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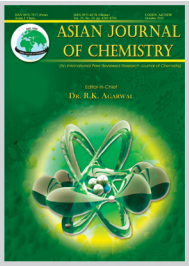

Synthesis, Crystal Structure and Biological Activity of 1-Cyano-*N*-phenylcyclopropanecarboxamide

YONG-LAI XUE[1], XING-HAI LIU[2,*] and YONG-GANG ZHANG[3]

[1]School of the Environment; Jiangsu University, Zhenjiang 212013, P.R. China
[2]College of Chemical Engineering and Material Science, Zhejiang University of Technology, Hangzhou 310014, Zhejiang, P.R. China
[3]Institute of Microbe, Shandong Academy of Science, Jinan, P.R. China

*Corresponding author: E-mail: xhliu@zjut.edu.cn

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A cyclopropane derivative, 1-cyano-*N*-phenylcyclopropanecarboxamide ($C_{11}H_{10}N_2O$) was synthesized and its structure was studied by X-ray diffraction, FTIR, ^{1}H NMR spectrum and MS. The crystals are monoclinic, space group Pbca with a = 10.0466(19), b = 9.6067(17), c = 20.790(3) Å, α = 90.00, β = 90.00, γ = 90.00°, V = 2006.5(6)Å^3, Z = 8, F(000) = 784.00, D_c = 1.233 g/cm^3, μ = 0.815 cm^{-1}, the final R = 0.0567 and wR = 0.1456. A total of 8716 reflections were collected, of which 1967 were independent (R_{int} = 0.045). Theoretical calculation of the title compound was carried out with B3LYP/6-31G (d.p.). The full geometry optimization was carried out using 6-31G(d.p.) basis set and the frontier orbital energy. The structure-activity relationship was also studied. The preliminary biological test showed that the synthesized compound is bioactive against the ketol-acid reductoisomerase of *Escherichia coli*.

Key Words: Synthesis, Therotical calculations, Crystal structure, Biological activity.

INTRODUCTION

Cyclopropane derivatives, a kind of highly bioactive compounds have been studied broadly for many years. Many high active compounds contain cyclopropane moiety, such as pyrethroids. A kind of cyclopropane derivatives with good activity of inhibiting ketol-acid reductoisomerase (KARI) were also synthesized[1-7]. In recent years, synthesis of broader spectrum and highly bioactive compounds, especially aromatic and heterocycle substituted amide, becomes the mainstream in the medicinal and agriculture chemistry field[8-12]. Some aromatic substituted cyclopropane compounds were synthesized and their herbicidal activity and ketol-acid reductoisomerase activity were tested. Then, the single crystal of the title compound was determined and theoretical study results were used to study the structure-activity relationship of this compound. The preliminary biological test showed that the 1-cyano-*N*-phenylcyclopropanecarboxamide synthesized compound has a strong and slow binding activity to inhibit *Escherichia coli* ketol-acid reductoisomerase.

EXPERIMENTAL

Melting points determined by a Yanaco MP-241 apparatus and uncorrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as KBr tablets. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ advantage LC/mass detector instrument. Crystallographic data of the compound collected on a Rigaku Saturn CCD diffractometer. All chemicals were of AR grade.

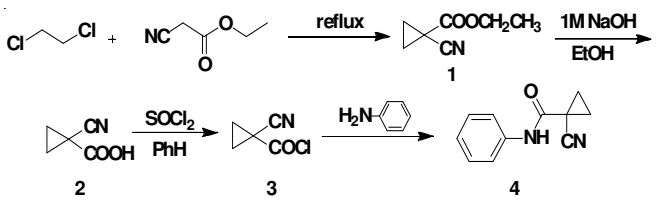
Crystal structure determination: The crystal of 1-cyano-*N*-phenylcyclopropanecarboxamide with dimensions of 0.12 mm × 0.08 mm × 0.06 mm was mounted on a Rigaku Saturn CCD area-detector diffractometer with a graphite-monochromated MoK_α radiation (λ = 0.71073Å) by using a phi and scan modes at 294(2) K in the range of 3.1° ≤ θ ≤ 27.7°. The crystal belongs to monoclinic system with space group Pbca and crystal parameters of a = 10.0466(19) Å, b = 9.6067(17) Å, c = 20.790(3) Å, α = 90°, β = 90°, γ = 90°, V = 2006.5(6) A^3, D_c = 1.233 g/cm^3. The absorption coefficient μ = 0.0815 mm^{-1} and Z = 8. The structure was solved by direct methods with SHELXS-97[13] and refined by the full-matrix least squares method on F^2 data using SHELXL-97. The empirical absorption corrections were applied to all intensity data. H atom of N-H was initially located in a difference Fourier map and were refined with the restraint Uiso(H) = 1.2 Ueq(N). Other H atoms were positioned geometrically and refined using a riding model, with d(C---H) = 0.93-0.97 Å and Uiso(H) = 1.2 Ueq(C) or 1.5 Ueq (Cmethyl). The final full-matrix least squares refinement gave R = 0.0567 and wR = 0.1456.

Therotical calculations: On the basis of the above crystal structure, the isolated molecule was selected as the initial structure, while DFT-B3LYP/6-31G (d.p.)[14] methods in Gaussian 03 package[15] were used to optimize the structure of the 1-cyano-*N*-phenylcyclopropanecarboxamide. Vibrational analysis showed that the optimized structures were in accordance with the minimum points on the potential energy surfaces. All the convergent precisions were the system default values and all the calculations were carried out on the Nankai Stars supercomputer at Nankai University.

Synthesis: A modified two-phase procedure was applied. Ethyl cyanacetate (22.6 g, 0.2 mol), 1,2-dichloroethane (160 g, 0.2 mol), potassium carbonate (220 g, 1.6 mol) and catalytic amount of Bu_4NHSO_4 (1.0 g) were vigorously refluxed in 1,2-dichloroethane for 6 h after which the reaction mixture was poured into water (800 mL). The product was extracted with ether (5 × 100 mL), combined extracts were dried over $MgSO_4$ then the solvent was removed on a rotary evaporator and the reside was distilled under pressure: b.p. 115-118/15 mmHg.

An ester (0.03 mol) was added to a *ca.* 15 % aqueous solution containing 3 mol equivalents of sodium hydroxide and a suspension was vigorously stirred at ambient temperature for 2 days until a homogenous solution was formed. The solution was extracted with ether (2 × 50 mL) to remove traces of unreacted ester, the water phase was acidified with concentrated hydrochloric acid and a free acid was extracted with ether (3 × 100 mL). The combined extracts were dried over $MgSO_4$ then the solvent was removed on a rotary evaporator[16]. Yields 51 %.

To a benzene solution (25 mL) of cyanocyclopropane carboxylic acid (7.50 mmol) was added thionyl chloride (30 mmol) and the mixture was refluxed for 2 h to give acid chloride. Then add acid chloride drop by drop to aniline (7.50 mmol), then vigorously stirred at ambient temperature for 4 h (**Scheme-I**). The yield was 85.6 % with m.p. (85-86) ºC.



Scheme-I Synthesis route of the title compound

^{1}H NMR ($CDCl_3$, 300 MHz): 1.61-1.83 (m, 4H, CH_2), 7.15 (d, *J* = 7.573 Hz, 1H, ArH), 7.31 (d, *J* = 3.893 Hz, 1H, ArH), 7.66 (d, *J* = 1.938 Hz, 1H, ArH), 8.50 (s, 1H, ArH), 8.68 (s, 1H, NH).

IR (KBr, ν_{max}, cm^{-1}): 3249 (-NH), 3191,3127(cyclopropane, CH), 2239 (C=N), 1680 (C=O), 1595, 1536, 1488 (Ar C-C), 751, 693 (Ar C-H).

ESI-MS: 185.41[M-1]$^-$: Elemental analysis(calc.): C: 70.95 (70.94); H 5.41 (5.41); N 15.04 (15.39).

RESULTS AND DISCUSSION

The IR spectrum of the title compound tested shows absorption bands at 3249 cm^{-1} originating from the stretching vibration of NH. The strong band at 2239 cm^{-1} can be assigned to the CN strentching vibration. The strong band at 1680 cm^{-1} can be assigned to the C=O strentching vibration. So the absorption of the phenyl ring at 1595, 1536, 1488 cm^{-1}.

Structure of the title compound: Crystallographic and refinement parameters are given in Table-1. The selected bond lengths and bond angles are listed in Tables 2-4. The structure was solved by direct methods. Anisotropic displacement parameters were applied to all nonhydrogen atoms in full-matrix least-square refinements based on F^2. The hydrogen atoms were set in calculated positions with a common fixed isotropic thermal parameter. The intermolecular hydrogen bonds are shown in Table-5.

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

Items	Values
Empirical formula	$C_{11}H_{10}N_2O$
Formula weight	186.21
Crystal system	Orthorhombic
Unit cell dimensions	
a (Å)	10.0466(19)
b (Å)	9.6067(17)
c (Å)	20.790(3)
Unit cell angles (º)	
α	90
β	90
γ	90
Volume (Å^3)	2006.5(6)
Z	8
Temperature (K)	294(2)
Space group	Pbca
Wavelength (Å)	0.71073
Calculated density (g/cm^3)	1.233
Absorption coefficient (mm^{-1})	0.082
F(000)	784
Crystal size (mm)	0.12 × 0.08 × 0.06
Theta range for data collection (º)	3.1–27.7
Reflections collected	8716
Independent reflections	1967 [$R_{(int)}$ = 0.045]
Final R indices [I > 2σ(I)]	R_1 = 0.0567, wR_2 = 0.1457

TABLE-2
SELECTED BOND LENGTHS [Å] FOR THE TITLE COMPOUND

Bond lengths	X-ray crystal
O1-C1	1.2274(18)
N1-C6	1.419(2)
C1-C2	1.496(2)
C8-C9	1.373(3)
N1-C1	1.344(2)
N2-C5	1.139(2)
C2-C4	1.506(3)
C2-C3	1.523(3)
C3-C4	1.454(3)
C9-C10	1.374(3)

The molecular structure and atom labels are shown in Fig. 1. The one-dimensional linework of hydrogen bonds (dashed lines) is illustrated in Fig. 2 respectively.

In Table-3, the results indicate that the lengths of three C-N bond C5-N2, C6-N1 and N1-C1 are 1.139 Å, 1.419 Å and 1.344 Å respectively, which are all longer than those in the single heterocycle ring[17,18], but the bond length of C5-N2 is also longer than the double C-N bond[19].

TABLE-3
SELECTED BOND ANGLES [°] FOR THE TITLE COMPOUND

Bond angles	X-ray crystal
C1-N1-C6	125.25(14)
O1-C1-C2	120.93(17)
C1-C2-C3	116.16(17)
C2-C3-C4	60.73(16)
N2-C5-C2	178.2(2)
C8-C9-C10	119.5(2)
N1-C6-C11	119.50(15)
O1-C1-N1	123.61(17)

TABLE-4
SELECTED BOND ANGLES [°] TORSIONAL ANGELS (°) FOR THE TITLE COMPOUND

Bond angles	X-ray crystal
C1-N1-C6-C7	-45.2(2)
C6-N1-C1-O1	-5.1(2)
O1-C1-C2-C3	-54.9(2)
N1-C1-C2-C4	-171.51(18)
C1-N1-C6-C11	137.99(18)
C1-N1-C1-C2	176.90(16)
C7-C6-C11-C10	0.3(2)
C1-C2-C4-C3	-104.6(2)

TABLE-5
HYDROGEN-BOND DISTANCE (Å) OF THE TITLE COMPOUND

D H A	D-H	H···A	D···A	D-H···A
N1 H1…O1	0.85(2)	2.02(2)	2.8446(19)	163.8(16)

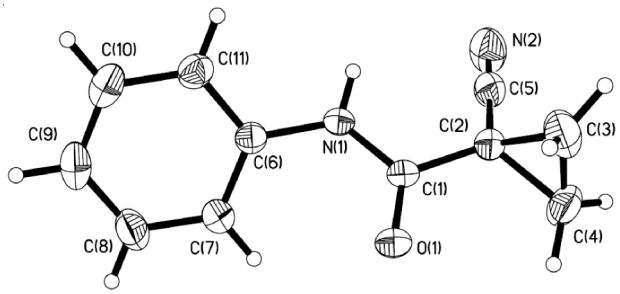


Fig. 1. Molecular structure of the title compound

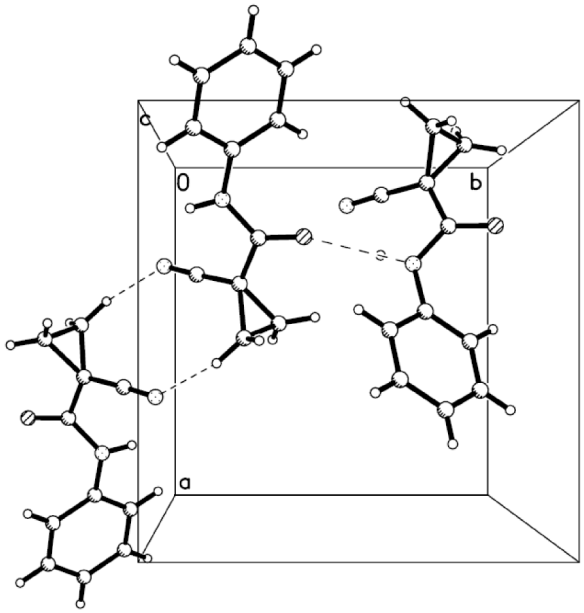


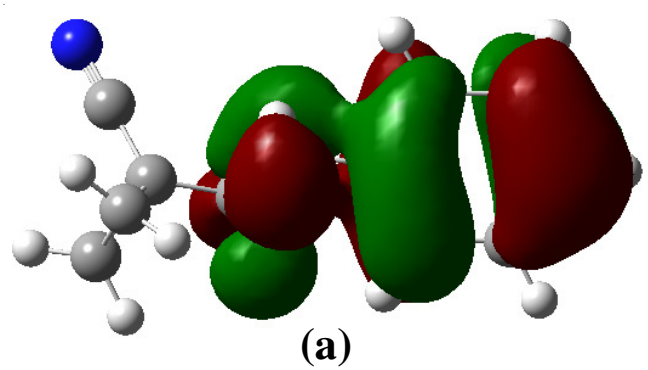
Fig. 2. Two-dimensional network of hydrogen bonds (dashed lines)

In the molecular structure of title compound, acyl group is not planar with amide group and the torsional angle of O1-C1-N1-H1 is 158.7. In the molecular structure of title compound, the two ring (benzene ring, cyclopropane ring) are nearly vertically with θ angle of 78.8º (benzene ring *vs.* cyclopropane ring). The C1-C3 cyclopropane ring is fairly planar with plane equation -0.976x + 8.757y + -8.307z = 1.4514, the largest deviation from the least squares plane is -0.0290 Å and the mean deviation from the plane is 0.0139 Å. The C6-C11 phenyl ring is fairly planar with plane equation-4.828x + 4.632y + 15.230z = 11.0585, the mean deviation from the plane is 0.0015 Å.

The title compound has an extensive one dimension chain polymer of hydrogen bonding involving the atoms, N and O. In the bc plane, they are linked together by N1 H1…O1, hydrogen bonds.

Biological activity: Gerwick *et al.*[20] reported that the inhibition of E. *coli* ketol-acid reductoisomerase is time-dependent. To characterise the steady-state inhibition constant, *Escherichia coli* ketol-acid reductoisomerase was preincubated for 10 min with NADPH, Mg^{2+} and the title compound, then the reaction was initiated with hydroxypyru-vate. Under these conditions, the change in A_{340} was found to be linear with time. The primary bioassay shows the title compound exhibits a strong inhibiting activity towards ketol-acid reductoisomerase, which reaches 77.23 % at 200 µg/mL.

Molecular frontier orbital energy analysis: According to the frontier molecular orbital theory, HOMO and LUMO are the most important factors that affect the bioactivity. HOMO has the priority to provide electrons, while LUMO can accept electrons firstly[21]. Thus study on the frontier orbital energy can provide useful information about the biological mechanism. Taking DFT result for example, the geometry of the frame of the title compound is hardly influenced by the introduction of either cycan group or cyclopropane ring (Fig. 3). The HOMO of the title compound is mainly located on the aromatic ring and amide group. While, the LUMO of the title compound is located on the aromatic ring, amide group, cycan group and cyclopropane ring. The fact that the title compound has strong affinity suggests the importance of the frontier molecular orbital in the π-π stacking or hydrophobic interactions. This also implies that the orbital interaction between the title compound and the aromatic ring or some other side of residue chains of *Escherichia coli* ketol-acid reductoisomerase receptors is dominated by π-π or hydrophobic interaction among the frontier molecular orbitals.



(a)

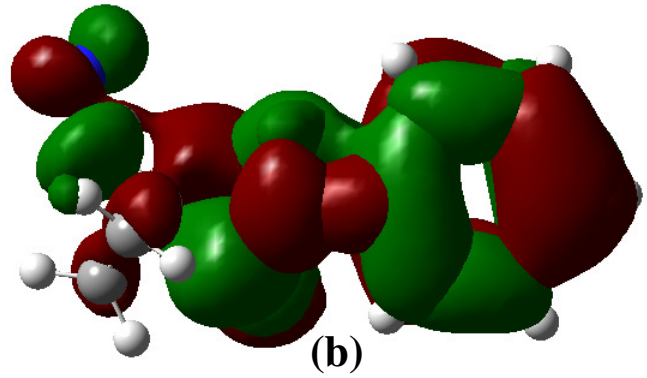


Fig. 3. Frontier molecular orbitals of title compound: (a) HOMO of the title compound; (b) LUMO of the title compound

Supplementary material

CCDC 814948 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/ retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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