negative charge up to the C(4)-C(5) bond of the dithiolium ring.



(**4**) (**5**)

Scheme 2

The molecular structure of the new mesoionic phenolates was proved by analytical and spectral data and by the following chemical transformation: treatment of an acetone suspension of the mesoionic compounds **5** with 70% perchloric acid regenerates the 1,3-dithiolium

perchlorates **4** in quantitative yields (Scheme 2). The UV-Vis absorption spectra of the mesoionic phenolates has shown that the yellow color 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 (ca. 405 nm) was proved by measurements at different concentrations; it was observed that the molar extinction coefficient remained constant regardless of the concentration variations.

Experimental

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; their results were found to be in good agreement (±0.30%) with the calculated values. Mass spectra were recorded on a Finnigan MAT 90X spectrometer.

1-(5-Bromo-2-hydroxyphenyl)-1-oxopropan-2-yl-(3-methylpiperidin-1-yl)-1-carbodithioate (**3a**)*; General Procedure:*

To a solution of 2-bromo-1-(5-bromo-2-hydroxyphenyl)propan-1-one (3.08 g, 0.01 mol) in acetone (30 mL) a solution of 3-methylpiperidinium *N*-(3-methylpiperidinyl)carbodithioate (**2**) (2.75 g, 0.01 mol) in acetone-water (1:1, 50 mL) was added. After 5 min under stirring at rt the precipitate was filtered, washed with water and dried off. Recrystallization from *i*-propyl alcohol (50 mL) gave colorless crystals; yield 2.81 g (70%). Mp 61-62 °C. IR (ATR): 2915, 2841, 1633, 1468, 1343, 1226, 1175, 933, 861, 747, 622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, 3H, CH_3), 1.22 (m, 1H), 1.57 (d, 3H, CH_3), 1.76 (m, 4H), 2.84 (m, 1H, m),

3.16 (m, 1H), 4.37 (m, 1H), 5.18 (m, 1H), 5.74 (q, 1H, H-2), 6.87 (d, ^4J = 1.4 Hz, 1H, H_{ar}), 7.54 (dd, ^3J = 7.9 Hz, ^4J = 1.4 Hz 1H, H_{ar}), 8.03 (d, ^4J = 1.4 Hz, 1H, H_{ar}), 11.60 (s, 1H, OH). MS (ESI, $C_{16}H_{20}{}^{79}BrNO_2S_2$): *m/z* = 401 ($M^+$).

1-(3,5-Dibromo-2-hydroxyphenyl)-1-oxopropan-2-yl-(3-methylpiperidin-1-yl)-1-carbodithioate (**3b**):

Yield 81%. Mp 128-129 °C. IR (ATR): 2893, 1634, 1428, 1315, 1221, 1154, 997, 860, 771, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, 3H, CH_3), 1.23 (m, 1H), 1.58 (d, 3H, CH_3), 1.76 (m, 4H), 2.83 (m, 1H, m), 3.17 (m, 1H), 4.37 (m, 1H), 5.19 (m, 1H), 5.77 (q, 1H, H-2), 7.84 (d, ^4J = 2.3 Hz, 1H, H_{ar}), 8.13 (d, ^4J = 2.3 Hz, 1H, H_{ar}), 12.64 (s, 1H, OH). MS (ESI, $C_{16}H_{19}{}^{79}Br_2NO_2S_2$): *m/z* = 479 ($M^+$).

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-oxopropan-2-yl-(3-methylpiperidin-1-yl)-1-carbodithioate (**3c**):

Yield 84%. Mp 112-113 °C. IR (ATR): 2895, 1637, 1434, 1346, 1226, 1148, 998, 854, 756, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, 3H, CH_3), 1.22 (m, 1H), 1.57 (d, 3H, CH_3), 1.76 (m, 4H), 2.27 (s, 3H, CH_3), 2.84 (m, 1H, m), 3.16 (m, 1H), 4.37 (m, 1H), 5.18 (m, 1H), 5.84 (q, 1H, H-2), 7.54 (d, ^4J = 2.2 Hz, 1H, H_{ar}), 7.76 (d, ^4J = 2.2 Hz, 1H, H_{ar}), 12.48 (s, 1H, OH). MS (ESI, $C_{17}H_{22}{}^{79}BrNO_2S_2$): *m/z* = 415 ($M^+$).

4-(5-Bromo-2-hydroxyphenyl)-5-methyl-2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium perchlorate (**4a**); *General Procedure:*

To a mixture of H_2SO_4–AcOH (1:3, 3 mL) carbodithioate **3a** (0.4 g, 1 mmol) were added in several portions. The reaction mixture was stirred for 30 min at 80 °C. After cooling to room temperature, $HClO_4$ (70%, 0.5 mL) was added and the crude **4a** was precipitated with water (100 mL). This was filtered off, dried, and recrystallized from EtOH (30 mL) to give the pure product as colorless crystals; yield 0.34 g (70%).

Mp 141-142 °C. IR (ATR): 3251, 2932, 1562, 1521, 1495, 1391, 1262, 1098, 1048, 816, 619 cm^{-1}. ^1H NMR (300 MHz, DMSO- d_6): δ = 0.96 (m, 3H, CH_3), 1.22 (m, 1H), 1.89 (m, 4H), 2.19 (s, 3H, CH_3), 3.45 (m, 1H), 3.49 (m, 1H), 3.82 (m, 2H), 7.09 (d, ^4J = 2.2 Hz, 1H, H_{ar}), 7.58 (d, ^3J = 8.6 Hz, 1H, H_{ar}); 7.55 (dd, ^3J = 8.6 Hz, ^4J = 2.2 Hz, 1H), 10.02 (1H, s, OH). MS (ESI, $C_{16}H_{19}{}^{79}BrClNO_5S_2$): *m/z* = 384 ($M^+$- ClO_4).

4-(3,5-Dibromo-2-hydroxyphenyl)-5-methyl-2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium perchlorate (**4b**):

Yield 60%. Mp 168-169 °C. IR (ATR): 3572, 3126, 1574, 1530, 1446, 1257, 1069, 620 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.98 (m, 3H, CH_3), 1.24 (m, 1H), 1.90 (m, 4H), 2.29 (s, 3H, CH_3), 3.47 (m, 1H, m), 3.50 (m, 1H), 3.83 (m, 2H), 7.45 (d, ^4J = 1.7 Hz, 1H, H_{ar}), 7.80 (d, ^4J = 1.7 Hz, 1H, H_{ar}), 10.10 (1H, s, OH). MS (ESI, $C_{16}H_{18}{}^{79}Br_2ClNO_5S_2$): *m/z* = 462 ($M^+$-$ClO_4$).

4-(3-Bromo-2-hydroxy-5-methylphenyl)-5-methyl-2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium perchlorate (**4c**):

Yield 89%. Mp 160-161 °C. IR (ATR): 3514, 3126, 1574, 1530, 1446, 1257, 1069, 620 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.98 (m, 3H, CH_3), 1.24 (m, 1H), 1.90 (m, 4H), 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.47 (m, 1H, m), 3.50 (m, 1H), 3.83 (m, 2H), 5.58 (1H, s, OH), 6.99 (d, ^4J = 2.2 Hz, 1H, H_{ar}), 7.36 (d, ^4J = 2.2 Hz, 1H, H_{ar}). MS (ESI, $C_{17}H_{21}{}^{79}BrClNO_5S_2$): *m/z* = 398 ($M^+$-$ClO_4$).

4-Bromo-2-[5-methyl-2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium-4-yl]phenolate (**5a**)*; General Procedure:*

To a saturated sodium hydrogencarbonate solution (30 mL) perchlorate **4a** (0.48 g, 1 mmol) 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 DMF gave yellow crystals; yield 0.38 g (100%).

Mp 201-202 °C (dec). IR (ATR): 1540, 1441, 1263, 721, 621 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.96 (m, 3H, CH_3), 1.22 (m, 1H), 1.89 (m, 4H), 2.19 (s, 3H, CH_3), 3.45 (m, 1H), 3.49 (m, 1H), 3.82 (m, 2H), 7.00 (d, ^4J = 2.3 Hz, 1H, H_{ar}), 7.50 (d, ^3J = 8.7 Hz, 1H, H_{ar}); 7.53 (dd, ^3J = 8.7 Hz, ^4J = 2.3 Hz, 1H). MS (ESI, $C_{16}H_{18}{}^{79}BrNOS_2$): *m/z* = 383.

4,6-Dibromo-2-[5-methyl-2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium-4-yl]phenolate (**5b**):

Yield 100%. Mp 130-131 °C (dec). IR (ATR): 3291, 3091, 2942, 1436, 1262, 854, 721, 664 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.96 (m, 3H, CH_3), 1.22 (m, 1H), 1.89 (m, 4H), 2.26 (s, 3H, CH_3), 3.46 (m, 1H, m), 3.49 (m, 1H), 3.82 (m, 2H), 7.44 (d, ^4J = 1.8 Hz, 1H, H_{ar}), 7.78 (d, ^4J = 1.8 Hz, 1H, H_{ar}). MS (ESI, $C_{16}H_{17}{}^{79}Br_2NOS_2$): *m/z* = 461.

6-Bromo-4-methyl-2-[5-methyl-2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium-4-yl]phenolate (**5c**):

Yield 100%. Mp 151-152 °C (dec). IR (ATR): 2851, 1461, 1263, 1203, 853, 792, 576 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.97 (m, 3H, CH_3), 1.24 (m, 1H), 1.89 (m, 4H), 2.18 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.45 (m, 1H, m), 3.50 (m, 1H), 3.81 (m, 2H), 6.99 (d, ^4J = 2.1 Hz, 1H, H_{ar}), 7.36 (d, ^4J = 2.1 Hz, 1H, H_{ar}). MS (ESI, $C_{17}H_{20}{}^{79}BrNOS_2$): *m/z* = 397.

Conclusions

The synthesis of a new class of 4-[2-(3-methylpiperidin-1-yl)-1,3-dithiol-2-ylium-4-yl] phenolates has been accomplished by the heterocyclization of the corresponding phenacyl carbodithioates. The latter compounds have been synthesized following regioselective bromination of various propiophenones.

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