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Synthesis and Antifungal Activity of 2-Chloro-N-phenylbenzamide

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In the present study, 2-chloro-N-phenylbenzamide was synthesized by the ammonolysis of 2-chlorobenzoyl chloride. Its structure was confirmed by IR and ^{1}H NMR. Its antifungal activity against *Sclerotinia sclerotiorum* and *Botrytis cinerea* has been determined in the laboratory. The results showed that it had good antifungal activity against the two different pathogenic fungi of plants. Its median effective concentrations (EC_{50}) reached 6.4 and 28.3 mg L^{-1}, respectively.

Key Words: Antifungal activity, 2-Chloro-N-phenylbenzamide, Synthesis.

INTRODUCTION

Sclerotinia sclerotiorum is an important disease of cole[1]. For a long period, benzimidazole fungicides have been mostly used to control it. However, in recent years, it has developed resistance to them[2-6]. Moreover, its scope of resistance continues to expand and now has included many new fungicides[7-9]. Similarly, *Botrytis cinerea* is a pathogenic fungus of plants which has serious harm to vegetables and flowers. Over the past decades, synthetic fungicides including carbendazim have been used to control it. Nevertheless, the development of its resistance to all these fungicides has reduced the efficacy of fungicidal treatment[10-16]. Thus, new fungicides are continually necessary.

Chalcone (1,3-diphenylprop-2-en-1-one) is a natural compound existing in many plants and has certain antifungal activity[17-20]. Therefore, 2-chloro-N-phenylbenzamide was synthesized based on it. Meanwhile, its antifungal activity has been evaluated in the laboratory to find novel fungicides with high effect and low toxicity.

EXPERIMENTAL

Sclerotinia sclerotiorum and *Botrytis cinerea* were obtained from the Chinese Academy of Agricultural Sciences. They were preserved at 4 ºC. All chemicals and solvents were purchased from commercial sources unless specified otherwise. IR spectra were recorded on a Thermofisher Nicolet-6700 spectrophotometer. ^{1}H NMR spectra were taken on a Varian Unity Inova-400 instrument using deuteron-chloroform as the solvent.

Synthesis of target compound: 2-Chloro-N-phenylbenzamide was synthesized according to the reaction shown in Fig. 1. Benzenamine (0.02 mol) and pyridine (0.02 mol) were dissolved in CH_2Cl_2 (25 mL). The mixture was stirred and heated to 35-45 ºC. 2-Chlorobenzoyl chloride (0.02 mol) was added slowly to the mixture under stirring until the reaction was complete. The precipitate was filtered and washed with distilled water. The pure compound was obtained by recrystallization in anhydrous ethanol.

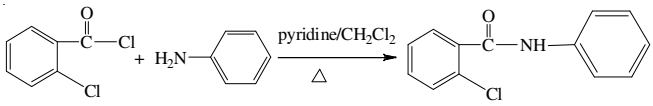

Fig. 1. Synthetic method of 2-chloro-N-phenylbenzamide

The synthesized compound (2-chloro-N-phenylbenzamide): Grey crystal, yield: 86.3 %, m.p. 114-116 ºC; IR (KBr, ν_{max}, cm^{-1}): 3239, 3042, 1641, 1600, 1548, 1489, 1444, 1330, 1050, 779, 761, 717, 692, 652, 588; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (s, 1H), 7.77 (dd, *J* = 1.6 Hz, 2.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.45 (s, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 2 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H).

Assay of antifungal activity: The antifungal activity of the synthesized compound against *Sclerotinia sclerotiorum* and *Botrytis cinerea* was determined using the plate growth rate method[21].

The synthesized compound and carbendazim (purity 90 %) were dissolved in dimethyl sulfoxide, respectively. The two solutions were diluted into five different concentrations with distilled water, respectively. They were added to the sterile culture medium (PDA) at 45 ºC, mixed to homogeneity and transferred to sterile petri dishes to solidify. A mycelium agar

TABLE-1
ANTIFUNGAL ACTIVITY OF 2-CHLORO-N-PHENYLBENZAMIDE AGAINST *Sclerotinia sclerotiorum*

	2-Chloro-N-phenylbenzamide					Carbendazim				
Concentration (mg L^{-1})	100	50	25	12.5	6.3	50	25	12.5	6.3	3.1
Inhibition of growth* (%)	92.6	84.4	75.4	60.5	51.8	94.1	85.5	74.9	61.1	49.5
Regressive equation (Y = aX + b)			Y = 1.1612X + 4.0624					Y = 1.2683X + 4.3132		
EC_{50} (mg L^{-1})			6.4					3.5		
(95 % CL)			(3.9-8.9)					(2.3-4.6)		
Correlative coefficient (r)			0.9555					0.9614		
χ^2			0.627					0.605		

*Based on the mean of triplicates.

TABLE-2
ANTIFUNGAL ACTIVITY OF 2-CHLORO-N-PHENYLBENZAMIDE AGAINST *Botrytis cinerea*

	2-Chloro-N-phenylbenzamide					Carbendazim				
Concentration (mg L^{-1})	100	50	25	12.5	6.3	100	50	25	12.5	6.3
Inhibition of growth* (%)	90.1	67.0	39.6	23.6	13.2	91.3	75.6	48.5	36.7	19.4
Regressive equation (Y = aX + b)			Y = 1.9763X + 2.1321					Y = 1.7924X + 2.6384		
EC_{50} (mg L^{-1})			28.3					20.8		
(95 % CL)			(24.4-32.8)					(17.6-24.3)		
Correlative coefficient (r)			0.9778					0.9647		
χ^2			4.295					3.092		

*Based on the mean of triplicates.

disc (5 mm in diameter) of the target fungi was placed in the center of PDA plates. They were incubated at 28 ºC in the dark until the target fungi used as the controls covered the surface of these plates. Control groups were treated with the corresponding solutions without the synthesized compound or carbendazim. The experiment for each concentration was replicated three times. The diameter of the fungi in the cultures was measured and the inhibition of growth was calculated according to the formula of Abbott. EC_{50} values were calculated with the Statistics Package for the Social Sciences (SPSS) based on probit analysis.

RESULTS AND DISCUSSION

Antifungal activity against *Sclerotinia sclerotiorum*: The synthesized compound was submitted to laboratorial bioassay compared with the efficient fungicide carbendazim. The results are presented in Table-1. It had good antifungal activity against *Sclerotinia sclerotiorum*. Its EC_{50} value was 6.4 mg L^{-1}. The results of regressive and correlative analysis indicated that the correlation was significant between concentration and efficacy. Its correlative coefficient was 0.9555. Chi square test demonstrated that the results were reliable (χ^2 = 0.627, df = 3, $p > 0.05$).

Antifungal activity against *Botrytis cinerea*: As shown in Table-2, the synthesized compound was subjected to laboratorial bioassay using the efficient fungicide carbendazim as the comparative standard. Its EC_{50} value reached 28.3 mg L^{-1}. The results of regressive and correlative analysis revealed that the correlation was very significant between concentration and efficacy. The correlative coefficient was 0.9778. As for the results of *Sclerotinia sclerotiorum*, chi square test also showed that the results were reliable (χ^2 = 4.295, df = 3, $p > 0.05$).

The target compound (2-chloro-N-phenylbenzamide) has been successfully synthesized by means of the ammonolysis of 2-chlorobenzoyl chloride and its structure has also been confirmed with the aid of IR and ^{1}H NMR.

The results of laboratory bioassay have clearly demonstrated the antifungal activity of 2-chloro-N-phenylbenzamide against *Sclerotinia sclerotiorum* and *Botrytis cinerea*. Although its antifungal activity was inferior to the comparative standard, its structure is simple and its chemical synthesis is easy. Therefore, on the basis of it, more derivatives may be further synthesized to survey quantitative structure-activity relationships and find novel fungicides with high effect and low toxicity as well as safety to non-target organisms. Meanwhile, these results suggested that the design and synthesis of the compound may be conducive to the antifungal activity of analogues of chalcone. The compound is also promising in the agricultural chemistry field because its antifungal activity against the two different pathogenic fungi of plants was close to the efficient fungicide carbendazim.

However, in order to realize the industrialization of the compound as a fungicide there is large amounts of research work to be done. Its antifungal spectrum needs to be determined. Its mode of action and its safety to humans and non-target organisms also needed for further investigation.

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