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Synthesis, Structure, and Spectroscopic Properties of Isotianil as a Bactericide

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Abstract—Isotianil [*N*-(2-cyanophenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide] has been synthesized in a good yield with high purity by reaction of the key intermediate product, *N*-(2-carbamoylphenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide, with thionyl chloride in *N*,*N*-dimethylformamide at 60°C. The structure of isotianil was studied by X-ray analysis. It crystallized in triclinic space group $P\bar{1}$ with a = 11.459(3), b = 12.632(3), c = 22.528(5) Å, α = 78.897(3), β = 81.730(3), γ = 71.493(3)°, Z = 10.

Keywords: bactericide, isotianil, intermediate, organic synthesis, X-ray analysis

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INTRODUCTION

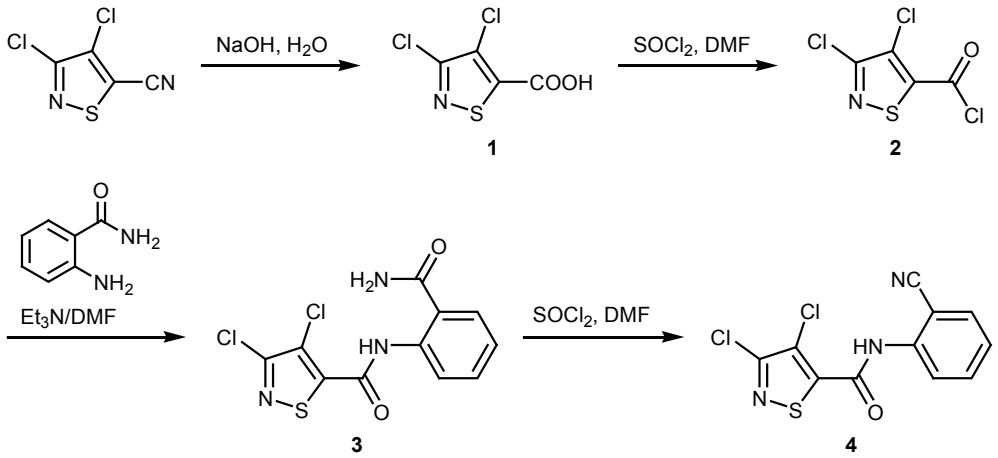
Isotianil is an environmentally friendly bactericide that is used mainly for the prevention and control of rice blast by stimulating the natural defense mechanism of rice itself [1–4]. In 2002, Himmler reported a synthetic route to isotianil via a one-pot reaction starting from isatoic anhydride [5]. Treatment of isatoic anhydride with ammonia in the presence of *N*,*N*-dimethylformamide gave 2-aminobenzamide, which was directly reacted with 3,4-dichloro-1,2-thiazole-5-carbonyl chloride to obtain *N*-(2-carbamoylphenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide, and the latter was treated with thionyl chloride to afford the target isotianil. The reaction of 2-cyanobenzylamine with 3,4-dichloro-1,2-thiazole-5-carbonyl chloride in the presence of pyridine or 4-dimethylaminopyridine also afforded isotianil [3, 6]. However, the reported syntheses of isotianil have problems such as low yields along with low purity. Herein, we report a synthetic route to isotianil with high purity and high yield and its molecular structure according to single-crystal X-ray diffraction data.

RESULTS AND DISCUSSION

As shown in Scheme 1, the starting material was 3,4-dichloro-1,2-thiazole-5-carbonitrile which was converted to 3,4-dichloro-1,2-thiazole-5-carboxylic acid (**1**) in quantitative yield by hydrolysis in aqueous sodium hydroxide. Treatment of compound **1** with thionyl chloride in DMF afforded intermediate 3,4-dichloro-1,2-thiazole-5-carbonyl chloride (**2**) which reacted with 2-aminobenzamide in DMF at 60°C to give the key intermediate product, *N*-(2-carbamoylphenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide (**3**), in a good yield. The target isotianil (**4**) was readily obtained by treatment of **3** with thionyl chloride in DMF. In the ^{1}H NMR spectrum of **3**, the signal at δ 7.20–7.15 ppm was assigned to protons of the NH_2 group, and signals in the region δ 7.52−8.26 ppm were attributed to aromatic protons. The ^{13}C NMR spectrum of isotianil showed two signals at δ_C 157.35 and 116.89 ppm due to C=O and C≡N carbons, respectively. In the ^{1}H NMR spectrum of **4**, the peaks in the range δ 7.49–7.92 ppm were attributed to aromatic protons, and the singlet at δ 11.04 ppm was assigned to the NH proton, similar to that in compound **3** (δ 10.56 ppm). The IR spectrum of **4** showed absorption bands at 3321 (N–H), 1650 (C=O), and 2224 cm^{-1} (C≡N). The UV–Vis absorption spectra of **3** and **4** in acetonitrile at room temperature showed strong bands at λ 210 (**4**) and ~270 nm (**3**) due to π→π* transition and at λ 283 (**4**) and 382 nm (**3**) due to *n*→π* transition (see Supplementary Materials).

The molecular structure of compound **4** was further confirmed by X-ray crystallography (Fig. 1). Selected bond lengths and angles are accordingly given in Table 1, and the hydrogen bond parameters are listed in Table 2. The C^4–O^1 bond length [1.220(10) Å] indicates double-bond character of the carbon–oxygen

Scheme 1.



bond, in agreement with the data for structurally related *N*-arylbenzamides and 2-aminobenzophenones {1.226(2) Å [7, 8]}. The C^{11}–N^3 bond length is 1.180(12) Å, which indicates the triple-bond character, as in the structure of 2-acetamidobenzonitrile {1.138(3) Å [9]}. The C^1–Cl^1 and C^2–Cl^2 bond lengths are 1.720(10) and 1.708(9) Å, respectively. The $C^{10}C^{11}N^3$ bond angle is 177.3(13)° which is typical of a C–C≡N group. The dihedral angle between the benzene and isothiazole ring planes is 5.1(10)°, and the torsion angle $C^3C^4N^2C^5$ is 178.2(10)°, i.e., the isothiazole and benzene rings are nearly coplanar.

The packing view of compound **4** is shown in Fig. 2. The crystal packing of **4** is governed by weak intermolecular N–H···O and N–H···Cl hydrogen-bonding interactions (Table 2). The H···O distances range from 2.28 to 2.38 Å, as in *N*-(4-chlorophenyl)-4-nitrobenzamide (2.29 Å) [10]. The bond angles N–H···O and N–H···Cl are in the range 127.2–134.0°. Furthermore, classical N–H···Cl (H···Cl ~2.61 Å) hydrogen bonds also contribute to stabilization of the crystal structure of **4**.

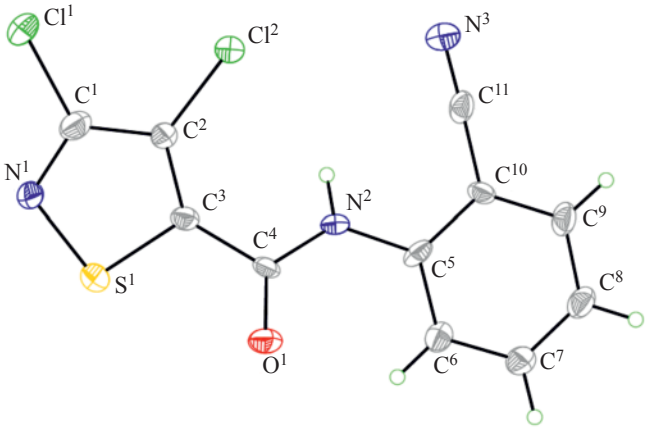


Fig. 1. Structure of the molecule of *N*-(2-cyanophenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide (**4**) according to the X-ray diffraction data. One molecule in the asymmetric unit is shown with non-hydrogen atoms represented as thermal displacement ellipsoids with a probability of 50%.

EXPERIMENTAL

All solvents were purified by routine procedures and distilled under dry nitrogen before use. Sodium hydroxide, thionyl chloride, and 2-aminobenzamide were purchased from Alfa Aesar and were used without

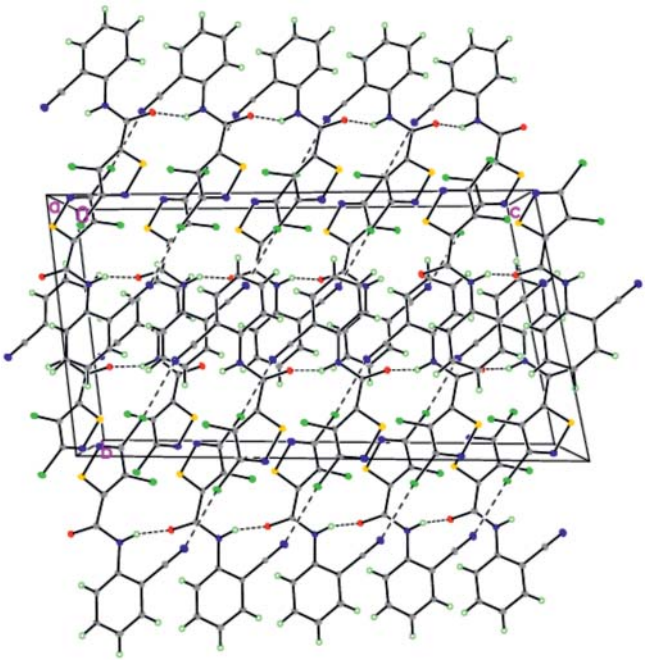


Fig. 2. Crystal packing of isotianil (**4**) viewed along the *a* axis. Dashed lines indicate N–H···O and N–H···Cl hydrogen bonds.

Table 1. Selected bond lengths (*d*) and bond angles (ω) for compound **4**

Bond	*d*, Å	Bond angle	ω, deg
S^1–N^1	1.653(8)	$N^1S^1C^3$	95.7(4)
S^1–C^3	1.710(9)	$C^1N^1S^1$	108.1(7)
O^1–C^4	1.220(10)	$C^4N^2C^5$	127.6(8)
N^3–C^{11}	1.180(12)	$N^1C^1Cl^1$	118.2(8)
N^2–C^4	1.350(10)	$C^3C^2Cl^2$	128.0(8)
N^2–C^5	1.404(11)	$O^1C^4N^2$	125.2(9)
Cl^1–C^1	1.720(10)	$O^1C^4C^3$	118.8(9)
Cl^2–C^2	1.708(9)	$N^3C^{11}C^{10}$	177.3(13)

Table 2. Parameters of hydrogen bonds in the crystal structure of isotianil (**4**)

D–H···A	D–H, Å	H···A, Å	D···A, Å	Angle DHA, deg
N^2–H^2···O^5	0.86	2.38	2.983(11)	127.2
N^2–H^2···Cl^5	0.86	2.59	3.238(8)	133.3
N^5–H^5···O^1	0.86	2.28	2.938(11)	134.0
N^5–H^5···Cl^4	0.86	2.63	3.236(8)	128.0
N^8–H^8···O^4 [a]	0.86	2.33	2.964(12)	130.9
N^8–H^8···Cl^6	0.86	2.61	3.240(8)	130.5
N^{11}–H^{11}···O^3 [b]	0.86	2.31	2.948(12)	131.5
N^{11}–H^{11}···Cl^8	0.86	2.62	3.235(8)	129.7
N^{14}–H^{14}···O^4	0.86	2.36	2.961(11)	127.7
N^{14}–H^{14}···Cl^{10}	0.86	2.59	3.225(8)	131.3

Symmetry operation: [a] $x, y, z + 1$; [b] $x - 1, y, z$.

Table 3. Crystallographic data for isotianil (**4**) and details of X-ray diffraction experiment

Formula	$C_{11}H_5Cl_2N_3OS$	d_{calc}, g/cm^3	1.638
Molecular weight	298.14	Temperature, K	296(2)
Crystal system	Triclinic	$F(000)$	1500
Space group	$P\bar{1}$	μ(Mo K_α), mm^{-1}	0.698
a, Å	11.459(3)	Total number of reflections	19220
b, Å	12.632(3)	Number of independent reflections	13313
c, Å	22.528(5)	R_{int}	0.0301
α	78.897(3)	Number of parameters	812
β	81.730(3)	R_1,[a] wR_2[b] [$I > 2\sigma(I)$]	0.0556, 0.1472
γ	71.493(3)	R_1, wR_2 (all reflections)	0.2555, 0.2795
V, Å^3	3022.4(12)	GoF[c]	0.852
Z	10		

[a] $R_1 = ||F_o| - |F_c||/|F_o|$.
[b] $wR_2 = [w(|F_o^2| - |F_c^2|)^2/w|F_o^2|^2]^{1/2}$.
[c] GoF = $[w(|F_o| - |F_c|)^2/(N_{obs} - N_{param})]^2$.

further purification. 3,4-Dichloro-1,2-thiazole-5-carbonitrile was purchased from Jiangsu Furun Chem. Co. Ltd. and used after recrystallization. The melting points were determined in capillaries using an X4 digital melting-point apparatus and are uncorrected. The NMR spectra were recorded on a Bruker ALX 400 spectrometer operating at 400 and 101 MHz for ^{1}H and ^{13}C, respectively; the chemical shifts are given with reference to tetramethylsilane. The infrared spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrophotometer. Elemental analyses were carried out using a Perkin Elmer 2400 CHN analyzer. Electronic absorption spectra were obtained on a Shimadzu UV-2600 spectrophotometer.

3,4-Dichloro-1,2-thiazole-5-carboxylic acid (1). 3,4-Dichloro-1,2-thiazole-5-carbonitrile (5.0 g, 0.028 mol) was added to a solution of sodium hydroxide (2.8 g, 0.070 mol) in distilled water (10 mL). The mixture was stirred under reflux, and the progress of reaction was monitored by TLC. After 6 h, the mixture was acidified with dilute aqueous HCl (2 M) to pH ~3. The product (a creamy-white solid) was filtered off, thoroughly washed with distilled water, and dried under reduced pressure in a desiccator. Yield 5.25 g (95%), mp 177–179°C. ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 165.32 s, 160.07 s, 148.95 s, 113.88 s. Found, %: C 26.57; H 0.63; N 15.57. $C_4HCl_2N_2O_2S$. Calculated, %: C 26.81; H 0.56; N 15.64.

3,4-Dichloro-1,2-thiazole-5-carbonyl chloride (2). 3,4-Dichloro-1,2-thiazole-5-carboxylic acid (**1**, 5.0 g, 0.025 mol) was slowly added in portions with stirring to thionyl chloride (5.1 mL, 0.070 mol). *N*,*N*-Dimethylformamide was then added, and the mixture was refluxed with stirring for 2 h. After completion of the reaction (TLC), the mixture was cooled to room temperature and evaporated under reduced pressure to afford light yellow powder. Found, %: C 20.83; N 12.12. $C_4Cl_3N_2OS$. Calculated, %: C 20.85; N 12.16.

***N*-(2-Carbamoylphenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide (3).** A solution of 2-aminobenzamide (3.4 g, 0.025 mol) in triethylamine (5 mL) was added dropwise to a solution of **2** (2.8 g, 0.070 mol) in DMF (2 mL). The mixture was stirred at 60°C for 3 h (TLC), ethyl acetate and distilled water were added, and the organic phase was separated, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from dichloromethane. Yield: 6.03 g (83%). yellow powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20–7.15 m (2H, NH_2), 7.52 d (1H, H_{arom}, J = 7.5 Hz), 7.75 d (2H, H_{arom}, J = 11.5 Hz), 8.26 s (1H, H_{arom}), 10.56 s (1H, NH). IR spectrum (KBr), ν, cm^{-1}: 3428 (N–H), 1725 (C=O), 1387 (C=N). Found, %: C 41.77; H 2.24; N 13.26. $C_{11}H_7Cl_2N_3O_2S$. Calculated, %: C 41.79; H 2.23; N 13.29.

***N*-(2-Cyanophenyl)-3,4-dichloro-1,2-thiazole-5-carboxamide (4, isotianil).** Thionyl chloride (3 mL) was added dropwise with vigorous stirring to a solution of **3** (5.0 g, 0.015 mol) in DMF (5 mL). The mixture was stirred at 60°C for 2 h (TLC), and distilled water (20 mL) was added with stirring over a period of 1 h. The gray solid was filtered off and washed with distilled water (3×15 mL) and petroleum ether (3×15 mL). An additional amount of the product was isolated from the filtrate by extraction with ethyl acetate (15 mL). The extract was washed with brine (2×15 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Yield 6.03 g (83%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.49 t (1H, H_{arom}, J = 7.6 Hz), 7.71 d (1H, H_{arom}, J = 8.0 Hz), 7.82–7.75 m (1H, H_{arom}), 7.92 d (1H, H_{arom}, J = 7.8 Hz), 11.04 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 157.35 s, 156.16 s, 148.10 s, 139.06 s, 134.59 s, 133.91 s, 127.67 s, 126.72 s, 121.50 s, 116.89 s, 108.87 s. IR spectrum (KBr), ν, cm^{-1}: 3321 (N–H), 2224 (C≡N), 1650 (C=O). Found, %: C 44.33; H 1.67; N 14.12. $C_{11}H_5Cl_2N_3OS$. Calculated, %: C 44.31; H 1.69; N 14.09.

X-Ray diffraction data. The crystallographic data for isotianil (**4**) and experimental details are summarized in Table 3. The X-ray reflection intensities were measured on a Bruker SMART APEX 2000 CCD diffractometer at 293(2) K (Mo K_α radiation, graphite monochromator, λ 0.71073 Å). The collected frames were processed with SAINT software [11]. The data were corrected for absorption using SADABS [12]. The structure was solved by the direct method and was refined against F^2 by the full-matrix least-squares method using SHELXTL software package [13, 14]. All non-hydrogen atoms were refined anisotropically. The positions of all hydrogen atoms were generated geometrically (C_{sp^3}—H 0.96, C_{sp^2}–H 0.93 Å), assigned isotropic thermal parameters, and allowed to ride on their respective parent carbon atoms before the final cycle of least-squares refinement. The crystallographic data were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1973435) and are available at https://www.ccdc.cam.ac.uk/.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S107042802010022X and are accessible for authorized users.

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