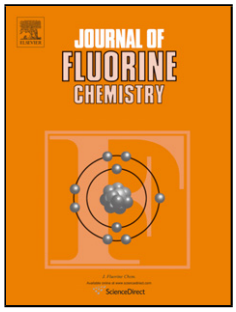

Title: Synthesis and fungicidal activity of fluorine-containing chlorothalonil derivatives

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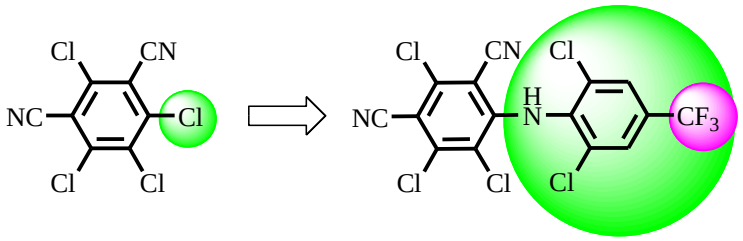
Graphical abstract



Chlorothalonil

3j containing 2,6-Cl2-4-CF_3 phenyl group showing good control against SCR

Graphical synopsis

Chlorothalonil, a commercialized fungicide with very low cost, was employed as the starting material to achieve a series of novel *N*-diphenylamines with excellent fungicidal activity against Southern Corn Rust. Trifluoromethyl group on 4-position of substituted phenyl plays an important role in enhancing the biological activity of target compounds.

Highlights

► Application of the strategies of Intermediate Derivatization Method. ► Trifluoromethyl, a very strong electron withdrawing group, plays an important role on fungicidal activity. ► Characterization of target compounds using ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, elemental analysis, HRMS and X-ray. ► Excellent fungicidal activity against *Puccinia polysora*. ► Detailed structure and activity relationship of target compounds.

Synthesis and fungicidal activity of fluorine-containing chlorothalonil derivatives

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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.

Keywords: Fluorine-containing chlorothalonil derivatives; IDM; Synthesis; Fungicidal activity

[1]

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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 mentioned-above 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**.

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 Table 1 and Table 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 zero 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 zero (**3f** versus **3d**). However, when we inserted an additional F atom on 3-position (based on **3d** structure**)** to obtain compound **3g,** 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 **3h** had much greater fungicidal activity compared with **3e**, (**3h** 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 **3h** 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 listed in Table 2. Compared with **3j**, which has 1,3-disubstituted CN, **3m** and **3n** have less fungicidal activities than **3j**, indicating that 1,3-disubstituted CNs is optimal position.

To further verify whether the effect of lipophilic property of substituents on biological activity, we calculated the CLogP parameter of all compounds including chlorothalonil and fluazinam, using ChemDraw software. As shown in

Tables 1 and 2, CLogP is less than 7 in the majority of compounds. Compounds with greater than 7 of CLogP are **3j**, **3k**, **3m** and **3n**. Interestingly, **3j**, the most active compound, has the highest CLogP value in all new compounds except **3k**, indicating that biological activity of SCR is positively related to the CLogP. However, the unexpected lower activity but high CLogP value of **3k** may be due to the presence of trifluoromethoxyl group, which is an electronic donating group. It is noted that although compounds **3j**, **3m** and **3n** have comparable CLogP values, their biological activities decreased according to the order of **3j**, **3m** and **3n**. This may be due to the position difference of two CNs of chlorothalonil, which plays an important role in controlling the biological activity in this particular case. The optimal 1,3-disubstituted position of compound **3j** represents the optimized steric configuration which allows the entry of this drug into the active site of targeted enzyme.

Based on the discussions above, a clear cut, well-defined and direct relationship between chemical structure and biological activity is on the horizon. It is summarized in the following (decreasing order of activity).

(1) for substituted position and numbers of substituents on benzene ring

2,6-Cl2-4-CF_3 >> 2,6-F2-4-NO_2 > 2-Cl-6-F-4-NO_2 >> 2,3,4-F3≈2,4-F3≈ 2,6-F2 >>

2,6-Br2-4-OCF_3≈2-Cl-4-CF_3≈3-CF_3≈4-CF_3≈4-OCF_3

(2) Different position of two CNs and halogen atoms attached to chlorothalonil

1,3-disubstituted >> 1,2-disubstituted > 1,4-disubstituted

Cl>>F

Fluorine as a unique atom can modulate the physical properties of molecules. The introduction of fluorine into organic molecules may increase the lipophilic properties and enhance the rate of plant cell penetration and transportation of drug into the active sites. Therefore, fungicidal activities are enhanced by introducing fluorine into compounds of interest in general [16, 17]. However, the correlation of physical and structural properties of these new compounds to the biological activity ascribes to the combination of many complicated factors including steric, electronic and lipophilic factors rather than a single factor as represented in this study.

3. Conclusions

In this study, 14 new fluorine-containing chlorothalonil derivatives were synthesized by using *intermediate derivatization method* (IDM). Their fungicidal activity against corn rust was tested in order to obtain the optimized structure. This study reveals that both number and position of fluorine atoms are critical to afford optimized structures. It has been shown that compound **3j** (R^1=R^2=R^3=Cl, R^n =2,6-Cl2-4-CF_3) is the optimal molecule with the promising fungicidal activity, 70% control against SCR at 6.25 mg/L concentration, much higher than chlorothalonil and fluazinam, highlighting the importance of CF_3 on 4-position of substituted phenyl ring. This study also demonstrates that fluorine-containing chlorothalonil derivatives can be used as lead compounds for developing novel fungicides to control SCR. Further synthesis and structure optimization studies are needed and are currently in progress.

4. Experimental

All starting materials and reagents used are commercially available and were utilized without further purification (except as indicated). Melting points were determined using a Büchi melting point apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded with a Mercury 300 MHz ^{1}H (75MHz ^{13}C, 282 MHz ^{19}F) spectrometer with deuterochloroform as the solvent and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded using a Bruke micrOTOF-Q III mass spectrometer. Elemental analyses were determined using a Yanaco MT-3CHN elemental analyzer. X-ray was recorded with XtaLAB mini. All plant and bacteria materials were obtained from the Agrochemical Discovery Department in Shenyang Research Institute of Chemical Industry.

The protective activity *in vivo* was determined as follows: whole corn plant was used in experiments; with the various compounds dissolved in a proper solvent to obtain a master solution; the proper solvent was selected from acetone, methanol, DMF and according to their dissolving capability in the sample. The ratio of solvent and testing solution (v/v) is equal to or less than 5%. The master solution was diluted with H20 containing 0.1% tween-80 to achieve the testing solution with the desired concentration. The testing solution was sprayed onto the host plant by means of a special plant sprayer. The plants were inoculated with the fungi within 24 hours of being sprayed. According to the specific infectious characteristics of the fungus, the plant was then stored in a humidity controlled

chamber, and transferred to a greenhouse after infection is noted. The other non-infected plants were placed in the greenhouse directly. The activity of the compounds was ascertained by direct careful observation after 7 days.

*4.1. General synthetic procedure for title compounds **3a-3g, 3j** and **3l-3n**.* [15, 18-20]

Substituted aniline (5μmol) was dissolved in 5 mL of DMF, and sodium hydroxide (10 μmol) was added to the solution. The solution was stirred for 10 min, and corresponding intermediate phthalonitrile (or isophthalonitrile or terephthalonitrile) (5 μmol) was then added. The reaction mixture was stirred at 60 ^{o}C and monitored by TLC. After completion of the reaction (2 hours), the mixture was then added to 50 mL water and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine, dried (anhydrous magnesium sulfate), and filtered. The filtrate was then evaporated and the crude product was purified via silica gel column chromatography, using a 1:4 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range: 60-90 ^{o}C) of the eluting solution to obtain the title compound **3;** except for **3h, 3i** and **3k**.

*4.1.1. 2,4,5-trichloro-6-(3-(trifluoromethyl)phenylamino)isophthalonitrile (**3a**)*

yield 68%, mp 236-238^{o}C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 7.12 (s, 1H, NH), 7.28-7.40 (m, 1H, Ph-6-H), 7.41-7.52 (m, 2H, Ph-2,4-2H), 7.54-7.62 (m, 1H, Ph-5-H). Anal. Calcd. for $C_{15}H_5Cl_3F_3N_3$: C, 46.13; H, 1.29; N, 10.76. Found: C, 46.19; H, 1.16; N, 10.84; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -7.74.

*4.1.2. 2,4,5-trichloro-6-(4-(trifluoromethyl)phenylamino)isophthalonitrile (**3b**)*

yield 60%, mp 186-187^{o}C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.06 (br, 1H, NH), 6.51(d, *J*=5.7Hz, 2H, Ph-2,6-2H), 7.52(d, *J*=5.7Hz, 2H, Ph-3,5-2H). Anal. Calcd. for $C_{15}H_5Cl_3F_3N_3$: C, 46.13; H, 1.29; N, 10.76. Found: C, 46.18; H, 1.13; N, 10.88; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -7.51.

*4.1.3. 2,4,5-trichloro-6-(4-(trifluoromethoxy)phenylamino)isophthalonitrile (**3c**)*

yield 59%, mp 204-206^{o}C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 7.09 (s, 1H, NH), 7.22-7.32 (m, 4H, Ph-2,3,5,6-4H). Anal. Calcd. for $C_{15}H_5Cl_3F_3N_3O$: C, 44.31; H, 1.24; N, 10.34. Found: C, 44.41; H, 1.11; N, 10.40; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -2.88.

*3.1.4. 2,4,5-trichloro-6-(2,4-difluorophenylamino)isophthalonitrile (**3d**)*

yield 71%, mp 206-208°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.88 (s, 1H, NH), 6.99 (t, 2H, Ph-5,6-2H, *J*=8.1Hz), 7.32 (d, 1H, Ph-3-H, *J*=2.4Hz). Anal. Calcd. for $C_{14}H_4Cl_3F_2N_3$: C, 46.90; H, 1.12; N, 11.72. Found: C, 46.98; H, 1.01; N, 11.79; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -60.59, -51.53.

*4.1.5. 2,4,5-trichloro-6-(2,6-difluorophenylamino)isophthalonitrile (**3e**)*

yield 70%, mp 264-266°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.70 (s, 1H, NH), 7.07 (t, 2H, Ph-3,5-2H, *J*=8.1Hz), 7.37 (m, 1H, Ph-4-1H). Anal. Calcd. for $C_{14}H_4Cl_3F_2N_3$: C, 46.90; H, 1.12; N, 11.72. Found: C, 46.96; H, 0.98; N, 11.80.

*4.1.6. 2,4,5-trichloro-6-(2-chloro-4-(trifluoromethyl)phenylamino)isophthalonitrile (**3f**)*

yield 75%, mp 166-168°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 7.00 (s, 1H, NH), 7.20 (d, 1H, Ph-6-H, *J*=8.4Hz), 7.57 (dd, 1H, Ph-5-H, ^{3}J=8.4Hz, ^{4}J=1.5Hz), 7.78 (s, 1H, Ph-3-H). Anal. Calcd. for $C_{15}H_4Cl_4F_3N_3$: C, 42.39; H, 0.95; N, 9.89. Found: C, 42.30; H, 1.09; N, 9.77.

*4.1.7. 2,4,5-trichloro-6-(2,3,4-trifluorophenylamino)isophthalonitrile (**3g**)*

yield 52%, mp 182-184°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.87 (s, 1H, NH), 7.05-7.09 (m, 2H, Ph-5,6-2H). Anal. Calcd. for $C_{14}H_3Cl_3F_3N_3$: C, 44.66; H, 0.80; N, 11.16. Found: C, 44.60; H, 0.95; N, 11.08; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -100.90, -84.15, 75.93.

*4.1.8. 2,4,5-trichloro-6-(2,6-dichloro-4-(trifluoromethyl)phenylamino)isophthalonitrile (**3j**)*

yield 66%, mp 201-203°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.91 (s, 1H, NH), 7.72 (s, 2H, Ph-3,5-2H). Anal. Calcd. for $C_{15}H_3Cl_5F_3N_3$: C, 39.21; H, 0.66; N, 9.15. Found: C, 39.28; H, 0.55; N, 9.24; ^{13}C NMR (DMSO, 75MHz) δ: 115.52, 120.30 (q, *J* = 33.0 Hz), 121.40, 121.68, 121.86, 124.03(t, *J* = 3.75 Hz), 124.15, 125.45, 126.85, 134.87,

140.29, 149.89, 150.12; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -7.77; HRMS for $C_{15}H_3Cl_5F_3N_3$: 456.8722; Found: 457.8813；The molecular structure of **3j** was also confirmed by X-ray single-crystal diffraction (Fig. 6) [21].

*4.1.9. 4-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2,5,6-trifluoroisophthalonitrile (**3l**)*

yield 57%, mp 128-130°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.31(br, 1H, NH), 7.66(s, 2H, Ph-3,5-2H). Anal. Calcd. for $C_{15}H_3Cl_2F_6N_3$: C, 43.93; H, 0.74; N, 10.25. Found: C, 43.85; H, 0.86; N, 10.19; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -88.46, -46.13, -7.58.

*4.1.10. 3,4,5-trichloro-6-(2,6-dichloro-4-(trifluoromethyl)phenylamino)phthalonitrile (**3m**)*

yield 52%, mp 202-204°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.49 (br, 1H, NH), 7.69 (s, 2H, Ph-3,5-2H). Anal. Calcd. for $C_{15}H_3Cl_5F_3N_3$: C, 39.21; H, 0.66; N, 9.15. Found: C, 39.29; H, 0.80; N, 9.05.

*4.1.11. 2,3,5-trichloro-6-(2,6-dichloro-4-(trifluoromethyl)phenylamino)terephthalonitrile (**3n**)*

yield 55%, mp 138-140°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.56 (br, 1H, NH), 7.65 (s, 2H, Ph-3,5-2H). Anal. Calcd. for $C_{15}H_3Cl_5F_3N_3$: C, 39.21; H, 0.66; N, 9.15. Found: C, 39.13; H, 0.79; N, 9.06; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 111.13, 112.08, 119.33, 120.45, 124.06, 125.92 (q, J = 3.75 Hz), 126.01, 126.82, 128.38, 129.94, 131.97, 136.04, 136.18, 142.03.

*4.2. General synthetic procedure for title compounds **3h** and **3i*** [15]

To the mixture of **3e** or intermediate **1** (2.0mmol) obtained according to the method described in section *3.1. General synthetic procedure* in concentrated sulfuric acid (20 mL) was added nitric acid fuming (d=1.52, 10 mL) drop wise during 20 minutes with stirring sufficiently. Further stirred at room temperature for an hour, the reacting mixture was poured into ice-water, the resulting precipitate was collected by filtration, washed with water sufficiently to get compound **3h** or **3i** as pale white solid.

*4.2.1. 2,4,5-trichloro-6-(2,6-difluoro-4-nitrophenylamino)isophthalonitrile (**3h**)*

Yield 58%, mp 204-206°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.70 (s, 1H, NH), 7.97-8.01 (dd, 2H, Ph-3,5-2H, ^{3}J=10.8Hz, ^{4}J=3.0Hz). Anal. Calcd. for $C_{14}H_3Cl_3F_2N_4O_2$: C, 41.67; H, 0.75; N, 13.88. Found: C, 41.60; H, 0.66; N, 13.96.

*4.2.2. 2,4,5-trichloro-6-(2-chloro-6-fluoro-4-nitrophenylamino)isophthalonitrile (**3i**)*

yield 63%, mp 197-199°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.86 (s, 1H, NH), 8.05 (dd, 1H, Ph-5-H, ^{3}J=9.9Hz, ^{4}J=2.7Hz), 8.28 (d, 1H, Ph-3-H, J=2.4Hz). Anal. Calcd. for $C_{14}H_3Cl_4FN_4O_2$: C, 40.03; H, 0.72. Found: C, 40.17; H, 0.66; ^{19}F NMR ($CDCl_3$, 282MHz) δ: -56.13.

4.3. Synthesis for title compound

*2, 4, 5-trichloro-6-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)isophthalonitrile (**3k**)* [15]

For the mixture of **3c** obtained in section *3.1. General synthetic procedure* (2.0mmol) and *N*-Bromosuccinimide (NBS) in carbon tetrachloride (20 mL) was added benzoyl peroxide (5% weigh of intermediate **3k-1**) with stirring. The reacting mixture was heated to reflux for 5 hours and then was cooled to room temperature; the resulting filtrate was collected by filtration, evaporated under reduced pressure to get compound **3k** as pale white solid.

Yield 69%, mp 171-173°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 6.97(br, 1H, NH), 7.56(s, 2H, Ph-3,5-2H). Anal. Calcd. for $C_{15}H_3Cl_5F_3N_3O$: C, 37.89; H, 0.64; N, 8.84. Found: C, 37.82; H, 0.66 N, 8.95.

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[21] The atomic coordinates for **3j** have been deposited at the Cambridge Crys- tallographic Data Centre. CCDC ID: 977468 contains the supplementary crys- tallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Figures and Tables

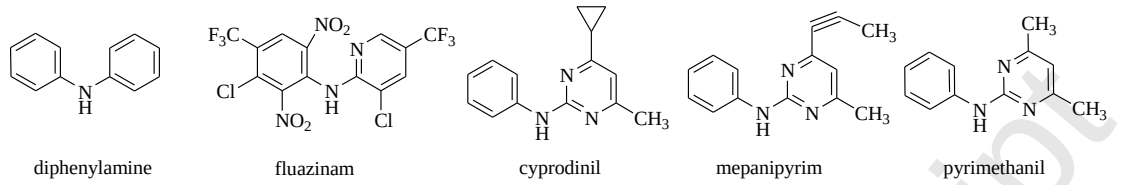

Figure 1. Commercial diarylamine compounds

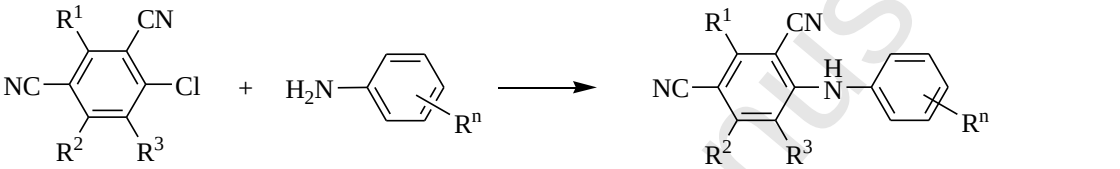

Figure 2. Synthesis scheme of compounds **3a-3g, 3j** and **3l**

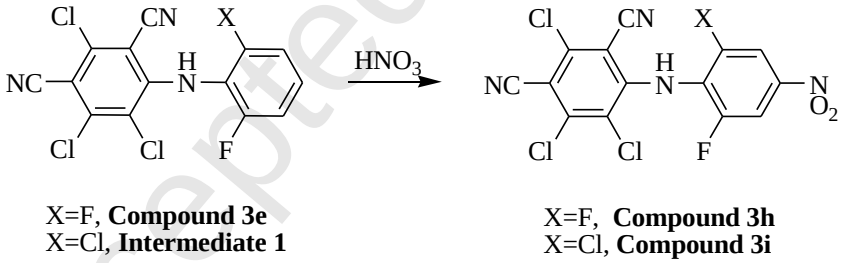

Figure 3. Synthesis scheme of compounds **3h** and **3i**

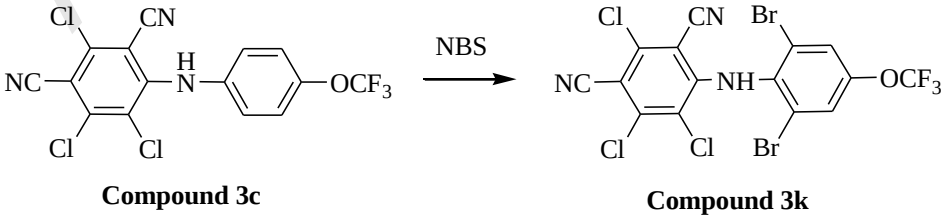

Figure 4. Synthesis scheme of compound **3k**

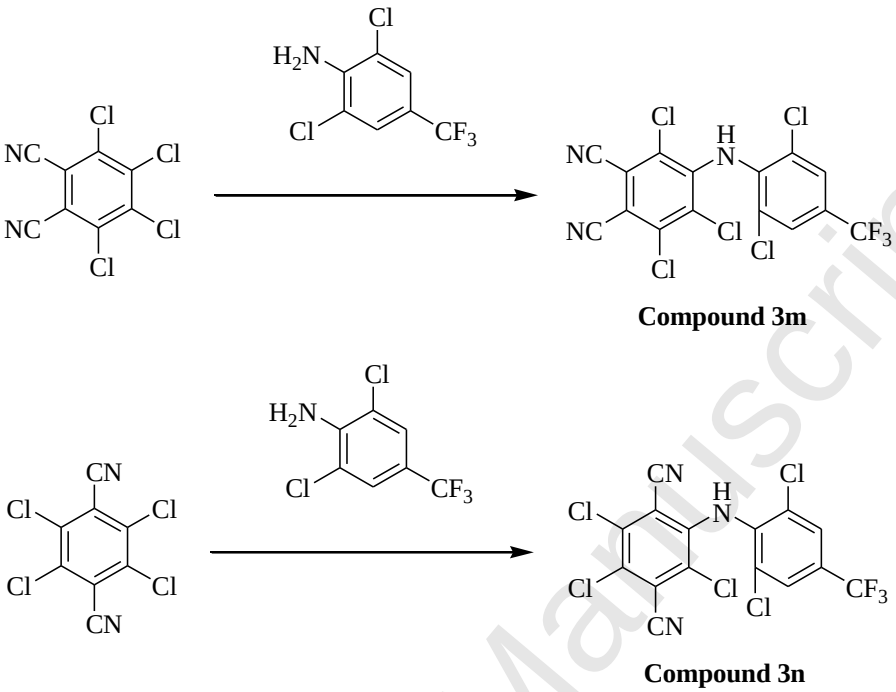

Figure 5. Synthesis scheme of compounds **3m** and **3n**

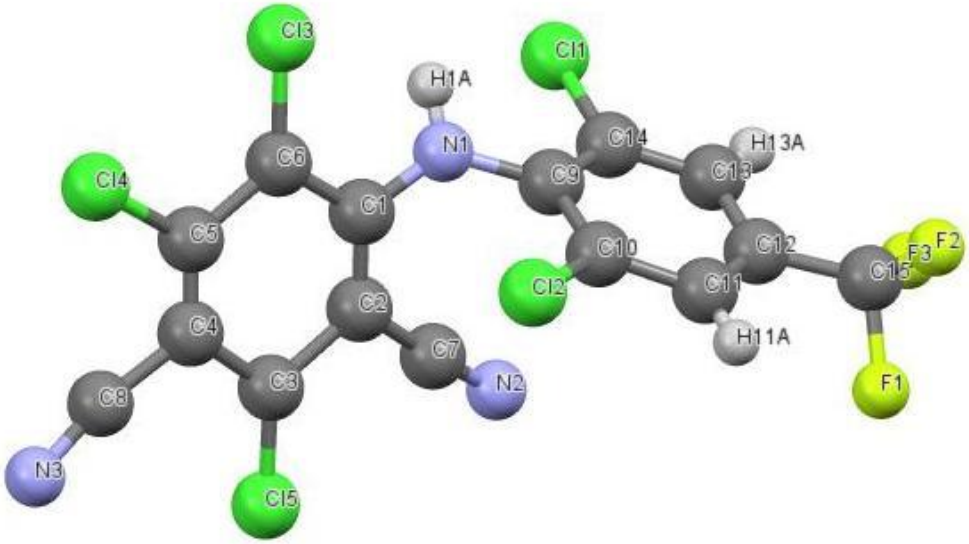

Figure 6. X-ray single-crystal diffraction of **3j**

Table 1

Chemical structures and fungicidal activity of compounds **3a** to **3l**

Compound	$R^1=R^2=R^3$	R^n	CLogP	Fungicidal Activity against SCR (% control at given concentration mg L^{-1})			
				400	100	25	6.25
3a	Cl	3-CF_3	6.14960	0	/[a]	/	/
3b	Cl	4-CF_3	6.14962	0	/	/	/
3c	Cl	4-OCF_3	6.26621	0	/	/	/
3d	Cl	2,4-2F	5.52539	100	0	/	/
3e	Cl	2,6-F2	5.52539	98	0	/	/
3f	Cl	2-Cl-4-CF_3	6.86318	0	/	/	/
3g	Cl	2,3,4-F3	5.52859	98	30	0	/
3h	Cl	2,6-F2-4-NO_2	5.31092	100	95	30	0
3i	Cl	2-Cl-6-F-4-NO_2	5.88092	100	80	50	30
3j	Cl	2,6-Cl2-4-CF_3	7.57637	100	100	98	70
3k	Cl	2,6-Br2-4-OCF_3	7.75021	0	/	/	/
3l	F	2,6-Cl2-4-CF_3	6.18637	100	20	0	/
chlorothalonil			3.47	50	/	/	/
fluazinam			5.96488	100	90	30	10

[a] stands for no data.

Table 2
Chemical structures and fungicidal activity of compounds **3m** to **3n**

Compound	Position of di-CN	$R^1=R^2=R^3$	R^n	CLogP	Fungicidal Activity against SCR (% control at given concentration mg L^{-1})			
					400	100	25	6.25
3j	1,3-disubstituted	Cl	2,6-Cl2-4- CF_3	7.57637	100	100	98	70
3m	1,2-disubstituted	Cl	2,6-Cl2-4- CF_3	7.59637	100	50	0	/[a]
3n	1,4-disubstituted	Cl	2,6-Cl2-4- CF_3	7.57637	100	0	/	/

[a] stands for no data.