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Design, Synthesis and Antifungal Activity of Novel Benzoylcarbamates Bearing a Pyridine Moiety

Fu-Xian Wan [1], Jian-Hua Wang [2], Yan-Hua Shi [1], Li-Zhi Niu [1] and Lin Jiang [1,*]

[1] College of Chemistry and Material Science, Shandong Agricultural University, Tai'an 271018, China; wfx@sdau.edu.cn (F.-X.W.); syh1234hz@163.com (Y.-H.S.); null1ee27@163.com (L.-Z.N.)
[2] College of Agronomy, Shandong Agricultural University, Tai'an 271018, China; jhwangjh@163.com
* Correspondence: jiangl@sdau.edu.cn; Tel.: +86-0538-8249248

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Abstract: Many natural and synthetic pyridine derivatives have good biological activity, and are widely used in the fields of pesticides and medicines. On the other hand, carbamate fungicides possess some unique properties, such as high efficiency, strong selectivity, low toxicity, and environmental friendliness, and are often used to control many plant diseases. Therefore, discovering novel pyridine-based carbamates is of great significance. In this paper, we chose the excellent fungicides tolprocarb and picarbutrazox as lead compounds, integrating benzoyl, carbamate, and pyridinyl moieties into a molecule. Thus, we designed and synthesized a series of substituted benzoyl carbamates containing a pyridine ring, and evaluated the in vitro antifungal activity. The target compounds exhibited moderate to strong bioactivity against *Botrytis cinerea*, among which the compounds **4d**, **4f**, **4g**, and **4h** exhibited significant activity with EC_{50} values (the concentration resulting in a 50% inhibition) of 6.45–6.98 μg/mL, and their activities were near or superior to that of chlorothalonil. Additionally, **4h** exhibited moderate activity against *Sclerotinia sclerotiorum* with an EC_{50} value of 10.85 μg/mL.

Keywords: pyridine; benzoyl; carbamate; synthesis; bioactivity; antifungal activity

1. Introduction

Sclerotinia sclerotiorum and *Botrytis cinerea* are two common plant pathogenic fungi that greatly influence the yield and quality of fruits and vegetables. The effective method for controlling such fungi is to employ chemical fungicides such as carbendazim, thiophanate-methyl, boscalid, and tebuconazole [1,2]. However, the unreasonable use of fungicides has resulted in serious resistances in recent years. Therefore, developing novel and effective antifungal agents is critical to the control of plant diseases.

Pyridine derivatives are important nitrogen-based heterocyclic compounds and are widely distributed in nature, e.g., nicotine, anabasine, pyridoxine, nicotinic acid, and nicotinamide. Many natural and synthetic pyridine derivatives show broad biological activity, including antifungal [3], anticancer [4], antivirus [5], anti-inflammatory [6], antitubercular [7], insecticidal [8], and herbicidal [9] activities. Additionally, pyridine is the bioisotere of benzene, but its electron density and hydrophobic constant are lower than those of benzene, thus pyridine derivatives often have high bioactivity and a notable systemic character [10]. Therefore, pyridine derivatives often serve as medicines and pesticides. Recently, two novel pyridine-based carbamate fungicides, picarbutrazox and pyribencarb, were respectively developed by Nippon Soda Co., Ltd. and Kumiai Chemical Industry Co., Ltd. [11,12]. In addition, diethofencarb, tolprocarb, and benthiavalicarb-isopropyl are also carbamate fungicides [13–15]. These carbamate fungicides possess some unique properties such as strong selectivity, low toxicity, and environmental friendliness, and are commonly used to control many

plant diseases, e.g., *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Plasmopara viticola*, and *Phytophthora capsici*. On the other hand, some benzoyl carbamates exhibit high antifungal activity. For example, Li et al. designed and synthesized a series of aryl carbamic acid-5-aryl-2-furanmethyl esters [16], and three of them displayed notable antifungal activity against four fungi; the morphologic results suggested that the compound can disturb the cell wall formation of fungi.

Inspired by the above findings, and based on our previous studies on the synthesis and bioactivity of pyridine-based compounds [17,18], we herein chose tolprocarb and picarbutrazox as lead compounds, integrated benzoyl, carbamate, and pyridinyl moieties into one molecule by the method of active substructure combination, and designed and synthesized ten substituted benzoyl carbamates containing a pyridine ring. In the target molecule, benzoyl is directly linked to the carbamate moiety, whereas pyridinyl is linked to the carbamate via two carbon atoms, which can enhance the flexibility of the molecule. Thus, the affinity between the target molecule and fungus might be increased [19]. Moreover, we also evaluated their antifungal activity against *Sclerotinia sclerotiorum* and *Botrytis cinerea*. Figure 1 shows the design strategy of the target compounds.

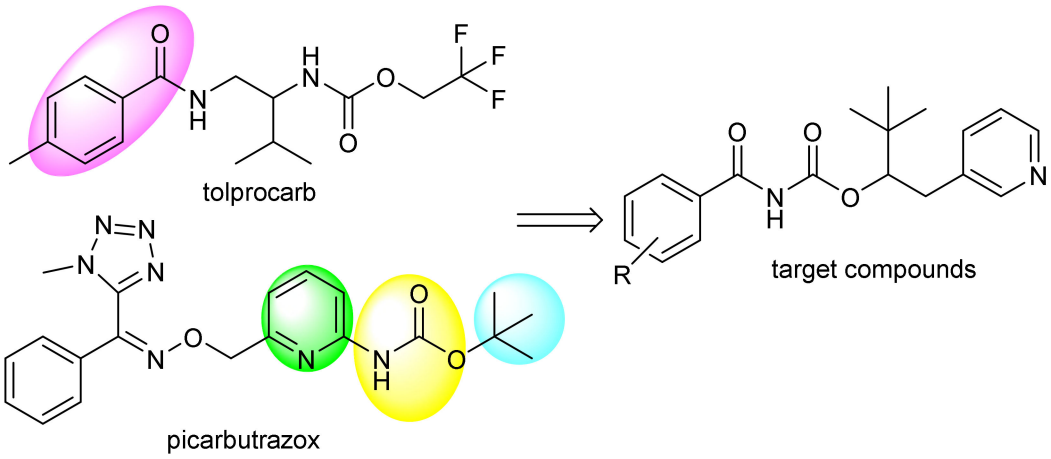


Figure 1. Rational design of novel benzoylcarbamates.

2. Materials and Methods

2.1. Synthesis

Melting points were measured on an X-4 melting point apparatus (Beijing Tech Instrument Co., China). ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AM-400 spectrometer (Bruker Co., Switzerland) with tetramethylsilane as an internal standard (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz). IR spectra were performed on a Nicolet 380 infrared spectrophotometer (Nicolet Co., America) using potassium bromide pellets. Elemental analyses were carried out with an Elementary Vario EL III analyzer (Elementar Co., Germany).

All reagents and solvents were commercially available; 1,2-dichloroethane and tetrahydrofuran were dried and redistilled before use.

2.1.1. Synthesis of 3,3-Dimethyl-1-(pyridin-3-yl)butan-2-one (**1**)

The 3,3-Dimethyl-1-(pyridin-3-yl)butan-2-one (**1**) was prepared as a pale yellow oil (yield 83%) according to a previous method [20].

2.1.2. Synthesis of 3,3-Dimethyl-1-(pyridin-3-yl)butan-2-ol (**2**)

To a solution of 3,3-Dimethyl-1-(pyridin-3-yl)butan-2-one (1.77 g, 10 mmol) in methanol (10 mL), sodium borohydride (0.74 g, 20 mmol) was added in portions under stirring conditions at 0 °C. The resulting suspension was stirred constantly for 2 h at the same temperature. Then, water (5 mL)

was added for extraction with ethyl acetate (3 × 10 mL). The combined organic phase was dried over sodium sulphate and the solvent was removed to yield a white solid, which was purified by silica gel chromatography with ethyl acetate/petroleum ether (*V*:*V* = 1:3) as eluent to generate intermediate **2** (1.52 g). Yield 85%, m.p. 113–114°C. ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9H, $C(CH_3)_3$), 2.46–2.54 (m, 1H, CH_2), 2.87 (d, *J* = 14 Hz, 1H, CH_2), 3.40 (d, *J* = 10 Hz, 1H, CH), 4.85 (bs, 1H, OH), 7.20–8.43 (m, 4H, Py-H). IR (KBr)v_{max} 3350 (O–H), 2961(C–H), 1386 and 1365 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81; found: C 73.92, H 9.25, N 7.58%.

2.1.3. General Procedure for the Synthesis of Substituted Benzoyl Isocyanate (**3**)

A solution of appropriate substituted benzamide (10 mmol) in anhydrous1,2-Dichoroethane (6 mL) was cooled to 0 °C, and oxalyl dichloride (2.05 g, 16 mmol) was slowly added under stirring. The reaction proceeded under stirring at room temperature for 1 h, followed by refluxing for 3–4 h. The solvent was distilled off under vacuum, to yield corresponding benzoyl isocyanate [21,22]. Crude isocyanates were directly used for the next reaction.

2.1.4. General Procedure for the Synthesis of Substituted Benzoylcarbamates (**4a**–**4j**)

To a mixture of benzoyl isocyanate freshly prepared as above (9 mmol) in dry tetrahydrofuran (12 mL), a solution of 3,3-Dimethyl-1-(pyridin-3-yl)butan-2-ol (1.62 g, 9 mmol) in dry tetrahydrofuran (20 mL) was slowly added under stirring. After stirring at room temperature for 3 h, the solvent was evaporated to yield a crude product. Further purification was performed by silica gel chromatography with ethyl acetate/petroleum ether (*V*:*V* = 1:2) as eluent, and target compounds were obtained as white solids.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl benzoylcarbamate (4a). Yield 82%, m.p. 153–154°C. ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$), 2.78–2.84 (m, 1H, CH_2), 2.98 (d, *J* = 14.0 Hz, 1H, CH_2), 5.01 (q, *J* = 8.0 Hz, 1H, CH), 7.19–7.72 (m, 7H, Ar-H), 8.38 (bs, 1H, NH), 8.45 (s, 2H, Py-H). ^{13}C NMR ($CDCl_3$) δ 165.50, 151.35, 150.36, 147.77, 136.72, 133.67, 133.28, 132.69, 128.61, 127.82, 123.48, 83.02, 35.04, 33.35, 25.96. IR (KBr)v_{max} 3285 (N–H), 1753 (C=O of carbamate), 1683 (C=O of benzoyl), 1397 and 1371 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{19}H_{22}N_2O_3$: C 69.92, H 6.79, N 8.58; found: C 69.65, H 6.54, N 8.72%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (2-methylbenzoyl)carbamate (4b). Yield 87%, m.p. 157–158°C. ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H, $C(CH_3)_3$), 2.31 (s, 3H, CH_3), 2.72–2.79 (m, 1H, CH_2), 2.97 (dd, *J* = 2.4, 11.6 Hz, 1H, CH_2), 4.98 (q, *J* = 8.4 Hz, 1H, CH), 7.18–7.61 (m, 6H, Ar-H), 8.17 (bs, 1H, NH), 8.31 (s, 1H, Py-H), 8.43 (s, 1H, Py-H). ^{13}C NMR ($CDCl_3$) δ 168.26, 150.83, 150.22, 147.65, 136.74, 136.29, 134.72, 133.42, 130.99, 126.91, 125.71, 123.58, 82.38, 35.02, 33.23, 25.95, 19.98. IR (KBr)v_{max} 3285 (N–H), 1770 (C=O of carbamate), 1700 (C=O of benzoyl), 1395 and 1365 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23; found: C 70.75, H 7.04, N 8.12%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (3-methylbenzoyl)carbamate (4c). Yield 84%, m.p. 147–148°C. ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$), 2.38 (s, 3H, CH_3), 2.78–2.84 (m, 1H, CH_2), 2.98 (dd, *J* = 2.4, 12.0 Hz, 1H, CH_2), 5.01 (q, *J* = 8.0 Hz, 1H, CH), 7.19–7.64 (m, 6H, Ar-H), 8.31 (bs, 1H, NH), 8.39 (d, *J* = 4.8 Hz, 1H, Py-H), 8.45 (d, *J* = 1.6 Hz, 1H, Py-H). ^{13}C NMR ($CDCl_3$) δ 164.93, 151.34, 150.77, 148.19, 143.87, 136.79, 130.45, 129.61, 127.93, 123.65, 83.47, 35.28, 33.61, 26.19, 21.75. IR (KBr)v_{max} 3273 (N–H), 1757 (C=O of carbamate), 1679 (C=O of benzoyl), 1396 and 1365 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23; found: C 70.81, H 7.14, N 8.06%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (4-methylbenzoyl)carbamate (4d). Yield 82%, m.p. 151–153°C. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, $C(CH_3)_3$), 2.40 (s, 3H, CH_3), 2.78–2.84 (m, 1H, CH_2), 2.98 (dd, *J* = 2.4, 12.0 Hz, 1H, CH_2), 5.00 (q, *J* = 8.0 Hz, 1H, CH), 7.22–7.62(m, 6H, Ar-H), 8.11 (bs, 1H, NH), 8.42–8.46 (m, 2H, Py-H). ^{13}C NMR ($CDCl_3$) δ 164.75, 151.16, 150.59, 148.01, 143.69, 136.61, 130.27, 129.43, 127.75, 123.47, 83.29, 35.10, 33.43, 26.01, 21.57. IR (KBr)v_{max} 3280 (N–H), 1740 (C=O of carbamate), 1678 (C=O of benzoyl), 1396 and 1368 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23; found: C 70.24, H 7.35, N 8.29%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (2-methoxybenzoyl)carbamate (4e). Yield 80%; m.p. 98.9–99.4°C. ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$), 2.78–2.84 (m, 1H, CH_2), 2.99 (dd, J = 2.8, 11.6 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 5.01 (q, J = 8.0 Hz, 1H, CH), 7.09–7.63 (m, 6H, Ar-H), 7.90 (bs, 1H, NH), 8.43–8.48 (m, 2H, Py-H). ^{13}C NMR ($CDCl_3$) δ 164.69, 151.07, 150.49, 147.95, 136.64, 134.92, 133.56, 129.74, 123.45, 123.25, 119.39, 119.16, 112.89, 83.29, 55.48, 35.06, 33.35, 25.97. IR (KBr)v_{max} 3307(N–H), 1770 (C=O of carbamate), 1697 (C=O of benzoyl), 1394 and 1363 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{20}H_{24}N_2O_4$: C 67.40, H 6.79, N 7.86; found: C 67.65, H 6.86, N 7.54%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (2-chlorobenzoyl)carbamate (4f). Yield 87%, m.p. 119–120 °C. ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H, $C(CH_3)_3$), 2.72–2.78 (m, 1H, CH_2), 2.96 (dd, J = 2.4, 12.0 Hz, 1H, CH_2), 4.95 (q, J = 8.4 Hz, 1H, CH), 7.19–7.59 (m, 6H, Ar-H), 8.29 (s, 1H, Py-H), 8.42 (s, 1H, Py-H) 8.75 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 166.32, 150.61, 150.19, 147.58, 136.73, 134.59, 133.41, 131.57, 130.54, 129.78, 129.20, 126.91, 123.54, 82.91, 35.01, 33.25, 25.90. IR (KBr)v_{max} 3225(N–H), 1759 (C=O of carbamate), 1683 (C=O of benzoyl), 1395 and 1365 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{19}H_{21}ClN_2O_3$: C 63.24, H 5.87, N 7.76; found: C 62.94, H 5.71, N 7.98%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (3-chlorobenzoyl)carbamate (4g). Yield 84%, m.p. 117–118°C. ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H, $C(CH_3)_3$), 2.71–2.77 (m, 1H, CH_2), 2.96 (dd, J = 2.4, 11.6 Hz, 1H, CH_2), 4.93 (q, J = 8.4 Hz, 1H, CH), 6.86–7.57 (m, 6H, Ar-H), 8.32 (s, 1H, Py-H), 8.41 (s, 1H, Py-H), 9.40 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 164.38, 151.39, 150.34, 147.76, 136.78, 134.99, 134.72, 133.63, 132.62, 129.87, 128.11, 125.99, 123.47, 83.41, 35.02, 33.34, 25.93. IR (KBr)v_{max} 3265(N–H), 1748 (C=O of carbamate), 1683 (C=O of benzoyl), 1395 and 1366 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{19}H_{21}ClN_2O_3$: C 63.24, H 5.87, N 7.76; found: C 63.10, H 5.96, N 7.88%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (4-chlorobenzoyl)carbamate (4h). Yield 82%, m.p. 129–131°C. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, $C(CH_3)_3$), 2.77–2.83 (m, 1H, CH_2), 2.98 (d, J = 14.4 Hz, 1H, CH_2), 4.99 (q, J = 8.4 Hz, 1H, CH), 7.21–7.64 (m, 6H, Ar-H), 8.41–8.44 (m, 2H, Py-H), 8.77 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 164.82, 151.44, 150.36, 147.75, 139.11, 136.85, 133.70, 131.57, 129.38, 128.85, 123.52, 83.32, 35.02, 33.36, 25.94. IR (KBr)v_{max} 3369 (N–H), 1776 (C=O of carbamate), 1689 (C=O of benzoyl), 1390 and 1367 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{19}H_{21}ClN_2O_3$: C 63.24, H 5.87, N 7.76; found: C 63.65, H 5.83, N 7.98%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (2-bromobenzoyl)carbamate (4i). Yield 84%; m.p. 114–115°C. ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H, $C(CH_3)_3$), 2.72–2.79 (m, 1H, CH_2), 2.97 (d, J = 13.6 Hz, 1H, CH_2), 4.98 (q, J = 8.4 Hz, 1H, CH), 7.17–7.60 (m, 6H, Ar-H), 8.42 (s, 1H, Py-H), 9.35 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 150.45, 150.37, 147.89, 136.77, 136.62, 133.35, 132.97, 131.64, 128.96, 127.43, 123.31, 118.86, 83.23, 35.03, 33.29, 25.93. IR (KBr)v_{max} 3260 (N–H), 1769 (C=O of carbamate), 1702 (C=O of benzoyl), 1394 and 1363 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{19}H_{21}BrN_2O_3$: C 56.31, H 5.22, N 6.91; found: C 56.68, H 5.20, N 7.14%.

3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl (4-bromobenzoyl)carbamate (4j). Yield 87%, m.p. 132–134°C. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, $C(CH_3)_3$), 2.77–2.83 (m, 1H, CH_2), 2.98 (dd, J = 2.4, 12.0 Hz, 1H, CH_2), 4.99 (q, J = 8.4 Hz, 1H, CH), 7.21–7.63 (m, 6H, Ar-H), 8.39 (bs, NH), 8.43 (s, 2H, Py-H). ^{13}C NMR ($CDCl_3$) δ 164.76, 151.24, 150.44, 147.86, 136.77, 133.63, 132.02, 131.90, 129.42, 127.71, 123.50, 83.44, 35.03, 33.89, 25.96. IR (KBr)v_{max} 3230 (N–H), 1770 (C=O of carbamate), 1690 (C=O of benzoyl), 1393 and 1365 (C–H of *t*-butyl) cm^{-1}. Analysis calculated for $C_{19}H_{21}BrN_2O_3$: C 56.31, H 5.22, N 6.91; found: C 56.12, H 5.26, N 6.98%.

2.2. Biological Assay

The in vitro fungicidal activity of compounds **4a**–**4j** against *Sclerotinia sclerotiorum* and *Botrytis cinerea* were measured by the mycelium growth rate method [23]. On the basis of pre-test results, PDA (potato glucose agar) cultures containing five concentrations (5, 10, 25, 50, and 100 μg/mL) of tested compound were prepared, and then inoculated with 5 mm plugs of the tested fungus. These cultures were incubated at 25 ± 1 °C, and the incubation times were 48 h for *S. sclerotiorum*, and 72 h for *B. cinerea*. Moreover, three fungicides, diethofencarb, carbendazim, and chlorothalonil, were provided as

the positive controls, and sterile water was treated as the blank control. The bioassay was performed three times. The inhibition rate was calculated by the following formula. Lastly, the EC_{50} value (the concentration resulting in a 50% inhibition) was obtained by DPS Software (Table 1).

$$\text{Inhibition rate} = \frac{D_0 - D_1}{D_0} \times 100\% \quad (1)$$

Table 1. Antifungal activities of compounds **4a–4j** (EC_{50}).

Compd.	R	EC_{50} (μg/mL), 95% CL	
		S. sclerotiorum	*B. cinerea*
4a	H	12.67 (8.98–17.89)	13.03 (12.02–14.11)
4b	2-CH_3	14.96 (10.42–19.48)	10.50 (8.49–14.03)
4c	3-CH_3	15.89 (13.19–19.40)	8.04 (6.54–11.68)
4d	4-CH_3	13.18 (9.06–18.21)	6.70 (4.03–11.02)
4e	2-OCH_3	14.06 (10.82–19.74)	7.84 (5.50–10.90)
4f	2-Cl	11.84 (8.04–17.90)	6.98 (6.24–7.79)
4g	3-Cl	12.41 (8.19–18.80)	6.81 (5.39–9.60)
4h	4-Cl	10.85 (6.57–17.92)	6.45 (5.44–7.65)
4i	2-Br	12.98 (9.26–16.64)	9.80 (6.48–13.16)
4j	4-Br	11.25 (7.40–17.78)	7.95 (5.21–12.15)
Diethofencarb		2.95 (1.24–5.08)	4.72 (2.49–7.15)
Chlorothalonil		9.97 (7.51–13.22)	6.56 (4.95–9.70)
Carbendazim		0.24 (0.20–0.28)	19.20 (13.27–27.89)

EC_{50}: Concentration resulting in a 50% inhibition; 95% CL: 95% confidence interval of EC_{50}.

In which D_0 is the expansion diameter of the mycelia in the blank test, and D_1 is that in the presence of the tested compound.

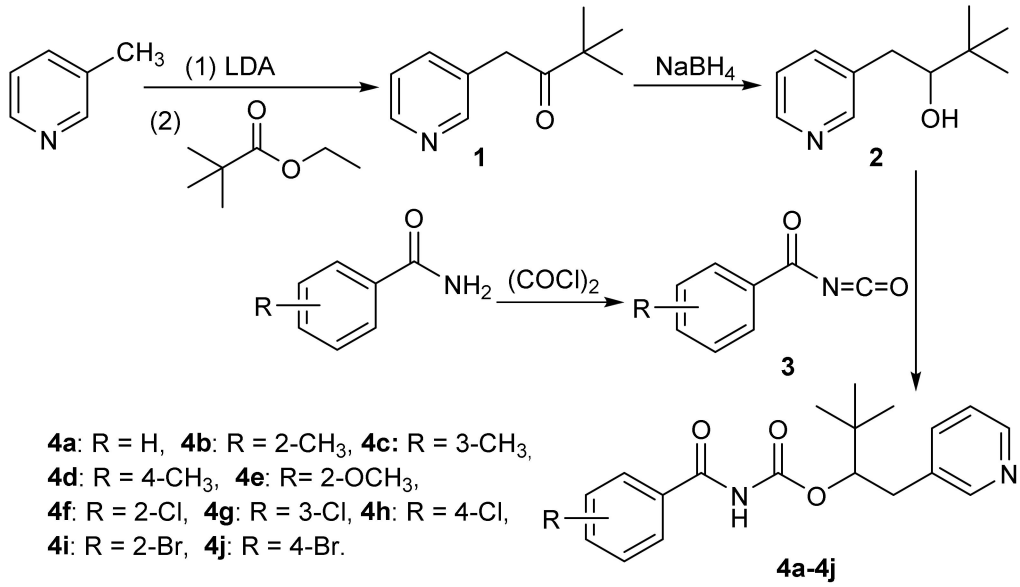
3. Results and Discussion

3.1. Chemistry

Target compounds **4a–4j** were synthesized according to the method depicted in Scheme 1. The starting material, 3-methylpyridine lost a proton under the catalysis of lithium diisopropylamide (LDA) and gave 3-pyridylmethyl lithium, followed by the treatment with ethyl 3,3-dimethylpropionate to yield 3,3-Dimethyl-1-(pyridin-3-yl) butan-2-one (**1**). Then, **1** was reduced by sodium borohydride to provide the key intermediate 3,3-dimethyl-1-(pyridin-3-yl)butan-2-ol (**2**). Finally, **2** reacted with freshly prepared substituted benzoyl isocyanate (**3**) in anhydrous tetrahydrofuran to yield the substituted benzoylcarbamate (**4**).

Target compounds were identified by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. In ^{1}H NMR spectra, the singlet of methyl protons of *t*-butyl moiety was observed at δ 1.02–1.07 ppm. The methine proton can form an ABX system with its two neighboring methylene protons, thus its signal was split into a quartet around δ 5.0 ppm, while the signals of methylene protons were split into two groups of multiplet near δ 2.80 and 2.98 ppm, respectively. A broad peak in the range of δ 7.90 to 9.40 ppm was ascribed to the presence of the NH proton. The signals of protons of pyridinyl and benzyl rings appeared in the range of δ 6.86–8.45 ppm. In ^{13}C NMR spectra, the signal for the carbonyl carbon of benzoyl was observed at δ 164.38 to 166.32 ppm, whereas that of carbamate occurred at around δ 151.00 ppm. The peak at δ 82.91–83.47 ppm corresponded to the methine carbon, whereas the peak near δ 35.00 ppm corresponded to the methylene carbon. The signal of the methyl carbon of *t*-butyl was observed at δ 25.90–26.19 ppm. In their IR spectra, the absorption peak around 3250 cm^{-1} could be assigned to the N–H stretching vibration; the strong absorption peaks of carbamate and benzoyl

C=O were observed at 1740–1776 cm^{-1} and 1679–1702 cm^{-1}, respectively. The bending vibration of *tert*-butyl displayed two peaks near 1390 and 1365 cm^{-1} [24].



Scheme 1. Synthetic route for target compounds **4a**–**4j.**

3.2. Antifungal Activity

The in vivo antifungal activities of target compounds against *S. sclerotiorum* and *B. cinerea* are summarized in Table 1. Compounds **4a**–**4j** demonstrated moderate antifungal activities against *S. sclerotiorum*, with EC_{50}values of 10.85–15.89 μg/mL. Comparing their EC_{50}values with diethofencarb (2.95 μg/mL), chlorothalonil (9.97 μg/mL), and carbendazim (0.24 μg/mL),it might be found that their activity was lower than those of the controls. On the other hand, the synthesized compounds displayed moderate to strong antifungal activities toward *B. cinerea*, the EC_{50}values of which were in the range of 6.45–13.03 μg/mL. Interestingly, compounds **4d**, **4f**, **4g**, and **4h** elicited significant activities with EC_{50} values of 6.45–6.98 μg/mL, indicating that their activities were near or superior to that of chlorothalonil (EC_{50}, 6.56 μg/mL), and much higher than that of carbendazim (EC_{50}, 19.20 μg/mL). However, their activities were lower than that of diethofencarb (EC_{50}**,** 4.72 μg/mL). In general, compound **4h** possessed the best activity against both *S. sclerotiorum* and *B. cinerea*, and the EC_{50} values were 10.85 and 6.45 μg/mL, respectively.

We analyzed the relationship between the activity and structure of the target compounds and found that the types of substituent at the benzene ring (R), including the electron-donating group (CH_3 or OCH_3) and the electron-withdrawing group (Cl or Br), had an inconspicuous effect on antifungal activity. However, the positions of the substituent had a notable effect on the activity, and the compounds, and compounds with the substituent at the 4-position possessing higher activity than those with the substituent at the 2- or 3-position. Compounds **4d** (R = 4-CH_3), **4h** (R = 4-Cl), and **4j** (R = 4-Br), for example, exhibited stronger activity against the two tested fungi in comparison to their 2- or 3-position analogues. On the other hand, due to the introduction of a chlorine atom at the 4-position of the benzene ring, compound **4h** had a suitable oil–water partition coefficient (Log P), therefore, it might easily access the cell wall of fungi and play an effective role in antifungal activity [16,25].

4. Conclusions

We designed and synthesized ten 3,3-Dimethyl-1-(pyridin-3-yl)butan-2-yl-substituted benzoylcarbamates and evaluated their antifungal activities against *S. sclerotiorum* and *B. cinerea*. Some compounds, such as **4d**, **4f**, **4g**, and **4h,** exhibited significant activity against *B. cinerea*.

Generally, compound **4h** displayed the best activity against both tested fungi. Due to its favorable pharmacophore (4-chlorophenyl) in the molecule and sufficient antifungal activity, **4h** possesses value for further structural optimization and bioactivity research.

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