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Synthesis and bioactivity of *N*-cyclopropanecarboxyl-*N*′-pyridin-2-yl thiourea derivatives and related fused ring compounds

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Abstract

Cyclopropanecarboxylic acid or 2,2-dimethyl cyclopropanecarboxylic acid was used as a leading compound for its biological activity. Six new *N*-(substituted) cyclopropanecarboxyl-*N*′-pyridin-2-yl thioureas were prepared. Compound **5** was obtained by oxidizing cyclization of compound **4** in the presence of bromine in chloroform solution. The structures of **4** and **5** were confirmed by ^{1}H NMR and elemental analysis. The preliminary biological tests indicate that compound **4b** and **4e** have excellent herbicidal activity, and compound **4c** and **4f** have excellent fungicidal activity.

Keywords: Cyclopropanecarboxylic acid; Heterocycle; Thiourea; Biological activity; Pyridine

Cyclopropane derivatives have several biological activities. 2,2-Dichloro-3,3-dimethylcyclopropane-carboxylic acid is an effective inducer against the rice blast fungus [1,2]. 1-Aminocyclopropane-1-carboxylic acid (ACC) is an intermediate in the biosynthesis of the ripening hormone ethylene [3], a component of bacterial phytotoxines, and an intermediate in the biosynthesis of azetidine-2-carboxylic acid [4]. Thus it is very important to synthesize other new compounds containing cyclopropane and study their biological activities.

Acyl thiourea derivatives has many biological activities, for example, they have been used as bactericides, fungicides and insecticides in many plants [5,6]. A pyridine ring is often used as an active component in pesticide discovery [7]. The title compound **4** *N*-cyclopropanecarboxyl-*N*′-pyridin-2-yl thiourea contains all these three active parts and may show some biological activity. In the presence of bromine, six new compounds **5** *N*-(5,6,7,8-tetrahydro-[1,2,4]thiadiazolo[2,3-a]pyridin-2-ylidene)cyclopropanecarboxamide were obtained by oxidizing cyclization of compounds **4**. The structures of **4** and **5** were confirmed by ^{1}H NMR and elemental analysis.

The preliminary biological tests indicate that compound **4b** and **4e** have excellent herbicidal activity. Compound **4c** and **4f** have good fungicidal activity.

1. Experimental

Melting points were determined with a Thomas–Hoover melting point apparatus. ^{1}H NMR spectra were determined with a Bruker AC-P200 in $CDCl_3$ solution. Chemical shifts were reported in ppm(δ) downfield from Me_4Si. Elemental

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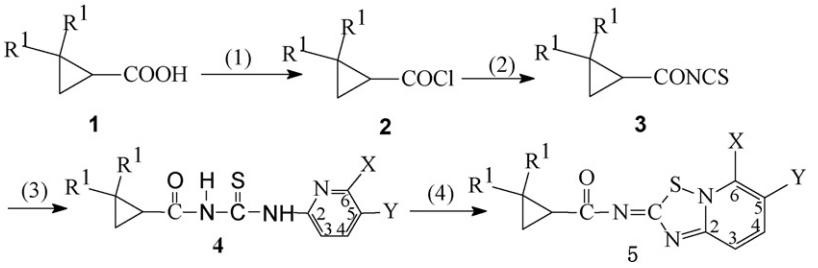

Scheme 1. Condition and regent: (1) $SOCl_2$, (2) NaSCN, (3) amino-pyridine, CH_3CN (4) Br_2. For compounds **4**(**a**–**f**) and **5**(**a**–**f**): (a) R^1 = H, X = H, Y = H; (b) R^1 = H, X = CH_3, Y = H; (c) R^1 = H, X = H, Y = Br, (d) R^1 = CH_3, X = H, Y = H; (e) R^1 = CH_3, X = CH_3, Y = H; (f) R^1 = CH_3, X = H, Y = Br.

analysis were performed on Yanaco Chn Cor Der MF-3 apparatus. All of the solvents were analytically pure. Cyclopropane carboxylic acid and 2,2-dimethyl cyclopropane were synthesized according to the references [8,9].

To a solution of cyclopropane carboxylic acid (or 2,2-dimethylcyclopropane carboxylic acid) (3 mL, 0.038 mol), was added $SOCl_2$ (0.068 mol, 5 mL) at 343 K in a dropwise way. Then it was reacted at 353 K for 2 h until no gas was given out. The excessive $SOCl_2$ was then removed by rotary distillation, the residue was subjected to distillation to give compound **2** (3.12 g, bp 118–119 °C), yield 79%. The reaction steps were shown in Scheme 1.

To a solution of NaSCN (0.5 g, 6 mmol) in dry CH_3CN (10 mL) was added compound **2** 0.36 mL (4.5 mmol) in dry CH_3CN (3 mL) dropwise. 30 min later, the solution was heated to refluxing and remined refluxing for 3 h. Then the solution was cooled to room temperature. After filtering, the solvent was removed by rotary distillation to give yellow solid **3**.

To the above product, was added substituted amino pyridine (5 mmol) and dry CH_3CN (10 mL). The mixture remained refluxing for 5–8 h. The reaction mixture was cooled in refrigerator overnight. Then the mixture was filtered, the resulting product was recrystallized to give compound **4a**.

Compounds **4b**–**f** were synthesized by the same method.

To a solution of compound **4** in $CHCl_3$ (5 mL), was added Br_2 (1 mmol) in $CHCl_3$ (5 mL) at 0 °C in a dropwise way. The mixture was stirred at room temperature for a few hours, then the solution was remained in the refrigerator overnight. The mixture was filtered, the resulting product was recrystallized (CH_3CN and $(CH_3)_2SO$) to give compounds **5a**–**f**.

The physical constant and ^1H NMR of compounds **4a**–**f** and **5a**–**f** are shown in Table 1 and Table 2 respectively.

2. Results and discussion

In the synthesis of cyclopropane carbonyl chloride, we found that the best ratio between $SOCl_2$:cyclopropane carbonic acid was 1.13–1.15. The reason is: (1) the molar ratio of the reaction is 1:1. In order to rise the conversion

Table 1
Physical and elemental analysis data of compounds **4** and **5**.

Products	mp (°C)	Yield (%)	Color	Elemental analysis (%) C H N
4a	198–199	74.5	White	54.44(54.29) 5.17(5.01) 18.72(18.99)
4b	144–145	71.3	White	56.38(56.15) 5.72(5.57) 17.99(17.86)
4c	141–142	66.8	White	40.28(40.01) 3.62(3.34) 14.24(14.00)
4d	92–93	73.4	White	57.62(57.81) 6.23(6.06) 16.66(16.85)
4e	138–139	67.9	White	43.92(43.91) 4.31(4.30) 12.81(12.80)
4f	232–233	75.6	Yellow	48.62(48.63) 5.97(5.99) 15.13(15.12)
5a	154–155	57.81	Yellow	54.52(54.79) 4.38(4.11) 19.01(19.18)
5b	161–162	62.4	Yellow	56.44(56.65) 4.53(4.72) 18.16(18.03)
5c	168–169	67.2	Yellow	44.35(44.17) 3.46(3.68) 12.69(12.88)
5d	158–159	57.2	Yellow	58.04(58.30) 5.43(5.26) 17.16(17.00)
5e	213–214	64.7	Yellow	59.65(59.74) 5.62(5.79) 15.96(16.08)
5f	216–233	73.5	Yellow	44.06 (44.18) 3.63(3.71) 12.66(12.88)