Synthesis and Antifungal Activity of 5,6-Dihydro-3-methyl-1,4-dioxin-2-carboxamides

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Seven *N*-aryl-5,6-dihydro-3-methyl-1,4-dioxin-2-carboxamides were prepared as potential fungicides. The fungicidal activity of the dioxincarboxamides was evaluated against bean rust, a major disease of cereal crops. Structure−activity relationships for the screened compounds are discussed. The fungicidal activity of the dioxincarboxamides is correlated with that of the structurally similar commercial fungicide, carboxin.

Keywords: *Dioxincarboxamides; fungicides; bean rust*

INTRODUCTION

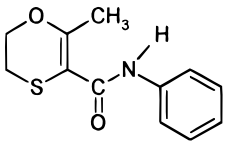
Carboxin (5,6-dihydro-2-methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide) (Vitavax) (Figure 1) is a well-established systemic fungicide (von Schmeling and Kulka, 1966). It is the active ingredient of several effective seed treatment fungicides that are commercially available and used worldwide to control smut and rust diseases of agricultural crops (Davis et al., 1972; von Schmeling et al., 1966). Because of its success in crop protection, a great deal of synthetic work has been done aimed at creating various analogues of carboxin, some of which have also become commercial fungicides (Kawada, 1980; Reinbergs et al., 1968; Roy, 1980; Uchida et al., 1983; White and Thorn, 1975).

Our interest in carboxin analogues was aroused by the prospect of obtaining novel fungicidally active compounds by replacing the sulfur atom in the oxathiin ring by an oxygen atom, thus forming a dioxin ring. Although several dioxincarboxamides have been reported by Kuznetsov et al. (1976), their compounds were missing the strategically important methyl group adjacent to the carboxamide function. These authors do not report fungicidal properties associated with their dioxincarboxamides.

In the present work, we synthesized a series of 5,6-dihydro-3-methyl- 1,4-dioxin-2-carboxamides (Figure 2) and measured their fungicidal activity against bean rust, one of the most important diseases of cereals (Royle, 1990).

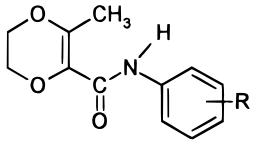
EXPERIMENTAL PROCEDURES

Chemistry. Synthesis of the title compounds was achieved according to the method outlined in Scheme 1. The dioxincarboxamides **4a**−**g** were prepared by the reaction of 1,2-ethanediol with propargyl chloride followed by cyclization with sodium hydroxide to give 2,3-dihydro-5-methyl-1,4-dioxin **1**, then acylation with trifluoroacetic anhydride to give the 2-trifluoroacetyl dioxin **2**, which was hydrolyzed to give the corresponding carboxylic acid **3**, then treated with thionyl chloride to give the acid chloride, which was reacted with a suitably substituted aniline to give the title compounds. The physical properties of the dioxincarboxamides are found in Table 1. The structural determination of the synthesized compounds was based on their infrared and ^{1}H NMR spectra



Carboxin

Figure 1. Structure of the commercial fungicide carboxin.



Dioxincarboxamides

Figure 2. Structure of the fungicide candidates, dioxincarboxamides.

Scheme 1. Synthesis of 5,6-Dihydro-3-methyl-1,4-dioxin-2-carboxamides 4a−g

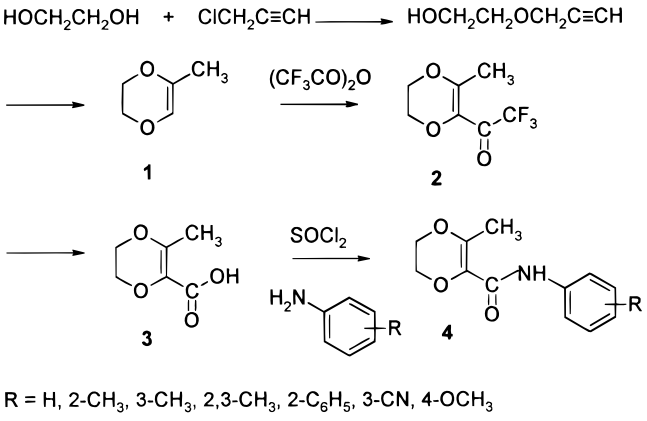


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Table 1. Physical Properties and Spectral Data of Dioxincarboxamides 4a−g

compd	R	mp (°C)	^{1}H NMR ($CDCl_3$) (ppm)
4a	H	85−87	8.0 (s, 1H), 7.1−7.6 (m, 5H), 4.0 (s, 4H), 2.2 (s, 3H)
4b	2-CH_3	70−72	8.1 (s, 1H), 7.0−7.7 (m, 4H), 4.0 (s, 4H), 2.3 (s, 3H), 2.2 (s, 3H)
4c	3-CH_3	71−73	8.0 (s, 1H), 7.1−7.8 (m, 4H), 4.0 (s, 4H), 2.3 (s, 3H), 2.2 (s, 3H)
4d	2,3-CH_3	oil	8.1 (s, 1H), 7.0−7.8 (m, 3H), 4.0 (s, 4H), 2.3 (s, 6H), 2.2 (s, 3H)
4e	2-C_6H_5	oil	8.5 (s, 1H), 7.2−7.7 (m, 9H), 3.8-4.2 (m, 4H), 2.2 (s, 3H)
4f	3-CN	160−163	8.3 (s, 1H), 7.2−7.8 (m, 4H), 4.0 (s, 4H), 2.2 (s, 3H)
4g	4-OCH_3	59-61	8.1 (s, 1H), 6.9−7.6 (m, 4H), 4.0 (s, 4H), 3.8 (s, 3H), 2.2 (s, 3H)

Table 2. Fungicidal Screening Results of Dioxincarboxamides 4a−g

		% inhibition ± SD[a] of bean rust			
compd	R	1000 ppm	500 ppm	250 ppm	100 ppm
4a	H	100 ± 0	100 ± 0	88 ± 8	67 ± 8
4b	2-CH_3	100 ± 0	79 ± 6	67 ± 6	17 ± 3
4c	3-CH_3	100 ± 0	100 ± 0	100 ± 0	79 ± 8
4d	2,3-CH_3	100 ± 0	100 ± 0	88 ± 6	75 ± 4
4e	2-C_6H_5	50 ± 8	17 ± 6	17 ± 5	17 ± 4
4f	3-CN	0 ± 0			
4g	4-OCH_3	0 ± 0			
carboxin		100 ± 0	100 ± 0	100 ± 0	67 ± 6

[a] SD, standard deviation.

(Table 1). Yields of dioxincarboxamides **4a−g** were in the range 50−68%.

Biology. Data on the fungicidal activity of compounds **4a−g** are presented in Table 2. The activity of the dioxincarboxamides against bean rust was determined by inoculating 7−10-day-old pinto beans with the fungus *Uromyces phaseoli* by spraying the leaf surfaces with 85 mg of spores and 10 drops of Tween 20 surfactant per liter of water. After inoculation, the plants were immediately placed in a temperature−humidity-controlled chamber at 21 °C for 24 h for infection to occur. The plants were then placed in the greenhouse for 24 h and sprayed to runoff with a solution of each compound dissolved in a minimum volume of acetone and diluted with water containing a wetting agent. Ten days after treatment, percentage disease control was compared to a treatment in the absence of the experimental compound and estimated with Abbott's formula (Abbott, 1925). Four replicates were included in the evaluation. The commercial fungicide, carboxin, was tested for comparative purposes under the same conditions as the dioxincarboxamides.

Melting points were determined in open glass capillaries and are uncorrected.

^{1}H NMR spectra were recorded on a Varian EM-360L (60 MHz) spectrometer in $CDCl_3$ using TMS as internal reference; chemical shifts are expressed in parts per million.

2,3-Dihydro-5-methyl-6-(trifluoroacetyl)-1,4-dioxin (2). 2-(2-Propynyloxy)ethanol and 5,6-dihydro-2-methyl-1,4-dioxin (**1**) were prepared according to the procedure of Bottini et al. (1965). Trifluoroacetic anhydride (12.64 g, 60.2 mmol) was added dropwise to a stirred mixture of **1** (3.00 g, 30.0 mmol) and pyridine (4.87 g, 61.3 mmol) in dichloromethane (20 mL) at room temperature, and the solution was allowed to stand for 1 day. After reaction, the mixture was added to an aqueous 10% sodium carbonate solution (20 mL). After washing with water (2 × 30 mL), the dichloromethane layer was dried with sodium sulfate, and the solvent was evaported to give **2**: yield, 1.96 g (33.3%, based on **1**); bp 85 °C/15 Torr; ^{1}H NMR ($CDCl_3$) 4.0 (s, 4H), 2.4 (s, 3H) ppm.

5,6-Dihydro-3-methyl-1,4-dioxin-2-carboxylic Acid (3). To a solution of **2** (1.96 g, 10 mmol) in toluene (50 mL) was added powdered potassium hydroxide (100 g, 18 mmol). The mixture was refluxed for 7 h with stirring and then acidified with dilute hydrochloric acid and extracted with dichloromethane. After drying with sodium sulfate, the solvent was removed under reduced pressure to give **3**: yield, 1.00 g (69%, based on **2**); mp 120 °C; ^{1}H NMR ($CDCl_3$) 8.2 (bs, 1H), 4.0 (s, 4H), 2.4 (s, 3H) ppm.

Dioxincarboxamides 4a−g. A mixture of dioxincarboxylic acid **3** (1.44 g, 10 mmol) and thionyl chloride (5 mL) was refluxed for 1.5 h and then concentrated under reduced pressure. The resulting acid chloride was dissolved in diethyl ether (20 mL) and cooled to 10 °C while 20 mmol of an appropriately substituted aniline dissolved in diethyl ether (20 mL) was added dropwise. After stirring for 2 h at room temperature, water (50 mL) was added and the mixture was extracted with diethyl ether. The organic layer was separated and washed with dilute hydrochloric acid. After drying with sodium sulfate, the solvent was removed under reduced pressure, leaving a solid. The products **4a−g** were washed with hexane and filtered, giving yields of 50−68% based on **3**.

RESULTS AND DISCUSSION

Melting points of dioxincarboxamides **4a−g**, obtained by the reaction of 5,6-dihydro-3-methyl-1,4-dioxin-2-carboxylic acid (**3**) with various aromatic amines, are shown in Table 1. Seven compounds were prepared in which the substituent and its position on the aromatic ring were varied to determine the effect this would have on the fungicidal properties of this class of compounds. Nuclear magnetic resonance spectra of the dioxincarboxamides showed the protons of the dioxin ring as a singlet at 4 ppm in all cases except **4e**, in which the substituent is a phenyl group in the ortho position (Table 1). In that case, a multiplet at 4 ppm was observed in the spectrum. Furthermore, a strong absorption in the infrared spectra of dioxincarboxamides was observed in the region 1660−1685 cm^{-1}, indicative of an amide carbonyl group.

Several dioxincarboxamides demonstrated fungicidal properties. The 3-methyl analogue **4c** showed higher activity against bean rust than the commercial fungicide, carboxin. On the other end of the scale, the 3-CN and 4-OCH_3 analogues (**4f** and **4g**, respectively) both failed to demonstrate fungicidal activity even at the highest application rate of 1000 ppm. Replacing O for S (**4a** versus carboxin) appears to retain fungicidal activity.

The substitution of oxygen for sulfur in the heterocyclic ring represents an example of an approach that is commonly known as bioisosterism. The 1,4-dioxin ring is a bioisosteric analogue of the 1,4-oxathiin ring. The idea of bioisosterism is one of the most successful techniques of bioactive compound design (Lipinski, 1986).

Aside from the expected fungicidal properties, dioxincarboxamides have also demonstrated usefulness as plant growth retardants, particularly on wheat and barley (Dekeyser and Blem, 1991).

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