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Communication

Synthesis and Crystal Structure of 1-(3-fluorophenyl)-3-(3,4,5-trimethoxybenzoyl)thiourea

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Abstract: The title thiourea was synthesized by reaction of 3,4,5-trimethoxybenzoyl isothiocyanate with 3-fluoroaniline. The 3,4,5-trimethoxybenzoyl isothiocyanate was produced *in situ* by reaction of 3,4,5-trimethoxybenzoyl chloride with ammonium thiocyanate in dry acetonitrile. The structure was confirmed by the spectroscopic, elemental analysis and single crystal X-ray diffraction data. It crystallizes in the monoclinic space group $P2_1/c$ with unit cell dimensions $a = 13.0966(9)$, $b = 16.6460(13)$, $c = 7.8448(5)$, $\beta = 106.721(5)^\circ$, $V 1637.9(2) \text{ \AA}^3$, $Z = 4$.

Keywords: Synthesis; 1-(3-fluorophenyl)-3-(3,4,5-trimethoxybenzoyl)thiourea; crystal structure

1. Introduction

Thiourea derivatives are extremely versatile building blocks for the synthesis of a variety of heterocyclic compounds and possess a wide spectrum of bioactivities. N, N-Dialkyl-N-aryl thioureas are efficient ligands for the separation of platinum group metals [1]. 1,3-Dialkyl or diaryl thioureas exhibit significant antifungal activity against plant pathogens *Pyricularia oryzae* and *Drechslera oryzae* [2]. N-aryl-N-phenyl thioureas have been developed as anion-binding site in a hydrogen-bonding receptor [3], calix [4] arenes containing thioureas as neutral receptors towards α ,

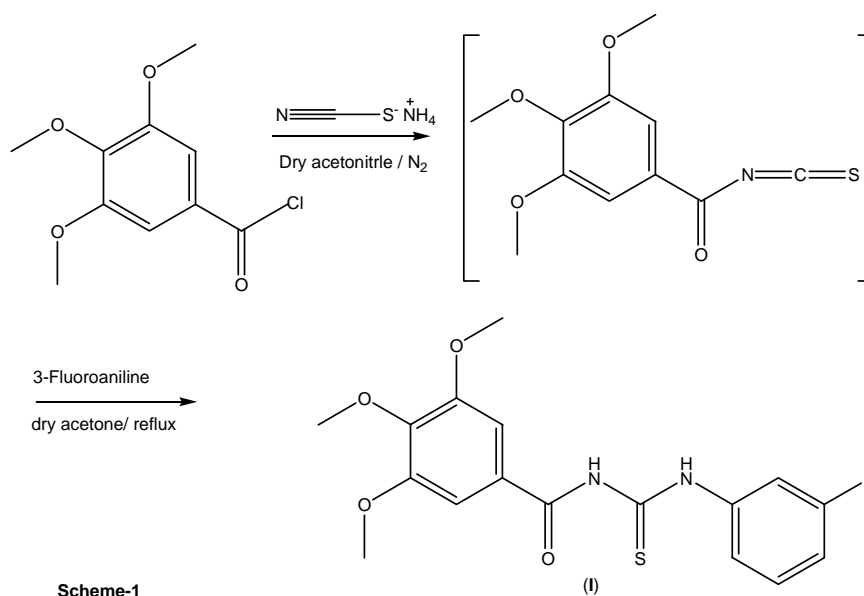
α -dicarboxylate anions [4], and N-4-substitued-benzyl-N-ter-butylbenzyl thioureas as vanilloid receptors ligands and antagonists in rat DRG neurons [5]. 1-Benzoyl-3-(4,6-disubstituted-pyrimidinyl)thioureas have shown excellent herbicidal activity [6]. Acyl thioureas are well known for their superior pesticidal, fungicidal, antiviral and 1-Acyl-3-(2'-aminophenyl) thioureas as anti-Intestinal Nematode Prodrugs [7]. Thioureas have widely been used in enantioselective synthesis, such as in nitro-Mannich reactions, aza-Henry reaction, and the Michael Addition [8]. Symmetrical and asymmetrical phenethyl thioureas, 5-halo-substituted thiophene pyridyl thioureas and heterocyclic thioureas are non-nucleoside inhibitors of HIV-1 reverse transcriptase [9]. Condensation of thiourea derivatives with carbonyl compounds have been used in the synthesis of 1-aryol-3-aryl-4-substituted imidazole-2-thiones [10], 2-(aroylimino)-3-aryl-4-methyl/phenyl-1,3-thiazolines [11].

Synthesis of title thiourea was carried out in continuation of our interest in the synthesis of thioureas as intermediates towards synthesis of novel heterocycles and for the systematic study of their bioactivity and complexation behavior.

2. Results and Discussion

Commercial 1-(3,4,5-trimethoxy)benzoic acid was converted into corresponding acid chloride by treatment with thionyl chloride. 1-(3,4,5-trimethoxy)benzoyl isothiocyanate was produced *in situ* by reaction of acid chloride with ammonium thiocyanate in dry acetonitrile under nitrogen. It was treated with an equimolar quantity of 3-fluoroaniline in acetonitrile to afford the title thiourea in high yield [19] (scheme 1).

Scheme 1. Synthetic route to 1-(3-fluorophenyl)-3-(3,4,5-trimethoxybenzoyl)thiourea.



In the IR spectrum absorptions were observed at 3350 cm^{-1} , 3280 cm^{-1} for free and associated NH, at 1638 cm^{-1} for carbonyl and at 1240 cm^{-1} for thiocarbonyl, at 1586 cm^{-1} for C=C and 1150 cm^{-1} for C-N stretchings respectively. The characteristic broad singlets at δ 9.17 and 4.61 for HN(1) and HN(3), were observed in ^1H NMR. The carbonyl and thiocarbonyl peaks were observed at δ 176.3 and 178.2

respectively, in ^{13}C NMR. In the mass spectrum the molecular ion peaks and base peak derived from aroyl group were observed.

2.1. Crystal Structure Determination

Bond lengths and angles of the title compound are in the usual ranges. The dihedral angle between the two aromatic rings is 89.9° . Two of the three methoxy groups lie in the plane of the ring to which they are attached [torsion angles: C27-O2-C23-C22 $0.12(19)^\circ$, C29-O4-C25-C26: $13.69(18)^\circ$], whereas the third one is twisted out of the ring plane [C28-O3-C24-C25 $76.18(15)^\circ$]. The molecular conformation is stabilized by an intramolecular N-H...O hydrogen bond. The crystal packing shows an intermolecular N-H...O hydrogen bond (Table 1). A search in the Cambridge Crystallographic Database for the fragment Ph-C(O)-N-C(S)-N-Ph yielded 116 hits. In all of them, the torsion angle O=C-N-C adopts a cis conformation. The values range from -13 to 24° . The C-N-C=S torsion angle on the other hand is trans in all structures spanning a 40° range at 180° . The S=C-N-Car torsion angle is again cis (-15 to 10.1°). The values of the title compound agree well with these [O1-C2-N2-C1 $-3.4(2)^\circ$, S1-C1-N2-C2 $-177.99(11)^\circ$, S1-C1-N1-C11 $-3.6(2)^\circ$].

Table 1. Hydrogen bonds for (3) [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
N(1)-H(1)...O(1)	0.839(18)	1.937(17)	2.6415(14)	140.9(16)
N(2)-H(2)...O(3)#1	0.848(17)	2.165(17)	2.9190(15)	148.0(16)

Symmetry transformations used to generate equivalent atoms: #1 $-x+1, -y+1, -z+1$

The molecular structure of the title compound **1** along with the atom-numbering scheme is depicted in Figure 1.

Figure 1. Perspective view of the title compound.

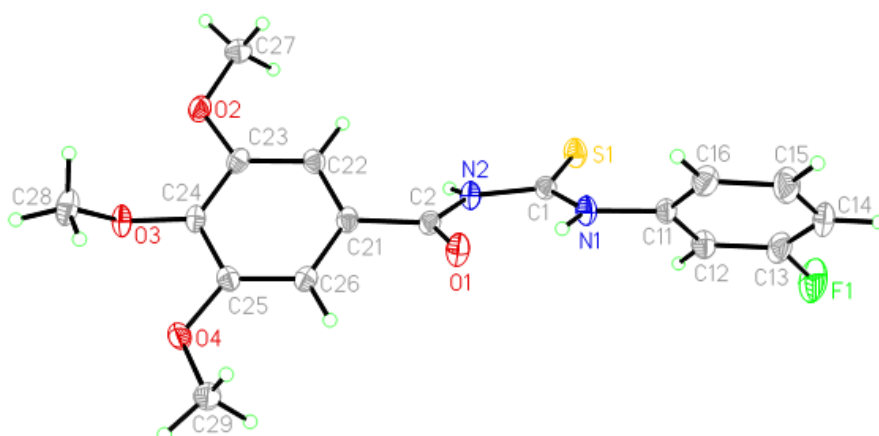
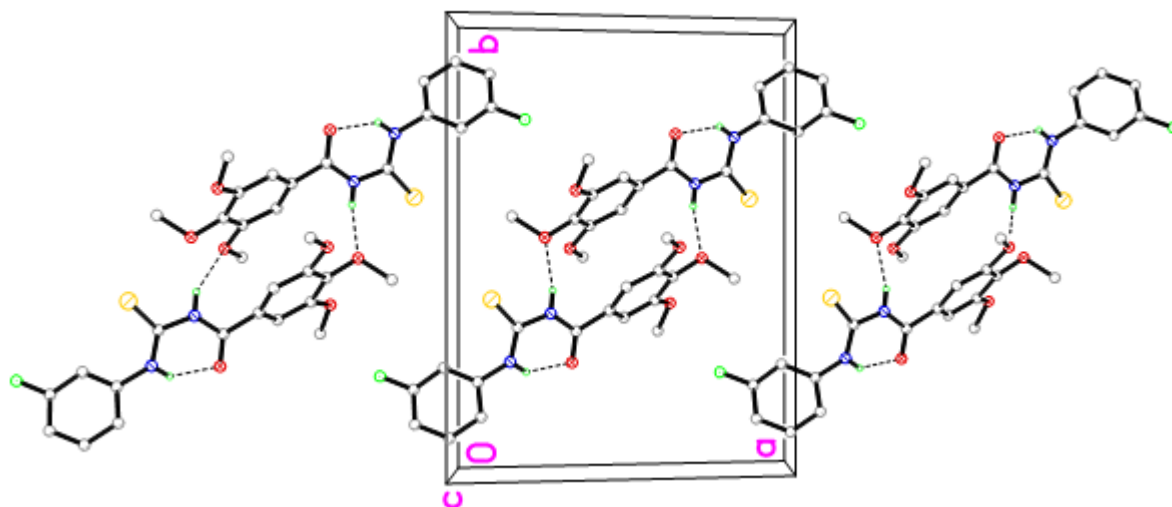


Figure 2. A packing diagram of the title compound **1** with view onto the ab plane. H atoms bonded to C omitted for clarity. Hydrogen bonds drawn as dashed lines.



3. Experimental Section

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^1H NMR spectra were determined as CDCl_3 solutions at 300 MHz using a Bruker AM-300 spectrophotometer. FT IR spectra were recorded using an FTS 3000 MX spectrophotometer, Mass Spectra (EI, 70 eV) on a GC-MS instrument. All compounds were purified by thick layer chromatography using silica gel from Merck.

3.1. Synthesis of 1-(3-fluorophenyl)-3-(3,4,5-trimethoxybenzoyl)thiourea

A solution of 1-(3,4,5-trimethoxy)benzoyl chloride (10 mmol) in acetonitrile (50 mL) was added dropwise to a suspension of ammonium thiocyanate (10 mmol) acetonitrile (30 mL) and the reaction mixture was refluxed for 30 min. After cooling to room temperature, a solution of the 3-fluoroaniline in (10 mmol) acetonitrile (10 mL) was added and the resulting mixture refluxed for 3 h. The reaction mixture was poured into cold water and the precipitated thiourea was recrystallized from aqueous ethanol. m.p. 169–171 °C. IR (KBr) cm^{-1} : 3350, 3280 (N-H), 1638 (C=O), 1586 (C=C), 1240 (C=S), 1150 (C-N), 862, 822, 770; ^1H NMR (CDCl_3) δ : 1.21 (9H, s, $\text{CH}_3 \times 3$), 9.67 (1H, brs, NH), 4.18 (1H, brs, NH), 6.25–7.57 (m, 3H, Ar). ^{13}C NMR (CDCl_3) δ 28.1, 39.4, 124.46, 126.91, 127.13, 128.7, 129.0, 133.75, 137.62, 176.4 (C=S), 177.8 (C=O); EIMS: m/z 304 [M^+] 306 [M^{+2}], 247, 219, 85, 57; *Anal.* Calcd. for $\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{N}_2\text{OS}$, C, 47.22; H, 4.62; N, 9.18; S, 10.51% found C, 47.03; H, 4.71, N, 9.23; S, 10.49%.

3.2. X-ray data collection and structure refinement

Crystallographic data were recorded on a STOE IPDS-II diffractometer [13] using Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) at $T = 173 \text{ K}$. An absorption correction was applied using the MULABS [14] option in PLATON [15]. The structure was solved by direct methods [16] and refined by full-matrix

least-squares using SHELXL-97 against F^2 using all data [16]. All non-H atoms were refined anisotropically. H atoms were positioned geometrically at distances of 0.95 Å (aromatic CH) and 0.98 Å (methyl groups) from the parent C atoms; a riding model was used during the refinement process and the Uiso(H) values were constrained to be 1.2 Ueq(aromatic C) or 1.5 Ueq(methyl C). The H atoms bonded to N were freely refined.

CCDC reference number: CCDC 815333. Copies of the data can be obtained, free of charge, on application to CHGC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Crystal data. $C_{17}H_{17}FN_2O_4S$, 364.39 g mol⁻¹. Monoclinic, $P2_1/c$ (no. 14), $a = 1309.66(9)$, $b = 1664.60(13)$, $c = 784.48(5)$ pm, $\beta = 106.721(5)$, $V = 1637.9(2) \times 10^6$ pm³, $Z = 4$. Diffractometer IPDS-II, Stoe Darmstadt; Mo-K α (graphite monochromator, $\lambda = 71.073$ pm); $T = 173(2)$ K; $6.94^\circ \leq 2\theta_{\max} \leq 51.24^\circ$; $-15 \leq h \leq 15$, $-20 \leq k \leq 20$, $-8 \leq l \leq 9$; $\rho_{\text{calc}} = 1.478$ g cm⁻³; 15402 reflections measured of which 3057 were symmetrically independent; $R_{\text{int}} = 0.0480$; $F(000) = 760$; $\mu = 0.234$ mm⁻¹. 238 refined parameters; R values: R_1/wR_2 for 2614 reflections with $[I_0 > 2\sigma(I_0)]$: 0.0289 / 0.0751, for all data: 0.0358 / 0.0770; $S_{\text{all}} = 1.031$; $\Delta\rho(\text{min/max})$: -0.236×10^{-6} pm⁻³ / 0.236×10^{-6} pm⁻³.

4. Conclusions

Synthesis, characterization and crystal structure of a novel thiourea derivative has been carried out which is an intermediate step towards a diversity of heterocycles.

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