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COMMUNICATION

Synthesis, Crystal Structure and Bioactivities of *N*-(2,6-Difluorobenzoyl)-*N*′-[5-(Pyrid-4-yl)-1,3,4-Thiadiazol-2-yl]Urea

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Abstract *N*-(2,6-difluorobenzoyl)-*N*′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea, **3**, has been synthesized by reaction of 2-amino-5-(pyrid-4-yl)-1,3,4-thiadiazole with 2,6-difluorobenzoyl isocyanate, and its structure was characterized with X-ray crystallographic, NMR, MS and IR techniques. It crystallizes in the triclinic space group $P-1$, with $a = 7.0821(9)$ Å, $b = 9.4896(13)$ Å, $c = 11.6594(15)$ Å, $\alpha = 82.311(2)°$, $\beta = 82.328(2)°$, and $\gamma = 87.641(2)°$. In the title compound, the urea scaffold in each molecule is essentially planar due to the presence of intramolecular N–H···O hydrogen bond. The molecules are linked by intermolecular complementary N–H···O hydrogen bonds into centrosymmetric $R_2^2(8)$ dimers. Intermolecular π–π stacking interactions are also present. The preliminary bioassay shows that the title compound exhibits excellent fungicidal activities against *Rhizoctonia solani*, *Botrytis cinerea* and *Dothiorella gregaria*.

Keywords Thiadiazole · Urea · Synthesis · Crystal structure · Biological activities

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Introduction

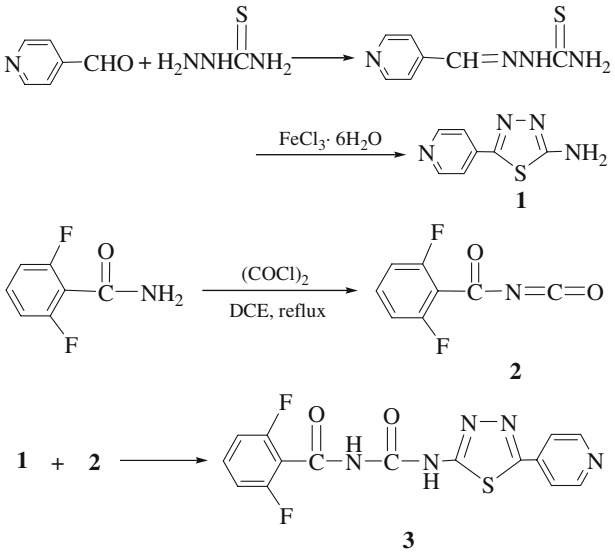
1,3,4-Thiadiazole derivatives have been attracting widespread attention due to their significant bioactivities [1–5]. Aroyl ureas have been found to possess diverse biological effects, such as fungicidal, insecticidal, plant-growth regulating and other pharmacological activities [6–9]. In general, pyridine can serve as effective bioisostere of benzene in drug design and considerable interest has been shown in pyridine derivatives in the field of modern agrochemistry and medicinal chemistry because substitution of benzene by pyridine may result in the good biological activity and low toxicity of molecules containing pyridyl moiety [10, 11]. It is therefore worth investigating aroyl ureas incorporating both a 1,3,4-thiadiazole nucleus and a pyridyl group. In view of our extensive interest, we would like to investigate this class of urea derivatives.

In this contribution, we report the preparation, crystal structure together with plant-growth regulating and fungicidal activities of *N*-(2,6-difluorobenzoyl)-*N*′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea **3**, as part of our ongoing structural studies as well as to provide a basis for consideration for the stereochemical structure-activity relationships. The synthetic route of the title compound is outlined in Scheme 1.

Experimental

Instruments

The infrared spectrum was recorded in the range of 4000–400 cm^{-1} on a Nicolet NEXUS 470 FT-IR spectrophotometer, using KBr pellets. ^1H NMR spectrum was obtained on a Varian Mercury Plus-400 MHz Spectrometer



Scheme 1 Procedure of preparing the title compound **3**

with TMS as internal standard and DMSO-d_6 as the solvent. Mass spectra were recorded on a Finnigan Trace Mass Spectrometer. Elemental analysis was performed by a Vario EL III analyzer. Melting point was determined by an X-4 microscopic melting-point apparatus and uncorrected.

Single crystal X-ray data were collected on a BRUKER SMART APEX-CCD diffractometer equipped with a graphite-monochromated Mo$K\alpha$ radiation. The structure was solved by direct Fourier methods. Full-matrix least-squares refinement was based on F^2 with SHELXL-97 [12].

Synthesis of the Compound

All chemicals used for the preparation of the compound were of reagent grade quality. Solvents were dried by standard methods and distilled prior to use. The required 2-amino-5-(pyrid-4-yl)-1,3,4-thiadiazole **1** was obtained via the oxidative cyclization of thiosemicarbazone in the presence of ferric chloride hexahydrate according to the literature method [13]. 2,6-Difluorobenzoyl isocyanate **2** was synthesized by refluxing 2,6-difluorobenzamide and an excess of oxalyl chloride in anhydrous 1,2-dichloroethane (DCE) by the reported procedure [14]. A solution of 1.83 g (10 mmol) of **2** in 5 mL of dry dimethylformide was added to a stirred solution of 1.78 g (10 mmol) of **1** in 12 mL of dry dimethylformide. The mixture was stirred overnight at room temperature, the solvent was removed by evaporation under reduced pressure, and the residue was recrystallized from ethanol/dimethylformide (1:2, v/v) to give the desired product **3**.

N-(2,6-difluorobenzoyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3) Color: white. Yield: 83%. m.p. >300 °C. *Anal.* required for $C_{15}H_9F_2N_5O_2S$: C, 49.86; H, 2.51; N, 19.38%. Found: C, 50.04; H, 2.37; N, 19.53%. IR (KBr pellets, cm^{-1}): ν (N–H) 3430, 3169, (C=O) 1724, 1691, (C–S–C) 699. ^{1}H NMR (DMSO-d_6): δ 7.28 (t, J = 8.4 Hz, 2H, aromatic H), 7.62–7.70 (m, 1H, aromatic H), 7.94 (d, J = 5.2 Hz, 2H, pyridyl 3,5-H), 8.75 (d, J = 5.2 Hz, 2H, pyridyl 2,6-H), 11.80 (s, 1H, NH), 12.14 (s, 1H, NH). EI-MS (m/z, %): 361 (M^+, 30), 342 (66), 205 (100), 177 (13), 141 (63), 113 (8), 78 (11).

A fully completed Crystallographic Information File deposited with the CCDC is available (Deposition CCDC No. 273315).

Results and Discussion

The data of ^{1}H NMR, IR, MS and elemental analysis for the product are in good agreement with the structure of the title compound **3**. Table 1 contains crystallographic data of compound **3**, Table 2 gives the selected bond lengths and angles. Table 3 enumerates the significant hydrogen bonds. The molecular structure of the title compound **3** is shown in Fig. 1.

In the title molecule, all of the C–N distances (Table 2) are between the normal C=N double bond (1.27 Å) and C–N single bond (1.47 Å), indicating all the N atoms are partially characterized by sp^2 hybridization. It is deduced that there exists some degree of π-electron delocalization around the urea scaffold. The urea linkage unit O(1)–C(7)–N(1)–C(8)–N(2)–H(2A) adopts the most stable conformation for the formation of an intramolecular N–H···O hydrogen bond (Fig. 2, Table 3) to give a planar six-membered ring specified as graph-set motif of S(6), which is essentially coplanar with the thiadiazole plane with a dihedral angle of only 8.62(14)°. Compared with unsubstitution or para-substitution [15] in the benzene moiety, the dihedral angle between the benzene ring with the urea scaffold increases to 42.66(15)°, thus the π-conjugation in the molecular structure is greatly weakened, as can be attributed to the existence of two F atoms substituted in the ortho-positions of the benzene ring. The three rings in the title molecule are not coplanar, the dihedral angles formed by the thiadiazole ring with the pyridine and benzene planes being 11.61(16)° and 39.94(16)°, respectively.

X-ray diffraction analysis reveals that pairs of N–H···O hydrogen bonds (N···O 2.867(3) Å, N–H···O 169.4°) occurring between centrosymmetrically related molecules result in the formation of $R_2^2(8)$ motifs [16, 17], where each H atom also participates in intramolecular **N**–H···F hydrogen bond, as shown in Fig. 2 and Table 3. The hydrogen-bond patterns, such as graph-set motifs of S(6) and $R_2^2(8)$, are similar to those reported in the previous literatures [18, 19]. Also present are intermolecular π–π stacking interactions [20] between parallel benzene rings

Table 1 Summary of crystallographic data and parameters of compound **3**

Empirical formula	$C_{15}H_9F_2N_5O_2S$
Formula weight	361.33
CCDC deposit no.	273315
Temperature	292(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P-1$
Unit cell dimensions	$a = 7.0821(9)$ Å
	$b = 9.4896(13)$ Å
	$c = 11.6594(15)$ Å
	$\alpha = 82.311(2)°$
	$\beta = 82.328(2)°$
	$\gamma = 87.641(2)°$
Volume	769.37(17) Å^3
Z	2
Density (calculated)	1.560 Mg m^{-3}
Absorption coefficient	0.254 mm^{-1}
$F(000)$	368
Crystal size	0.20 × 0.20 × 0.10 mm^3
θ range for data collection	1.78–25.00°
Index ranges	$-8 \le h \le 8$
	$-10 \le k \le 11$
	$-11 \le l \le 13$
Reflections collected	4097
Independent reflections	2679 [$R_{int} = 0.0888$]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2679/0/227
Goodness-of fit on F^2	1.030
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0465$, $wR_2 = 0.1103$
R indices	$R_1 = 0.0778$, $wR_2 = 0.1445$
Large diff. peak and hole	0.310 and −0.402 e Å^{-3}

Table 2 Selected bond lengths (Å) and angles (°) of compound **3**

Bond lengths			
C1−F1	1.335(4)	C9−N2	1.386(4)
C5−F2	1.361(4)	C9−N3	1.287(4)
C6−C7	1.500(4)	C9−S1	1.710(3)
C7−O1	1.204(3)	C10−N4	1.282(4)
C7−N1	1.386(4)	N3−N4	1.373(3)
C8−O2	1.197(3)	C10−S1	1.738(3)
C8−N2	1.369(3)	C13−N5	1.337(5)
C8−N1	1.384(4)	C14−N5	1.300(5)
Bond angles			
O1−C7−C6	122.9(3)	C8−N2−C9	122.6(3)
O1−C7−N1	123.1(3)	N3−C9−N2	119.3(3)
N1−C7−C6	114.0(3)	N3−C9−S1	115.6(2)
C8−N1−C7	128.2(2)	N2−C9−S1	125.1(2)
O2−C8−N1	122.3(3)	C9−S1−C10	86.03(14)
O2−C8−N2	122.4(3)	C11−C10−S1	124.0(2)
N2−C8−N1	115.2(3)	C14−N5−C13	115.6(3)

Table 3 Hydrogen-bonding Geometry (Å, °)

D−H···A	D−H	H···A	D···A	D−H···A	Symmetry codes
N1−H1···O2	0.86	2.02	2.867(3)	169.4	$1-x, 1-y, -z$
N2−H2A···O1	0.86	1.97	2.638(3)	133.7	x, y, z
N1−H1···F2	0.86	2.43	2.808(3)	107.1	x, y, z

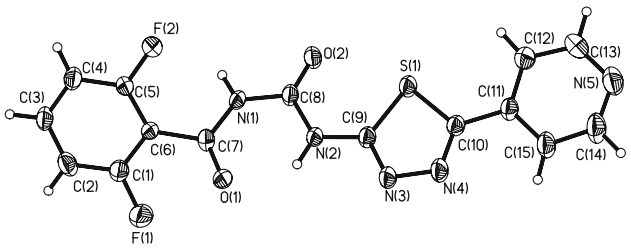


Fig. 1 Molecular structure of compound **3** showing the atomic labeling. Displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as spheres of arbitrary radii

(symmetry code: $1 - x$, $1 - y$, $1 - z$) of neighboring molecules. The centroid-to-centroid distance is 3.561(2) Å, the face-to-face distance and the slippage are 3.428(2) and 0.963(2) Å, respectively. However, π–π stacking is not found in the reported aroylurea structure [18, 19]. The different point is related to the substituted groups on the benzene ring. In the title molecular structure, there are two strong electron-attracting F atoms on the benzene ring, it might be helpful to forming π–π stacking interactions between parallel benzene rings. In conclusion, these intra- and intermolecular interactions, such as π–π stacking and hydrogen bonding, play a fundamental role in the three-dimensional organization of the molecules in solid state.

The plant-growth regulating and fungicidal activities of compound **3** were evaluated. The plant-growth regulating activity was tested at the concentration of 10 ppm according to a previously reported method [21]. The preliminary biological tests show that the title compound does not display distinct auxin activity towards wheat coleoptile and cytokinin activity towards cucumber cotyledon, giving only 11.6% and 8.5% promotion respectively. The fungicidal activity of the title compound was investigated at the concentration of 50 ppm according to the method of literature [22], and the results of preliminary bioassay indicate that it exhibits good inhibiting activity against the selected six kinds of fungi (*Fusarium oxysporium*, *Rhizoctonia solani*, *Botrytis cinerea*, *Gibberella zeae*, *Dothiorella gregaria* and *Colletotrichum gossypii*). The inhibitory ratios

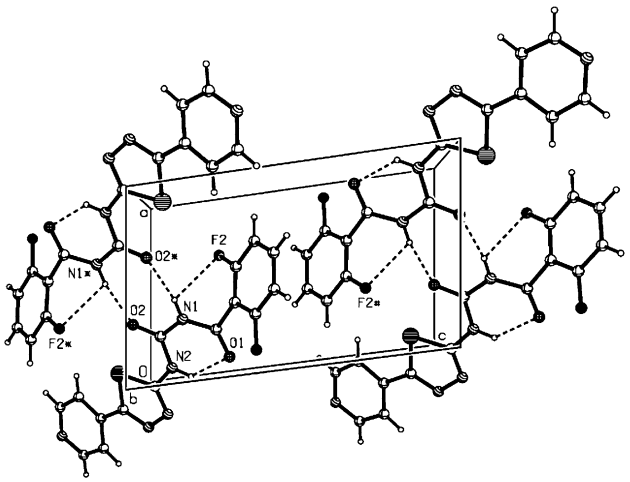


Fig. 2 Partial packing diagram of compound **3**. Dashed lines represent hydrogen-bonding interactions

are 78.2%, 95.1%, 100.0%, 82.1%, 90.5% and 80.0%, respectively.

Supplementary material

CCDC-273315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk, or by emailing 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.

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