1-Aryl-1,4-Dihydro-3-Acylhydrazinocarbonyl -6-Methylpyridazin-4-One and Their Biological Activity

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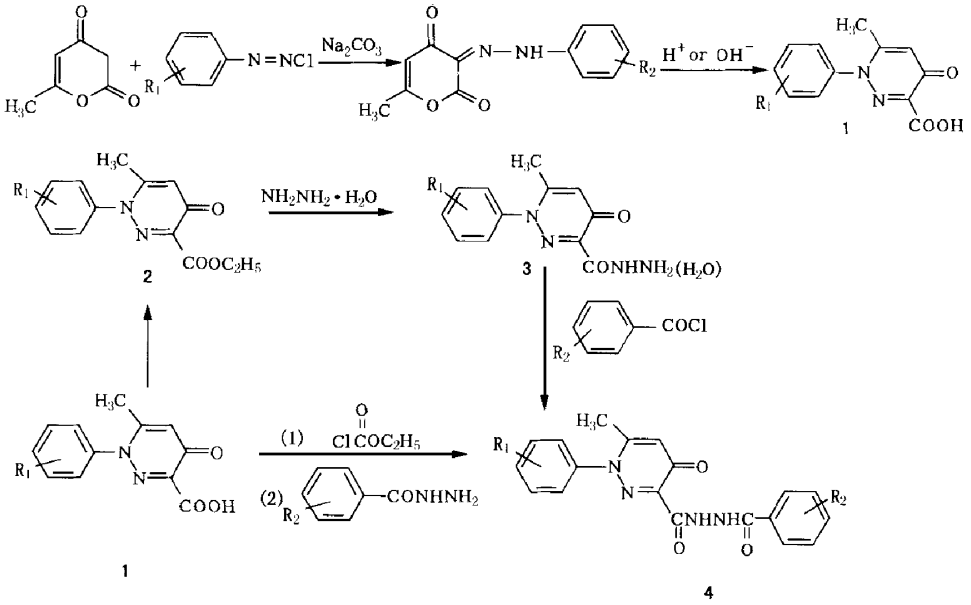
Abstract 1-aryl-1,4-dihydro-3-acylhydrazinocarbonyl-6-methylpyridazin-4-one (4) was synthesized by two methods. The better process was chosen to prepare a series of the target compound in order to find novel bio-active compounds. Their structures were confirmed by IR, ^{1}H NMR and elemental analysis. The preliminary bioassay showed that the title compounds possess promoting cucumber cotyledon root-formation activity. Some of the compounds exhibit antiviral activity against TMV and *Sheath blight* on rice.

Key words Pyridazinone; Synthesis; Antiviral activity; Plant growth regulating activity

1 Introduction

Pyridazine derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They were widely used in pharmaceuticals and agrochemicals [1,2]. Rohm-Haas Company had reported that pyridazines exhibit useful plant growth regulating effects [3,4]. It was reported that diacylhydrazines exhibit excellent insecticides [5~7]. In view of these facts and in continuation of our interest in the chemistry of pyridazines, it was contemplated to synthesize heterocycles containing both pyridazinone and diacylhydrazine moieties to obtain compounds possessing better biological activity.

The general synthetic strategy followed in the preparation of the title compound 4 is outlined in scheme I.



Scheme I

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2 Experiment

All melting points were determined on a Yanaco micro melting point apparatus and uncorrected. The IR spectra (KBr) were recorded on a Shimadzu IR-435 and ^{1}H NMR spectra on JEOL FX-90Q spectrometer (Chemical shift are in δ values. TMS was used as internal standard). Elemental (C, H and N) analysis were carried out on MT-3 analyzer. Mass spectra were recorded on HP-5988A.

2.1 1-(2-chlorophenyl)-1,4-dihydro-4-oxo-6-methyl pyridazine-3-carboxylic acid (1)

The compound was prepared by a previously described procedure[1,4,8], m. p. 161 ~ 162℃. (Yield 66.6%).

2.2 1-(2-chlorophenyl)-1,4-dihydro-3-ethoxycarbonyl-6-methyl pyridazine-4-one (2)

To a suspension of compound 1 1.2 g (5 mmol) and 0.7 mL of triethylamine in 30 mL of dichloromethane 0.52 mL (5.5 mmol) of ethyl chloroformate was added at -10℃. The suspension formed was stirred at room temperature for 20 min and to it 2 mL of ethanol was added. The mixture was stirred at room temperature for 20h. And to it 10 mL of water was added. The mixture was stirred at room temperature for 1 h. The dichloromethane was isolated and dried over magnesium sulfate and concentrated in vacuo. After recrystallization from ethyl acetate, 1.1 g of the desired product 2, corresponding to 75.3%, were obtained. m. p. 146 ~ 147℃. IR, ν/ cm^{-1} 1736.7, 1622.0 (CO); ^{1}H NMR, δ 1.4 (t, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.5 (q, 2H, CH_2), 6.7 (s, 1H), 7.6 (m, 4H, C_6H_4).

2.3 Hydrazide of 1-(2-chlorophenyl)-1,4-dihydro-3-carboxy-6-methylpyridazine-4-one (3)

0.44 g compound 2 was dissolved in a 1∶1 mixture of methanol and water (10 mL) and 0.5 mL of 50% hydrazine hydrate was added. The mixture was stirred for 7 h, during which period a pale-yellow solid separated. This solid was filtered and recrystallized from a 1∶1 mixture of methanol and water to give 0.41 g, corresponding to 93.2 %, of the hydrate of the desired product **3**. m.p. 218 ~ 220℃. IR, ν/cm^{-1} 3221.0, 3328.5 (N-H), 1647.5, 1621.7 (CO); ^{1}H NMR, δ 2.10 (s, 3H, CH_3), 6.70 (s, 1H), 7.6 (m, 4H, C_6H_4); MS, m/z 278 ($M^+ - H_2O$).

2.4 *N*-(2-chlorobenzoyl) hydrazine of 1-(2-chlorophenyl)-1,4-dihydro -3-carboxy-6-methylpyridazine-4-one (4b)

Method 1: To an ice cooled suspension of compound **3** 0.20 g and 0.15mL of triethylamine in 20 mL of dichloromethane, 0.12 g of 2 – chlorobenzoyl chloride in 4 mL of dichloromethane was added. The suspension formed was stirred at room temperature for 7 h and to it 4 mL of water was added. The mixture was stirred at room temperature for 1 h. The dichloromethane was isolated and dried over magnesium sulfate and concentrated in vacuo. After recrystallization from chloroform and petroleum ether, 0.28 g of the desired product **4b**, corresponding to 93.3% ,were obtained, m.p. 208 ~ 210 ℃

Method 2: To a suspension of compound **1** 0.27 g (mmol) and 0.15 mL of triethylamine in 8 mL dichloromethane, 0.12 mL of ethyl chloroformate was added at -10℃. The suspension formed was stirred at room temperature for 20 min and cooled to -10℃. To the mixture 0.17 g of 2-chlorobenzoyl hydrazine in 4 mL of tetrahydrofuran was added. The mixture was stirred for 22 h and to it 4 mL of water was added. The mixture was stirred at room temperature for 1 h. The dichloromethane was isolated and dried over magnesium sulfate and concentrated in vacuo. After recrystallization from chloroform and

petroleum ether, 0.33 g of the desired product **4b**, corresponding to 80.5%, was obtained, m.p. 208 ~ 210℃.

3 Results and discussion

3.1 Synthesis

The target compound is synthesized by two methods. First, compound **1** is esterificated and converted into ester **2**, which in turn is hydrazinolyzed by hydrazine hydrate and converted into hydrazide **3**, Compound **3** is reacted with an acylhalide to produce the target compound **4**. Second, in general terms, it is often useful to convert compound **1** into an acid halide, especially the acid chloride, which is reacted with an acylhydrazine to produce the target compound. But we found it was difficult to convert compound **1** into an acid halide using thionyl chloride, under the conditions used to prepare acid chlorides halide (reflux in the pure reagent or in a solvent such as benzene). The result is in accordance with literature [1]. We try to convert it into a mixed anhydride, which was prepared by reacting the free acid **1** or, preferably an amine salt, for example the triethylamine salt thereof, with an chloroformate ethyl ester, which in turn is reacted with an acylhydrazine to prepare the target compound in high yield.

Comparing these two methods, we found that the second process is convenient, simple and high yield. The reaction of compound **1** with various *o*-and *p*-substituted benzoyl hydrazine derivatives provided the target compounds **4a ~ r** by this methods. The physical constants and elemental analysis of these new compounds are recorded in Table 1.

Table 1　Physical constants and elemental analysis of new compounds **4**

No.	R_1	R_2	Formula	m.p./℃	Yield (%)	Elemental analysis (calcd., %)		
						C	H	N
4a	*o*-Cl	H	$C_{19}H_{15}ClN_4O_3$	194 ~ 196	81	59.50 (59.61)	4.13 (3.92)	14.35 (14.64)
4b	*o*-Cl	*o*-Cl	$C_{19}H_{14}Cl_2N_4O_3$	208 ~ 210	72	54.47 (54.68)	3.24 (3.36)	13.33 (13.43)
4c	*o*-Cl	4-N	$C_{18}H_{14}ClN_5O_3$	157 ~ 159	80	56.42 (56.31)	3.52 (3.65)	18.37 (18.25)
4d	*o*-Cl	*p*-OCH_3	$C_{20}H_{17}ClN_4O_4$	229 ~ 231	86	58.00 (58.18)	4.24 (4.12)	13.54 (13.58)
4e	*o*-Cl	*o*-OCH_3	$C_{20}H_{17}ClN_4O_4$	188 ~ 189	84	57.89 (58.18)	4.34 (4.12)	13.26 (13.58)
4f	*o*-Cl	2,4-2Cl	$C_{19}H_{13}Cl_3N_4O_3$	133 ~ 134	86	50.27 (50.50)	3.09 (2.89)	12.26 (12.40)
4g	H	H	$C_{19}H_{16}N_4O_3$	195 ~ 198	72	65.42 (65.52)	4.67 (4.60)	15.99 (16.10)
4h	H	4-N	$C_{18}H_{15}N_5O_3$	244 ~ 246	57	61.56 (61.87)	4.19 (4.30)	20.14 (20.05)
4i	2,6-2Cl	H	$C_{19}H_{14}Cl_2N_4O_3$	234 ~ 236	68	54.50 (54.68)	3.38 (3.36)	13.53 (13.43)
4j	*p*-Cl	H	$C_{19}H_{15}ClN_4O_3$	239 ~ 240	77	59.68 (59.61)	3.81 (3.92)	14.70 (14.64)
4k	*p*-Cl	2,4-2Cl	$C_{19}H_{13}Cl_3N_4O_3$	216 ~ 218	80	50.08 (50.50)	2.67 (2.88)	12.19 (12.40)
4l	*p*-Cl	*p*-F	$C_{19}H_{14}ClFN_4O_3$	> 240	79	56.91 (56.93)	3.48 (3.49)	13.75 (13.98)
4m	2,4,5-3Cl	H	$C_{18}H_{13}Cl_3N_4O_3$	254 ~ 256	71	50.27 (50.50)	3.09 (2.89)	12.26 (12.40)
4n	2,4,5-3Cl	4-N	$C_{18}H_{12}Cl_3N_5O_3$	259 ~ 261	81	47.44 (47.73)	2.80 (2.65)	15.43 (15.47)
4o	2,4,5-3Cl	2,4-2Cl	$C_{19}H_{11}Cl_5N_4O_3$	227 ~ 228	83	43.82 (43.80)	2.16 (2.11)	10.67 (10.76)
4p	*p*-Br	H	$C_{19}H_{15}BrN_4O_3$	240 ~ 241	81	53.00 (53.27)	3.64 (3.50)	12.94 (13.08)
4q	*o*-NO_2	H	$C_{19}H_{15}N_5O_5$	168 ~ 170	69	57.81 (57.97)	3.65 (3.84)	17.65 (17.87)
4r	2,4-2CH_3	H	$C_{21}H_{20}N_4O_3$	210 ~ 213	78	66.70 (66.96)	5.40 (5.34)	14.98 (14.94)

The spectra analysis of the new compounds are listed in Table 2. The infrared spectra of **4** exhibited

Table 2 ^{1}H NMR and IR data of the new compounds **4**

No.	^{1}H NMR (solvent), δ	IR, ν/cm^{-1}
4a	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.01 (m, 9H, C_6H_4, C_6H_5), 10.20 (s, 1H), 13.20 (bs)	1691.7, 1646.9, 1613.4 (C=O)
4b	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.00 (m, 8H, $2C_6H_4$), 9.60 (s, 1H), 13.20 (bs)	1 722.9, 1663.5, 1613.4 (C=O); 3162.5 (N-H)
4c	($DMSOd_6$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.60 ~ 8.00 (m, 9H, C_6H_4, pyridine-H), 8.80 (m, 2H, pyridine-H), 11.32 (bs), 12.00 (bs)	
4d	($CDCl_3$): 2.20 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 6.84 (s, 1H), 6.86 ~ 8.00 (m, 8H, C_6H_4), 9.20 (bs)	1679.3, 1646.8, 1616.4 (C=O)
4e	($CDCl_3$): 2.20 (s, 3H, CH_3), 4.10 (s, 3H, CH_3), 6.84 (s, 1H), 7.00 ~ 7.68 (m, 8H, C_6H_4), 8.32 (s, 1H), 11.20 (s, 1H)	1711.0, 1686.6, 1627.8 (C=O)
4f	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 7.92 (m, 7H, C_6H_4, C_6H_3), 9.52 (s, 1H)	1 695.2, 1640.5, 1608.8 (C=O); 3159.5 (N-H)
4g	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.00 (m, 10H, C_6H_5), 9.12 (s, 1H), 13.20 (bs)	1 703.3, 1663.5, 1616.0 (C=O); 3161.5 (N-H)
4h	($CDCl_3$ + $DMSOd_6$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.40 ~ 7.68 (m, 7H, C_6H_5, pyridine-H), 8.00 (m, 2H, pyridine-H), 8.80 (d, 1H)	1694.1, 1639.3, 1610.6 (C=O)
4i	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.00 (m, 9H, C_6H_4, C_6H_5), 9.92 (d, 1H), 13.20 (d, 1H)	1701.4, 1654.5, 1629.1 (C=O)
4j	($CDCl_3$ + $DMSOd_6$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.00 (m, 9H, C_6H_4, C_6H_5), 10.40 (bs, 1H), 12.80 (bs, 1H)	
4m	($CDCl_3$ + $DMSOd_6$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.36 ~ 8.00 (m, 7H, C_6H_2, C_6H_5), 10.80 (bs), 12.80 (bs)	
4n	($CDCl_3$ + $DMSOd_6$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.92 ~ 8.20 (m, 4H, C_6H_2, pyridine-H), 8.80 (m, 2H, pyridine-H)	1708.7, 1661.6, 1610.8 (C=O)
4p	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.00 (m, 9H, C_6H_4, C_6H_5)	
4q	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.36 ~ 8.40 (m, 9H, C_6H_4, C_6H_5), 10.20 (s, 1H), 13.20 (bs)	
4r	($CDCl_3$): 2.20 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.12 ~ 8.00 (m, 8H, C_6H_3, C_6H_5)	1 694.8, 1661.1, 1616.5 (C=O); 3198.0 (N-H)
4k	($CDCl_3$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.20 ~ 7.92 (m, 7H, C_6H_4, C_6H_3), 9.88 (bs, 1H)	1 707.1, 1676.1, 1628.5 (C=O); 3250.0 (N-H)
4o	($CDCl_3$ + $DMSOd_6$): 2.20 (s, 3H, CH_3), 6.84 (s, 1H), 7.28 ~ 8.00 (m, 5H, C_6H_2, C_6H_3), 11.20 (s, 1H), 12.64 (s, 1H)	1 712.9, 1670.5, 1636.0 (C=O); 3174 (N-H)

N-H stretching absorption bands in the region between 3100 ~ 3250 cm^{-1}, the absorption bands due to the C = O groups were observed in the range of 1610 ~ 1725 cm^{-1}. In the nuclear magnetic resonance spectra, the chemical shifts of the aromatic protons range from 7.00 ~ 8.30 ppm, the methyl group attached to the pyridazinone ring appeared as a single at 6.84 ppm and 10.00 ~ 13.00 ppm due to the N-H proton.

3.2 Biological activity

The preliminary biological tests are listed in Table 3 . Most of the products exhibit promoting

Table 3　Biological activity data of compounds **4**

No.	FW	GRE ± % (0 mg/L)	Antifungal activity % (*in vivo*) (500 mg/L)			
		Cucumber cotyledon	TMV	*Sclerotinia sclerotinia*	*Botrytis cinerea*	*Puccinia triticina*
4a	382.5	26.5	20	21	30.4	60
4b	417	68.7	40	30	32.1	10
4d	412.5	68.7	0	12	10.4	10
4e	412.5	38.6	15	20	8.6	30
4f	451.5	110.8	0	28	0	60
4g	348	56.6	70	10	0	10
4h	349.1	50.6	60	35	11.7	20
4i	417	86.7	0	30	29.1	0
4j	382.5	110.8	0	35	30.4	20
4m	451.5	104.8	0	40	30.4	30
4n	452.5	80.7	0	45	26.0	10
4p	428	56.6	40	18	30.4	20
4q	393	68.6	45	50	46.2	20
4r	376	68.6	0	21	20.5	10

Cucumber cotyledon root-formation activity, especially compound **4f** (R_1 = *o*-Cl, R_2 = 2, 4-2Cl), **4j** (R_1 = *p*-Cl, R_2 = H), **4m** (R_1 = 2, 4, 5-3Cl, R_2 = H), which showed over 100% promotion. We introduced fluoride atom into the compound and prepared compound **4l**, which can't dissolve in most of polar solvent, such as DMF, DMSO, methanol, ethanol etc., so the ^1H NMR and bioactive test can't be tested. Some of the compounds exhibit antiviral activity against TMV, especially compound **4g** and **4h**, which showed 70% and 60% inhibition respectably. Compound **4a** and **4f** were assessed for against *Sheath blight* on rice, they showed 84.6% and 79.0% inhibition respectably at 500 mg/L^{-1}. A further study of the promoting *Cucumber cotyledon* root-formation activity is underway.

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References

1 (a) Heinisch G., Koplent F. H.. *Prog. Med. Chem.*, 1992, 29: 141
(b) Heinisch G., Koplent F. H.. *Prog. Med. Chem.*, 1990, 27: 1
2 Sha J. J.. Foreign New Pesticide Handbook, Beijing: Chemical Industry Press, 1993, 10: 130 (in Chinese)
3 Fujimoto T. T. (Rohm and Haas Company). Ger Offen 2 808 795, 1978
4 Fujimoto T. T. (Rohm and Haas Company). US 4 344 934, 1982
5 Hsu. Adan Chi-Tung. (Rohm and Haas Company). EP 0 232 075, 1987
6 Hsu. Adan Chi-Tung (Rohm and Haas Company). EP 0 245 950, 1987
7 Hsu. Adan Chi-Tung (Rohm and Haas Company). EP 0 253 468, 1987
8 Li Z.M., Zou X.J., Yao E.Y. *et al*.. *Yingyong Huaxue of China*, 1993, 10 (6): 86 ~ 88
9 Raymond N.. Castle, Heterocyclic Compounds: Pyridazines, Vol 28, John wiley & Sons. Inc. 1973: 414

1-芳基-1,4-二氢-6-甲基-3-酰肼羰基-4-哒嗪酮及其生物活性

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摘 要 用两种方法合成了 1-芳基-1,4-二氢-6-甲基-3-酰肼羰基-4-哒嗪酮 (4)。选择了较好的一种方法合成了一系列的目标化合物以期找到具有生物活性的新型化合物。生测结果表明,标题化合物对黄瓜子叶生根具有较高的促进生长作用,一些化合物对烟草花叶病毒 (TMV)和水稻纹枯病具有较高的抑制作用。

关键词 哒嗪酮;合成;抗病毒活性;植物生长调节活性