One-Pot Regioselective Synthesis of Novel Oximino Ester-Containing 1-Aryl-4-chloro-3-oxypyrazoles as Potential Fungicides

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A novel, functional-group-tolerant, and highly regioselective one-pot synthesis of six 4-chloro-1-aryl-3-oxypyrazoles, **8a**–**8f**, containing an oximino ester moiety has been developed. Their structures were characterized by ^{1}H- and ^{13}C-NMR, IR, MS, and elemental analyses. The regioselectivity of the reaction was also determined by single-crystal X-ray diffraction analysis of product **8d**. The reaction pathway, proposed with the aid of DFT calculations, likely proceeds *via* a DMF-catalyzed mechanism, which involves an electrophilic attack by $SOCl_2$ and two nucleophilic substitutions by benzyl bromide (BnBr) and Cl^-, respectively, as the key steps. A preliminary *in vitro* bioassay indicated that most compounds exhibited good fungicidal activities against *Sclerotinia sclerotiorum* and *Gibberella zeae*. Especially, **8d** and **8e** displayed higher or similar fungicidal activities compared with pyraclostrobin at the concentration of 10 μg/ml.

Introduction. – Since the discovery of the strobilurin fungicide azoxystrobin (**1**) by *Syngenta* scientists in 1992 (*Fig. 1*) [1], this novel fungicide class, developed from natural fungicidal strobilurin A, oudemansin A, and myxothiazol A, has occupied an important position in agrochemical market due to its lower mammalian toxicity, broad spectrum, and higher fungicidal activity [2–6]. Pyraclostrobin (**2**), kresoxim-methyl (**3**), and trifloxystrobin (**4**, *Fig. 1*), three representatives in the strobilurin family containing methoxy carbamate or oximino ester moieties, play significant roles [7–10]. Generally, the chemical structure of strobilurin fungicides can be characterized by three parts: *i*) a methyl (*E*)-2-(methoxyimino)acetate or isosteric methyl (*E*)-2-methoxyacrylate moiety as pharmacophore, *ii*) an aromatic bridge, and *iii*) a side chain. Analysis of the mode of action revealed that these strobilurins inhibited the mitochondrial respiration by binding their pharmacophore to the ubiquinol-oxidation center (Qo site) of cytochrome bc1–enzyme complex of a fungus where electron transfer took place [11][12]. Therefore, researchers have mainly focused on keeping the pharmacophore but changing the side chain, and some new strobilurins have been commercialized [13–15]. To prevent the resistance of pathogens to chemicals and develop more efficient fungicides, we have also devoted considerable efforts. Bioactive (alkyl)oxy acetate, thiazolidine-2-thione, and *O*-acetylated glucopyranosyl or benzoyl moieties were introduced into the 1-aryl-3-methoxy-1*H*-pyrazole structure of pyraclostrobin (**2**) to

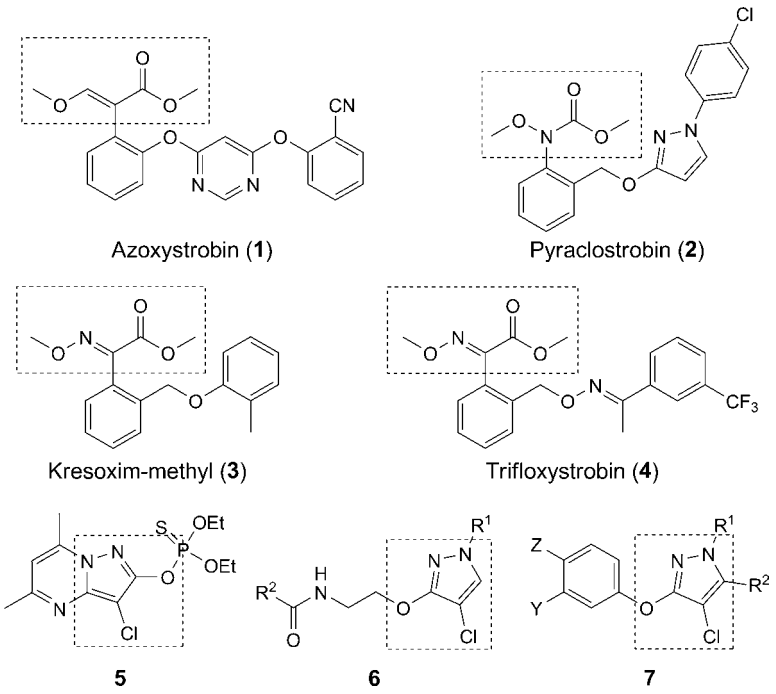


Fig. 1. *Representative strobilurin fungicides and 4-chloro-3-oxypyrazoles*

replace its methoxycarbamate pharmacophore, which could not be synthesized in an environmentally friendly way, and several novel 1,5-diaryl-3-oxypyrazoles with good fungicidal activity were reported [16–19].

On the other hand, since the preparation of compound **5** (*Fig. 1*) in 1969 for the control of susceptible and resistant pasture mosquitoes [20], the 4-chloro-3-oxypyrazoles have attracted enormous attention due to their diverse biological features such as antimicrobial (*e.g.*, **6**) and herbicidal (*e.g.*, **7**) activities [21][22]. Introduction of Cl-atom can indeed led to a better fungicidal efficacy and plant systemicity. In continuation of our program toward the preparation of fungicidal 1-aryl-3-oxypyrazole derivatives, the oximino ester pharmacophores of **3** and **4**, as well as Cl were introduced into the 1-aryl-3-oxypyrazole structure of **2** according to the principles of active parts combination, and novel 1-aryl-3-(arylmethoxy)-4-chloropyrazoles **8** were designed (*Fig. 2*).

Herein, we report a novel, highly regioselective, and functional-group-tolerant method to prepare six oximino ester-containing 4-chloro-1-aryl-3-(arylmethoxy)pyrazoles **8a**–**8f** in one step from readily accessible 1-aryl-1*H*-pyrazol-3-ols. The regioselectivity of the reaction was established by single-crystal X-ray diffraction analysis of **8d**. The reaction mechanism was also proposed with the help of DFT calculations. A preliminary *in vitro* bioassay indicated that most compounds displayed good fungicidal activity against *Sclerotinia sclerotiorum* and *Gibberella zeae*, especially

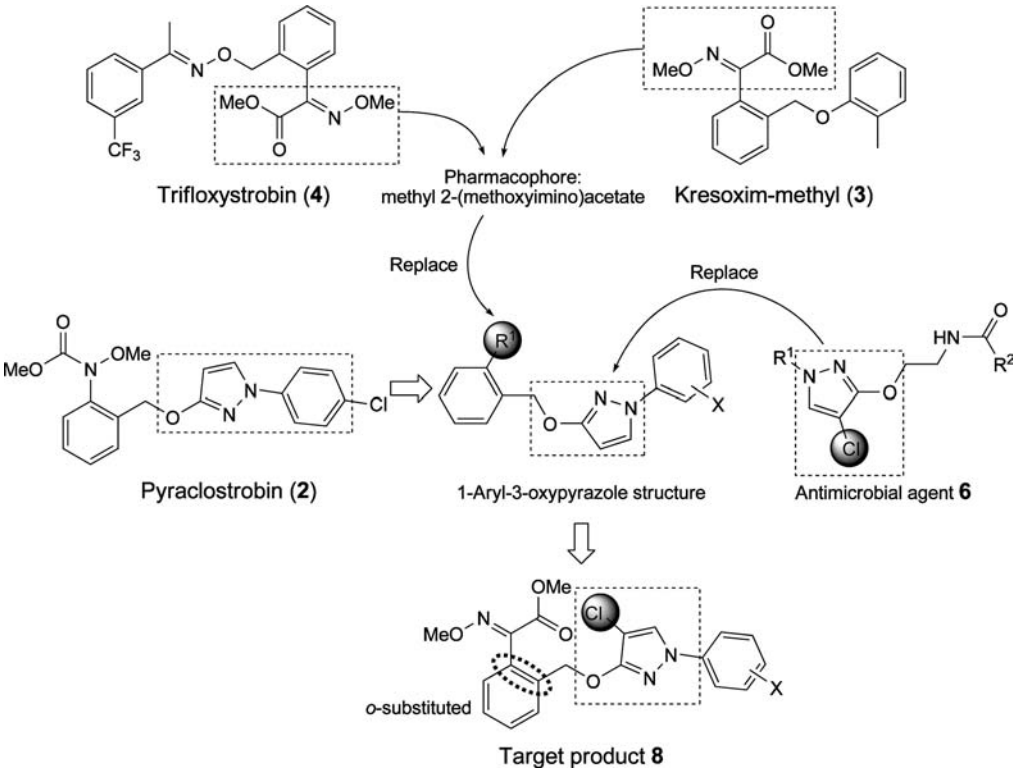
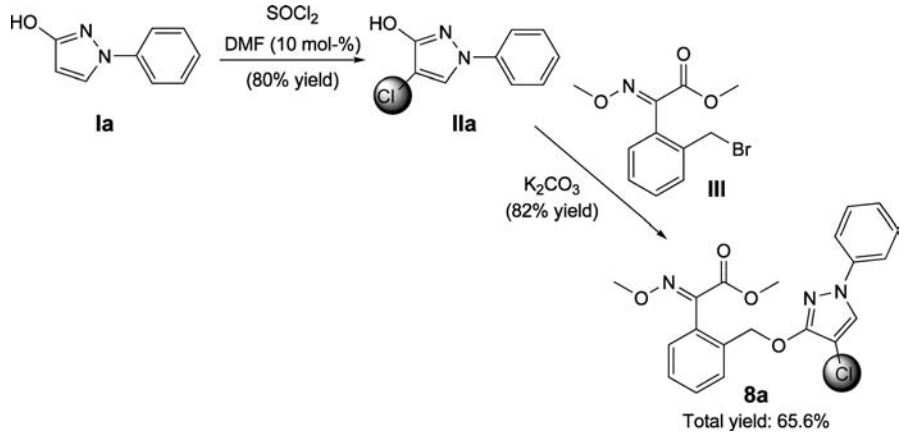


Fig. 2. *Design strategy for the target compound* **8**

8d and **8e**, which showed a higher or similar activity as compared with pyraclostrobin at a concentration of 10 μg/ml.

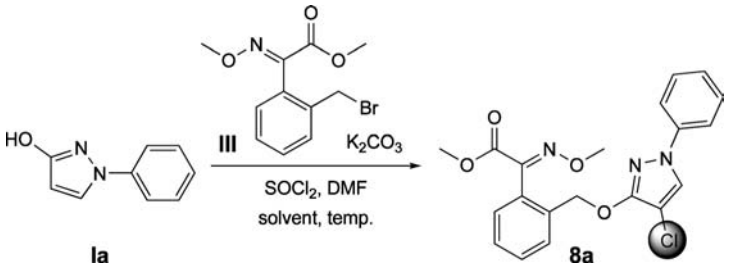
Results and Discussion. – *Synthesis.* Recently, we have reported details of the DMF-catalyzed 4-chlorination of 1-aryl-1*H*-pyrazol-3-ols [23]. Therefore, the reaction sequence depicted in *Scheme 1* was first proposed for the synthesis of the target product **8a**. In the presence of a catalytic amount of DMF, 1-phenyl-1*H*-pyrazol-3-ol (**Ia**) was heated to reflux in $SOCl_2$, and 4-chlorinated product **IIa** was isolated in 80% yield, with high regioselectivity for monochlorination at C(4). Then, 82% yield of **8a** was obtained by the reaction of **IIa** with bromobenzyl derivative **III** in the presence of K_2CO_3 in boiling acetone. Although **8a** was prepared by this approach, it required two time-consuming, purification processes *via* column chromatography, and the total yield was only 65.6%. To address this problem, a one-pot synthesis (*Table 1*) was proposed. However, since compound **III** contains many functional groups, such as alkoxy, ester, imino, and aryl groups, *i.e.*, both electron-donating and -withdrawing groups, the regioselective formation of the 4-chlorinated product **8a** seemed not so easy to accomplish.

Scheme 1. *Synthesis of Target Product* **8a**



Unexpectedly, a better yield, *i.e.*, 80% (*Table 1*, *Entry 1*), of **8a** was obtained by the one-pot reaction of **Ia**, **III**, K_2CO_3, and $SOCl_2$ in boiling $CHCl_3$ by using DMF (10 mol-%) as catalyst. HPLC Analysis of the reaction mixture indicated that this reaction was completed within 6 h without the formation of other chlorinated products. However,

Table 1. *One-Pot Synthesis of the Target Product* **8a**[a])



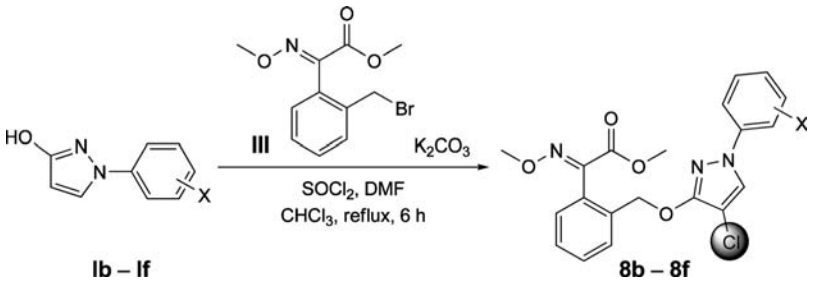
Entry	DMF [equiv.]	Solvent	Temp.	Time [h]	Yield of isolated **8a** [%]
1	0.1	$CHCl_3$	reflux	6	80
2	0.15	$CHCl_3$	reflux	6	80
3	–	$CHCl_3$	reflux	6	32
4	0.1	CH_2Cl_2	reflux	6	38
5	0.1	CCl_4	reflux	6	42
6	0.1	Acetone	reflux	6	45
7	0.1	MeCN	reflux	6	50
8	0.1	$CHCl_3$	r.t.	6	15
9	0.1	–	reflux	6	40

[a]) The reaction was carried out with **Ia** (1.0 mmol), **III** (1.05 mmol), K_2CO_3 (1.5 mmol), $SOCl_2$ (5.0 mmol), and DMF (0–0.15 mmol) in a solvent and monitored by HPLC.

the yield was not improved by increasing the amount of DMF, and this reaction turned out to proceed with lower yield when using CH_2Cl_2, CCl_4, acetone or MeCN instead of $CHCl_3$ as solvent (38–50%; *Table 1*, *Entries 4–7*). Furthermore, the reaction did not run well at room temperature (15%; *Table 1*, *Entry 8*) or without DMF or solvent (32–40%; *Table 1*, *Entries 3* and *9*).

Similar results were obtained starting from 1-aryl-1*H*-pyrazol-3-ols **Ib** and **Ic** with electron-donating Me and CF_3O groups, and **Id**–**If** with electron-withdrawing F, Cl, or CF_3 groups at various positions of the 1-phenyl ring, giving yields of 75 and 76% (*Table 2*, *Entries 1* and *2*) and 80–83% (*Table 2*, *Entries 3–5*) yield of **8b** and **8c** and **8d**–**8f**, respectively. All these examples revealed this one-pot synthesis to be a versatile method with a good functional-group tolerance. The regioselectivity of the reaction and the structures of the products **8** were unequivocally determined by NMR spectroscopy and single-crystal X-ray diffraction analysis of **8d** (*Fig. 3*).

Table 2. *One-Pot Synthesis of the Target Products* **8b–8f** [a])



Entry	Substrate	X	Yield [%] (isolated product)
1	**Ib**	*m*-Me	76 (**8b**)
2	**Ic**	*p*-CF_3O	75 (**8c**)
3	**Id**	*p*-Cl	82 (**8d**)
4	**Ie**	*m*-CF_3	83 (**8e**)
5	**If**	*m*-CF_3-*p*-F	80 (**8f**)

[a]) The reaction was carried out with **Ib**–**If** (1.0 mmol), **III** (1.05 mmol), K_2CO_3 (1.5 mmol), $SOCl_2$ (5.0 mmol), and DMF (0.1 mmol) in boiling $CHCl_3$ and monitored by HPLC.

Structures. Compound **8d** crystallizes in the monoclinic space group $P2_1/n$. The detailed crystal and structure refinement data for **8d** are compiled in *Table 4* in the *Exper. Part*. In the crystal structure of **8d** (*Fig. 3*), the bond length of C(3)–Cl(2) is 1.736(4) Å, representing a typical aryl–Cl bond length, and the value is similar to those (1.738(4) Å) reported for other related derivatives [23]. The bridge benzene ring *A* (C(11)–C(16)) and the terminal benzene ring *B* (C(1)–C(6)) are connected to the pyrazole ring *C*, twisted by 77.20° and 20.93°, respectively, whereas they form a dihedral angle of 56.48°. The ester and methoxyimino groups are almost coplanar, twisted by 60.98° and 59.52°, 9.08°, and 5.73°, 19.94°, and 19.52°, respectively, from the planes of the rings *A*, *B*, and *C*. The intramolecular C–H···O and C–H···N H-bonds result in the

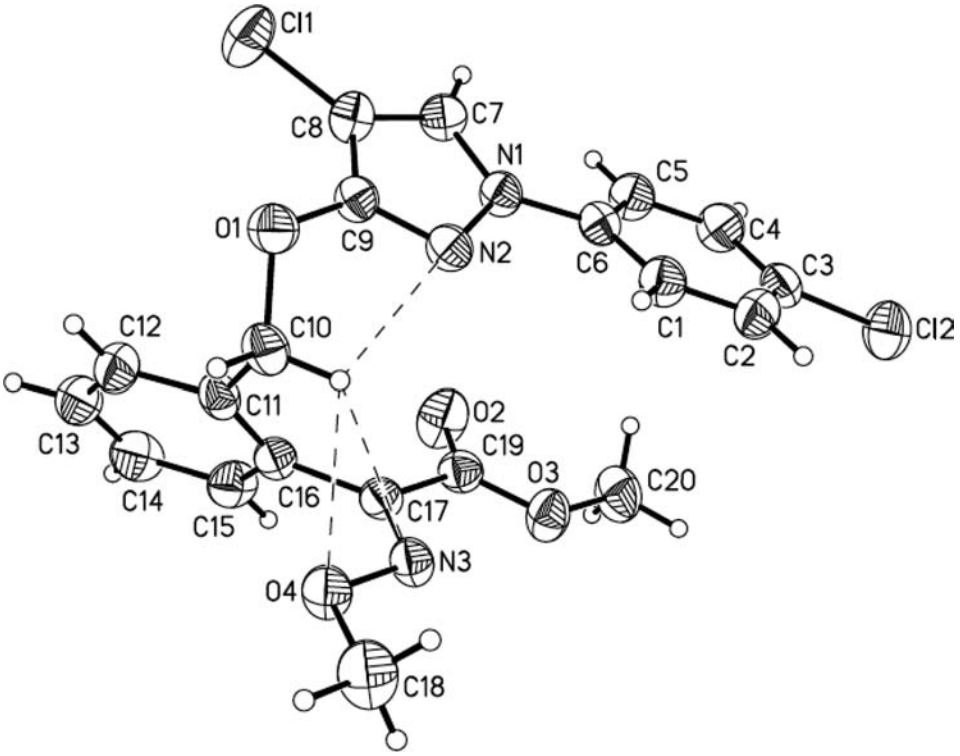


Fig. 3. *X-Ray crystal structure of* **8d**

formation of three non-planar pseudo-rings *D* (N(2)/C(9)/O(1)/C(10)/H(10B)), *E* (N(3)/C(17)/C(16)/C(11)/C(10)/H(10B)), and *F* (O(4)/N(3)/C(17)/C(16)/C(11)/C(10)/H(10B)) of envelope conformations, with O(1), N(3), and O(4) atoms displaced by 0.415, 0.951, and 1.988 Å, respectively, from the plane of the other ring atoms. In the crystal, the molecules form intermolecular C–H⋯O H-bonds (*Fig. 4*) and C–H⋯π stacking interactions (*Fig. 5*), one is between the MeO H-atom and the center of ring *B* (C(20)–H(20B)⋯*Cg*(1)), and the others from a phenyl H-atom to the center of ring *A* (C(2)–H(2B)⋯*Cg*(2) and C(4)–H(4A)⋯*Cg*(2)).

In conclusion, 1-aryl-1*H*-pyrazol-3-ols **I** containing aryl and OH groups, with electron-donating and -withdrawing groups, as well as bromobenzyl compound **III** containing alkoxy, ester, imino, halogen, and phenyl groups, were all compatible with this one-pot reaction, and the procedure led to the regioselective formation of the 4-chlorinated products **8** in good yields. Significantly, this method does not involve tedious steps of protection and deprotection of functional groups.

Reaction Mechanism. The following results were also obtained in studies to elucidate the mechanism of this one-pot reaction: *1*) with a catalytic amount of DMF, a higher yield of **8a** (80%) was obtained than without DMF; *2*) the nucleophilic substitution with elimination of HBr occurred between the OH group of **Ia** and bromobenzyl derivation **III**; *3*) to determine whether the $SOCl_2$–DMF complex **SD**

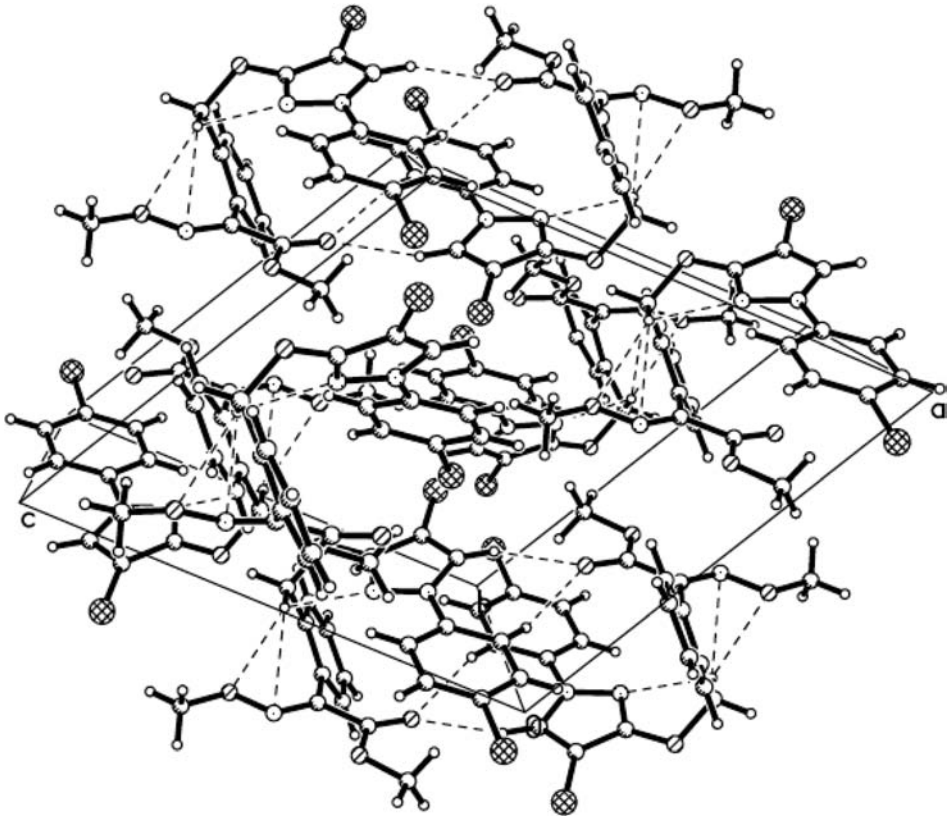
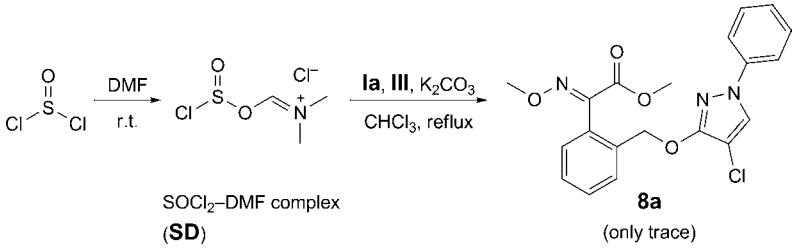


Fig. 4. *A packing diagram of* **8d**

was the chlorinating species (*Scheme 2*), **SD** was prepared [24] and allowed to react with **Ia**, **III**, and K_2CO_3 in boiling $CHCl_3$. However, only a trace of product **8a** was detected by HPLC. Therefore, it seems most likely that **Ia** reacts with $SOCl_2$ and **III** first, and then the reaction with the catalyst DMF occurs; *4*) the 4-chlorination likely proceeds *via* nucleophilic attack by Cl^-, because $SOCl_2$ is normally a source of Cl^-, and

Scheme 2. *Reaction of* **Ia**, **III**, *and* K_2CO_3 *with* $SOCl_2$*–DMF complex* **SD** *in boiling* $CHCl_3$



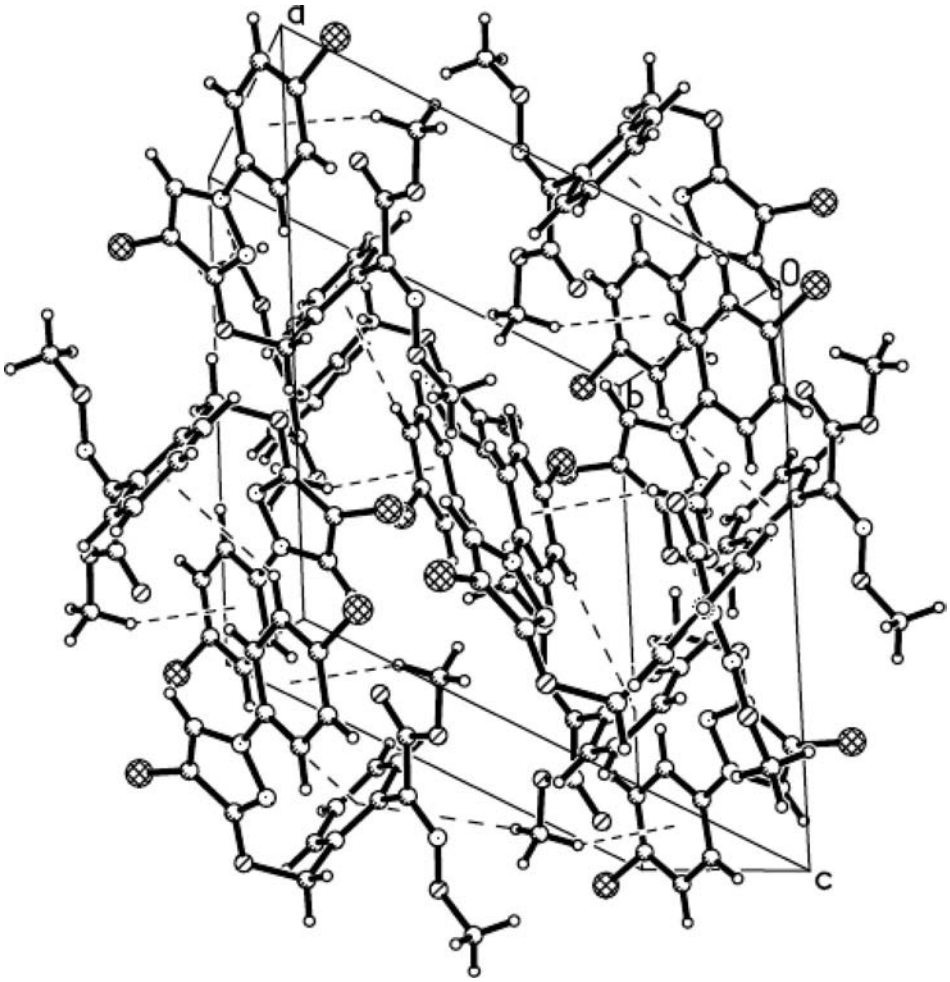
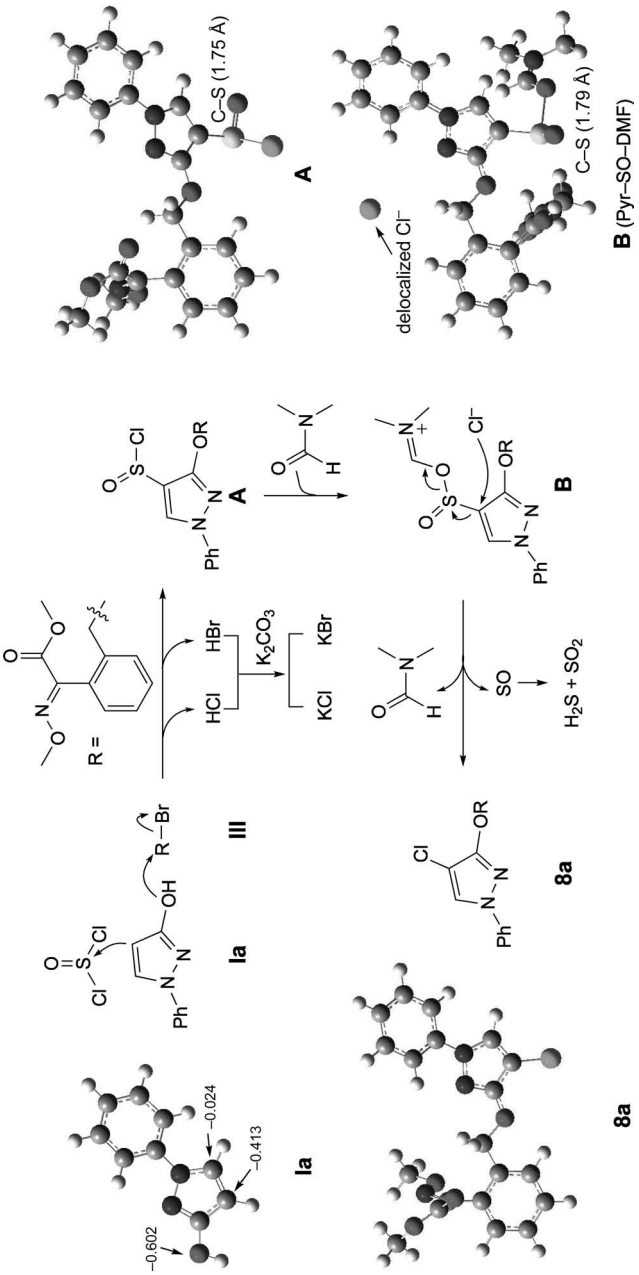


Fig. 5. *Intermolecular C–H···π interactions of* **8d**

the intermediacy of Cl^- is feasible; *5*) elemental sulfur was isolated during the column chromatographic purification of **8a**.

We propose a catalytic mechanism for the formation of **8a** from **Ia** and **III**, which was also illustrated with the aid of density-functional theory (DFT) calculations (*Scheme 3*). The calculations were carried out in the ground-state (*in vacuo*) with Gaussian 09 software by using B3LYP/6-31G* method [25–28]. As can be seen from the NBO (natural bond orbital) charges of **Ia**, the initial electrophilic attack of $SOCl_2$ occurs at the more electron-rich C(4) atom (−0.413; C(5) −0.024). Meanwhile, the nucleophilic substitution of the negatively charged O-atom (−0.602) to **III** occurs competitively, releasing one molecule of HBr and generating an active intermediate **A** [29][30]. This step involves a concerted sulfonylation/alkylation. Subsequently, an intermediate **B** is formed *via* complexation of **A** with DMF, and Cl^- takes part in the

Scheme 3. *Proposed Reaction Pathway for the Formation of* **8a** *with the Aid of DFT Calculations*



nucleophilic substitution of the SO-DMF group. Then, product **8a** is formed *via* extrusion of SO and regeneration of DMF. The longer C–S bond in **B** (1.79 Å) than in **A** (1.75 Å) makes the bond rupture more easy when the nucleophilic substitution takes place. In this reaction, K_2CO_3 is an acid-binding agent, and the catalyst DMF acts an electron-withdrawing group to improve the reaction rate and, additionally, as a leaving group upon protonation. Sulfur monoxide (SO) has been suggested as a product in other redox reactions of $SOCl_2$, but detection of SO has not been possible due to its ready disproportionation to SO_2 and elemental sulfur [31–34]. Indeed, elemental sulfur was isolated, which indicated the possible involvement of SO in the reaction.

With the help of DFT calculations, the probability and position of this chlorination on the pyrazole ring can be proposed. Related studies on the introduction of Cl or other halogen atoms to other heterocycles, such as isoxazole, isothiazole, imidazole, and thiazole, should also be calculated first, and then achieved. These works are underway in our laboratory and will be reported in due course.

Fungicidal Activity Studies. Compounds **8a**–**8f** were screened for bioactivity against two fungi, *Sclerotinia sclerotiorum* and *Gibberella zeae*, at a dosage of 10 μg/ml each. As can be seen from *Table 3*, most compounds have moderate fungicidal activities, except **8d** (X = *p*-Cl; 100%, 81%) with excellent inhibitory activity and **8e** (X = *m*-CF_3; 86%, 74%) with a level similar to that of pyraclostrobin. The products containing substituent X with electron-withdrawing properties, such as F (*i.e.*, **8f**; 78%, 67%), Cl (*i.e.*, **8d**; 100%, 81%), and CF_3 (*i.e.*, **8e**, 86%, 74%; and *i.e.*, **8f**, 78%, 67%) groups showed higher activities than those with electron-donating Me (*i.e.*, **8b**, 61%, 46%) and CF_3O (*i.e.*, **8c**, 63%, 50%) groups. However, switching X from Cl to the strong electron-withdrawing F or CF_3 groups without full consideration of the electronic effects had negative impact on the inhibition rates, as seen in the comparison of compounds **8d** *vs.* **8e** and **8f**. This might imply that Cl could balance the HLB (hydrophilic-lipophilic balance) value and increase the systemic of molecule within plant. Moreover, classical intramolecular (C–H···O, C–H···N) and intermolecular (C–H···O) H-bonds (*Figs. 3* and *4*, resp.) formed in the crystal of **8d** seem to have an impact on improving the hydrophilicity of molecule. The present work indicated that **8d** and **8e** could be used as potential lead compounds for further studies of novel fungicides. The enhancement of bioactivity requires a reasonable design of molecules,

Table 3. *Antifungal Activity of the Tested Compounds* (10 μg/ml)

Compounds	X	Inhibition [%][a]	
		S. sclerotiorum	*G. zeae*
8a	H	65	51
8b	*m*-Me	61	46
8c	*p*-CF_3O	63	50
8d	*p*-Cl	100	81
8e	*m*-CF_3	86	74
8f	*m*-CF_3, *p*-F	78	67
Pyraclostrobin	–	96	71

[a]) 0, No activity, and 100, total kill.

such as full consideration of H-bonds and electronic effects of substituents, combination of heterocycle and pharmacophore, and introduction of halogen such as Cl to balance the HLB value of molecule and enhance the plant systemicity.

Conclusions. – In summary, we have developed a simple and efficient method to prepare six novel oximino ester-containing 4-chloro-1-aryl-3-oxypyrazoles, **8a**–**8f**, in one step from readily accessible 1-aryl-1*H*-pyrazol-3-ols, **Ia**–**If**, bromobenzyl compound **III**, and $SOCl_2$. The DMF-catalyzed reaction mechanism proposed on the basis of DFT calculations involves an electrophilic attack by $SOCl_2$, and two nucleophilic substitutions by **III** and Cl^-, respectively, as the key steps. Good functionality tolerance and high regioselectivity for monochlorination at C(4) render this method useful for the synthesis of these 4-chloro-3-oxypyrazole strobilurins. The fungicidal activities of **8a**–**8f** were tested *in vitro* against *Sclerotinia sclerotiorum* and *Gibberella zeae*, and **8d** displayed a higher fungicidal activity, whereas **8e** exhibited a similar level, as compared with pyraclostrobin. This implies that full consideration of the electronic effects, and introduction of halogen such as Cl to balance the HLB value and enhance the plant systemicity are important for improving their fungicidal activities. Further introduction of halogen to the pyrazole ring or other heterocycles, and the investigation of bioactivities are underway in our laboratory and will be reported in due course.

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Experimental Part

General. All reagents used were of anal. grade, and solvents were dried by standard methods and distilled before use [35]. Compounds **Ia**–**If** [36] and **III** [12] were prepared according to the published procedures. TLC: Precoated silica-gel plates (*Merck* silica gel *60* F_{254}); detection by UV light. M.p.: *X-4* Microscope electrothermal apparatus; uncorrected. IR Spectra: *Nicolet* 380 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker* spectrometer, at 400 and 100 MHz, resp.; in $CDCl_3$ or (D_6)DMSO; chemical shifts δ in ppm rel. to TMS as internal standard, and coupling constants J in Hz. MS: *Agilent* 1100 Series *LC/MSD Trap SL*. Elemental analyses: *Vario EL III* elemental analyzer.

*General Procedure for the Synthesis of Methyl (*2E*)-2-(2-{[(1-Aryl-4-chloro-1*H*-pyrazol-3-yl)oxy]-methyl}phenyl)-2-(methoxyimino)acetate* **8a**–**8f** [40]. To a soln. of *1-aryl-1*H*-pyrazol-3-ol* (**Ia**–**If**; 1.0 mmol) and *methyl (*2E*)-2-(2-[bromomethyl)phenyl]-2-(methoxyimino)acetate* (**III**; 0.3 g, 1.05 mmol) in $CHCl_3$ (20 ml) was added K_2CO_3 (0.21 g, 1.5 mmol). Then, $SOCl_2$ (5 ml) and a cat. amount of DMF (0.1 mmol) were added. The mixture was heated to reflux for 6 h (reaction monitored by HPLC), and then K_2CO_3 was filtered off. The solvent was evaporated under reduced pressure. The residue was dispersed in H_2O (200 ml) and extracted with AcOEt (3×15 ml). The org. phase was separated, dried (Na_2SO_4), and then concentrated to dryness. It was then purified by flash column chromatography (CC; silica gel; AcOEt/petroleum ether (PE) 1:12 (*v*/*v*)) to afford target product **8a**–**8f**.

*Methyl (*2E*)-2-(2-{[(4-Chloro-1-phenyl-1*H*-pyrazol-3-yl)oxy]methyl}phenyl)2-(methoxyimino)acetate* (**8a**). Yield: 0.32 g (80%). White solid. M.p. 104–105°. IR (KBr): 3147, 2949, 2895, 1734, 1598, 1557, 1511, 1463, 1438, 1406, 1356, 1323, 1223, 1122, 1063, 1012, 984, 947, 895, 862, 795, 756, 684. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.73 (*s*, CH); 7.63–7.19 (*m*, 9 arom. H); 5.25 (*s*, CH_2); 4.04 (*s*, MeO); 3.84 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.3; 158.9; 149.4; 139.7; 134.8; 130.1; 129.5; 129.4; 128.9; 128.5; 128.1; 125.7; 125.6; 117.6; 98.3; 69.5; 63.9; 53.1. ESI-MS: 400.11 ($[M+H]^+$), 422.09 ($[M+Na]^+$). Anal. calc. for $C_{20}H_{18}ClN_3O_4$ (399.83): C 60.08, H 4.54, N 10.51; found C 59.83, H 4.58, N 10.57.

*Methyl (*2E*)-2-[2-({[4-Chloro-1-(3-methylphenyl)-1*H*-pyrazol-3-yl]oxy}methyl)phenyl]-2-(methoxyimino)acetate* (**8b**). Yield: 0.31 g (76%). White solid. M.p. 108–109°. IR (KBr): 3133, 2946, 2820,

1719, 1583, 1548, 1490, 1442, 1407, 1375, 1352, 1325, 1254, 1218, 1114, 1067, 1018, 952, 871, 823, 786, 728, 690. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.69 (*s*, CH); 7.62 – 7.20 (*m*, 8 arom. H); 5.23 (*s*, CH_2); 4.04 (*s*, MeO); 3.84 (*s*, MeO); 2.42 (*s*, Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 162.3; 159.0; 149.4; 138.2; 137.4; 134.7; 131.3; 130.1; 129.8; 129.5; 128.9; 128.5; 128.1; 125.6; 119.8; 116.1; 98.6; 69.5; 63.9; 53.1; 20.4. ESI-MS: 414.11 ($[M+H]^+$), 436.09 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{20}ClN_3O_4$ (413.85): C 60.95, H 4.87, N 10.15; found C 60.74, H 4.82, N 10.21.

*Methyl (2*E*)-2-{2-[({4-Chloro-1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazol-3-yl}oxy)methyl]phenyl}-2-(methoxyimino)acetate* (**8c**). Yield: 0.36 g (75%). White solid. M.p. 149 – 150°. IR (KBr): 3144, 2946, 1722, 1607, 1558, 1507, 1441, 1393, 1370, 1298, 1261, 1208, 1146, 1115, 1063, 1017, 957, 842, 808, 759, 728, 685. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.71 (*s*, CH); 7.62 – 7.21 (*m*, 8 arom. H); 5.24 (*s*, CH_2); 4.04 (*s*, MeO); 3.84 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.3; 159.2; 149.4; 146.6; 146.6; 138.2; 134.7; 130.1; 129.5; 128.9; 128.5; 128.2; 125.7; 122.2; 118.6; 99.0; 69.6; 63.9; 53.0. ESI-MS: 484.09 ($[M+H]^+$), 506.06 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{17}ClF_3N_3O_5$ (483.82): C 52.13, H 3.54, N 8.68; found C 52.35, H 3.60, N 8.61.

*Methyl (2*E*)-2-[2-({[4-Chloro-1-(4-chlorophenyl)-1*H*-pyrazol-3-yl]oxy}methyl)phenyl]-2-(methoxyimino)acetate* (**8d**). Yield: 0.36 g (82%). White solid. M.p. 147 – 148°. IR (KBr): 3140; 2940; 1721; 1594; 1547; 1495; 1437; 1355; 1327; 1253; 1217; 1114; 1063; 1016; 959; 829; 785; 723; 689. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.68 (*s*, CH); 7.61 – 7.20 (*m*, 8 arom. H); 5.23 (*s*, CH_2); 4.03 (*s*, MeO); 3.84 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.3; 159.0; 149.4; 138.2; 134.7; 131.0; 130.1; 129.5; 128.9; 128.5; 128.2; 125.6; 118.6; 98.8; 69.5; 63.9; 53.1. ESI-MS: 434.07 ($[M+H]^+$), 456.05 ($[M+Na]^+$). Anal. calc. for $C_{20}H_{17}Cl_2N_3O_4$ (434.27): C 55.31, H 3.95, N 9.68; found C 55.52, H 3.91, N 9.62.

*Methyl (2*E*)-2-{2-[({4-Chloro-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-3-yl}oxy)methyl]phenyl}-2-(methoxyimino)acetate* (**8e**). Yield: 0.39 g (83%). White solid. M.p. 119 – 120°. IR (KBr): 3140, 2946, 1730, 1598, 1562, 1518, 1458, 1406, 1358, 1328, 1306, 1226, 1169, 1122, 1067, 1014, 948, 889, 794, 758, 692. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 (*s*, CH); 7.79 – 7.21 (*m*, 8 arom. H); 5.26 (*s*, CH_2); 4.05 (*s*, MeO); 3.85 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.3; 159.3; 149.4; 140.0; 134.5; 130.2; 130.1; 129.5; 129.0; 128.5; 128.2; 125.6; 122.1; 122.0; 120.1; 114.3; 99.6; 69.7; 63.9; 53.1. ESI-MS: 468.10 ($[M+H]^+$), 490.08 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{17}ClF_3N_3O_4$ (467.83): C 53.91, H 3.66, N 8.98; found C 54.12, H 3.60, N 8.92.

*Methyl (2*E*)-2-{2-[({4-Chloro-1-[4-fluoro-3-(trifluoromethyl)phenyl]-1*H*-pyrazol-3-yl}oxy)methyl]phenyl}-2-(methoxyimino)acetate* (**8f**). Yield: 0.39 g (80%). White solid. M.p. 101 – 102°. IR (KBr): 3140, 2946, 1734, 1602, 1563, 1518, 1459, 1407, 1372, 1359, 1330, 1308, 1226, 1173, 1122, 1068, 1017, 952, 843, 792, 753, 696. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*s*, CH); 7.75 – 7.24 (*m*, 7 arom. H); 5.60 (*s*, CH_2); 4.01 (*s*, MeO); 3.89 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.1; 162.8; 149.0; 147.8; 139.7; 130.6; 130.4; 130.2; 129.9; 129.6; 128.7; 128.4; 127.4; 125.7; 63.9; 53.1; 30.9. ESI-MS: 486.09 ($[M+H]^+$), 508.07 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{16}ClF_4N_3O_4$ (485.82): C 51.92, H 3.32, N 8.65; found C 51.71, H 3.37, N 8.72.

Fungicidal Assays. The fungicidal activities of compounds **8a** – **8f** against fungi *Sclerotinia sclerotiorum* and *Gibberella zeae* were evaluated as described in [17][37]. The compounds to be tested were dissolved in acetone and added to a sterile agarized *Czapek-Dox* medium at 45°. In preliminary screenings, compounds were used in a concentration of 10 µg/ml. The control sample contained only 1 equiv. of acetone. The media were poured onto 8-cm *Petri* dishes (10 ml for each dish) and, after 2 d, inoculated with 5-mm PDA (potato dextrose agar) discs with overgrown mycelium. In the case of *Sclerotinia sclerotiorum*, the medium was inoculated by a prick of laboratory needle containing fungus spores. The *Petri* dishes were incubated at r.t. in the dark. After 4 d, the diameters of the inoculation of the cultures were measured. The percentage inhibition of fungal growth was determined by comparison between the development of fungi colonies on media containing compounds and on the control. Three replicates of each test were carried out.

X-Ray Crystallography. Suitable crystals of **8d** were obtained by slow evaporation of EtOH soln. at r.t. Further details of the data collection are compiled in *Table 4*. Crystal data[1]) were collected on a *Nonius CAD-4* diffractometer by using MoK_α (0.71073 Å) radiation. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares on F^2 for all data using SHELXL-97

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[1]) CCDC-949755 (**8d**) contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 4. *Crystallographic Data for Compound* **8d**

Empirical formula	$C_{20}H_{17}Cl_2N_3O_4$
CCDC No.	949755
Formula weight	434.27
Temp. [K]	293(2)
Wavelength [Å]	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions:	
a [Å]	11.516(2)
b [Å]	16.498(3)
c [Å]	12.093(2)
α [°]	90.00
β [°]	118.28(3)
γ [°]	90.00
Volume [Å^3]	2023.3(7)
Z	4
$\rho_{calc.}$ [g cm^{-3}]	1.426
μ [mm^{-1}]	0.353
$F(000)$	896
Crystal size [mm^3]	$0.10 \times 0.20 \times 0.30$
θ Range [°] for data collection	2.01 to 25.36
Index ranges	$0 \le h \le 13$, $0 \le k \le 19$, $-14 \le l \le 12$
Reflections collected	3899
Independent reflections	3709 ($R_{int} = 0.0921$)
Max. and min. transmission	0.9656/0.9015
Data/restraints/parameters	3709/0/262
Goodness-of-fit on F^2	1.006
Final R indices [$I > 2\sigma(I)$]; R_1, wR_2	0.0627, 0.1601
R_1, wR_2 (all data)	0.1026, 0.1799
Largest diff. peak and hole [e · Å^{-3}]	0.224 and -0.351

[38][39]. All non-H-atoms were refined anisotropically, and the H-atoms were added at calculated positions. The isotropic temp. factors were fixed to 1.2 times (1.5 times for Me group) the equivalent isotropic displacement parameters of the C-atom the H-atom is attached to.

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