4-(7-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(pyridin-2-yl)thiazol-2-amine: Chiral Crystal from Achiral Molecule①

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ABSTRACT The title compound 4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(pyridin-2-yl) thiazol-2-amine was synthesized by reacting 2-bromo-1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)ethanone with 1-(pyridine-2-yl)thiourea, and its crystal was determined by single-crystal X-ray diffraction. The crystal belongs to the monoclinic system, chiral space group *C*2 with a = 18.1328(14), b = 5.5969(5), c = 19.2195(15) Å, β = 115.5420(10)°, V = 1759.9(2) Å^3, Z = 4, F(000) = 744, $C_{19}H_{19}N_3O_2S$, M_r = 353.43, D_c = 1.334 g/cm^3, S = 1.15, μ = 0.201 mm^{-1}, the final R = 0.035 and wR = 0.111 for 2307 observed reflections ($I > 2\sigma(I)$). The *Flack* parameter is –0.03(10). The preliminary bioassay result indicated that the title compound exhibits strong insecticidal activity (93.75% mortality) against *Mythimna separate* at the concentration of 1.000 g/L.

Keywords:4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(pyridin-2-yl)thiazol-2-amine, chiral crystal structure, synthesis, insecticidal activity

1 INTRODUCTION

Thiazole derivatives have attracted extensive interest of synthetic researchers because of their insecticidal, antibacterial, antiviral and other biological activities[1-3]. Furan phenol is an important intermediate to synthesize carbofuran, carbosulfan, benfuracarb and other carbamate pesticides[4]. Recently, some chiral crystals have been formed from achiral molecules which contained chiral nitrogen like 2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-methyl/*N*-ethylcarbamate ($P2_12_12_1$)[5-6]. In the previous paper[7], we have reported the synthesis and crystal structure of 4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(4-chlorobenyl)thiazol-2-amine (*C*2/*c*) which exhibits insecticidal activity against *Aphis fabae*. However, in this paper, the crystal of 4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(pyridin-2- yl)thiazol-2-amine (**3**) reported is chiral, which is formed from achiral molecules through self-assembly. And compound **3** exhibits insecticidal activity against *Mythimna separate*. The synthesis route of **3** is depicted in Scheme 1.

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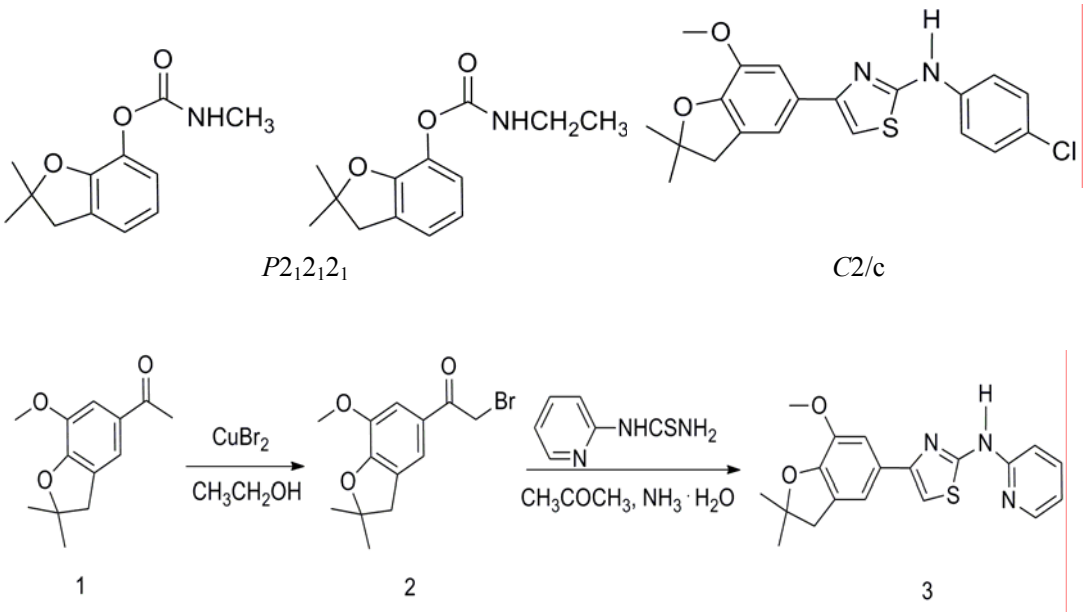

Scheme 1. Synthetic route of the title compound (3)

2 EXPERIMENTAL

2. 1 Instruments and general methods

Melting point was measured on an X-4 electrothermal digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Bruker advance instrument with TMS as internal standard at 400 MHz with the chemical shifts (δ) expressed in ppm. MS spectra were recorded on an Agilent 1100 LC/MS instrument. The data of elemental analysis were recorded on a VARIO EL III elemental analyzer. Crystal data were obtained on a Bruker AXS SMART 1000 CCD X-diffractometer. TLC was performed on E-Merck precoated 60 F_{254} plates and the spots were rendered visible by exposure to UV light or iodine. Every starting material was obtained from commercial suppliers and purified according to the literature procedures.

2. 2 Synthesis of the title compound

Synthesis of **3**: A solution of 2-bromo-1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)ethanone[7] (2.0 mmol) and 1-(pyridin-2-yl)thiourea (1.8 mmol) in acetone (20 mL) were stirred and heated under reflux for 2 h (monitored by TLC). Then the reaction mixture was cooled and filtered to obtain 4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(pyridin-2-yl)thiazol-2-amine hydrobromide, neutralized with ammonia and recrystallized from ethanol to obtain compound **3**. Yield: 86.5%, m.p.: 200.3–201.4 ℃. ^{1}H NMR($CDCl_3$, 400 MHz) δ: 1.50 (s, 6H, 2×CH_3), 2.98 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.53 (d, J = 7.2 Hz, 1H, pyridine 3-H), 6.83 (t, J = 7.2 Hz, 1H, pyridine 5-H), 6.88 (s, 1H, thiazole 5-H), 7.29–7.30 (m, 2H, Ph-H), 7.39 (t, J = 7.2 Hz, 1H, pyridine 4-H), 8.33–8.35 (m, 1H, pyridine 6-H), 10.46 (br, 1H, NH). EI-MS(m/z): 354.1($M + H^+$). Anal. Calcd. (%) for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89; S, 9.07. Found (%): C, 63.41; H, 5.62; N, 11.97; S, 8.95.

2. 3 X-ray structure determination

The crystals suitable for X-ray structure determination were obtained by the slow evaporation of ethanol solution for about fifteen days at room temperature. A white single crystal with dimensions of 0.45mm × 0.43mm × 0.34mm was selected and mounted in air onto thin glass fibers. X-ray intensity data were measured at 293(2) K on a Bruker AXS SMART 1000 CCD diffractometer equipped with a graphite-monochromatic Mo$K\alpha$ (λ = 0.71073 Å) radiation. A total of 2689 reflections were collected in the range of $1.17<\theta<25.99°$ (index ranges: $-19\leqslant h\leqslant 22$, $-6\leqslant k\leqslant 6$, $-21\leqslant l\leqslant 23$) by using an ω-φ scan mode with 3330 independent ones (R_{int} = 0.0193), of which 2307 with $I > 2\sigma(I)$ were con-

sidered as observed and used in the succeeding refinements. Corrections for incident and diffracted beam absorption effects were applied using SADABS[8]. The structure was solved by direct methods with SHELXS-97[9] and refined by full-matrix least-squares techniques on F^2 with SHELXL-97[10]. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were added according to theoretical models. The final refinement gave $R = 0.035$, $wR = 0.111$ ($w = 1/[\sigma^2(F_o^2) + (0.0644P)^2 + 0.0786P]$, where $P = (F_o^2 + 2F_c^2)/3$) for 2307 observed reflections with $I > 2\sigma(I)$. $(\Delta/\sigma)_{max} = 0.001$, $S = 1.15$, $(\Delta\rho)_{max} = 0.216$ and $(\Delta\rho)_{min} = -0.206$ e/Å^3. The selected bond lengths and bond angles are listed in Table 1.

Table 1. Selected Bond Lengths (Å) and Bond Angles (°)

Bond	Dist.	Bond	Dist.	Bond	Dist.
S(1)–C(13)	1.723(3)	C(5)–C(6)	1.401(3)	C(14)–N(1)	1.302(3)
S(1)–C(14)	1.727(3)	C(5)–C(12)	1.477(3)	C(14)–N(2)	1.370(3)
C(1)–O(2)	1.371(3)	C(7)–C(8)	1.542(4)	C(15)–N(2)	1.377(3)
C(1)–C(6)	1.386(3)	C(8)–O(1)	1.473(4)	C(15)–C(16)	1.384(4)
C(1)–C(2)	1.390(4)	C(8)–C(10)	1.503(4)	C(16)–C(17)	1.362(5)
C(2)–O(1)	1.362(3)	C(8)–C(9)	1.516(4)	C(17)–C(18)	1.364(6)
C(2)–C(3)	1.379(4)	C(11)–O(2)	1.432(3)	C(18)–C(19)	1.354(5)
C(3)–C(4)	1.380(4)	C(12)–C(13)	1.351(4)	C(19)–N(3)	1.349(4)
C(3)–C(7)	1.507(4)	C(15)–N(3)	1.318(4)		
C(4)–C(5)	1.391(3)	C(12)–N(1)	1.383(3)		
Angle	(°)	Angle	(°)	Angle	(°)
C(13)–C(12)–N(1)	114.1(2)	N(2)–C(14)–S(1)	124.73(19)	N(3)–C(19)–C(18)	123.9(4)
C(13)–C(12)–C(5)	126.9(2)	N(3)–C(15)–N(2)	117.6(3)	C(14)–N(1)–C(12)	110.9(2)
N(1)–C(12)–C(5)	119.0(2)	N(3)–C(15)–C(16)	123.2(3)	C(14)–N(2)–C(15)	128.9(2)
C(12)–C(13)–S(1)	111.5(2)	N(2)–C(15)–C(16)	119.2(3)	C(15)–N(3)–C(19)	116.5(3)
C(13)–C(12)–N(1)	114.1(2)	C(17)–C(16)–C(15)	118.5(4)	C(2)–O(1)–C(8)	107.3(2)
N(1)–C(14)–N(2)	119.9(2)	C(16)–C(17)–C(18)	119.4(4)	C(1)–O(2)–C(11)	117.20(19)
N(1)–C(14)–S(1)	115.36(19)	C(19)–C(18)–C(17)	118.4(3)		

2. 4 Measurement of the insecticidal activity

The insecticidal test of compound **3** was carried out according to the previous procedure[11] with the following insect specy: *Nephotettix cincticeps*. The mortality was determined by the number of live and dead insects as follows:

$$M = \frac{\bar{N}_1}{N_0} \times 100\%$$

in which M is the mortality, N_0 is the total number of live insects for the test, and $\bar{N}_1$ is the average number of dead insects.

3 RESULTS AND DISCUSSION

The ^{1}H NMR and EI-MS for the product are in good agreement with the structure of compound **3**. The ^{1}H NMR spectrum shows singlets at δ 1.50, 2.98 and 3.83 due to the CH_3, CH_2 and OCH_3, respectively. A broad singlet at δ 10.46 is corresponding to the NH proton and the other singlet at δ 6.88 to the thiazole ring. A doublet at δ 6.53 (J = 7.2 Hz) results from the pyridine 3-H. Pyridine 5-H and pyridine 4-H both show triplet at δ 6.83 (J = 7.2 Hz) and δ 7.39 (J = 7.2 Hz), respectively. A multiplet in the range of δ 7.29–7.30 is owing to the aromatic protons on the benzfuran ring, and the other multiplet falling in the δ 8.33–8.35 region corresponds to the pyridine 6-H. Mass spectrum of compound **3** shows the molecular ion peak is located at m/z 354.

X-ray diffraction crystal structure of compound **3** is shown in Fig. 1. The atoms of C(4), C(5), C(6), C(1), C(2), C(3), C(7) and O(1) are nearly on one plane (plane equation $0.7960(6)x + 0.6047(8)y - 0.0266(72)z = 1.452$), with the maximum deviation of 0.0036 Å for C(7), and the mean deviation to be

0.0019(3) Å. As shown in Table 1, the C(1)–O(2) and C(2)–O(1) bonds are 1.371(3) and 1.362(3) Å, respectively, shorter than the typical C–O single bond[12], which are caused by the conjugation with benzofuran. Similarly, the bond length of C(14)–N(2) is 1.370(3) Å and that of C(15)–N(2) is 1.377(3) Å, both shorter than the typical C–N single bond[12]. The dihedral angle between the thiazole and pyridine rings is 1.008(1)°, so they are nearly coplanar, and that between the thiazole and benzofuran rings is 2.769(8)°.

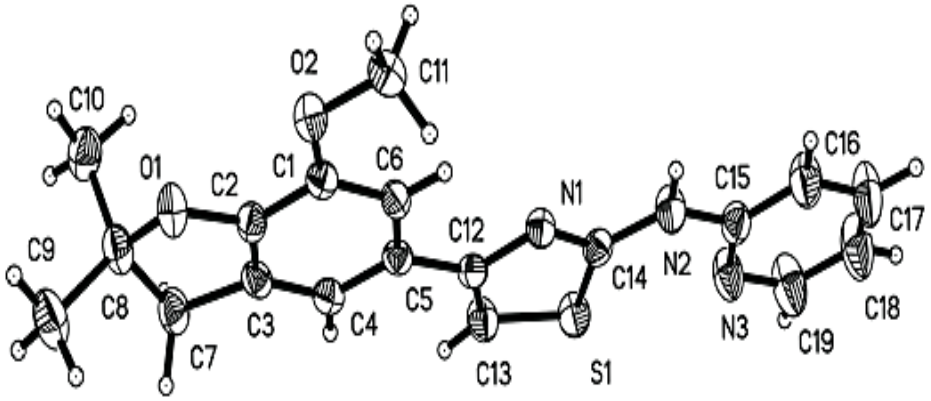

Fig. 1. X-ray crystal structure of the title compound (3)

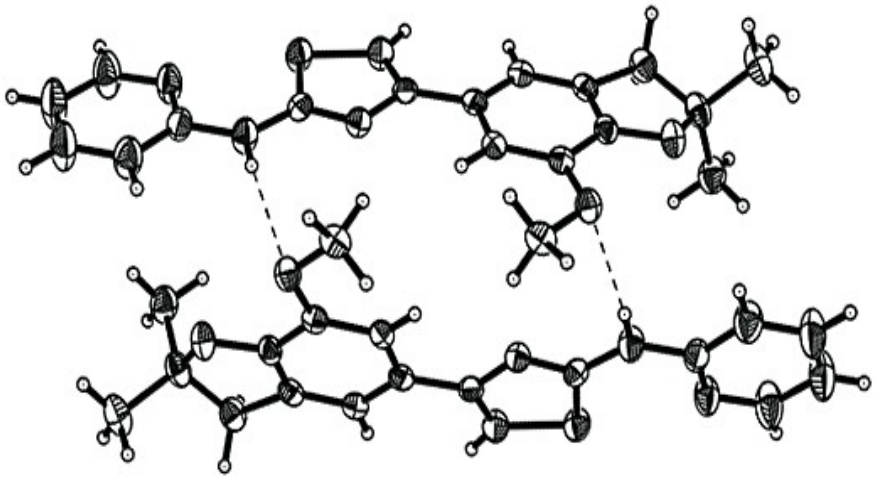

Fig. 2. Hydrogen bonds between adjacent molecules

If the nitrogen atom attaches three different atoms or substituents, and its unbonding electron pair can be looked as the forth substituent in three-dimensional space, the nitrogen compound will have a taper structure. As the molecule is lack of symmetrical faction, it should have chirality when the three atoms or substituents are different. However, the chiral tertiary amine enantiomer can not be split as the activation energy of inversion of the configuration is low as 21 kJ·mol^{-1}, so the configuration can be transformed 10^2–10^5 times in a second[13]. The stable chiral tertiary amine can be split if the configuration is prevented to inverse as the nitrogen is located in a ring or on the bridge, like Tröger base[13]. The crystal structure of compound **3** is stabilized by an intermolecular hydrogen bond N–H···O (N(2)–H(2C)···O(2): N(2)–H(2C): 0.86 Å, H(2C)···O(2): 2.22 Å, N(2)···O(2): 3.032(3) Å, ∠N(2)–H(2A)···O(2) 156.3°). The combination of two N–H···O hydrogen bonds between adjacent

molecules generates a cyclic centrosymmetric $R_2^2(18)$ (as shown in Fig. 2), so different substituents of nitrogen atom can not reverse, and the nitrogen atom becomes the chiral nitrogen virtually. The crystal configuration of compound **3** was successfully determined by refining the *Flack* parameter (–0.03(10)).

The result of preliminary bioassay indicated that the title compound exhibits strong insecticidal activity (93.75% mortality) against *Mythimna separate* at the concentration of 1.000 g/L.

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