European Journal of Chemistry

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Synthesis, crystal structure and antioxidant evaluation of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide

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RESEARCH ARTICLE

doi 10.5155/eurjchem.11.2.156-159.1981

Received: 23 March 2020
Received in revised form: 09 May 2020
Accepted: 10 May 2020
Published online: 30 June 2020
Printed: 30 June 2020

KEYWORDS

Thiourea
Benzoylthiourea
Antioxidant activity
Benzamide derivative
Single crystal structure
1-Piperazinecarboxaldehyde

ABSTRACT

New benzoylthiourea derivative, *N*-(4-formylpiperazine-1-carbonothioyl)benzamide was prepared by the reaction of benzoylisothiocyanate with 1-piperazinecarboxaldehyde in acetone as solvent. The compound was characterized by FT-IR and multinuclear ^{1}H and ^{13}C NMR spectroscopy techniques. The benzoylthiourea molecule was obtained in crystalline form by recrystallization in DMSO. Single crystal X-ray diffraction study indicates that compound crystallized in triclinic crystal system and crystal data for $C_{13}H_{15}N_3O_2S$, space group P-1 (no. 2), a = 7.3016(9) Å, b = 7.7380(9) Å, c = 12.9815(16) Å, α = 103.581(4)°, β = 102.153(4)°, γ = 102.409(4)°, V = 669.46(14) Å^3, Z = 2, T = 296(2) K, μ(MoKα) = 0.243 mm^{-1}, *Dcalc* = 1.376 g/cm^3, 31184 reflections measured (6.72° ≤ 2Θ ≤ 53.46°), 2822 unique (R_{int} = 0.0582) which were used in all calculations. The final R_1 was 0.0501 (>2σ(I)) and wR_2 was 0.1493 (all data). Intramolecular N-H···O hydrogen bond is stabilized the trans geometry of the thiono and the carbonyl groups. The heterocyclic piperazine ring makes a dihedral angle of 48.50(15)° with the benzene ring. Antioxidant test by DPPH method showed that compound exhibits good antioxidant activity of about 75%.

Cite this: *Eur. J. Chem.* **2020**, *11(2)*, 156-159 **Journal website**: www.eurjchem.com

1. Introduction

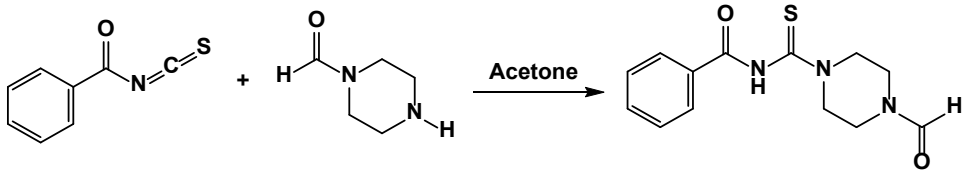
The synthesis and design of new benzoylthiourea derivatives including heterocyclic rings have motivated thiourea derivatives chemistry applications in many fields in coordination chemistry as well as biological activities [1-4]. Some thiourea derivatives containing pyridine moieties have been synthesized and screened for antitumor, these compounds also showed stronger anti-inflammatory activity than ibuprofen [5]. On the other hand, thiourea derivatives have been used as agrochemicals such as fungicides, insecticides and herbicides [6-8]. The benzoyl thiourea ligands involving thiocarbonyl moieties could lead to complexation as mono or bidentate ligands with a series of hard and soft metal cations [9-11]. In recently years, one interesting application of current interest is the use of thiourea derivatives as ion sensors due to the strong anion binding ability, more than those of the corresponding urea. A number of carbonoylthiourea derivatives were used for the extraction of some metals ions such as gold(III), copper(II) and cobalt(III) [12,13]. Some of benzoyl thiourea derivatives such as 3-aroyl-1-(4-sulfamoylphenyl) thiourea derivatives containing sulfonamide moiety were also evaluated for their antioxidant activity using the ferric reducing/antioxidant power (FRAP) assay and its capacity for reducing ferric ion was more than ascorbic acid [14]. These potential applications of thiourea derivatives have driven the growth for the synthesis of new thiourea derivatives. In the present study, the vibrational frequencies (FT-IR), multinuclear (^{1}H and ^{13}C) NMR and molecular structure of the new benzoyl thiourea, *N*-(4-formylpiperazine-1-carbonothioyl)benzamide were reported.

2. Experimental

2.1. Materials and methods

The chemical materials and the solvents that have been used in this study were available from Sigma-Aldrich and were used without further purification. FT-IR spectrum (400-4000 cm^{-1}) of the title compound has been recorded by Perkin-Elmer spectrum spectrometer with a resolution of 4 cm^{-1} in solid phase at room temperature. The experiments of multinuclear (^{1}H and ^{13}C) NMR were performed on a Bruker 600 MHz instrument in deuterated DMSO solvent. The X-ray single crystal diffraction measurement was performed on a Bruker D-QUEST diffractometer at 296(2) K. The intensity data was collected using graphite monochromated with λ = 0.71073 Å.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.11.2.156-159.1981



Scheme 1. Reaction scheme for the synthesis of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide.

The structure was solved by direction method and refined by full matrix least-squares against F^2 for all data using SHELXTL-97 program [15]. The carbon and hydrogen atoms were positioned geometrically (C-H = 0.93-0.97 Å) and constrained to ride on their parent atoms with U_{iso}(H) = 1.2U_{eq}(C). Hydrogen atoms on the nitrogen were located in difference Fourier map and refined freely with using SHELXL instruction DFIX 0.87 0.01.

2.2. Synthesis of N-(4-formylpiperazine-1-carbonothioyl) benzamide

A freshly prepared solution of benzoylisothiocyanate (0.03 mol) in dry acetone was added to solution of 1-piperazine carboxaldehyde (0.03 mol, 3.42 g) in 50 mL acetone and the resulting mixture refluxed for about 4 h and filtered into a beaker and left to evaporate at room temperature. The filtrate gave precipitate after 7 days of evaporation. Color: White. Yield: 85%. M.p.: 446.2-447.2 K. FT-IR (KBr, ν, cm^{-1}): 3271 (N-H), 1693 (C=$O_{aldehyde}$), 1661 (C=O_{amide}), 1239 (C-N), 2874 (C-$H_{aldehyde}$), 859 (C=S). ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 10.90 (1H, s, NH), 8.08 (1H, s, H-C=O), 7.96 (2H, d, *J* = 8.4 Hz, C_6H_5), 7.62 (1H, t, *J* = 7.8 Hz, C_6H_5), 7.52 (2H, t, *J* = 7.8 Hz, C_6H_5), 4.19 (2H, m, -CH_2-), 3.48 (6H, m, -CH_2-). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 51.32 (CH_2), 49.87 (CH_2), 133.04 (Ar-C), 133.0 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 161.6 (C=$O_{aldehyde}$), 164.5 (C=O_{amide}), 180.8 (C=S). Anal. calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 55.70; H, 5.12; N, 14.89%.

2.3. Antioxidant studies

The free radical stock solution of 2,2-diphenyl-1-picryl hydrazyl (DPPH, 97% purity) was prepared daily at the concentration of 0.4 g in 1000 mL methanol and protected from the light (A_{DPPH} = 1.012). The sample solution of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide was prepared in dimethyl sulfoxide solvent (*C* = 15 mg/5 mL). 1 mL from solution of DPPH was mixed with 100 µL from the stock solution of the new synthesized benzoylthiourea compound. The mixture was shaken well and kept in the dark at room temperature for 2 h. The absorbance of the mixture was recorded at 517 nm by using spectrophotometer (A_{Sample} = 0.250). The percentage reduction of the DPPH was calculated using the Equation (1).

$$\text{DPPH Scavenging Activ. (\%)} = [(A_{DPPH} - A_{Sample})/(A_{DPPH})] \times 100 \quad (1)$$

3. Results and discussion

3.1. Synthesis and characterization

The synthesis of new benzoylthiourea derivatives including aldehyde group are quite important and interesting for preparation of a variety of derivatives. Therefore, the solution mixture of benzoylisothiocyanate with 1-piperazine carboxaldehyde in acetone gave homogenous colorless solution after refluxed for about 4 h (Scheme 1).

The micro-elemental analysis data of the precipitate is in agreement with the expected formula of *N*-(4-formyl piperazine-1-carbonothioyl)benzamide. The infrared spectrum of the compound showed the stretching frequencies of *ν*(N-H) and *ν*(C=O)$_{aldehyde}$ at 3271 and 1693 cm^{-1}, respectively, whereas the stretching frequency of *ν*(C=O)$_{amide}$ absorbed near 1661 cm^{-1}. The frequencies of 1239 and 859 cm^{-1} in the spectrum are assigned for *ν*(C–N) and *ν*(C=S) stretching vibration, respectively. The lower stretching vibration of *ν*(C=S) than the normal value of 1050-1200 cm^{-1} is mainly due to the conjugated resonance and tautomerism effect within the amide-thioamide groups. A similar conjugated resonance effect on *ν*(C=S) stretching mode was reported for other class of thiourea derivatives [16,17]. The characteristic frequency of *ν*(C–H) stretching for the aldehyde group appeared at 2874 cm^{-1}. ^{1}H NMR spectrum shows the amide proton H-N-C=O chemical shift at δ 10.90 ppm, the downfield position for this proton than the normal value of δ 5-8 ppm is due to electronegative of oxygen and sulfur atoms of the carbony and thiono groups, further decreases the electron density on the amide proton. The aldehyde proton was observed at δ 8.08 ppm. The protons chemical shifts of the methylene groups (–CH_2–) of the piperazine ring appeared as distinctive multiplet in the range of δ 3.48 to 4.19 ppm. The protons chemical shifts of the phenyl ring appeared in the normal range between δ 7.49 to 7.96 ppm. The ^{13}C chemical shifts of C=S and C=O were observed at δ 180.84 and 164.54 ppm, respectively. The aldehyde carbon chemical shift of C=O appeared at δ 161.68 ppm. The aromatic carbon chemical shifts occurred in the range of δ 128.8-133.0 ppm. The aliphatic carbons chemical shift of the piperazine ring appeared in the normal range of δ 49.87-51.32 ppm.

3.2. Single crystal structure of N-(4-formylpiperazine-1-carbonothioyl)benzamide

The X-ray investigation of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide showed the molecular structure as determined in the crystalline phase. The crystal and the refinement data are shown in Table 1. The asymmetric unit consists one molecule of *N*-(4-formylpiperazine-1-carbono thioyl)benzamide. Figure 1 shows the molecular structure and atomic numbering scheme.

The thiono and the carbonyl groups are *trans* positioned with respect to N2-C8 bond with C7-N2-C8-S1 torsion angle of 123.2(2)°. The heterocyclic piperazine ring adopts a chair conformation and is twisted relative to the thiourea fragment (S1/N1/N2/C8), forming a dihedral angle of 26.39°. The benzene ring (C1-C6) forms a dihedral angle of 56.07° with the last mean planes of the thiourea moiety. The carbonyl of the amide group C=O [1.211(8) Å] and C=S [1.690(6) Å] bond lengths are comparable to those reported for *N*-(4-methoxybenzoyl)-*N*`-(3-hydroxyphenyl)thiourea [1.221(19) Å, 1.674(18) Å, respectively] [1]. The other bond lengths and angles are in normal ranges and comparable to those in 1-(4-chlorobenzoyl)-3-cyclohexyl-3-methylthiourea [18] as shown in Table 2.

The *trans* geometry of the molecule is stabilized by intramolecular hydrogen bond C10–H10A···O1 (Table 3), resulting in the formation of a pseudo-eight-membered ring (C10/H10A/O1/C7/N2/C8/N1/C9).

Table 1. Crystal data and structure refinement of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide.

Crystal parameters	Data/values	
CCDC. deposition number	1990392	
Moiety formula	$C_{13}H_{15}N_3O_2S$	
Formula weight	277.34	
Temperature	296(2) K	
Wavelength, λ	0.71073 Å	
Crystal system	Triclinic	
Space group	Pī	
Unit cell dimensions	a = 7.3016(9) Å	α = 103.581(4)°
	b = 7.7380(9) Å	β = 102.153(4)°
	c = 12.9815(16) Å	γ = 102.409(4)°
Volume	669.46(14) Å^3	
Z	2	
D_{calc}	1.376 Mg/m^3	
Absorption coefficient	0.243 mm^{-1}	
F(000)	292	
Crystal dimension	0.18 × 0.21 α 0.34 mm	
Theta range for data collection	2.97 to 26.73°	
Reflections measured	31185	
Ranges/indices (h,k,l)	-9, 9; -9, 9; -16, 16	
Completeness to theta	26.73° to 99.6%	
Max. and min. transmission	0.9575 and 0.9026	
Independent reflections	2823 [R(int) = 0.0582]	
Data / restraints / parameters	2823 / 1 / 176	
Refinement method	Full-matrix least-squares on F^2	
Goodness of fit on F^2	1.114	
R1, wR2 (I≥2σ(I))	R1 = 0.0503, wR2 = 0.1419	
R1, wR2 indices (all data)	R1 = 0.0676, wR2 = 0.1540	
Largest diff. peak and hole	0.378 and -0.264 e.Å^{-3}	

Table 2. Selected bond lengths and angles (Å, °) of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide.

Bond	Length (Å)	Bond	Angles (°)
S1-C8	1.690(6)	C8-N1-C12	120.8(5)
O1-C7	1.211(8)	C8-N1-C9	125.0(5)
O2-C13	1.229(9)	C12-N1-C9	112.7(5)
N1-C8	1.323(8)	C8-N2-C7	121.5(5)
N1-C12	1.464(8)	C13-N3-C11	122.9(6)
N1-C9	1.466(8)	C13-N3-C10	121.9(6)
N2-C8	1.395(8)	C11-N3-C10	115.2(5)
N2-C7	1.399(9)	N1-C8-N2	117.1(5)
N3-C13	1.332(9)	N1-C8-S1	124.3(5)
N3-C11	1.441(9)	N2-C8-S1	118.6(4)
N3-C10	1.468(8)	N1-C9-C10	111.2(5)

Table 3. Hydrogen geometric parameters (Å, °) of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide *.

D—H···A	D—H	H···A	D···A	∠D—H···A
C10—H10A···O1	0.97	2.60	3.212(3)	122
N2—H2A···O2 [i]	0.87(3)	2.22(3)	3.065(3)	164(3)
C2—H2···O2 [i]	0.93	2.37	3.257(3)	160
C12—H12B···O2 [ii]	0.97	2.51	3.411(3)	154

* Symmetry codes: [i] 1+*x*, 1+*y*, *z*, [ii] -1-*x*, -1-*y*, -*z*.

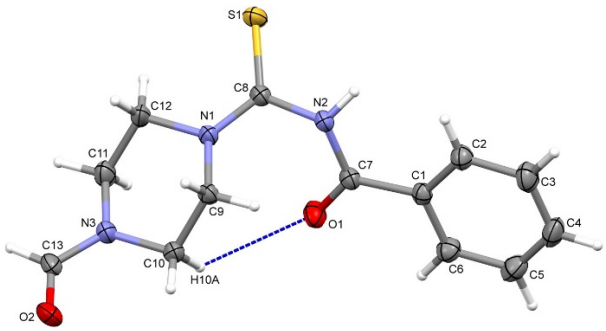


Figure 1. The molecular structure of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide with 50% probability displacement ellipsoids. The dashed line indicates an intramolecular hydrogen bond.

The molecules are linked by N2–H2A···O2, C2–H2···O2 and C12–H12B···O2 intermolecular hydrogen bonds to form infinite one-dimensional chains along *ab* face (Figure 2).

3.3. Antioxidant evaluation

Antioxidant properties of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide due to donate a hydrogen atoms of the amide H–N–C=O or aldehyde group to the stable free radical 2,2-diphenyl-1-picrylhydrazyl to forms non-radical DPPH-H and the color of the reaction mixture changes from purple to yellow when the DPPH radical is scavenged. The DPPH scavenging activity of the synthesized benzoylthiourea compound was 75.29 % indicting good antioxidant properties, compared to its analogs of the other benzoylthiourea derivatives [14].

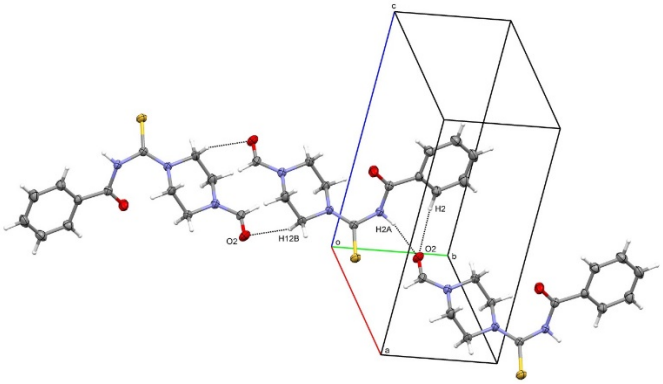


Figure 2. Molecular packing of *N*-(4-formylpiperazine-1-carbonothioyl)benzamide, viewed down the *c* axis. The dashed lines denote N–H···O and C–H···O hydrogen bonds.

4. Conclusions

The benzoylthiourea compound namely *N*-(4-formyl piperazine-1-carbonothioyl)benzamide was successfully synthesized and confirmed its structure by spectroscopic techniques (FT-IR, ^{1}H and ^{13}C NMR). The molecular structure of the newly benzoylthiourea compound was also determined using X-ray crystallography technique and the compound showed good antioxidant activity of about 75%.

Acknowledgements

The author would like to thank Ministry of Higher Education of Malaysia and University Kebangsaan, Malaysia for the facilities and financial support. I would like also to thank the Ministry Education of Libya and Bani Waleed University for their support to carry out this work.

Supporting information

CCDC-1990392 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Sample of the compound is available from the author.

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