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Synthesis and fungicidal activity of fluorine-containing chlorothalonil derivatives

Aiying Guan, Changling Liu *, Guang Huang, Huichao Li, Shulin Hao, Ying Xu, Yong Xie, Zhinian Li

State Key Laboratory of the Discovery and Development of Novel Pesticide, Shenyang Research Institute of Chemical Industry Co. Ltd., Shenyang 110021, China

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ABSTRACT

Fourteen new fluorine-containing chlorothalonil derivatives were synthesized by using intermediate derivatization method (IDM) in order to discover novel antifungal compounds for controlling corn rust. The structures of synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, elemental analysis, HRMS and X-ray. The bioassay results indicated that compound 2,4,5-trichloro-6-(2,6-dichloro-4-[trifluoromethyl]phenylamino)isophthalonitrile (**3j**, R^n is 2,6-Cl2-4-CF_3) had the optimal structure with best fungicidal activity against corn rust (98%, 70% controls) at 25 and 6.25 mg/L concentration, respectively, much better than chlorothalonil and fluazinam, highlighting the importance of trifluoromethyl group on 4-position of benzene ring. The structure–activity relationship of the synthesized compounds was discussed as well.

1. Introduction

Rust disease is an entire family of plant diseases caused by rust fungi, which infect and harm the stem, leaves, and fruit of cereal crops. Because of the rule of epidemic of region, when rust diseases take hold in an agricultural region, tremendous yield reductions will follow [1]. At present, the fungicides used to control rusts are generally triazole compounds. However, their single structure type, combined with the characteristics of high variability in rust disease, leads easily to pesticide resistance in affected plants [2]. Therefore it is particularly important to discover and develop new fungicides with different modes of action to control rust diseases. Chlorothalonil has a broad spectrum of fungicidal activity [3] with a relatively low cost, and it is commercially available in a large scale. Based on these features, we chose chlorothalonil as the key intermediate to develop novel bioactive compounds using intermediate derivatization method (IDM), developed by our research group [4–6]. It is well known that many fluorine-containing compounds exhibit significant agricultural bioactivities due to the fluorine atom's unique properties [7]. For example, the trifluoromethyl group, considered a 'pseudo-halogen', has been found to impart unique biological activity [8]. On the other hand, some commercial diarylamine compounds (Fig. 1), specifically diphenylamine, were used to control storage related diseases in fruits and vegetables [9]. Furthermore, *N*-phenylpyridinamines including fluazinam [10], *N*-phenylpyrimidinamines including cyprodinil [11], pyrimethanil [12], and mepanipyrim [13], have been proven to be effective against many diseases. In particular, fluazinam shows broad-spectrum control against diseases in field crops. However, none of the above-mentioned compounds are effective against rust disease. More importantly, these structure types have no similarities to other commercialized fungicides, e.g., triazoles, benzimidazoles and diethofencarb, implying that compounds containing diarylamine may overcome the resistance of these marketed fungicides [14]. Therefore, in this study, in order to discover new *N*-diphenylnamine leads or compounds with promising and effective control of rust disease, a series of *N*-diphenylnamine fluorine-containing chlorothalonil derivatives were designed, synthesized and bio assayed. The structure–activity relationships of these compounds are discussed as well.

2. Results and discussion

2.1. Synthesis

The general synthesis route of these targeted compounds is described in Figs. 2–5. Fig. 2 shows the synthesis process of compounds **3a–3g, 3j** and **3l**. Fig. 3 summarizes the synthesis process of compounds **3h** and **3i**. Fig. 4 explains the synthesis procedure of compound **3k**. Fig. 5 displays the synthesis procedure of compound **3m** and **3n**.

* Corresponding author. Tel.: +86 2485869078; fax: +86 2485869137.
E-mail address: liuchangling@vip.163.com (C. Liu).

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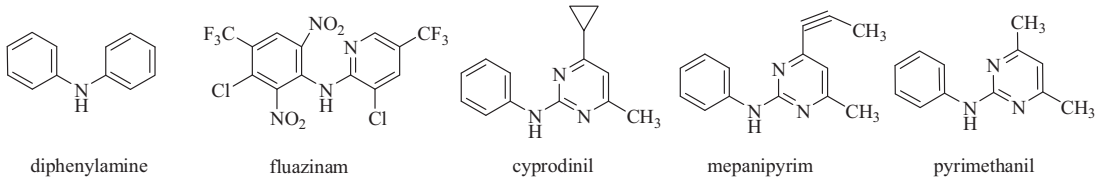

Fig. 1. Commercial diarylamine compounds.

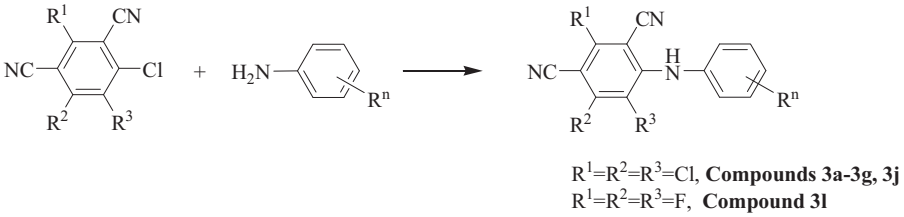

Fig. 2. Synthesis scheme of compounds **3a–3g, 3j** and **3l**.

2.2. Fungicidal activity

The fungicidal activity of the above compounds against southern corn rust (SCR-*Puccinia polysora*) *in vivo* was determined at the concentration ranging from 6.25 to 400 mg/L, using fluazinam and chlorothalonil which is the parental structure in the series as the reference standards, in accordance to the methods reported in a previous study [15], and the results are listed in Tables 1 and 2. Some of the synthesized compounds exhibited potential activity against SCR. Particularly **3j**, having strong electron withdrawing group CF_3 on 4-position, displayed best fungicidal activity (98% control at 25 mg/L and 70% control at 6.25 mg/L), much higher than chlorothalonil (50% at 400 mg/L) and fluazinam (30% control at 25 mg/L and 10% control at 6.25 mg/L).

2.3. Exploration of structure–activity relationship

In order to provide better references for following optimization combating SCR, the detailed SAR was further discussed and summarized here.

Using available materials we started with synthesizing the compounds **3a** (R^n = 3-CF_3), **3b** (R^n = 4-CF_3) and **3c** (R^n = 4-OCF_3), which all have single substituent containing fluorine atom. However, this first step did not result in observable and effective control of SCR as shown in Table 1, since all of these compounds demonstrated virtually no activity against SCR even at a high concentration of 400 mg/L. Yet useful information delivered from these data highlights that introducing a single F-containing group CF_3 (strong electron-withdrawing group) or OCF_3 (electron-donating group), into 4-position alone, did not increase the fungicidal activity of the molecule. Nor did the introduction of a single F-containing group CF_3 at the 3-position. The analysis of these results prompted us to further employ F atom(s) into two positions on the benzene ring simultaneously, leading to the generation of the compounds **3d** (R^n = 2,4-F2) and **3e** (R^n = 2, 6-F2). To our surprise, the fungicidal activity of these two compounds against SCR increased remarkably from 0 to near 100% at 400 mg/L, indicating that introduction of two fluorine atoms into this system dramatically increases fungicidal activity. Of interest, when 4-F was replaced with 4-CF_3 (while keeping 2-position fixed as halogen), the activity decreased to 0 (**3f** versus **3d**). However, when we inserted an additional F atom on 3-position (based on **3d** structure**)** to obtain compound **3 g,** this modification did not exhibit any obvious increase in fungicidal activity, showing that too many fluorine atoms may not be good for increasing the fungicidal activity.

Thus, we carried out a subtle refinement of **3e** with R^n of 2,6-F2, by inserting NO_2 on 4-positon, obtained compound **3 h** had much greater fungicidal activity compared with **3e**, (**3 h** 95% control of SCR at 100 mg/L versus **3e** 98% at 400 mg/L). Further, by changing 2-F to 2-Cl we observed a decrease of anti-fungal activity at 100 mg/L (**3i** 80% versus **3 h** 95%). However, compound **3j** (R^n = 2,6-Cl2-4-CF_3) demonstrated the highest fungicidal activity (70% at 6.25 mg/L) that was superior to other tested compounds, indicating that 4-CF_3 plays an important role in the efficacy as a fungicide. In order to confirm the importance of 4-CF_3 at 4-position, we turned 4-CF_3 into 4-OCF_3 and kept 2,6-position constant as halogen atoms to obtain **3k**. The results displayed that compound **3k** is much less effective in the control of SCR than **3j** (**3k** 0 versus **3j** 100% at 400 mg/L), underscoring the importance of CF_3 on 4-position of substituted phenyl ring for targeting SCR. Interestingly, when all chlorine atoms on chlorothalonil were substituted with F atoms (**3l**), we expected that the activity would be enhanced, but the result was opposite: **3l** exhibited lower fungicidal activity than **3j** (**3l** 20% versus **3j** 100% at 100 mg/L) indicating that the fluorine atoms at chlorothalonil side do not help to increase the fungicidal activity.

Finally to investigate the role of CNs of chlorothalonil, **3m** and **3n** compounds with 1,2-disubstituted and 1,4-disubstituted CN, respectively, were synthesized and bioassayed, the results are

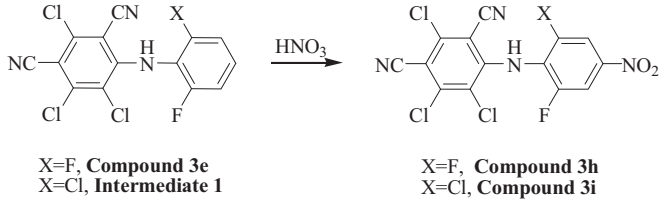

Fig. 3. Synthesis scheme of compounds **3h** and **3i**.

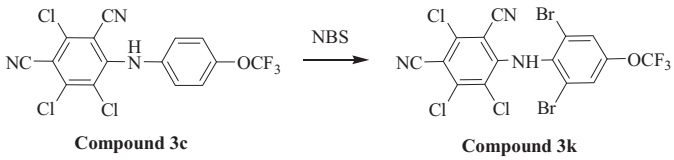

Fig. 4. Synthesis scheme of compound **3k**.