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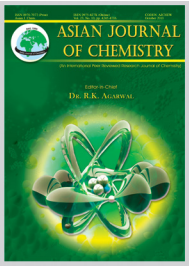

Synthesis, Crystal Structure and Biological Activity of 1-Cyano-*N*-(4-bromophenyl)cyclopropanecarboxamide

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A cyclopropane derivative, 1-cyano-*N*-(4-bromophenyl)cyclopropanecarboxamide ($C_{11}H_9N_2OBr$) was synthesized and its structure was studied by X-ray diffraction, FTIR, ^1H NMR spectrum and MS. The crystal is triclinic, space group P-1 with a = 8.902(4), b = 10.944(5), c = 12.733(6) Å, α = 103.753(8), β = 106.812(9), γ = 104.004(9)°, V = 1087.1(9) Å^3, Z = 4, F(000) = 528, D_c = 1.620 g/cm^3, the final R = 0.0604 and wR = 0.1197. A total of 5404 reflections were collected of which 3790 were independent (R_{int} = 0.0578). There are two intramolecular hydrogen bonds in the crystal lattice. The preliminary biological test showed that the synthesized compound had weak activity against the KARI of *Escherichia coli*.

Key Words: Synthesis, Crystal structure, Biological activity.

INTRODUCTION

Cyclopropane derivatives[1], as a kind of highly bioactive compounds, have been studied broadly for many years. The amide compounds exhibited broad biological spectrum, such as insecticidal activities[2], herbicidal activities[3], anti-HBV acitivities[4], antitumor activities[5], fungicidal activities[6], *etc*. Thus, the synthesis of broader spectrum and highly bioactive substituted cyclopropane compounds, especially aromatic and heterocycle substituted ones which are bioactive themselves, becomes the mainstream in the agriculture chemistry field.

In our search for compounds with biological activities, we have synthesized some aromatic substituted cyclopropane compounds and tested their herbicidal activity. Then, the single crystal of the title compound was determined. The preliminary biological test showed that the synthesized compound has a strong and slow binding activity to inhibit *Escherichia coli* KARI.

EXPERIMENTAL

Melting points determined by a Yanaco MP-241 apparatus and uncorrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as KBr tablets. ^1H 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.

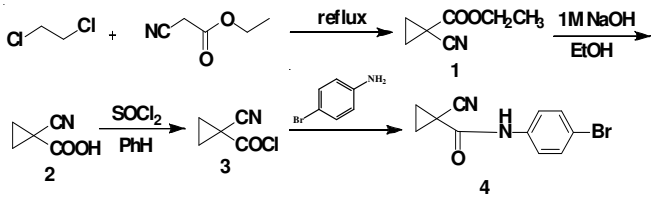
Crystal structure determination: The crystal of 1-cyano-*N*-(4-bromophenyl)cyclopropanecarboxamide with dimensions of 0.12 mm × 0.08 mm × 0.06 mm was mounted on a Bruker Smart 2000-detector diffractometer with a graphite-monochromated MoK_α radiation (λ = 0.71073 Å) by using a phi and scan modes at 294(2) K in the range of 2.03° ≤ θ ≤ 25.1°. The crystal belongs to triclinic system with space group P-1 and crystal parameters of a = 8.902(4) Å, b = 10.944(5) Å, c = 12.733(6) Å, α = 103.753(8)°, β = 106.812(9)°, γ = 104.004(9)°, V = 1087.1(9) A^3, D_c = 1.620 g/cm^3. The absorption coefficient μ = 3.755 mm^{-1} and Z = 4. The structure was solved by direct methods with SHELXS-97[7] 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 located in a difference map and refined freely. All C-H atoms were generated by riding model with C-H distance fixed at 0.93 (phenyl group), 0.97 (methylene group).

Synthesis: 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 ºC/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. Yields 51 %.

To a benzene solution (25 mL) of cyanocyclopropanecarboxylic acid (7.50 mmol) was added thionyl chloride (30 mmol) and the mixture was refluxed for 2 h to give acid chloride. Then add dropwise the acid chloride to 4-bromoaniline (7.50 mmol), then vigorously stirred at ambient temperature for 4 h (**Scheme-I**). The yield was 93.1 % with m.p. (117-119) ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.59-1.72 (m, 4H, CH_2), 7.15-7.39 (m, *J* = 8.784 Hz, 4H, ArH), 8.05 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}) : 3347, 3093, 2236, 1692, 1598, 1525, 1489, 814; ESI-MS: 264.98, 197.95, 116.02, 80.99. Elemental analysis: C, 49.80; H, 3.28; N, 10.58; calculated from $C_{12}H_9N_2OBr$. Observed: C, 49.84; H, 3.42; N, 10.57.



Scheme-I Synthesis route of the title compound

RESULTS AND DISCUSSION

The IR spectrum of the present compound shows absorption bands at 3347cm^{-1} originating from the stretching vibration of NH. The strong band at 2236 cm^{-1} can be assigned to the CN stretching vibration. The strong band at 1692 cm^{-1} can be assigned to the C=O strentching vibration. The absorption of the phenyl ring is at 1598, 1525, 1489 cm^{-1}. In the ^{1}H NMR spectra of title compounds, the NH proton signals of title compound were observed at 8.05 ppm as single peak. The CH proton of benzene ring was appeared around δ 7.30 ppm as two double peak, which indicated the symmetry of CH group. The title compounds of mass spectra are molecular ion peak.

Structure of the title compound: Crystallographic and refinement parameters are given in Table-1. Coordinates and equivalent atomic displacement parameters of the nonhydrogen atoms are listed in Table-2. The selected bond lengths and bond angles listed in Table-3. 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-4.

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

Items	Values
Empirical formula	$C_{11}H_9N_2OBr$
Formula weight	265.11
Crystal system	Triclinic
Unit cell dimensions	
a (Å)	8.902(4)
b (Å)	10.944(5)
c (Å)	12.733(6)
Unit cell angles (º)	
α	103.753(8)
β	106.812(9)
γ	104.004(9)
Volume ($Å^3$)	1087.1(9)
Z	4
Temperature (K)	294(2)
Space group	P-1
Wavelength (Å)	0.71073
Calculated density (g/cm^3)	1.620
Absorption coefficient (mm^{-1})	3.755
F(000)	520
Crystal size (mm)	0.30 × 0.26 × 0.20
Theta range for data collection (º)	2.03 – 25.01
Reflections collected	5404
Independent reflections	3797[$R_{(int)}$ = 0.0578]
Final R indices [I>2σ(I)]	R_1 = 0.0604, wR_2 = 0.1197

TABLE-2
ATOMIC COORDINATES (× 10^4) AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS ($A^2 \times 10^3$) FOR THE PRESENT COMPOUND

Atom	x	y	z	U (eq)
Br(1)	667(1)	8225(1)	14163(1)	80(1)
O(1)	2862(8)	10304(6)	9900(5)	81(2)
N(1)	770(8)	8405(6)	9454(6)	49(2)
N(2)	-930(10)	7052(7)	6364(6)	65(2)
C(1)	1716(11)	9494(8)	11568(8)	58(3)
C(2)	1699(11)	9447(9)	12642(8)	61(3)
C(3)	664(13)	8325(10)	12684(8)	58(3)
C(4)	-346(12)	7276(8)	11707(8)	65(3)
C(5)	-272(12)	7335(8)	10653(8)	65(3)
C(6)	777(10)	8441(8)	10570(7)	43(2)
C(7)	1782(12)	9286(9)	9184(8)	52(3)
C(8)	1615(11)	8974(8)	7943(8)	46(2)
C(9)	2297(11)	10158(8)	7591(7)	56(3)
C(10)	3266(11)	9247(8)	7710(8)	60(3)
C(11)	206(12)	7903(9)	7057(8)	53(3)

TABLE-3
SELECTED BOND LENGTHS [Å] AND BOND ANGLES [º] FOR THE PRESENT COMPOUND

Bond lengths	X-ray crystal	Bond angles	X-ray crystal
Br(1)-C(3)	1.910(9)	C(7)-N(1)-C(6)	127.6(7)
O(1)-C(7)	1.220(9)	C(6)-C(1)-C(2)	121.8(9)
N(1)-C(7)	1.333(10)	C(3)-C(2)-C(1)	118.3(8)
N(1)-C(6)	1.410(10)	C(4)-C(3)-C(2)	121.8(9)
N(2)-C(11)	1.143(10)	C(4)-C(3)-Br(1)	119.3(8)
C(1)-C(6)	1.365(10)	C(5)-C(6)-N(1)	117.4(8)
C(1)-C(2)	1.385(11)	O(1)-C(7)-N(1)	123.6(8)
C(7)-C(8)	1.489(11)	O(1)-C(7)-C(8)	118.7(9)
C(8)-C(11)	1.436(12)	N(1)-C(7)-C(8)	117.6(8)
C(9)-C(10)	1.475(10)	C(11)-C(8)-C(7)	120.1(8)

TABLE-4
HYDROGEN BONDS FOR PRESENT COMPOUND [Å AND DEG.]

D-H...A	d(D-H)	d(H...A)	d(D...A)	< (DHA)
N(1)-H(1)...N(4)#1	0.86	2.50	3.283(10)	152.4
N(3)-H(3)...N(2)#1	0.86	2.44	3.246(10)	156.8

Symmetry transformations used to generate equivalent atoms: #1 -x, -y+1, -z+1

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

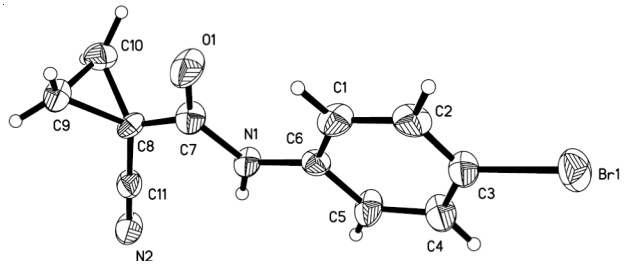


Fig. 1. Molecular Structure of the title compound

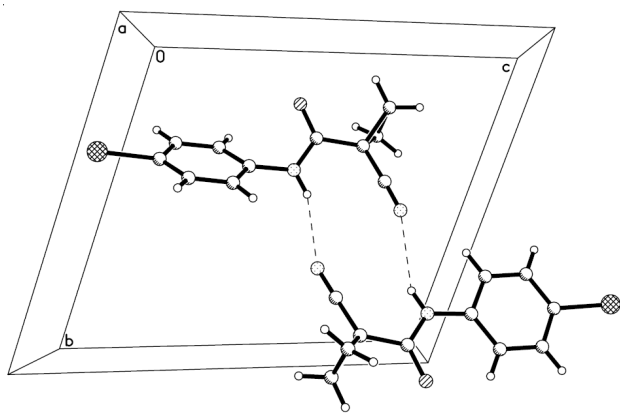


Fig. 2. Two-dimensional network of hydrogen bonds (dashed lines)

The X-ray analysis reveals that the benzene ring is planar. The carboxamide moiety is coplanar with the benzene ring [dihedral angle 8.6(14)]. The inter-atomic distance for C(18)-O(2) is 1.225(9), which shows it is a normal C=O double bond. The conformation of the N-H bond in the NH-C(O) segment of the structure is anti to the C=O bond, similar to that observed in 1-cyano-*N*-(*p*-tolyl)cyclopropanecarboxamide. As shown in Fig. 1. The X-ray analysis reveals that the structure has two independent molecules. The benzene ring is nearly vertical with cyclopropane ring. The angle of two ring is 92.8º. The amide bond is nearly coplanar with benzene ring [dihedral angle 3.0(14)]. X-ray analysis reveals that there are intermolecular hydrogen bonds N---H...N in the crystal lattice.

Biological activity: Gerwick *et al.*[8] reported that the inhibition of *E. coli* KARI is time-dependent. To characterise the steady-state inhibition constant, *Escherichia coli* KARI was preincubated for 10 min with NADPH, Mg^{2+} and the title compound, then the reaction was initiated with hydroxypyruvate. Under these conditions, the change in A_{340} was found to be linear with time. The primary bioassay shows the title compound exhibits a weak inhibiting activity towards KARI, which reaches 32.23 % at 200 μg/mL.

Supplementary material

CCDC-832173 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, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

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