Synthesis and Antifungal Activities of Some 2,6-Bis-(Un)Substituted Phenoxymethylpyridines

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Z. Naturforsch. **65c**, 433–436 (2010); received January 20/March 1, 2010

Several 2,6-bis-(un)substituted phenoxymethylpyridines were synthesized and evaluated *in vitro* against *Fusarium graminearum*, *Helminthosporium sorokinianum*, *Alternaria brassicae*, *Alternaria alternata*, and *Fusarium oxysporum* f. sp. *vasinfectum*. Among all derivatives, compound **3a** exhibited a broad-spectrum antifungal activity against the five phytopathogenic fungi.

Key words: 2,6-Bis-(Un)Substituted Phenoxymethylpyridines, Antifungal Activity, Phytopathogenic Fungi

Introduction

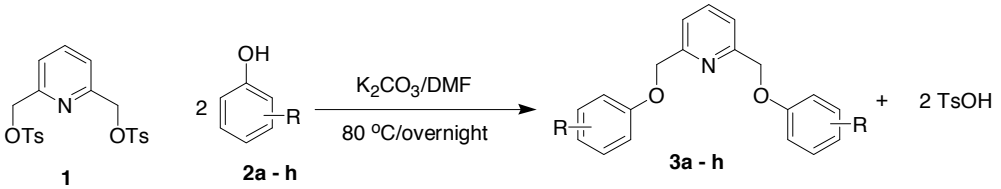
Recently, many reports have demonstrated that a number of biologically important molecules with pyridine scaffolds exhibit pharmacological activities, such as antimicrobial (De Almeida *et al*., 2007), antibacterial (Mishra *et al.*, 2008), antiangiogenic (Hayashi *et al*., 2009), anti-inflammatory and antioxidant activities (Gonzalez *et al*., 2009). However, to the best of our knowledge, little attention has been paid to the antifungal activities of the simple 2,6-bis-(un)substituted phenoxymethylpyridines. As a consequence and in continuation of our program aimed at the discovery and development of bioactive molecules (Xu *et al*., 2002, 2007, 2009; Xu and Xiao, 2009), here we report the synthesis and antifungal activities of some simple 2,6-bis(un)substituted phenoxymethylpyridines.

Experimental

*Synthesis of the 2,6-bis-(un)substituted phenoxymethylpyridines **3a–3h***

Eight simple 2,6-bis-(un)substituted phenoxymethylpyridines, **3a–3h** (Fig. 1), were prepared from 2,6-bis(*p*-tosyloxymethyl)pyridine (**1**) (Bradshaw *et al*., 1990) with the (un)substituted phenols **2a–2h** in the presence of potassium carbonate and dimethylformamide at 80 °C, as shown in Scheme 1, and characterized by proton nuclear magnetic resonance (^{1}H NMR), electron ionization mass spectrometry (EI-MS), infrared spectrometry (IR), and melting points.

3a: Yield 58%. – White solid. – M.p. 78–79 °C. – IR (KBr): ν = 2917, 2852, 1598, 1579, 1442, 1370, 1235, 1083, 1066 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (t, J = 7.6 Hz, 1H), 7.47 (d, J =



Scheme 1. Synthetic route of the 2,6-bis-(un)substituted phenoxymethylpyridines **3a–3h**.

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8.0 Hz, 2H), 7.32 (m, 2H), 6.99 (m, 8H), 5.22 (s, 4H). – EI-MS: *m/z* = 291 (M^+, 29).

3b: Yield 83%. – Yellow solid. – M.p. 136–139 °C. – IR (KBr): *v* = 2922, 2855, 1594, 1511, 1445, 1338, 1246, 1154, 1038 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.56 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 2H), 5.33 (s, 4H). – EI-MS: *m/z* = 381 (M^+, 2).

3c: Yield 78%. – Pale yellow solid. – M.p. 163–165 °C. – IR (KBr): *v* = 2910, 2838, 1589, 1510, 1442, 1375, 1251, 1171, 1111, 1054 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (m, 4H), 7.81 (t, *J* = 7.6 Hz,1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.09 (m, 4H), 5.30 (s, 4H). – EI-MS: *m/z* = 381 (M^+, 5).

3d: Yield 58%. – Pale yellow solid. – M.p. 115–116 °C. – IR (KBr): *v* = 2917, 2852, 1583, 1444, 1364, 1230, 1057 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 4H), 6.93 (m, 4H), 5.17 (s, 4H). – EI-MS: *m/z* = 359 (M^+, 23).

3e: Yield 72%. – White solid. – M.p. 104–105 °C. – IR (KBr): *v* = 2896, 2856, 1586, 1442, 1365, 1250, 1071 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.20 (m, 2H), 6.99 (m, 4H), 5.28 (s, 4H). – EI-MS: *m/z* = 359 (M^+, 20).

3f: Yield 71%. – Yellow solid. – M.p. 49–50 °C. – IR (KBr): *v* = 2922, 2852, 1583, 1447, 1366, 1256, 1158, 1077 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 2H), 6.80 (m, 6H), 5.20 (s, 4H), 2.33 (s, 6H). – EI-MS: *m/z* = 319 (M^+, 34).

3g: Yield 60%. – Yellow solid. – M.p. 176–177 °C. – IR (KBr): *v* = 2921, 2856, 1591, 1504, 1451, 1365, 1252, 1150, 1041 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 9.90 (s, 2H), 7.86 (d, *J* = 8.8 Hz, 4H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 4H), 5.29 (s, 4H). – EI-MS: *m/z* = 347 (M^+, 39).

3h: Yield 49%. – White solid. – M.p. 164–168 °C. – IR (KBr): *v* = 2954, 2861, 1579, 1450, 1367, 1249, 1185, 1070 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 4H), 6.80 (d, *J* = 8.8 Hz, 4H), 5.20 (s, 4H), 1.30 (s, 18H). – EI-MS: *m/z* = 403 (M^+, 0.5).

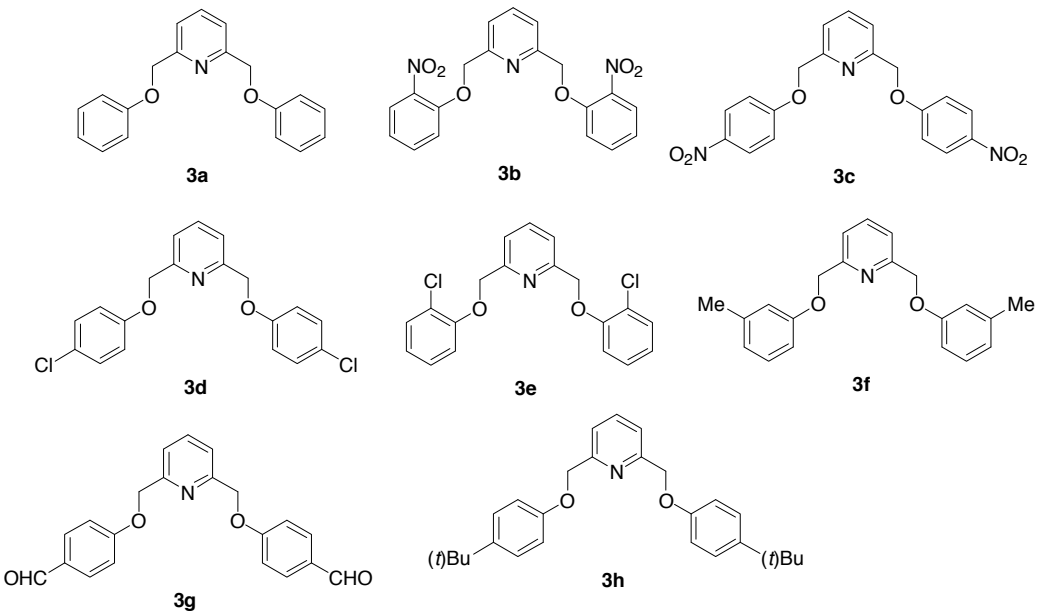

Fig. 1. Chemical structures of the 2,6-bis-(un)substituted phenoxymethylpyridines **3a**–**3h**.

Table I. Antifungal activities of the 2,6-bis-(un)substituted phenoxymethylpyridines **3a**–**3h** against phytopathogenic fungi at 100 μg/mL *in vitro*.

Compound	Inhibition rate (%)[a]				
	Fusarium graminearum	*Helminthosporium sorokinianum*	*Alternaria brassicae*	*Alternaria alternata*	*Fusarium oxysporum* f. sp. *vasinfectum*
3a	41.1 (± 3.1)	33.0 (± 2.1)	42.7 (± 1.0)	39.8 (± 1.2)	47.6 (± 2.1)
3b	4.5 (± 0.4)	7.0 (± 1.4)	5.4 (± 1.7)	6.2 (± 1.7)	5.2 (± 1.4)
3c	2.8 (± 1.0)	7.5 (± 1.9)	7.8 (± 4.2)	8.0 (± 2.9)	8.3 (± 1.2)
3d	12.8 (± 0)	5.4 (± 2.1)	8.5 (± 2.0)	5.8 (± 1.5)	7.1 (± 6.3)
3e	2.5 (± 0.5)	1.1 (± 0.9)	1.1 (± 2.9)	5.1 (± 0.6)	20.8 (± 0.8)
3f	16.0 (± 1.5)	6.6 (± 7.0)	10.1 (± 3.8)	28.6 (± 1.9)	4.8 (± 1.7)
3g	6.1 (± 0.4)	18.9 (± 4.9)	3.8 (± 2.1)	6.4 (± 0.8)	1.2 (± 1.7)
3h	22.0 (± 5.0)	10.9 (± 2.6)	0 (± 0)	9.6 (± 8.4)	21.4 (± 0)
Acetone[b]	0	0	0	0	0

[a] Values are means of three experiments, standard deviations are given in parentheses.
[b] Control.

*Antifungal assay of the 2,6-bis-(un)substituted phenoxymethylpyridines **3a**–**3h***

Subsequently, compounds **3a**–**3h** were screened *in vitro* for their antifungal activities against phytopathogenic fungi by the poisoned food technique (Xu *et al*., 2007). Five phytopathogenic fungi, namely *Fusarium graminearum*, *Helminthosporium sorokinianum*, *Alternaria brassicae*, *Alternaria alternata*, and *Fusarium oxysporum* f. sp. *vasinfectum*, were used for the biological assays. Potato dextrose agar (PDA) medium was prepared in flasks and sterilized. Compounds **3a**–**3h** were dissolved in acetone before mixing with PDA, and the final concentration of the test compounds in the medium was fixed at 100 μg/mL. The medium was then poured into sterilized Petri dishes. All types of fungi were incubated in PDA at (28 ± 1) °C for 5 d to get new mycelium for the antifungal assays. Then mycelium disks of approx. 5 mm diameter cut from the culture medium were picked up with a sterilized inoculation needle and inoculated in the centre of each PDA Petri dish. The inoculated Petri dishes were incubated at (28 ± 1) °C for 4 d. Acetone without any compound mixed with PDA served as control, while hymexazole (Binzhou De'dong Chemical Engineering Co., Ltd., Shandong province, China), a commercial agricultural fungicide, severed as positive control. For each treatment, three replicates were conducted. The radial growth of the fungal colonies was measured, and the data were statistically analyzed. The inhibitory effects of the test compounds on these fungi *in vitro* were calculated by the formula

$$\text{inhibition rate (\%)} = (C - T) \cdot 100/C,$$

where C represents the diameter of fungal growth on untreated PDA, and T represents the diameter of fungal growth on treated PDA.

Results and Discussion

As indicated in Table I, some 2,6-bis-(un)substituted phenoxymethylpyridines (Fig. 1) showed certain antifungal activity at 100 μg/mL. For example, compounds **3a** and **3h** inhibited the growth of *F. graminearum* by 41.1% and 22.0%, respectively; compounds **3a** and **3g** inhibited the growth of *H. sorokinianum* by 33.0% and 18.9%, respectively; compound **3a** inhibited the growth of *A. brassicae* by 42.7%; compounds **3a** and **3f** inhibited the growth of *A. alternata* by 39.8% and 28.6%, respectively; compounds **3a**, **3e**, and **3h** inhibited the growth of *F. oxysporum* f. sp. *vasinfectum* by 47.6%, 20.8%, and 21.4%. Interestingly, among all the 2,6-bis-(un)substituted phenoxymethylpyridine derivatives, compound **3a** exhibited broad-spectrum antifungal activities against the above-mentioned five phytopathogenic fungi, and the percentage inhibitions of **3a** on the growth of *F. graminearum*, *H. sorokinianum*, *A. brassicae*, *A. alternata*, and *F. oxysporum* f. sp. *vasinfectum* were 41.1%, 33.0%, 42.7%, 39.8%, and 47.6%, respectively.

From the comparative study, some structure-activity relationships of the 2,6-bis-(un)substituted phenoxymethylpyridines **3a**–**3h** could be drawn as follows:

(1) It doesn't matter whether electron-donating groups (like in **3f** and **3h**) or electron-withdrawing groups (like in **3b**–**3e**, and **3g**) were introduced at the phenyl ring of **3a**, the inhibition rates of the corresponding compounds were all lower than that of **3a**.

(2) Especially when the nitro group was introduced at the phenyl ring of **3a**, the corresponding inhibition rates of **3b** and **3c** were less than 10% against the five tested phytopathogenic fungi.

(3) 2,6-Bis(4-*t*-butylphenoxymethyl)pyridine (**3h**) displayed no inhibitory activity at all against *A. brassicae*.

In conclusion, eight simple 2,6-bis-(un)substituted phenoxymethylpyridines, **3a**–**3h**, were synthesized and evaluated *in vitro* against *Fusarium graminearum*, *Helminthosporium sorokinianum*, *Alternaria brassicae*, *Alternaria alternata*, and *Fusarium oxysporum* f. sp. *vasinfectum*. Among all the derivatives, compound **3a** exhibited broad-spectrum antifungal activities against the above-mentioned five phytopathogenic fungi.

Acknowledgement

This work has been supported by the program for New Century Excellent University Talents, State Education Ministry of China (NCET-06-0868).

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