Synthesis of Novel Fluorine-Containing 1,3-Dithiolium Derivatives

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The synthesis of 4-(5-fluoro-2-hydroxyphenyl)-2-N,N-diethylamino-1,3-dithiol-2-ylium perchlorate has been accomplished by the acid-catalyzed cyclization of 1-(5-fluoro-2-hydroxyphenyl)-1-oxaethan-2-yl-N,N-diethylamino-1-carbodithioate. The structure of the new phenacyl carbodithioate was confirmed by X-ray analysis. Conversion of the 1,3-dithiolium perchlorate into a mesoionic derivative was achieved in a basic environment.

Keywords: fluorine derivatives, dithiocarbamate, 1,3-dithiolium salt, mesoionic phenolate, X-ray crystallography, medicinal chemistry, drug design

Before the middle of the last century, it was inconceivable that the introduction of fluorine into natural products would result in beneficial biological properties. The carbon-fluorine bond is one of the strongest chemical bonds, and its biological formation/cleavage would require extremely activated intermediates that are difficult to generate under biological conditions [1]. This quite rare grouping can be, however, of great value for the rational design of molecules with a particular reactivity and biological activity. In the last twelve years, several reviews covering various areas of the use of fluorine substitution in pharmaceuticals have been published [2-9]. Fluorine is making a great impact in pharmaceuticals not only in the fast-growing number of fluorinated drugs but also in the development of health care products. Thus, three out of the five top-selling pharmaceuticals contain fluorine. In 2008 atorvastatin (**1**) was registered as the best-selling drug globally (fig. 1); it is used for treatment of high cholesterol and triglyceride levels and prevention of heart attacks and strokes. The antibacterial ciprofloxacin (**2**) should also be mentioned. About one-third of the top-performing drugs currently on the market contain fluorine atoms in their structure. This fact suggests a well-established role of fluorine in medicinal chemistry and drug design.

Both structures depicted in figure 1 contain a heterocyclic core. Heterocyclic compounds are of great importance and hence widely used by the drug industry [10, 11]. In chemical and/or pharmaceutical research,, a great deal of attention is currently being focused on nitrogen- and sulfur-containing heterocycles [12-22]. A 1,3-dithiolium derivative has been reported to exhibit biological activity against gram-positive and gram-negative bacteria [23]. Besides the biological interest in the 1,3-dithiolium derivatives, these compounds are known to be reactive at the C(2)-position towards nucleophiles [24]. Investigations on a series of (1,3-dithiolium-2-yl)phenolates showed that 1,3-dithiolium ions can also serve as acceptor moieties in intramolecular charge-transfer systems [25, 26]. *N,N*-Dialkylamino carbodithioates represent the main precursors for 1,3-dithiol-2-ylium systems bearing a *N,N*-dialkylamino moiety at the 2-position [27]. In view of the above facts, we report here the synthesis of a new class of fluorine-containing 1,3-dithiolium derivatives.

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 AV-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. MS: Finnigan MAT 90X, electron impact (EI, 70 eV). Electrospray ionization (ESI): ThermoFisher Scientific LTQ-Orbitrap Velos. Typical spray voltage in positive ion mode was 2.3-2.8 kV.

Synthesis

The synthetic pathway used to obtain fluorinated derivatives **3-5** is based on a method previously used by our research group [28-31] and is presented in Scheme 1.

1-(5-Fluoro-2-hydroxyphenyl)-1-oxaethan-2-yl-N,N-diethylamino-1-carbodithioate **3**

To a solution of 2-bromo-1-(5-fluoro-2-hydroxyphenyl) ethan-1-one (**1**) (1.16g, 5mmol) in acetone (10mL), a solution of sodium *N,N*-diethyldithiocarbamate trihydrate (1.13g, 5mmol) in acetone/water (10mL/10mL) was added. The resulting mixture was refluxed for 10 min, cooled to room temperature and poured into water (200mL) with vigorous stirring. The precipitate thus formed was vacuum-filtered and recrystallized from ethanol, yielding 1.05g (70%) of yellow crystals; m.p. = 107-109°C.

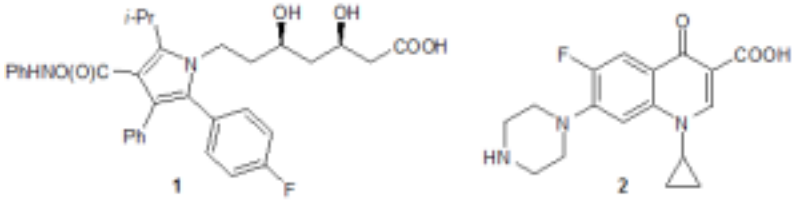

Fig. 1. Structures of atorvastatin (1) and ciprofloxacin (2)

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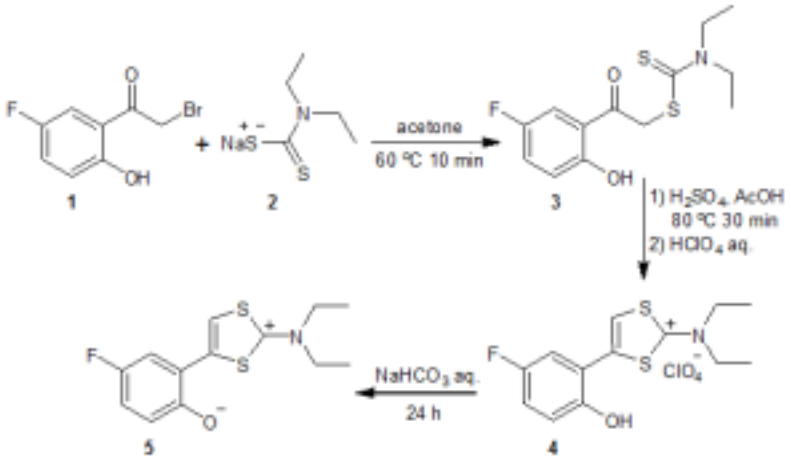

Scheme 1. Synthesis of fluorinated derivatives **3-5**

^{1}H NMR ($CDCl_3$) *d* 1.28 (t, 3H, ^3J = 7.1 Hz), 1.37 (t, 3H, ^3J = 7.1 Hz), 3.82 (q, 2H, ^3J = 7.1 Hz), 4.02 (q, 2H, ^3J = 7.1 Hz), 4.85 (s, 2H), 6.98 (dd, 1H, ^3J = 9.3 Hz, ^4J = 4.5 Hz), 7.25 (ddd, 1H, ^3J = 7.7, 9.3 Hz, ^4J = 3.0 Hz), 7.67 (dd, 1H, ^3J = 9.0 Hz, ^4J = 3.0 Hz), 11.62 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) *d* 11.5, 12.6, 44.0, 47.2, 50.4, 115.1, 118.5, 119.9, 124.4, 154.8, 158.6, 193.1, 198.4 ppm. ^{19}F NMR ($CDCl_3$) *d* -123.7 ppm. EI-MS (*m/z*): 301.1 (M^+), 154.1, 148.0, 139.0, 116.1.

4-(5-Fluoro-2-hydroxyphenyl)-2-N,N-diethylamino-1,3-dithiol-2-ylium perchlorate **4**

To a mixture of sulfuric and acetic acid (1mL/3mL), dithiocarbamate **3** (0.6g, 2mmol) was added and the resulting mixture was heated at 80°C for 30 min. The resulting solution was then allowed to cool to room temperature and poured into an aqueous solution of perchloric acid (1mL $HClO_4$ 70% and 75mL H_2O) with vigorous stirring. The resulting white precipitate was then filtered and recrystallized from ethanol, yielding 0.44g (57%) of a white crystalline solid; m.p. = 146-148°C. ^{1}H NMR (DMSO-*d*6) *d* 1.32-1.41 (m, 6H), 3.81-3.96 (m, 4H),), 7.01 (dd, 1H, ^3J = 9.0 Hz, ^4J = 4.8 Hz), 7.25 (ddd, 1H, ^3J = 8.1, 9.0 Hz, ^4J = 3.0 Hz), 7.55 (dd, 1H, ^3J = 9.6 Hz, ^4J = 3.0 Hz), 8.12 (s, 1H), 11.12 (s, 1H) ppm. ^{13}C NMR (DMSO-*d*6) *d* 10.2, 10.3, 53.0, 53.4, 114.4, 117.6, 117.7, 118.2, 120.2, 133.9, 150.1, 155.4, 186.4 ppm. ESI-MS (*m/z*): [M-ClO_4^-]: 284.0573 (calcd. 284.0575).

4-Fluoro-2-[2-N,N-diethylamino-1,3-dithiol-2-ylium-4-yl]phenolate **5**;

1,3-Dithiolium perchlorate **4** (0.38g, 1mmol) was added to a saturated solution of sodium hydrogen carbonate and the resulting suspension was stirred vigorously for 24 h. The solid was then filtered, washed with water and air-dried, yielding 0.25g (88%) of a yellow amorphous powder; m.p. = 239-241°C. ^{1}H NMR (DMSO-*d*6) *d* 1.29-1.41 (m, 6H), 3.76-3.93 (m, 4H), 6.74 (dd, 1H, ^3J = 9.1 Hz, ^4J = 5.0 Hz), 7.03 (m, 1H), 7.50 (dd, 1H, ^3J = 10.0 Hz, ^4J = 3.2 Hz), 7.96 (s, 1H) ppm. ^{13}C NMR (DMSO-*d*6) *d* 10.3, 10.4, 52.4, 52.9, 111.8, 114.1, 117.2, 118.1, 118.2, 136.8, 152.9, 156.5, 187.3 ppm.

X-ray Structure Determination of ***3****:*

Crystal data are summarized in table 1. The crystal was mounted in inert oil on a glass fibre and transferred to the cold gas stream of an Oxford Diffraction Xcalibur A diffractometer. Intensity measurements were performed using monochromated Mo *K*a radiation (l=0.71073 Å). Absorption corrections were based on multi-scans. The structure was refined anisotropically on F^2 using the program SHELXL-97 [32]. The hydroxyl hydrogen was refined freely; other hydrogen atoms were included using a riding model or rigid methyl groups.

CCDC-1440648 contains the supplementary crystallographic data for compound **3**. These data can be obtained

Empirical formula	$C_{13}H_{16}FNO_2S_2$	
Formula weight	301.39	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 4.83480(17) Å	α= 90°
	b = 24.8040(10) Å	β= 91.808(3)°
	c = 11.6730(4) Å	γ = 90°
Volume	1399.15(9) Å^3	
Z	4	
Density (calculated)	1.431 Mg/m^3	
Absorption coefficient	0.39 mm^{-1}	
F(000)	632	
Crystal size	0.25 x 0.20 x 0.10 mm^3	
Theta range for data collection	2.40 to 30.96°	
Reflections collected	36292	
Independent reflections	4186 [R(int) = 0.039]	
Completeness to theta = 30.00°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.988	
Data/parameters	4186/178	
Goodness-of-fit on F^2	1.08	
Final R indices [I >2sigma(I)]	R1 = 0.0376, wR2 = 0.0790	
R indices (all data)	R1 = 0.0471, wR2 = 0.0827	
Largest diff. peak and hole	0.49 and -0.28 e.Å^{-3}	

Table 1
CRYSTAL DATA AND STRUCTURE REFINEMENT

free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and discussions

The synthetic pathway for the synthesis of fluorine-containing 1,3-dithiolium derivatives is described in Scheme 1. Thus, 2-bromo-1-(5-fluoro-2-hydroxyphenyl)ethan-1-one (**1**) [33] reacts with the diethyldithiocarbamate anion to form the desired phenacyl carbodithioate **3**. The ^{1}H NMR spectrum indicates the presence of the diethylamino group in the form of two triplets corresponding to the two methyl groups (1.29 ppm and 1.37 ppm) and two quartets belonging to the two methylene units (3.82 ppm and 4.02 ppm). The singlet at 4.85 ppm corresponds to the methylene unit bound to the carbonyl group. The H-3, H-4 and H-6 hydrogen atoms of the aromatic ring all couple with each other, and also with the fluorine atom at position 5. Thus, the H-3 hydrogen atom can be found as a doublet of doublets at 6.98 ppm. It couples with the H-4 hydrogen atom (*ortho* coupling, ^3J = 9.3 Hz) and with the fluorine atom (*meta* coupling, ^4J = 4.5 Hz). The H-4 hydrogen atom at 7.25 ppm appears as a doublet of doublets of doublets. It is involved in two *ortho* couplings (H-3, ^3J = 9.3 Hz and F, ^3J = 7.7 Hz) and a *meta* coupling (H-5, ^4J = 3.0 Hz). The H-6 hydrogen atom at 7.67 ppm appears as a doublet of doublets because of an *ortho* coupling with the fluorine atom (^3J = 9.0 Hz) and a *meta* coupling with the H-4 hydrogen atom (^4J = 3.0 Hz). The sharp singlet at 11.62 ppm arises from the phenolic hydrogen atom, which forms an intramolecular hydrogen bond with the carbonyl group. The ^{13}C NMR spectrum also supports the formation of the desired phenacyl carbodithioate. The two signals at 11.9 ppm and 13.0 ppm belong to the two methyl groups, while the two nitrogen-bound methylene groups can be found at 47.6 ppm and 50.8 ppm. The thiocarbonyl and carbonyl carbon atoms can be found at 193.1 ppm and 198.4 ppm. The ^{19}F NMR spectrum places the fluorine atom at -123.7 ppm, a typical value for a fluorine atom bonded to an aromatic system. Single crystals suitable for X-ray determinations were obtained for dithiocarbamate **3** by recrystallization from ethanol. X-Ray analysis of these crystals confirms the proposed structure. The results are presented in figure 2.

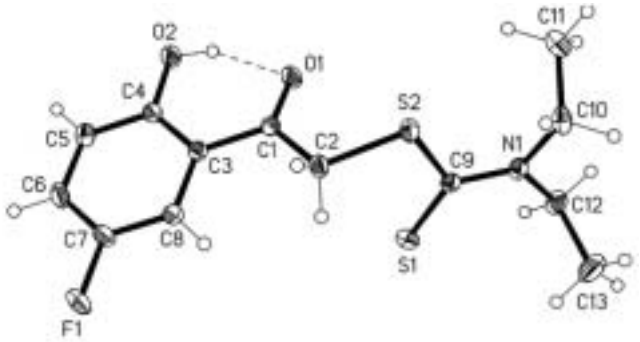

Fig. 2. Molecular structure of compound **3**. Ellipsoids represent 50% probability levels. Selected molecular dimensions (Å, °): N(1)-C(9) 1.3351(17), S(1)-C(9) 1.6789(13), S(2)-C(9) 1.7738(14), N(1)-C(9)-S(2) 112.88(10), N(1)-C(9)-S(1) 124.26(10), S(2)-C(9)-S(1) 122.87(8)

A strong intramolecular *hydrogen bond* O(2)–H(02)LO(1), with H–O 0.84(2) Å, angle 147(2)°, is observed for **3**. The data confirm the extended *p*-π conjugation at the level of the dithiocarbamate group [34]; the N(1) – C(9) bond length is 1.3351(17) Å, shorter than N(1)–C(10) and N(1)–C(12), which are essentially σ-bonds (1.4775(17), 1.4725(17) Å). The torsion angle between the plane of the aromatic ring and that of the planar section of the diethyldithiocarbamate moiety [C(1)-C(2)-S(2)-C(9)] is -93.86(10)°.

The cyclization reaction of 1-(5-fluoro-2-hydroxyphenyl)-1-oxaethan-2-yl-*N,N*-diethylamino-1-carbodithioate (**3**) to 4-(5-fluoro-2-hydroxyphenyl)-2-*N,N*-diethylamino-1,3-dithiol-2-ylium perchlorate (**4**) takes place in a sulfuric acid/acetic acid mixture [35], necessary for the protonation of the oxygen atom of the carbonyl group and the dehydration of the cyclic intermediate. This chemical transformation leads to important spectral changes. In the ^{1}H NMR spectrum, the singlet at 4.87 ppm (the methylene unit bound to the carbonyl group) disappears. At the same time, a new singlet, attributable to the 1,3-dithiolium ring hydrogen atom, appears at 8.12 ppm. The H-3 hydrogen atom can be found at 7.01 ppm as a doublet of doublets (^3J = 9.0 Hz and ^4J = 4.8 Hz), the H-4 hydrogen atom as a doublet of doublets of doublets at 7.25 ppm (^3J = 8.1, ^3J = 9.0 Hz and ^4J = 3.0 Hz) and the H-6 hydrogen atom as a doublet of doublets at 7.55 ppm (^3J = 9.6 Hz and ^4J = 3.0 Hz). The phenolic hydrogen atom, no longer part of a hydrogen bond with the carbonyl group, appears as a broad singlet at 11.12 ppm. The ^{13}C NMR spectrum reveals the disappearance of the two signals at 193.1 ppm and 198.4 ppm, belonging to the thiocarbonyl and carbonyl groups, a clear sign that the cyclization reaction had taken place. This is further confirmed by the appearance of a new signal at 186.4 ppm, which was attributed to the positive C-2 carbon atom of the 1,3-dithiolium ring.

1,3-Dithiolium perchlorate **4** can be converted to the mesoionic phenolate **5** in the presence of a weak base, such as sodium hydrogen carbonate. The reaction proceeds with evolution of carbon dioxide and a change of color from colourless to pale yellow; this compound displays the features of mesoionic derivatives [36, 37]. The ^{1}H NMR spectrum indicates the disappearance of the phenolic hydrogen atom.

Conclusions

The synthesis of 4-(5-fluoro-2-hydroxyphenyl)-2-*N,N*-diethylamino-1,3-dithiol-2-ylium perchlorate has been accomplished by the acid-catalyzed cyclization of the corresponding *N,N*-diethylaminocarbodithioate. The structure of this compound, 1-(5-fluoro-2-hydroxyphenyl)-1-oxaethan-2-yl-*N,N*-diethylamino-1-carbodithioate, was confirmed by X-ray analysis. Conversion of the 1,3-dithiolium perchlorate into a mesoionic derivative was achieved under weakly basic conditions. All new compounds were characterized using NMR spectroscopy.

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