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Synthesis, Structure and Biological Activities of 2,2-Dichloro-1-(4-ethoxyphenyl)-cyclopropanyl Substituted Piperidin-1-yl Ketone

NA-BO SUN*, JIAN-ZHONG JIN, CHAO LEI and WEI KE

College of Biology and Environmental Engineering, Zhejiang Shuren University, Hangzhou, 310015, P.R. China

*Corresponding author: E-mail: nabosun@gmail.com

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Ten new amide-type compounds, which are pyrethroids containing piperidine, are synthesized from 1-(4-ethyoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid and substituted piperidine. Their structures were confirmed by ^{1}H NMR, MS and elemental analysis. The crystal structure of **4a** and **4h** were determined by X-ray diffraction analysis. The bioassay results indicated that they showed moderate activity.

Key Words: Pyrethroid, Cycloprothrin, Piperidine, Synthesis, Structure.

INTRODUCTION

Cyclopropane derivatives, as a kind of highly bioactive compounds, have been studied broadly[1]. At the end of 1940s, cyclopropane compounds, such as pyrethroids, were marketed as low toxic insecticides. Since the first pyrethroids insecticide-Allethrin was found, a large variety of pyrethroids derivatives have been synthesized and lots of them, such as deltamethrin, cypermethrin, bifenthrin, fenvalerate, tefluthrin *etc.* are commercially available[2]. From then on, many biologically active and structurally stable cyclopropane compounds had been synthesized[3].

In recent years, synthesis of broader spectrum and highly bioactive substituted cyclopropane compounds, especially heterocycle substituted ones, becomes the main stream in the agriculture chemistry field. Also, from the structure-activity relationships of these pyrethroids, it is showed that the ester group was replaced by other functional groups, such as amide group from numerous reports. Due to the amide group exhibited the good biological activity, such as herbicidal activity, fungicidal activity, insecticide activity, *etc.*[4]. In line with our continuous efforts to synthesize bioactive lead compounds for crop protection, the title compounds were designed by introducing amide and piperidine pharmacophore into the cyclopropane scaffold and their biologicial activity tested. Then, the single crystal of the title compound was determined. The preliminary biological test showed that the synthesized compound has moderate fungicidal activity.

EXPERIMENTAL

Melting points were determined by an X-4 apparatus and uncorrected. ^{1}H NMR spectra were measured on a Bruker Avance 400 DMX instrument using TMS as an internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a HP 5989B mass detector instrument. Elemental analyses were performed on a Carlo erba EA1110 elemental analyzer. All the reagents are of analytical grade or freshly prepared before use.

To 1-(4-ethyoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (2.75 g, 10 mmol) was added thionyl chloride (20 mL) and the mixture was refluxed for 2 h to give acid chloride. To a mixture of compound **3** (8.8 mmol) and Et_3N (1.2 g,12 mmol) in CH_2Cl_2 (20 mL) was added 2. The mixture was stirred for 10-25 h. The corresponding amide precipitated immediately. The product was washed with HCl, dried and was purified by chromatography on silica gel using petroleum ether (60-90 ºC) and ethyl acetate as the eluent to afford the title compounds **4a-4j**.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl piperidin-1-yl ketone (4a). Colourless crystal; yield, 92 %; m.p., 121-123 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.41(t, J = 7.2 Hz, 3H, CH_3), 1.49-1.59 (m, 6H, piperdine H), 1.99 (d, J = 7.2 Hz, 1H, cyclopropane H), 2.35 (d, J = 7.2 Hz, 1H, cyclopropane H), 3.44-3.67 (m, 4H, piperdine H), 4.00-4.05 (m, 2H, CH_3CH_2O), 6.85-6.88 (m, 2H, Ph), 7.86-7.88 (m, 2H, Ph); Ms *m/z* (relative intensity/ %): 341([M-1]$^+$, 100), 306 (48), 277 (56), 222

(30), 193 (53), 165 (29), 131 (86), 112 (30), 97 (32), 84 (41); Anal. calcd. for $C_{17}H_{20}NO_2Cl_2$ (%): C 59.66, H 6.18, N 4.09, found: C 59.88, H 6.21, N 4.02.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 4-methylpiperidin-1-yl ketone (4b). Yellow crystal; yield, 64.6 %; m.p., 82-84; ^{1}H NMR ($CDCl_3$) δ: 0.83 (d, *J* = 7.2 Hz, 3H, CH_3), 1.40 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 1.48-1.63 (m, 5H, piperdine H), 1.99 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.53 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 3.57-3.70 (m, 4H, piperdine H), 4.01-4.05 (m, 2H, CH_3CH_2O), 6.80-6.82 (m, 2H, Ph), 7.85-7.87 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 355 ([M-1]$^+$, 100), 320 (63), 291 (60), 222 (76), 193 (81), 165 (29), 131 (35), 112 (44), 97 (63); Anal. calcd. for $C_{18}H_{23}NO_2Cl_2$(%): C 60.68, H 6.51, N 3.93, found: C 60.59, H 6.58, N 3.90.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 3-methylpiperidin-1-yl ketone (4c). Yellow crystal; yield, 60.5 %; m.p., 90-92 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.88 (d, *J* = 7.2 Hz, 3H, CH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 1.45-1.56 (m, 5H, piperdine H), 1.98 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.48 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 3.51-3.69 (m, 4H, piperdine H), 4.01-4.04 (m, 2H, CH_3CH_2O), 6.84-6.86 (m, 2H, Ph), 7.82-7.84 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 355 ([M-1]$^+$, 100), 320 (32), 291 (66), 222 (26), 193 (36), 165 (71), 131 (35), 112 (56), 97 (30), 84 (71); Anal. calcd. for $C_{18}H_{23}NO_2Cl_2$ (%): C 60.68, H 6.51, N 3.93, found: C 60.50, H 6.45, N 4.00.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 2-ethylpiperidin-1-yl ketone (4d). White crystal; yield, 93.5 %; m.p., 134-137 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, *J* = 7.2 Hz, 3H, CH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 1.50-1.63 (m, 8H, piperdine H and CH_2CH_3), 1.90 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.41 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 3.19-3.25 (m, 3H, piperdine H), 4.00-4.05 (m, 2H, CH_2O), 6.85-6.87 (m, 2H, Ph), 7.49-7.51 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 369 ([M-1]$^+$, 95), 340 (44), 220 (100), 195 (33), 162 (55), 140 (83), 131 (64), 84 (47); Anal. calcd. for $C_{19}H_{25}NO_2Cl_2$ (%): C 61.62, H 6.80, N 3.78, found: C 61.81, H 6.88, N 3.72.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 4-ethylpiperidin-1-yl ketone (4e). White crystal; yield, 86.4 %; mp, 125-128 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, *J* = 7.2 Hz, 3H, CH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 1.2-1.62 (m, 7H, piperdine H and CH_2CH_3), 1.90 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.41 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 3.19-3.25 (m, 4H, piperdine H), 4.01-4.05 (m, 2H, CH_3CH_2O), 6.84-6.86 (m, 2H, Ph), 7.45-7.47 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 369 ([M-1]$^+$, 93), 340 (30), 295 (34), 220 (100), 162 (69), 140 (68), 131 (87), 102 (28); Anal. calcd. for $C_{19}H_{25}NO_2Cl_2$ (%): C 61.62, H 6.80, N 3.78, found: C 61.75, H 6.86, N 3.73.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 2,6-dimethylpiperidin-1-yl ketone (4f). Colourless crystal; yield, 56.2 %; m.p., 124-127 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.11 (d, *J* = 7.2 Hz, 6H, CH_3), 1.41 (t, *J* = 6.8 Hz, 3H, CH_3CH_2O), 1.58-1.78 (m, 6H, piperidine H), 1.88 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.23-2.28 (m, 2H, piperidine H), 3.99-4.03 (m, 2H, CH_3CH_2O), 6.84-6.88 (m, 2H, Ph), 7.53-7.55 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 369 ([M-1]$^+$, 100), 258 (15), 234 (57), 222 (28), 195 (32), 165 (40), 140 (74), 131 (53), 112 (63), 97 (35); Anal. calcd. for $C_{19}H_{25}NO_2Cl_2$ (%): C 61.62, H 6.80, N 3.78; found: C 61.69, H 6.84, N 3.75.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 3,3-dimethylpiperidin-1-yl ketone (4g). White crystal; yield, 76.5; m.p. 110-112 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.72 (s, 6H, CH_3), 1.41 (t, *J* = 6.8 Hz, 3H, CH_3CH_2), 1.44-1.50 (m, 4H, piperidine H), 1.97 (d, *J* = 6.8 Hz, 1H, cyclopropane H), 2.40 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 3.10 (t, *J* = 8.4 Hz, 2H, piperidine H), 3.66 (s, 2H, piperidine H), 4.00-4.05 (m, 2H, CH_3CH_2O), 6.85-6.87 (m, 2H, Ph), 7.49-7.51 (m, 2H, Ph); Ms m/z (relative intensity/%): 369 ([M-1]$^+$, 100), 334 (30), 306 (21), 270 (26), 222 (30), 193 (17), 165 (29), 140 (63), 131 (38), 112 (35), 97 (14), 84 (33); Anal. calcd. for $C_{19}H_{25}NO_2Cl_2$ (%): C 61.62, H 6.80, N 3.78, found: C 61.58, H 6.83, N 3.77.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 2,3-dimethylpiperidin-1-yl ketone (4h). Colourless crystal; yield, 90.0 %; m.p., 159-161 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.85 (d, *J* = 6.8 Hz, 6H, CH_3), 1.41 (t, *J* = 6.8 Hz, 3H, CH_3CH_2O), 1.58-1.69 (m, 5H, piperidine H), 2.01 (d, *J* = 6.8 Hz, 1H, cyclopropane H), 2.32 (d, *J* = 6.8 Hz, 1H, cyclopropane H), 2.60-2.81 (m, 3H, piperidine H), 3.98-4.04 (m, 2H, CH_3CH_2O), 6.84-6.86 (m, 2H, Ph), 7.45-7.50 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 369 ([M-1]$^+$, 100), 334 (19), 306 (17), 270 (8), 222 (30), 195 (22), 165 (37), 140 (68), 131 (44), 112 (47), 98 (20), 84 (34); Anal. calcd. for $C_{19}H_{25}NO_2Cl_2$ (%): C 61.62, H 6.80, N 3.78; found: C 61.55, H 6.84, N 3.74.

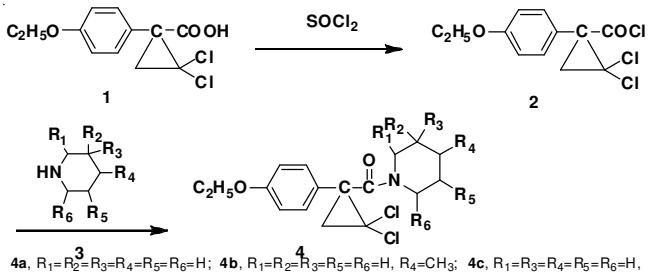
2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 3,5-dimethylpiperidin-1-yl ketone (4i). White crystal; yield, 64.8; m.p., 126-129 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.86 (d, *J* = 7.2 Hz, 6H, CH_3), 1.41 (t, *J* = 6.8 Hz, 3H, CH_3CH_2O), 1.61-1.69 (m, 4H, piperidine H), 1.91 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 1.91 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.51-2.67 (m, 3H, piperidine H), 3.99-4.07 (m, 2H, CH_3CH_2O), 6.85-6.87 (m, 2H, Ph), 7.42-7.49 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 369 ([M-1]$^+$, 100), 256 (95), 334 (33), 306 (29), 270 (36), 222 (36), 165 (37), 140 (67), 131 (46), 112 (39); Anal. calcd. for $C_{19}H_{25}NO_2Cl_2$ (%): C 61.62, H 6.80, N 3.78; found: C 61.66, H 6.85, N 3.72.

2,2-Dichloro-1-(4-ethoxyphenyl)cyclopropanyl 4-*tert*-butylpiperidin-1-yl ketone (4j). Yellow crystal; yield, 55.6 %; m.p., 113-115 ºC; ^{1}H NMR ($CDCl_3$) δ: 0.80 (s, 9H, CH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH_3), 1.60-1.73 (m, 5H, piperdine H), 1.99 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.35 (d, *J* = 7.2 Hz, 1H, cyclopropane H), 2.93-3.01 (m, 4H, piperdine H), 4.00-4.05 (m, 2H, CH_3CH_2O), 6.85-6.87 (m, 2H, Ph), 7.44-7.48 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 397([M-1]$^+$, 100), 362 (30), 334 (24), 298 (29), 222 (38), 168 (42), 131 (41), 102 (10); Anal. calcd. for $C_{21}H_{29}NO_2Cl_2$ (%): C 63.31, H 7.34, N 3.52, found: C 63.27, H 7.31, N 3.57.

Single crystal: The prism-shaped single crystal of the title compound was obtained by recrystallization from EtOH and CH_2Cl_2. The crystal with dimensions of 0.20 mm × 0.16 mm × 0.12 mm was mounted on a Bruker SMART 1000 CCD area-detector diffractometer[5] with a graphite-monochromated MoK_α radiation (λ = 0.71073Å) by using a Phi scan modes at 113 (2) K in the range of $2\theta \leq 55.0^o$. The calculations were performed with SIR97 program and the empirical absorption corrections were applied to all intensity data.

RESULTS AND DISCUSSION

The 1-(4-ethyoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid, prepared according the reference. Cyclopropanecarbonyl chloride was prepared from the cyclopropane dicarboxylic acid and $SOCl_2$, without isolation further reacted with substituted peridines at room temperature as shown in **Scheme-I**.



4a, $R_1=R_2=R_3=R_4=R_5=R_6=H$; **4b**, $R_1=R_2=R_3=R_5=R_6=H$, $R_4=CH_3$; **4c**, $R_1=R_3=R_4=R_5=R_6=H$, $R_2=CH_3$ **4d**, $R_2=R_3=R_4=R_5=R_6=H$, $R_1=CH_2CH_3$; **4e**, $R_1=R_2=R_3=R_5=R_6=H$, $R_4=CH_2CH_3$; **4f**, $R_2=R_3=R_4=R_5=H$, $R_1=R_6=CH_3$; **4g**, $R_1=R_4=R_5=R_6=H$, $R_2=R_3=CH_3$; **4h**, $R_3=R_4=R_5=R_6=H$, $R_1=R_2=CH_3$ **4i**, $R_1=R_3=R_4=R_6=H$, $R_2=R_5=CH_3$; **4j**, $R_1=R_2=R_3=R_5=R_6=H$, $R_4=C(CH_3)_3$

Scheme-I: Synthetic route of title compounds

Crystal structures of 4a: The crystal symmetry is monoclinic, space group $P2_1/n$, with a = 0.60819 (19) nm, b = 1.5592 (6) nm, c = 1.8000 (7) nm, α = 90º, β = 91.087 (14)º, γ = 90º, V = 1.7066 (10) nm^3, Z = 4,Dx = 1.332 Mg/m^3, μ = 0.39 mm^{-1}, R = 0.035, wR = 0.081. The single crystal of the title compounds was obtained and its structure is shown in Fig. 1. The torsion angles of C2-C1-C4-O1 and C3-C1-C4-O1 are 65.82 (17)º and 133.21 (14)º respectively. From the molecular structure, it can be seen that the piperidine ring is in the e-bond positions of chair conformation in the six membered ring.

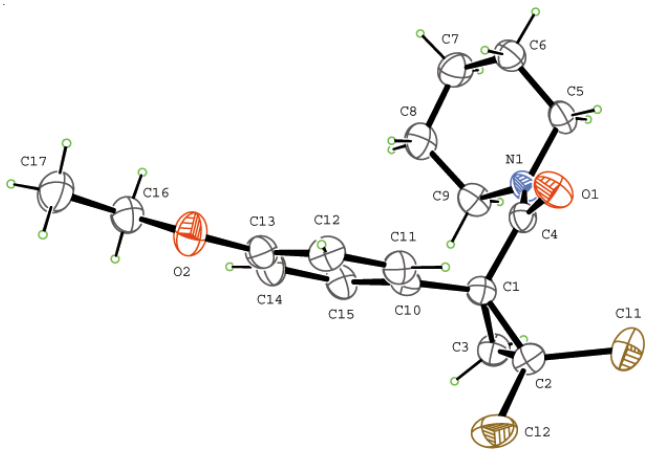


Fig. 1. Molecular structure of **4a**

Crystal structures of 4h: The crystal symmetry is monoclinic, space group $P2_1/n$, with a =1.1662 (5) nm, b = 1.6242 (8) nm, c = 1.1398 (5) nm, α = 90º, β = 115.078 (14)º, γ = 90º, V = 1.9553 (10) nm^3, Z = 4, Dx = 1.258 Mg/m^3, μ = 0.34 mm^{-1}, R = 0.034, wR = 0.085. The single crystal of the title compounds was obtained and its structure is shown in Fig. 2. The torsion angles of C2-C1-C4-O1 and C3-C1-C4-O1 are-125.0(2)º and -57.2(2)º respectively. From the molecular structure, it can be seen that the piperidine ring is in the e-bond positions of chair conformation in the six membered ring. The dihedral angle of cyclpopropane and phenyl is 55.68 (17)º. In addition, X-ray analysis reveals that there exist three intermolecular hydrogen bonds in the crystal. The intermolecular hydrogen bond lengths of C11-H···O1 is 3.322(2) Å.

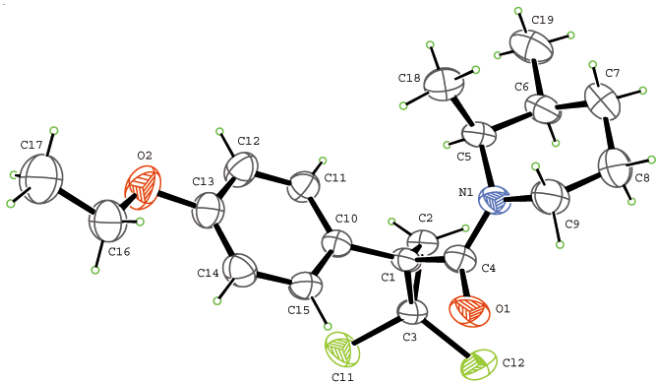


Fig. 2. Molecular structure of 4h

Fungicidal activity: The *in vivo* fungicidal results of all of the compounds against *Rhizoctonia solani, Pseudo-peronospora cubensis, Sphaerotheca fuliginea* and *Botrytis cinerea* were listed in Table-1. As shown in Table-1, all these compounds did not display obvious fungicidal activities against *Rhizoctonia solani, Pseudo- peronospora cubensis, Sphaerotheca fuliginea*. Among them, these compounds displayed the highest fungicidal activity against *Botrytis cinerea.* Compounds **4b**, **4c**, **4i** have fair to moderate fungicidal activity against *Botrytis cinerea*. at the concentration of 200 μg mL^{-1}.

TABLE-1
FUNGICIDAL ACTIVITIES OF 4 (INHIBITION/%)

Compd.	*Sphaerotheca fuliginea*	*Pseudo-peronospora cubensis*	*Botrytis cinerea*	*Rhizoctonia solani*
4a	0.00	0.00	17.25	0
4b	3.11	6.53	45.36	0
4c	0.00	7.58	59.85	0
4d	6.74	0.00	28.61	0
4e	8.79	3.21	30.80	0
4f	1.63	6.39	21.53	0
4g	0	0	0.00	0
4h	0	0	0.00	0
4i	0	0	43.66	0
4j	0	0	34.86	0

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