Regioselective Synthesis and Base Catalyzed Transacylation of Substituted 1*H*-Pyrazole-4-carboxamides

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New type of substituted 1*H*-pyrazole-4-carboxamides were obtained by regioselective synthesis under the catalysis of different bases. The structures of the title compounds were confirmed by elemental analysis, ^{1}H NMR, IR, MS and X-ray crystallography. Compounds 1 were transacylated into their corresponding amides 3 in the presence of sodium hydride. Preliminary bioassays indicated that some compounds showed fungicidal activities against *Rhizoctonia solani* and *Sclerotinia sclerotiorum*.

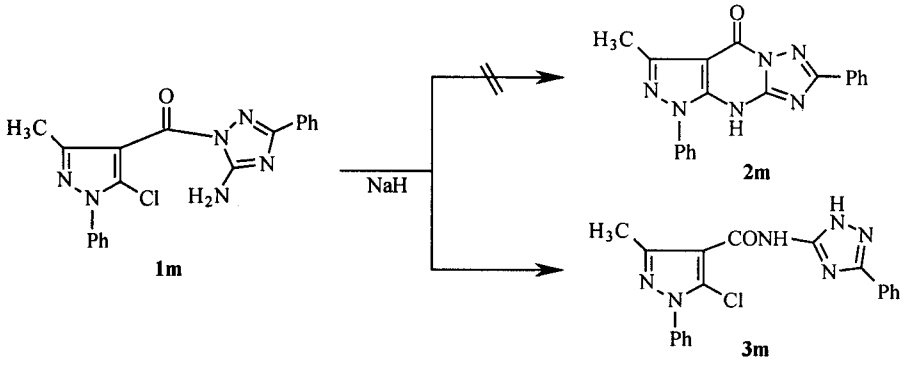
Keywords regioselectivity, 1*H*-pyrazole-4-carboxamide, transacylation, fungicidal activity

Introduction

Azolides are heterocyclic amides in which the amide nitrogen is part of an azole ring, such as imidazole, pyrazole, triazole, tetrazole and benzimidazole. They play an important role in the prevention of a number of plant diseases[1-3] and are attractive intermediates for heterocyclic synthesis.[4] Therefore, development of novel azolides is of great interest to both fused heterocyclic studies and pesticide application.

A series of 1*H*-pyrazole-4-carboxamides as intermediates of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine fused heterocyclic compounds were synthesized in our group.[4] When these substituted 1*H*-pyrazole-4-carboxamides **1** were treated with NaH in solution of THF, no fused heterocyclic products **2** but transacylated products **3** were obtained (Scheme 1). To our knowledge, this is the first report about such transacylation reaction. Herein, we will report the detailed experiment results.

Scheme 1



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Results and discussion

Compounds **1** and **3** were obtained by reaction of 1-substituent-3-methyl-5-chloropyrazole-4-formylchloride with 3-substituent-5-amino-4-cyanopyrazole or 3-substituent-5-amino-triazole (Table 1).

Table 1 Physical constants and elemental analyses of compounds **1** and **3**

Comp.	R^1	R^2	Formula	MS (*FW*)	Yield	mp	Elementary analysis (calcd.) (%)		
				$[M]^+$	(%)	(℃)	C	H	N
1a	CH_3	H	$C_{10}H_9N_6OCl$		54.1	148—150	45.09(45.38)	3.41(3.43)	31.78(31.75)
1b	CH_3	Ph	$C_{16}H_{13}N_6OCl$		53.7	222—224	56.15(56.39)	3.71(3.85)	24.61(24.66)
1c	CH_3	*o*-Cl-Ph	$C_{16}H_{12}N_6OCl_2$	374(375.3)	53.3	196—198	51.49(51.22)	3.38(3.22)	22.12(22.40)
1d	CH_3	MeS	$C_{11}H_{11}N_6OClS$		57.9	201—203	42.30(42.51)	3.46(3.57)	26.95(27.04)
1e	Ph	H	$C_{15}H_{11}N_6OCl$		52.8	172—174	55.04(55.14)	3.66(3.39)	25.39(25.72)
1f	Ph	Ph	$C_{21}H_{15}N_6OCl$		57.9	218—220	62.66(62.61)	3.78(3.75)	20.61(20.86)
1g	Ph	*o*-Cl-Ph	$C_{21}H_{14}N_6OCl_2$		44.9	182—184	57.81(57.68)	3.15(3.23)	19.11(19.22)
1h	Ph	MeS	$C_{16}H_{13}N_6OClS$	372(372.9)	56.3	221—223	51.67(51.55)	3.64(3.51)	22.64(22.54)
1i	CH_3	H	$C_8H_9N_6OCl$		52.7	174—176	39.90(39.93)	3.51(3.77)	34.43(34.92)
1j	CH_3	Ph	$C_{14}H_{13}N_6OCl$	316(316.8)	76.4	219—221	53.19(53.09)	3.94(4.14)	26.10(26.53)
1k	CH_3	CH_3	$C_9H_{11}N_6OCl$		53.2	192—193	42.42(42.45)	4.35(4.35)	32.85(33.00)
1l	Ph	H	$C_{13}H_{11}N_6OCl$		59.7	210—212	51.39(51.58)	3.55(3.66)	27.86(27.76)
1m	Ph	Ph	$C_{19}H_{15}N_6OCl$	378(378.9)	43.3	220—222	60.03(60.24)	4.02(3.99)	22.06(22.18)
1n	Ph	CH_3	$C_{14}H_{13}N_6OCl$		53.7	225—226	53.04(53.09)	4.33(4.14)	26.39(26.53)
3a	CH_3	H	$C_{10}H_9N_6OCl$		90.5[a]	216—218	45.45(45.38)	3.35(3.43)	31.54(31.75)
3b	CH_3	Ph	$C_{16}H_{13}N_6OCl$		94.7[a]	> 240	56.33(56.39)	3.77(3.85)	24.54(24.66)
3c	CH_3	*o*-Cl-Ph	$C_{16}H_{12}N_6OCl_2$	374(375.3)	90.4[a]	231—233	51.07(51.22)	3.08(3.22)	22.16(22.40)
3d	CH_3	MeS	$C_{11}H_{11}N_6OClS$		90.3[a]	237—239	42.60(42.51)	3.56(3.57)	27.06(27.04)
3e	Ph	H	$C_{15}H_{11}N_6OCl$		66.1[b]	175—177	55.35(55.14)	3.46(3.39)	25.49(25.72)
3f	Ph	Ph	$C_{21}H_{15}N_6OCl$		63.7[b]	> 240	62.35(62.61)	3.86(3.75)	20.65(20.86)
3g	Ph	*o*-Cl-Ph	$C_{21}H_{14}N_6OCl_2$		61.3[b]	208—210	57.55(57.68)	3.28(3.23)	18.94(19.22)
3h	Ph	MeS	$C_{16}H_{13}N_6OClS$	372(372.9)	63.6[b]	196—198	51.29(51.55)	3.41(3.51)	22.30(22.54)
3i	CH_3	H	$C_8H_9N_6OCl$		90.8[a]	270—272	39.61(39.93)	3.77(3.77)	35.39(34.92)
3j	CH_3	Ph	$C_{14}H_{13}N_6OCl$	316(316.8)	91.2[a]	276—278	53.02(53.09)	4.19(4.14)	26.05(26.53)
3k	CH_3	CH_3	$C_9H_{11}N_6OCl$		85.8[a]	248—250	42.15(42.45)	4.01(4.35)	32.60(33.00)
3l	Ph	H	$C_{13}H_{11}N_6OCl$		94.9[a]	293—295	51.62(51.58)	3.69(3.66)	27.31(27.76)
3m	Ph	Ph	$C_{19}H_{15}N_6OCl$	378(378.9)	85.7[a]	277—278	60.73(60.24)	4.00(3.99)	22.29(22.18)
3n	Ph	CH_3	$C_{14}H_{13}N_6OCl$		89.0[a]	255—257	52.78(53.09)	4.10(4.14)	26.38(26.53)

[a] Yield of Method A. [b] Yield of Method B.

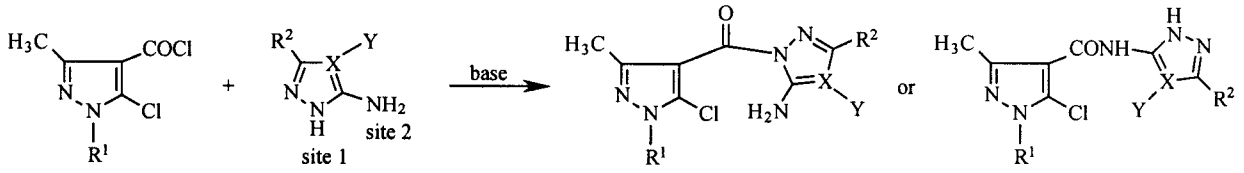
There are two sites in the candidates (aminopyrazole or aminotriazole) which can react with pyrazole-4-formylchloride. It is expected that the reaction will produce two kinds of different amides as shown in Scheme 2. Site 1 and site 2 have different reactivity, so using suitable solvent, catalyst and reaction temperature, either **1** or **3** can be synthesized by regioselective reaction.

The optimized condition for single **1** or **3** was found: THF as solvent, at room temperature, triethylamine or sodium hydride as catalyst, respectively.

The X-ray crystal structure determinations[5] of one pair of 1*H*-pyrazole-4-carboxamides (Fig. 1—2) indicated that **1** was the product when triethylamine was used as catalyst, and **3** was the product when sodium hydride was used as catalyst.

The reactivity of amide **1** can be explained[6] on the basis of the quasi-aromatic character of the azole π-system: the lone electron pair on the acyl-substituted nitrogen N(1) is part of the cyclic π-system of the azole units, leading to a partial positive charge on N(1) that

Scheme 2



4a (R^1=Me)
4b (R^1=Ph)

5a—n

1a—n

3a—n

a—h: X=C; Y=CN; R^1=Me, Ph; R^2=H, Ph, *o*-Cl-Ph, MeS
i—n: X=N; Y=H; R^1=Me, Ph; R^2=H, Me, Ph

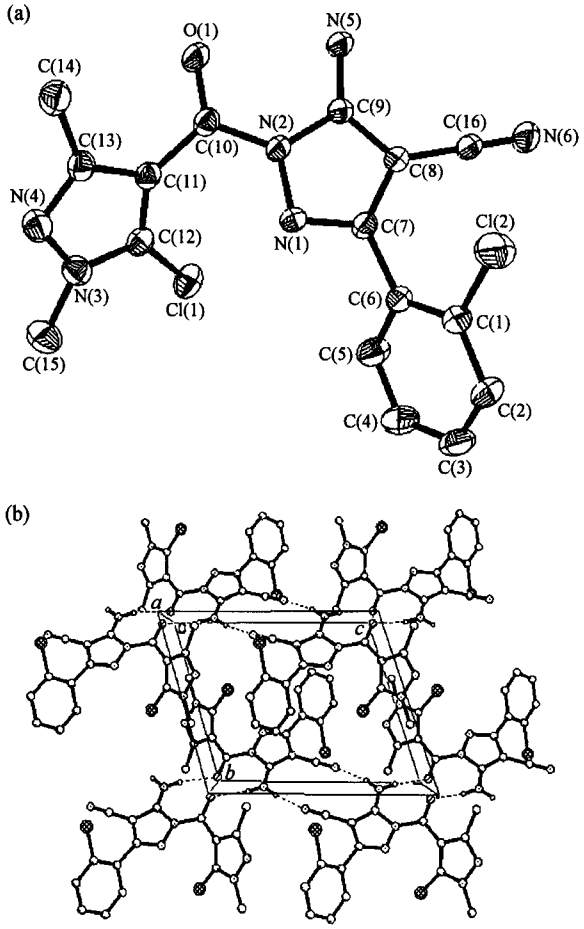


Fig. 1 ORPET drawing (a) and packing diagram (b) of 1-(1′ *H*, 3′-dimethyl-5′-chloropyrazole-4′-carbonyl)-3-(*o*-chlorophenyl)-5-amino-4-cyanopyrazole, **1c**.

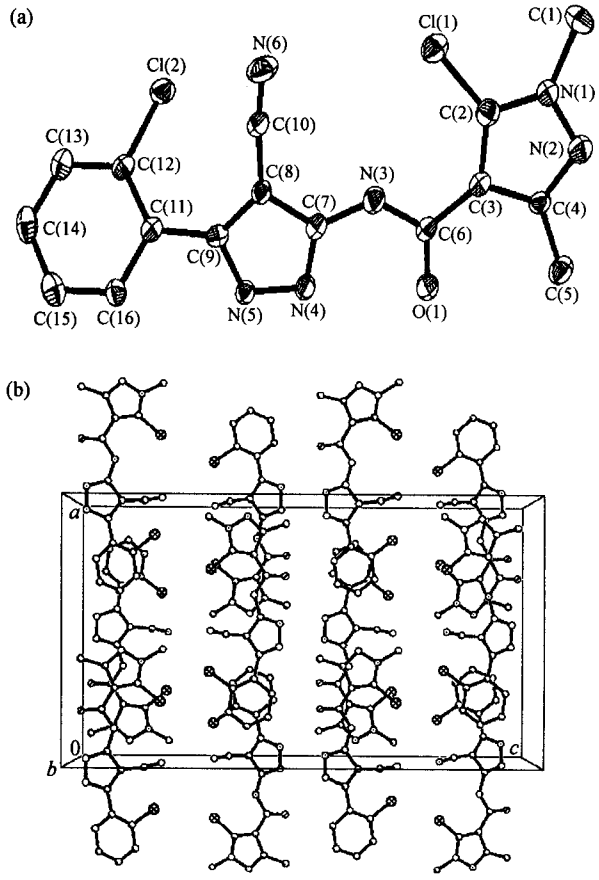


Fig. 2 ORPET drawing (a) and packing diagram (b) of *N*-(1′ *H*-3′-*o*-chlorophenyl-4′-cyanopyrazol-5′-yl)-1, 3-dimethyl-5-chloro-1*H*-pyrazole-4-carboxamide, **3c**.

interferes with the normal carboxamide resonance and takes an electron-withdrawing effect on the carbonyl group which makes this group more susceptible to nucleophilic attack. The reactivity graduation depends on the number and location of the nitrogen atoms in the azole rings, which in turn determines the electron-withdrawing effect on the carbonyl group as well as the effectiveness of the azole units as leaving groups.

1 and **3** have quite different physical properties (Table 1), quite different IR and ^{1}H NMR data (Table 2), but corresponding compounds have the same peak of $[M]^+$ in mass spectrometry (Table 1). In IR spectra of 1*H*-pyrazole-4-carboxamides, the C=O stretching vi-

bration occurred between 1675.2 and 1695.3 cm^{-1}. In ^1H NMR spectra, the peaks of most amino groups in **1** are broad singles (6.45—7.12). When they rearranged to **3**, the peaks of amino group disappeared and those of O = CNH proton appeared in lower fields, these of **3a—h** at 8.80—10.12, thses of **3i—n** at 11.50—13.80. Comparing the crystallography data, it can be found that there are remarkable inter- and intra-molecular hydrogen bonds in **1c** (Fig. 1b), but there are no hydrogen bonds in **3c** (Fig. 2b).

Table 2 IR and ^1H NMR data for compounds **1** and **3**

No.	IR ν (KBr, cm^{-1})			^1H NMR δ ($CDCl_3$)
	N—H	C≡N	C=O	
1a	3412.0	2215.0	1687.2	2.40(s, 3H, 3-CH_3), 3.92(s, 3H, 1-CH_3), 6.48(br.s, 2H, NH_2), 7.68(s, 1H, Py-H)
1b	3412.0	2283.0	1683.8	2.52(s, 3H, 3-CH_3), 3.88(s, 3H, 1-CH_3), 6.56(br.s, 2H, NH_2), 7.36—8.20(m, 5H, Ph)
1c	3389.0	2218.5	1680.3	2.40(s, 3H, 3-CH_3), 3.84(s, 3H, 1-CH_3), 6.72(br.s, 2H, NH_2), 7.32—7.60(m, 4H, Ph)
1d	3390.5	2217.0	1690.1	2.35(s, 3H, SCH_3), 2.50(s, 3H, 3-CH_3), 3.80(s, 3H, 1-CH_3), 6.50(br.s, 2H, NH_2)
1e	3405.5	2217.0	1679.3	2.38(s, 3H, 3-CH_3), 6.45(br.s, 2H, NH_2), 7.46—7.59(m, 5H, Ph), 7.58(s, 1H, Py-H)
1f	3408.5	2209.5	1682.1	2.45(s, 3H, 3-CH_3), 6.50(br.s, 2H, NH_2), 7.35—8.05(m, 10H, Ph)
1g	3402.5	2214.5	1687.9	2.44(s, 3H, 3-CH_3), 5.04(br.s, 2H, NH_2), 7.20—7.62(m, 9H, Ph)
1h	3384.5	2203.5	1678.8	2.24(s, 3H, 3-CH_3), 2.56(s, 3H, SCH_3), 3.32(br.s, 2H, NH_2), 7.40—7.56(m, 5H, Ph)
1i	3418.8		1682.4	2.32(s, 3H, 3-CH_3), 3.80(s, 3H, 1-CH_3), 6.28(br.s, 2H, NH_2), 7.47(s, H, Tri-CH)
1j	3410.0		1687.3	2.39(s, 3H, 3-CH_3), 3.66(s, 3H, 1-CH_3), 6.97(br.s, 2H, NH_2), 7.40—7.43(m, 5H, Ph)
1k	3416.0		1687.5	2.32(s, 3H, Tri-CH_3), 2.48(s, 3H, 3-CH_3), 6.72(br.s, 2H, NH_2), 7.46—7.56(m, 5H, Ph)
1l	3417.0		1695.3	2.42(s, 3H, 3-CH_3), 2.48(s, 3H, 3-CH_3), 3.80(s, 3H, 1-CH_3), 6.87(br.s, 2H, NH_2)
1m	3418.0		1684.7	2.48(s, 3H, 3-CH_3), 6.88(br.s, 2H, NH_2), 7.41—7.56(m, 6H, Ph), 8.00—8.03(m, 4H, Ph)
1n	3435.5		1688.6	2.32(s, 3H, Tri-CH_3), 2.48(s, 3H, 3-CH_3), 7.12(br.s, 2H, NH_2), 7.48—7.61(m, 5H, Ph)
3a	3372.5, 3178.5	2233.0	1675.2	2.60(s, 3H, 3-CH_3), 3.96(s, 3H, 1-CH_3), 7.40(s, 1H, Py-H), 8.04(s, 1H, NH), 9.20(s, 1H, O=CNH)
3b	3388.0, 3244.0	2210.5	1675.8	2.48(s, 3H, 3-CH_3), 3.92(s, 3H, 1-CH_3), 7.52—8.04(m, 5H, Ph), 8.04(s, 1H, NH), 10.12(s, 1H, O=CNH)
3c	3367.0, 3221.5	2212.5	1681.9	2.52(s, 3H, 3-CH_3), 3.92(s, 3H, 1-CH_3), 7.20(s, 1H, NH), 7.42—7.84(m, 4H, Ph), 10.00(s, 1H, O=CNH)
3d	3378.5, 3261.5	2221.5	1684.1	2.42(s, 3H, SCH_3), 2.59(s, 3H, 3-CH_3), 3.85(s, 3H, NCH_3), 6.80(s, 1H, NH), 9.60(s, 1H, O=CNH)
3e	3388.5, 3184.5	2215.5	1689.3	2.60(s, 3H, 3-CH_3), 7.56—7.72(m, 5H, Ph), 7.88(s, 1H, NH), 9.08(s, 1H, O=CNH)
3f	3376.0, 3074.0	2201.5	1683.9	2.60(s, 3H, 3-CH_3), 7.35—7.95(m, 10H, Ph), 8.04(s, 1H, NH), 8.90(s, 1H, O=CNH)

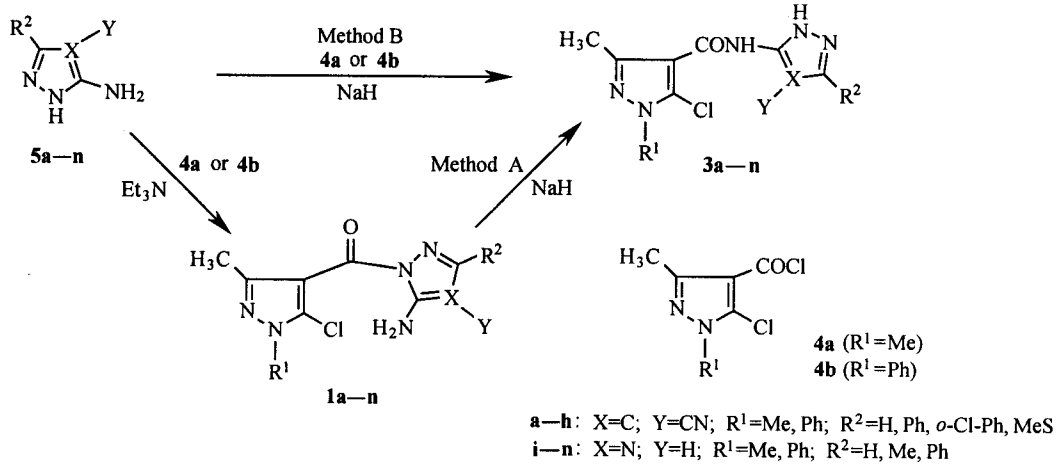
(Coutinued)

No.	IR ν (KBr, cm^{-1})			^1H NMR δ ($CDCl_3$)
	N—H	C≡N	C=O	
3g	3371.5, 3225.0	2203.8	1685.1	2.64(s, 3H, 3-CH_3), 7.28—7.60(m, 10H, Ph, NH), 8.96(s, 1H, O=CNH)
3h	3307.5, 3032.0	2227.0	1680.0	2.60(s, 6H, 3-CH_3, SCH_3), 7.50(s, 5H, Ph), 7.22(s, 1H, NH), 8.80(s, 1H, O=CNH)
3i	3391.0, 3238.0		1675.4	2.29(s, 3H, 3-CH_3), 3.76(s, 3H, 1-CH_3), 7.89(s, 1H, Tri-CH), 11.30(s, 1H, NH), 13.40(s, 1H, O=CNH)
3j	3389.0, 3257.0		1680.8	2.42(s, 3H, 3-CH_3), 3.81(s, 3H, 1-CH_3), 7.38—8.10(m, 5H, Ph), 11.02(s, 1H, NH), 12.90(s, 1H, O=CNH)
3k	3309.5, 3158.6		1675.8	2.30(s, 3H, Tri-CH_3), 2.42(s, 3H, 3-CH_3), 3.81(s, 3H, 1-CH_3), 10.42(s, 1H, NH), 11.58(s, H, O=CNH)
3l	3394.0, 3222.0		1676.3	2.42(s, 3H, 3-CH_3), 7.50—7.60(m, 5H, Ph), 11.52(s, 1H, NH), 13.40(s, 1H, O=CNH)
3m	3435.0, 3247.5		1675.6	2.42(s, 3H, 3-CH_3), 7.41—7.58(m, 10H, Ph), 11.52(s, 1H, NH), 13.80(s, 1H, O=CNH)
3n	3416.5, 3276.0		1678.7	2.32(s, 3H, Tri-CH_3), 2.48(s, 3H, 3-CH_3), 7.50—7.60(m, 5H, Ph), 10.22(s, 1H, NH), 11.50(s, 1H, O=CNH)

Tri: triazole, Py: pyrazole.

When using sodium hydride catalyzed **1m** to synthesize fused heterocyclic compound, its transacylated product **3m** rather than the expected fused heterocyclic product **2m** was obtained. To validate the catholicity of transacylation, **1a—d**, **1i—l**, and **1n** were tested with 2 eq. of NaH (Method A) respectively, and the results were alike. **3a—d**, **3i—l** and **3n** were obtained by this method in high yields (85%—95%) (Scheme 3 and Table 1). These experiments demonstrated that the acyl group could be transferred from the ring nitrogen to the exocyclic amino group. The study of transacylative mechanism is underway.

Scheme 3



Fungicidal activities of some compounds against *Rhizoctonia solani* and *Sclerotinia sclerotiorum* were evaluated *in vivo* at a concentration of 500 ppm by a preventive foliar application in a green house. The test result was shown in Table 3. Preliminary bioassays indicate that compounds **1i**, **1k**, **1l**, **1m**, **3j**, **3l** and **3m** have moderate inhibitory activities against Sclerotinia sclerotiorum, and **1j**, **3i** and **3j** have moderate inhibitory

activities against *Rhizoctonia solani*.

Table 3 Fungicidal activities of some compounds

	Inhibition rate (%)								
	1i	**1j**	**1k**	**1l**	**1m**	**3i**	**3j**	**3l**	**3m**
Sclerotinia sclerotiorum	50	< 50	75	70	70	< 50	70	75	70
Rhizoctonia solani	< 50	70	< 50	< 50	< 50	58.5	55.1	< 50	< 50

In conclusion, reaction of substituted 1*H*-pyrazole-4-formylchloride and aminopyrazole or aminotriazole leads to an acylation of the ring nitrogen using Et_3N as base, whereas acylation at the exocyclic amino group is achieved under the catalysis of NaH. Compound **1** can be transacylated into the corresponding exocyclic amide **3** using NaH as catalyst. Preliminary bioassay study showed that some compounds displayed inhibition to *Rhizoctonia solani* and *Sclerotinia sclerotiorum*.

Experimental

Instruments and reagents

Elemental analyses were carried out on a Yanaco MT-3 instrument. Melting points were determined with a model Yanaco MP-500 apparatus and uncorrected. Mass spectra were obtained on an HP 5989 mass spectrometer (EI). IR spectra were recorded on a Shimadzu-435 spectrometer in KBr pellets. ^1H NMR spectra were recorded on a Bruker AC-200Q spectrometer with TMS as internal standard. Exchangeable protons were detected by addition of D_2O. X-ray crystallography data were collected with a Bruker Smart 1000 CCD area detector system, using graphite monochromatized Mo K_α radiation ($\lambda = 0.071073$ nm). Column chromatography was performed on silica gel (200—300 mesh) purchased from Qingdao Chemical Company, China.

The solvents were available commercially and were purified according to conventional methods. Substituted 1*H*-pyrazole-4-formylchlorides and aminotriazoles were prepared according to the literature.[4]

Preparation of 1-(1′,3′-*dimethyl*-5′-*chloropyrazole*-4′-*carbonyl*)-3-(*o-clorophenyl*)-5-*amino*-4-*cyanopyrazole* (**1c**)

To a solution of **4a** (5.79 g, 0.03 mol) in dry THF (40 mL), Et_3N (4.55 g, 0.045 mol) and **5c** (6.55 g, 0.03 mol) were added in turn. The mixture was stirred at room temperature for 10 h, then the mixture was filtered and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (petroleum ether 60—90 ℃: ethyl acetate = 1:5) afforded compound **1c** (8.22 g, yield 53.3%). Single crystals were obtained from its ethyl acetate solution in the air naturally.

Compounds **1a—b** and **1d—n** were prepared in the same method as **1c**.

Preparation of N-(1′*H*-3′-*o-chlorophenyl*-4′-*cyanopyrazol*-5′-*yl*)-1,3-*dimethyl*-5-*chloro*-1*H*-*pyrazole*-4-*carboxamide* (**3c**) (Method A)

95% NaH (0.5 g, 0.02 mol) was added to a stirred solution of **1c** (3.75 g, 0.01 mol) in dry THF (40 mL). The mixture was stirred for 1.5 h at room temperature, and evaporated to dryness. Then water (40 mL) was added to the residue, and the solution was acidified to pH = 7 with 10% HCl. White precipitate was got, then dried and crystallized from ethyl acetate. 3.39 g of the desired product **3c**, corresponding to yield of 90.4%, was obtained.

Compounds **3a—3b**, **3d** and **3i—3n** were prepared in the same method as **3c**.

Preparation of N-(1′*H*-3′-*o-chlorophenyl*-4′-*cyanopyrazol*-5′-*yl*)-1-*phenyl*-3-*methyl*-5-*chloro*-1*H*-*pyrazole*-4-*carboxamide* (**3g**) (Method B)

To a solution of **4b** (7.65 g, 0.03 mol) in dry THF (40 mL), 95% NaH (1.5 g, 0.06 mol) and **5g** (6.55 g, 0.03 mol) were added in turn. The mixture was stirred at room temperature until compound **4b** was consumed (checked by TLC). The solvent was then evaporated to dryness. Water (40 mL) was added to the residue, and the mixture was acidified to pH = 7 with

10% HCl. White precipitate was got. The solid was dried and then recrystallized from ethyl acetate. 8.03 g of the desired product **3g**, corresponding to yield of 61.3%, was obtained.

Compounds **3e—3f**, **3h** and **3i—3n** were prepared in the same method as **3g**.

References

1 Yoshikawa, Y.; Tomiya, K.; Kitajima, T. *EP 841 336*, **1998** [*Chem. Abstr.* **1998**, *129*, 16051k].

2 Ohuchi, S.; Okada, S. *JP 10 338 589*, **1998** [*Chem. Abstr.* **1998**, *130*, 120912y].

3 Graneto, J.; Phillips, G. *US 5 093 347*, **1992** [*Chem. Abstr.* **1992**, *116*, 250506r].

4 Liu, Y. *Ph. D. Thesis*, Nankai University, Tianjin, **1999** (in Chinese).

5 Zhang, X. H.; Weng, L. H.; Jin, G. Y. *J. Crystal. Chem.* (in press).

6 (a) Staab, H. A., *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 351.
(b) Staab, H. A.; Rohr, W. *Newer Methods of Prepatative Organic Chemistry*, V, **1967**, p.61.

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