ヘテロ芳香族アルデヒドおよびケトン ピリミジニルヒドラゾン類の殺菌活性

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著者	小西, 和雄 倉賀野, 隆
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Original Article

Fungicidal Activity of Heteroaromatic Aldehyde and Ketone Pyrimidinylhydrazones*

Kazuo KONISHI and Takashi KURAGANO

Plant Protection Research Laboratories, Agro Division, Takeda Chemical Industries, Ltd., Yodogawa-ku, Osaka 532, Japan

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From the viewpoint of synthetic diversification, a variety of heteroaromatic isosters of fungicidal aromatic aldehyde and ketone 2-pyrimidinylhydrazones were prepared and their *in vitro* fungicidal activities were examined. Five-membered derivatives with methyl group(s) on the neighboring position(s) to the carbonyl group scarcely exhibited fungicidal activity against phytopathogenic fungi. On the other hand, 2-pyridyl derivatives, the representative of 6-membered heteroaromatic rings, displayed considerable activity even without a methyl group on the ring. The methyl group on the 5-membered rings may not function sterically in the vicinity of the hydrazone bond on consideration of their interior angles. The activity also observed for various other azinylhydrazones of methyl 2-pyridyl ketone may be attributed to the characteristic of α-acetylpyridine itself.

INTRODUCTION

A series of pyrimidinylhydrazones was recently described as a new class of fungicides that is curatively active against fungi pathogenic to plants[1-3]. From the viewpoint of synthetic diversification, we were led to prepare heteroaromatic isosters of the aromatic aldehyde and ketone derivatives reported in the previous papers[2,3] and represented by ferimzone.[1,3]

The thiosemicarbazones of 2-pyridyl ketones have been reported to show various bioactivities against protozoa,[4,5] insects[6-8] and fungi.[9] Expectation of other possible bioactivities prompted us to prepare a variety of hydrazones of methyl 2-pyridyl ketone (α-acetylpyridine) with aryl- and hetero-arylhydrazines including 2-pyrimidinylhydrazines.

In this report, synthetic variation of individual structural elements was undertaken to have a deeper insight into the structure-activity relationship.

* Studies on Fungicidal Pyrimidinylhydrazones (Part 3). For Part 2, see Ref. 3).

MATERIALS AND METHODS

1. *Synthesis of Compounds*

The following typical routes have been employed for synthesizing hydrazone derivatives (Fig. 1). Compounds were prepared by condensation of heteroaromatic carbonyl compounds **A** and 2-pyrimidinylhydrazines **B** or by reaction of methyl 2-pyridyl ketone **C** with aryl- or heteroarylhydrazines **D** according to the methods described in the previous reports.[1-3]

The condensation products were purified by silica gel column chromatography and/or recrystallization, and characterized by elemental analysis (C, H, N) and/or ^{1}H NMR spectral measurement.

1.1 General synthetic route I

Methyl 2,4-dimethyl-3-furyl ketone 4,6-dimethyl-2-pyrimidinylhydrazones (**3a, b**): A solution of methyl 2,4-dimethyl-3-furyl ketone (**A**: Ar=2,4-Me$_2$-3-Fr, R$_1$=Me; 1.38 g)[10] and 4,6-dimethyl-2-pyrimidinylhydrazine (**B**: R$_2$=R$_4$=Me, R$_3$=H; 1.79 g)[11-13] in ethanol (30 ml)

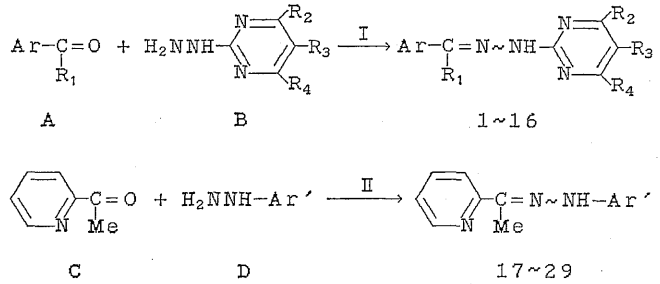


Fig. 1 General synthetic routes.

was boiled under reflux for 5 hr. Evaporation of the solvent *in vacuo* afforded an oily residue, which was composed of geometrical isomers (**3a**, **3b**). Column chromatography on silica gel (Kieaselgel 60, 70–230 mesh ASTM, Merck; eluent: $CHCl_3$) gave **3b** as a viscous, resinous matter in 39% yield (1.0 g) and then **3a** as a viscous, resinous matter in 16% yield (0.4 g).

3b: Anal. Found: C, 57.27; H, 6.19; N, 18.87, Calcd. for $C_{14}H_{18}N_4O \cdot 1/3\ CHCl_3$: C, 57.74; H, 6.20; N, 18.80%. ^1H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 8.20 (1H, bs, NH), 7.17 (1H, s, Fr-H), 6.52 (1H, s, Pm-H), 2.33 (6H, s, Me×2), 2.25 (3H, s, Me), 2.18 (3H, s, Me), 1.88 (3H, d, Me).

3a: Anal. Found: C, 63.71, H, 7.05; N, 21.03, Calcd. for $C_{14}H_{18}N_4O \cdot 1/3\ H_2O$: C, 63.71; H, 7.12; N, 21.20%. ^1H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 8.16 (1H, bs, NH), 7.05 (1H, s, Fr-H), 6.52 (1H, s, Pm-H), 3.40 (3H, s, Me), 2.38 (6H, s, Me×2), 2.20 (3H, s, Me), 2.08 (3H, d, Me).

Other compounds were prepared by similar reaction of heteroaromatic carbonyl compounds **A** with 2-pyrimidinylhydrazines **B**. The hydrazones thus obtained are tabulated in Table 1 along with their fungicidal activities.

1.2 General synthetic route II

Methyl 2-pyridyl ketone 4-chlorophenylhydrazone (**17**) *and its hydrochloride* (**18**): A solution of methyl 2-pyridyl ketone (**C**: 1.21 g) and 4-chlorophenylhydrazine (**D**: Ar=4-Cl-Ph) hydrochloride (1.79 g) in ethanol (20 ml) was boiled under reflux for 6 hr. After cooling the reaction mixture, the resulting precipitates were gathered by filtration and washed with ethanol. Recrystallization from ethanol gave **18** as orange needles in 35% yield (1.0 g), mp *ca.* 210°C. Anal. Found: C, 55.22; H, 4.62; N, 14.86, Calcd. for $C_{13}H_{12}N_3Cl \cdot HCl$: C, 55.33; H, 4.64; N, 14.89%.

The mother liquids of reaction and recrystallization were combined and condensed *in vacuo* to afford a solid residue, which was dissolved in hot aqueous ethanol. The solution was neutralized with a 10% solution of sodium bicarbonate to precipitate pale yellow crystals. Recrystallization from dilute ethanol gave **17** as pale yellow plates in 28% yield (0.84 g), mp 127–128°C. Anal. Found: C, 63.47; H, 4.71; N, 16.99, Calcd. for $C_{13}H_{12}N_3Cl$: C, 63.55; H, 4.92; N, 17.10%.

Other compounds were prepared by similar reaction of 2-pyridyl ketone **C** with heteroarylhydrazines **D**. The hydrazones thus obtained are tabulated in Table 2 along with their fungicidal activities.

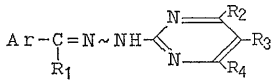
2. Fungicidal Activity

In vitro test results are shown in Tables 1 and 2 with MIC (μg/ml) against *Pyricularia oryzae* (Po), *Helminthosporium oryzae* (Ho), *Helminthosporium sigmoideum* var. *irregulare* (Hs) and *Phytophthora capsici* (Pc) or *Phytophthora infestans* (Pi) by the agar dilution method.

RESULTS AND DISCUSSION

The condensation employed here favored the formation of *E*-isomers, which, however, were accompanied with *Z*-isomers in some cases. The mixture ratios appeared to vary with the structure of ketones and also the reaction conditions. When accompanied, each isomer was separated from the other isomer by means of silica gel column chromatography and/or recrystallization. Each of the isomers appeared to be stable enough to stay at least in the process of separation and purification.

Table 1 Chemical structures and fungicidal activities of pyrimidinylhydrazones.



No.	Compounds[a]							*in vitro*[c]				
	Ar	R_1	R_2	R_3	R_4	Is[b]	mp (°C)	Po	Ho	Hs	Pc	Pi
1	Ar-1	H	H	H	H	*E*	180–182	>100	>100	—[d]	—	>100
2	Ar-2	Me	Me	H	Me	*E*	109–110	>100	>100	12.5	>100	—
3a	Ar-3	Me	Me	H	Me	*E*	oil[e,f]	25	>100	12.5	100	—
3b	Ar-3	Me	Me	H	Me	*Z*	oil[e,g]	50	>100	25	50	—
4	Ar-4	Me	H	H	H	*E*	oil[e]	>100	>100	>100	>100	—
5	Ar-4	Me	Me	H	Me	*E*	122–125	100	>100	50	>100	—
6	Ar-5	Me	Me	H	Me	*E*	oil[e]	>100	>100	>100	>100	—
7	Ar-6	Me	Me	H	Me	*E*	201–203	>100	>100	>100	>100	—
8	Ar-7	Me	Me	H	Me	*E*	118–119	>100	>100	>100	>100	—
9	Ar-8	H	H	H	H	*E*	208–209	50	50	—	—	6.25
10a	Ar-8	Me	H	H	H	*E*	149–152	50	50	—	—	6.25
10b	Ar-8	Me	H	H	H	*Z*	102–103	100	100	—	—	12.5
11	Ar-8	Me	Me	H	H	*E*	*ca.* 55[h]	50	25	25	12.5	—
12	Ar-8	Me	H	Me	H	*E*	*ca.* 116	50	25	50	6.25	—
13	Ar-8	Me	H	Cl	H	*E*	137–139[i]	50	50	50	6.25	—
14	Ar-8	Me	Me	H	Me	*E*	136	50	50	—	—	12.5
15	Ar-8	Me	Me	H	OH	*E*	160–162[i,15]	50	100	—	—	6.25
16	Ar-8	Me	Ph	H	OH	*E*	243–244	100	100	—	—	6.25

[a] Synthesized according to general synthetic route I. All new compounds exhibited satisfactory ^{1}H NMR and/or elemental analysis.
[b] Geometrical configuration (*E*/*Z*).
[c] MIC (μg/ml) against *Pyricularia oryzae* (Po), *Helminthosporium oryzae* (Ho), *Helminthosporium sigmoideum* (Hs) and *Phytophthora capsici* (Pc) or *Phytophthora infestans* (Pi) by the agar dilution method.
[d] Not tested.
[e] Viscous, resinous matter (not crystallized yet).
[f] +1/3 H_2O. [g] +1/3 $CHCl_3$. [h] +3H_2O. [i] +1/2 H_2O.

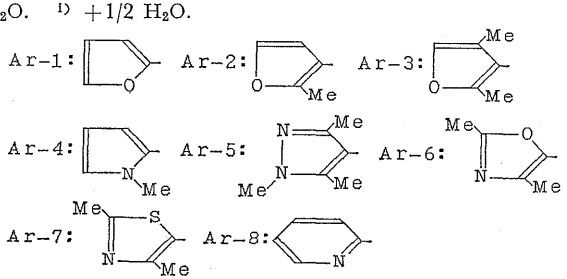
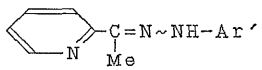
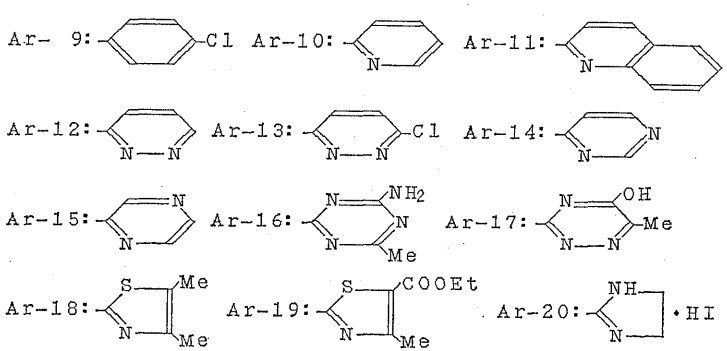


Table 2 Chemical structures and fungicidal activities of aryl- and heteroaryl-hydrazones.



No.	Compounds[a]			*in vitro*[c]				
	Ar′	Is[b]	mp (°C)	Po	Ho	Hs	Pc	Pi
17	Ar-9	*E*	127–128	50	>100	50	100	—[d]
18	Ar-9	*E*	*ca.* 210[e]	6.25	12.5	12.5	25	—
19	Ar-10	*E*	*ca.* 48[f]	50	25	25	6.25	—
20	Ar-11	*E*	145–148	50	25	25	25	—
21	Ar-12	*E*	165–168	25	25	25	6.25	—
22	Ar-13	*E*	*ca.* 170	50	50	50	12.5	—
23	Ar-14	*E*	191–193	50	50	25	6.25	—
24	Ar-15	*E*	*ca.* 154	50	25	50	6.25	—
25	Ar-16	*E*	277–278	>100	>100	—	—	6.25
26	Ar-17	*E*	264–267	>100	>100	—	—	12.5
27	Ar-18	*E*	*ca.* 107	25	50	25	25	—
28	Ar-19	*E*	233	>100	>100	—	—	50
29	Ar-20	*E*	270–272 (d.)	>100	>100	—	—	>100

[a] Synthesized according to general synthetic route II. All new compounds exhibited satisfactory ^{1}H NMR and/or elemental analysis.
[b] Geometrical configuration (*E*/*Z*).
[c] MIC (μg/ml) against *Pyricularia oryzae* (Po), *Helminthosporium oryzae* (Ho), *Helminthosporium sigmoideum* (Hs) and *Phytophthora capsici* (Pc) or *Phytophthora infestans* (Pi) by the agar dilution method.
[d] Not tested.
[e] Hydrochloride, [f] $+2H_2O$.



Configurational assignments of the hydrazones obtained here were performed by analogous comparison in the ^{1}H NMR chemical shifts of both isomeric imino protons and/or other means as detailed in the preceding paper.[3]

In the beginning, the heteroaromatic isosters of 5-membered ring derivatives such as furans, *N*-methylpyrrole, *N*-methylpyrazole, oxazole and thiazole were provided from the viewpoints of commercial availability and synthetic feasibility (**1–8**, Table 1). The results of the *in vitro* fungicidal test indicated that the fungicidal activities of the pyrimidinylhydrazones derived from these heterocycles were not so strong against *P. oryzae, H. oryzae, H. sigmoideum* and *P. capsici* or *P. infestans*. It is noticeable that **2** has the same nucleus as fenfuram,[14] one of carboxylic acid anilide fungicides. A similarity in the structural requirements for fungicidal activity has been pointed out between **2** and fenfuram in the preceding paper.[3] An introduction of another methyl group into the 4-position (**3a, 3b**) scarcely improved the activity contrary to our expectation. The azoles (**5–8**) with methyl group(s) in the neighboring position to the acetyl group were also equal or weaker in *in vitro* activity compared with the furan derivatives (**1–3**).

The above results may suggest that the methyl group neighboring to the acetyl group on the 5-membered rings has no sufficient effect on sterical congestion in the vicinity of the hydrazone bond on consideration of their interior angles, or that an introduction of hetero atom(s) into the ring is unfavorable to physicochemical properties to exert the activity.

Subsequently, the 2-pyridyl derivatives (**9–16**, Table 1) were provided as the representative of 6-membered ring isosters. The hydrazone derivatives (**9–16**) without a methyl group on the pyridine ring showed considerable activity against fungi, *P. capsici* or *P. infestans*, in particular. Even the aldehyde hydrazone (**9**) without any substituents on both the pyridine and pyrimidine rings exhibited the activity to some extent. However, the introduction of methyl group(s), a chlorine atom or a hydroxy group, or the substitution of the methyl group for the phenyl group on the pyrimidine ring resulted in neither improvement nor attenuation. The activity of the pyridine series was lenient to the kind and number of substituents although a slight difference was observed between *E*- and *Z*-isomers (**10a**, **10b**). Difficulty in synthesis prevented us from confirming the positive contribution of a neighboring methyl group on α-acetylpyridine to the fungicidal activity.

The finding that all of the 2-pyridine derivatives (**9–16**) showed potent fungicidal activity against *Phytophthorae* by the agar dilution method incited us to provide a variety of the hydrazones (**17–29**, Table 2) of methyl 2-pyridyl ketone (**C**) and to examine their antifungal activity. As a result, all of the azinylhydrazones (**19**, **21–26**) also exhibited potent fungicidal activity against *Phytophthorae*. This implies that the activity is characteristic of methyl 2-pyridyl ketone azinylhydrazones. Insecticidal activity, however, was not recorded in our screening system different from the cases with thiosemicarbazones.[6-8] Incidentally, in comparison between **17** and **18**, the water solubility affected potential fungicidal activity to a large extent by the agar dilution method.

The present study did not produce any compound worth for the field evaluation as a fungicide.

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要　　約

ヘテロ芳香族アルデヒドおよびケトン ピリミジニルヒドラゾン類の殺菌活性*

小西和雄，倉賀野隆

前2報の植物病原菌に殺菌活性を示した芳香族アルデヒドおよびケトンの2-ピリミジニルヒドラゾン類に対して，本報ではそれらのヘテロ環同族体を合成し，殺菌活性を調べた．5員環誘導体はカルボニル基の両隣接位にメチル基を備えても，なおほとんど不活性であったのに反して，6員環の代表として選んだ2-ピリジル誘導体ではメチル基なしでも一応の活性を示した．5員環は角度的にみてメチル基が立体的に十分に機能しえないためと推察され，2-ピリジル化合物は2-ピリミジニル以外の6員環ヘテロ芳香族ヒドラゾンに導いてもなお活性を保持したことから，隣接位のヘテロ芳香環窒素原子の存在に係わる2-ピリジル体固有の性質が活性に寄与しているものと推測された．しかし，今回の合成化合物の中には圃場試験での活性評価試験に値する候補化合物は見出せなかった．

* 殺菌性ピリミジルヒドラゾン類の研究（第3報）