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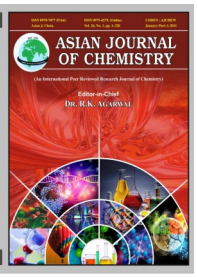

Synthesis, Supramolecular Structure, Antimicrobial and Plant-Growth Regulation Activities of N-Benzoylthiourea

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N-Benzoylthiourea has been synthesized and characterized by elemental analysis, IR and ^{1}H NMR etc. The X-ray crystallography of the compound indicates that the carbonyl group forms an intramolecular hydrogen bond with the N2-H2 group, which forms a six-membered ring (C7/N1/C8/N2/H2/O1) srtucture. Each molecule are linked by the intermolecular N2-H2A...S2 and N4-H4A...S1 hydrogen bonds to form a dimer, adjacent dimers are linked by the intermolecular N1-H1N...S2 and N3-H3N...S1 hydrogen bonds, leading to a hydrogen-bonded netty structure. The results indicated that the N-benzoylthiourea played the important role in plant-growth regulators and may be a potential source of active antimicrobial agents.

Keywords: Thiourea, Synthesis, Crystal structure, Antibacterial, Plant-growth regulation activity.

INTRODUCTION

Thiourea and its derivatives, especially acylthiourea, are extensively studied because of their biological activities such as herbicides, insecticides, plant-growth regulators, antifungal, antibacterial and pharmacodynamics[1-5]. Some thioureas are organic reaction catalyst in the metal-catalyzed asymmetric reduction of carbonyl compounds and carbonylative cyclization of *o*-hydroxyarylacetylenes[6,7]. With the rapid development of supramolecular chemistry, thioureas are one of many important neutral receptors because of their anion recognition properties[8-10], H-atom of thiourea group N-H bond form easily hydrogen bond, which recognize the anion by the interaction of the hydrogen bond and the anion. In a ^{13}C NMR study, the differences between the benzoyl (CO) chemical shift value of N-monosubstituted and N,N-disubstituted indicated the existence of an intramolecular hydrogen bond, namely between the benzoyl (CO) and the N-H group. The indication was also supported by the ^{1}H NMR spectrum[11]. Here we report synthesis and crystal structure of N-benzoylthiourea, $C_8H_8N_2OS$. Then tested it possessed prominent antimicrobial and plant growth regulation activities.

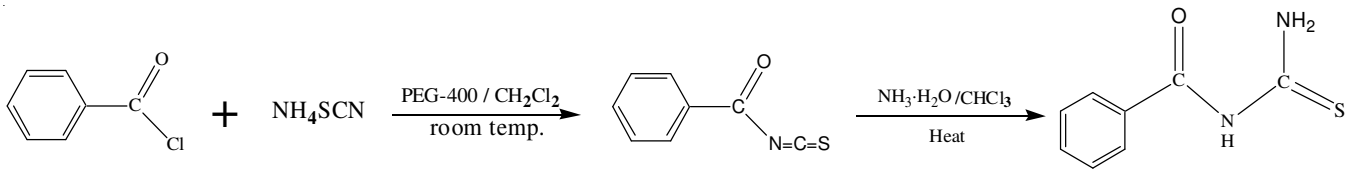
EXPERIMENTAL

All chemicals were of analytical reagent grade and were used without further purification. C, H and N analyses were obtained using a GmbH VarioEL V3.00 automatic elemental analysis instrument. The IR spectrum in the range of 4000-400 cm^{-1} was recorded with a VERTEX70 FT-IR spectrophotometer using KBr pellets. ^{1}H NMR spectrum was determined by German Bruker AVANCE DRX-400 spectrometers with TMS as internal standard and d_6-DMSO as solvent. X-ray single crystal structure determination was obtained on a Rigaku RAXIS-RAPID detector. Melting points were obtained by use of a X4 microscopic melting point apparatus made in Beijing Taike instrument limited company and were uncorrected.

The antimicrobial activities were determined using agar disc diffusion method by measuring the inhibition zone in mm. All organisms were obtained from the China Center of Industrial Culture Collection, including 2 bacterial stains: *Escherichia coli* ACCC11864 as gram-negative bacteria, *Bacillus subtilis* ACCC 01518 as gram-positive bacteria, 4 fungal stains: *Botrytis cinerea* ACCC35153, *Thanatephorus cucumeris* ACCC30367, *Phyricularia grisea* ACCC100762 and *Fusarium oxysporum* ACCC13422. Ampicillin and fluconazole were served as standard antibacterial and antifungal agents, respectively. The plant growth regulation activities were determined using in vitro plate method. The seeds of rape were brought from Seed store.

General procedure

Synthesis of N-benzoylthiourea: Benzoyl chloride (1.41 g, 10 mmol) was reacted with ammonium thiocyanate (1.14 g, 15 mmol) in CH_2Cl_2 (25 ml) solution under soild-liquid phase transfer catalysis, using polyethylene glycol-400 (0.18 g) as the catalyst, to give the corresponding benzoyl isothiocyanate.



Scheme-I: Synthetic scheme of the title compound.

The resulting mixture was evaporated to dryness using a rotatory evaporator and the residue was extracted with chloroform, to give the title compound. Yield 84.6 %. m.p. 386-388 K. Anal. Calcd. (%) for $C_8H_8N_2OS$: C, 53.31; H,4.47; N, 15.54. Found (%): C, 53.23; H, 4.58; N, 15.32. Selected IR data (cm^{-1}, KBr pellet): 3310, 3225(ν_{NH}), 1680($\nu_{C=O}$) and 1031($\nu_{C=S}$). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.53-7.87 (m, 5H,Ar-H), 9.98 (s, 1H, HN), 10.06 (s, 2H, H2N).

Colorless needle-shaped single crystals were obtained by slow evaporation of an chloroform solution after several weeks at room temperature. Synthetic scheme of the title compound was shown in **Scheme-I**.

X-ray structure determination: The colorless crystal with a dimension of 0.67 mm × 0.48 mm × 0.13 mm was placed on a Rigaku RAXIS-RAPID detector. Intensity data were collected with a graphite-monochromator MoKα radiation (λ = 0.71073 Å) at 153(2) K. The structure was solved by direct methods and refined by full matrix least squares on F^2 using the program. All hydrogen atoms were added theoretically. The final refinements converged at $R_1 = 0.0289$, $wR_2 = 0.0850$ with $\omega = 1/[\sigma^2(F_o^2) + (0.0526P)^2 + 0.2490P]$, where $P = (F_o^2 + 2F_c^2)/3$. All atoms were refined with anisotropic displacement parameters. The largest differential peak and hole were 0.359 and -0.277 e $Å^{-3}$. The structural plots were drawn with SHELXL 97 software package[12]. The crystal data and experimental parameters relevant to the structure determination are listed in Table-1.

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR THE TITLE COMPOUND

Empirical formula	$C_8H_8N_2OS$
Formula weight	180.22
Temperature (K)	153(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
Cell dimensions, (Å, deg)	a = 8.1862(4), b = 9.2399(5), c = 12.4921(8), α = 73.509(2), β = 87.766(2), γ = 70.556(2)
Volume ($Å^3$)	852.74(8)
Z	4
Density (calculated) (mg/m^3)	1.404
Absorption coefficient (mm^{-1})	0.329
$F_{(000)}$	376
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-16 \le l \le 16$
Reflections collected	8370/3864 [R(int) = 0.0205]
Independent reflections	3566
Data/restraints/parameters	3864/0/242
Goodness of fit indicator	0.996
R [$I > 2\sigma(I)$]	$R_1 = 0.0289$, $wR_2 = 0.0850$
Largest diff. peak and hole (e $Å^{-3}$)	0.359 and -0.277

Antimicrobial activity: The culture media used were nutrient agar and Sabourd's medium for bacteria and fungus strains, respectively. The hot nutrient agar and sabourd's medium solution was poured into sterilized petridishes and allowed to attain room temperature. Seed layer medium which contains the previously grown subculture was lawned into the Petri dishes. Cups were made using sterile borer of 5 mm diameter. To these cups 0.5 mL of the drug solution (50 µg/mL), standard solution were added and allowed to cool for 1 h to facilitate diffusion. The plate was incubated at 37 °C or 28 °C for 48 h. Zone of inhibition around wells were measured. All tests were repeated three times to confirm the results. The results are presented in Table-2.

Plant-growth regulators determination: The method of *vitro* plate was adopted. Twain's 80 was used as emulsifier, the compound was dissolved in the solution of N,N-dimethylformamide. Six kinds of solution were configurated with distilled water respectively (100, 10, 01.0, 0.1, 0.01, 0.001 mg L^{-1}). Put 10 mL solution with differents concentration into 9 mm culture plate (including 2 layers of filter paper), use equivalent emulsifier as contrast. 15-20 healthy seeds of Brassica napus were choosen and puted into every plate, The plates were incubated at 25 ± 5 °C for 72 h. Then for day light 8 h every day, examined after 5 d. Measured the growth of the root and the stem, calculated the percentage of plant growth regulator activity.

The promotion rate (the inhibition rate) = $(N-N_1)/N_1 \times 100$ %. N_1: The average of the length of rape root in distill water, N: The average of the length of rape root in compound solution All tests were repeated three times to confirm the results. The results are presented in Table-3.

TABLE-2
RESULTS OF ANTITUBERCULOSIS AND ANTIMICROBIAL ACTIVITIES FOR THE TITLE COMPOUND

Compound	Diameter of zone of inhibition (mm)					
	B. subtilis	*E. coli*	*B. cinerea*	*T. cucumeris*	*P. grisea*	*F. oxysporum*
N-Benzoylthiourea	8.9 ± 0.25	–	11.4 ± 0.35	12.9 ± 0.2	10.4 ± 0.35	7.8 ± 0.15
Ampicillin	10.3 ± 0.3	12.6 ± 0.5		–	–	–
Fluconazole	–	–	13.2 ± 0.6	14.9 ± 0.55	15.4 ± 0.6	14.2 ± 0.65

(– indicates no activity).

TABLE-3
DATA OF PLANT GROWTH REGULATION ACTIVITY OF TARGET FOR THE TITLE COMPOUND

C (mg L^{-1})	Indolylacetic acid	N-Benzoylthiourea
0.001	4.5 ± 0.1	-19.8 ± 0.11
0.01	6.9 ± 0.12	-22.0 ± 0.24
0.1	-12.5 ± 0.23	-39.3 ± 0.6
1.0	-62.1 ± 0.3	-11.7 ± 0.25
10	-85.9 ± 1.2	-37.5 ± 0.4
100	-98.1 ± 3.1	-73.6 ± 0.31

RESULTS AND DISCUSSION

Description of crystal structure: Selected bond lengths and angles are listed in Table-4. The data for hydrogen bonds are given in Table-5. The molecular structure with atom label1ing, two-dimensional mono-layer structure and its packing diagram along *c*-axis were shown in Figs. 1-3, respectively.

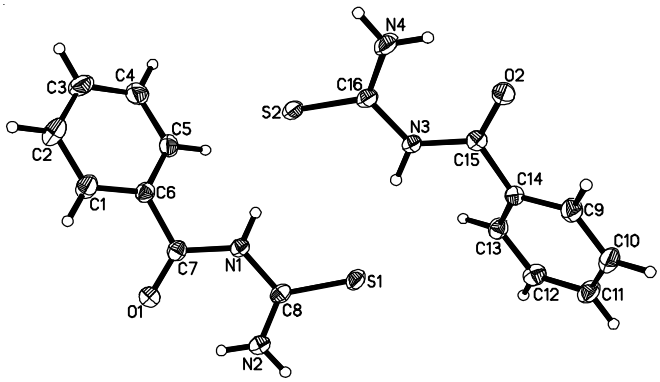


Fig. 1. Crystal structure and atom numbering of the title compound

The crystal structure of the title compound is built up by only the $C_8H_8N_2OS$ molecules. X-ray crystallographic analysis revealed the crystal structure of N-benzoylthiourea, which the carbonyl group forms an intramolecular hydrogen bond with the N2-H2 group, which forms a six-membered ring (C7/N1/C8/N2/H2/O1) srtucture. This is similar to that found in N-benzoyl-N'-(3-pyridyl)thiourea[13,14]. The C=O bond length is 1.22(3) Å, longer than the normal C=O bond length (1.20(3) Å), which is due to intramolecular hydrogen bond. The bond

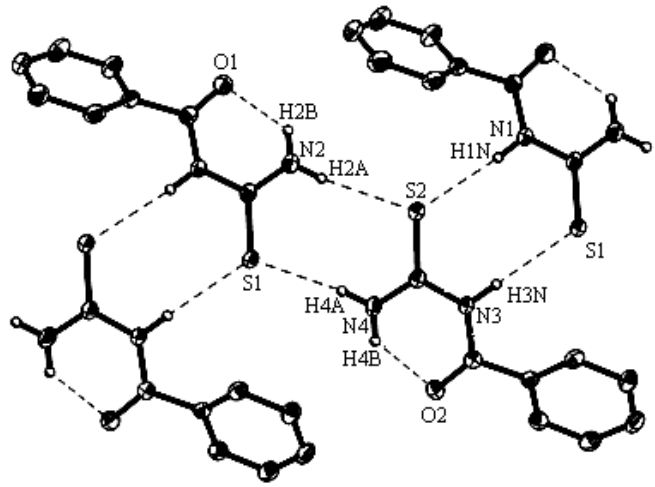


Fig. 2. The two-dimensional mono-layer netty structure. Hydrogen bonds are illustrated by dashed line

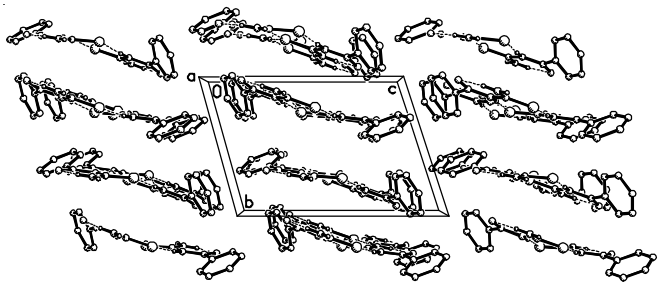


Fig. 3. Three-dimensional packing diagram of the title compound, H atoms are omitted for clarity

TABLE-4
SELECTED BOND DISTANCES (Å) AND ANGLES (º) FOR THE TITLE COMPOUND

Bond	Lengths	Bond	Lengths	Bond	Lengths
S1-C8	1.685(1)	N2-C8	1.314(2)	C3-C4	1.384(2)
O1-C7	1.220(1)	C1-C2	1.385(2)	C4-C5	1.392(2)
N1-C8	1.382(1)	C1-C6	1.392(2)	C5-C6	1.391(2)
N1-C7	1.384(1)	C2-C3	1.385(2)	C6-C7	1.491(2)
Bond	Angles	Bond	Angles	Bond	Angles
C8-N1-C7	126.9(1)	C6-C5-C4	119.6(1)	O1-C7-C6	122.2(1)
C2-C1-C6	120.12(1)	C5-C6-C1	119.9(1)	N1-C7-C6	114.7(1)
C1-C2-C3	119.9(1)	C5-C6-C7	121.9(1)	N2-C8-N1	118.3(1)
C4-C3-C2	120.2(1)	C1-C6-C7	18.1(1)	N2-C8-S1	123.45(9)
C3-C4-C5	120.2(1)	O1-C7-N1	123.0(1)	N1-C8-S1	118.25(8)

TABLE-5
DATA FOR HYDROGEN-BONDING INTERACTIONS (Å, º)

D-H···A	d(D-H)	d(H···A)	d(D···A)	∠D-H···A	Symmetry code
N1-H1N...S2	0.89	2.47	3.353(1)	176	x, y, z
N3-H3N...S1	0.91	2.50	3.401(1)	174	x, y, z
N2-H2B...O1	0.86	2.03	2.664(2)	131	x, y, z
N2-H2A...S2	0.87	2.61	3.447(1)	164	1 + x, y, z
N4-H4B...O2	0.87	1.95	2.621(2)	132	x, y, z
N4-H4A...S1	0.88	2.41	3.282(2)	173	-1 + x, y, z

lengths of intramolecular hydrogen bonds H2B...O1and H4B...O2 are 2.02(2) and 1.95(2) Å and the bond lengths of intermolecular hydrogen bonds H1N...S2, H3N...S1, H2A...S2, H4A...S1 are 2.47(2), 2.50(2), 3.56(2) and 2.41(2) Å, respectively. Fig. 2 is shown that four distinct hydrogen bonds occur in the crystal structure: which each pair molecules are linked by the intermolecular N2-H2A...S2 (-x+1, -y, -z+1), N4-H4A...S1 (x-1, y, z), hydrogen bonds to form a dimer, adjacent dimers are linked by the intermolecular N1-H1N...S2, N3-H3N...S1 hydrogen bonds, leading to a hydrogen-bonded netty structure[15-17].

Antimicrobial and plant-growth regulation activities: N-Benzyl thiourea has shown good antimicrobial activities as compared to their standard drugs but the antifungal activities are more prominent. Especially in plant pathogens, it reveals extraordinary disinfect abilities in cucumber gray mold, rice sheath blight disease, Rice blast and Fusarium Wilt of cotton. It also played the role of plant-growth regulators, at the concentration of 0.1 mg/L, 10 mg/L and 100 mg/L, it has prominent plant growth regulation activties. These results indicated the potential of the N-benzyl thiourea as antimicrobial and plant-growth regulators, in these aspects the research of the N-benzoylthiourea is suggested for further work.

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