한국농약과학회지 제4권 제2호(2000)
The Korean Journal of Pesticide Science
Vol. 4, No. 2, pp.72~75(2000)

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Synthesis and Herbicidal Activity of New *N*-{5-[(Pyrazolylmethyl)oxy]phenyl}imides

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Abstract : 3,4-Dimethyl-*N*-[4-chloro-2-fluoro-5-{(pyrazolylmethyl)oxy}phenyl]maleimides or 3,4,5,6-tetrahydro-*N*-[4-chloro-2-fluoro-5-{(pyrazolylmethyl)oxy} phenyl]phthalimides were prepared and evaluated their herbicidal activities under paddy conditions. Those compounds which have *N*-methyl-5-pyrazolylmethyloxy moiety showed good tolerance in transplanted rice and strong herbicidal activities on barnyardgrass below 60 g/ha of dose.(Received May 12, 2000, accepted June 23, 2000)

Key words : *N*-Phenyl imides, Protox inhibitor, pyrazole, herbicide, rice, barnyardgrass.

N-Phenyl imides are bleaching herbicides that act by interrupting chlorophyll biosynthesis *via* inhibiting the activity of the protoporphyrinogen oxidase (protox, EC 1.3.3.4) (Dayan and Duke, 1997). The chemical structure of protox herbicudes has some similiarities, N-C(=O)- group bound to a hydrophobic alkyl ; and N-(5- propargyloxy or 5-alkoxycarbonyl)phenyl. Also, many kinds of pyrazoles were developed as agrochemicals (Kobayashi, 1989) and 3-aryl pyrazoles, although they has no N-C(=O)-group, were developed as protox inhibiting herbicides (Woodard *et al.*, 1994).

In the course of our program to develop new herbicides, we were interested in the syntheses and herbicidal activities of the *N*-{5-[(pyrazolylmethyl)oxy] phenyl}imides **6**, **7** and **8**, the combined structure of *N*-phenyl imide and pyrazole. It was envisioned that heterocycles like pyrazole in place of 5-propargyloxy or 5-alkoxycarbonyl groups could enhance the biological activity.

Pyrazoles were prepared from phenyl methyl ketones or alkyl methyl ketones, as described in **Scheme 1**. The base-catalyzed condensation of 2,4-dichlorophenyl methyl ketone with diethyl oxalate gave **1** which was reacted with hydrazine hydrate to afford 5-methoxycarbonyl pyrazole **2**. When *N*-methylation of pyrazole **2** was carried out with dimethyl sulfate in the presence of base, a mixture of *N*-methyl pyrazole isomers (**3** and **3'**) were obtained with variable product ratios. When the reaction was performed in the absence of base with an excess amount of dimethyl sulfate (4 equiv.) in refluxing acetonitrile, 5-alkoxycarbonyl-1-methyl-pyrazole (**3**) was exclusively produced. Two isomers can be separated using silica gel column chromatography and identified; the characteristic H^1 NMR peak of *N*-methyl-3-(2,4-dichlorophenyl)-5-methoxycarbonylpyrazole (**3**) appeared at δ 4.24 (s, 3H, NCH_3), and that of *N*-methyl-5-(2,4-dichlorophenyl)-3-methoxycarbonyl-pyrazole (**3'**) appeared at δ 3.81 (s, 3H, NCH_3) (Tensmeyer and Ainsworth, 1966). Chlorination of **3** with N-chlorosuccinimide (NCS) in DMF at 80°C, followed by reduction of alkoxycarbonyl group with $LiAlH_4$ afforded the alcohol **4**. Chlorination of alcohol **4** with methansulfonyl chloride in the presence of triethylamine afforded the 5-chloromethyl-1-methylpyrazole **5**, which was coupled with 3,4-dimethyl-*N*-(4-chloro-2-fluoro-5-hydroxy phenyl) maleimide or 3,4,5,6-tetrahydro-*N*-(4-chloro-2-fluoro-5-hydroxyphenyl)phthalimide in the presence of sodium hydride in DMF to give the desired products **6** or **7**, respectively. Similarly, compounds **8** were prepared by the same procedure from the pyrazole isomer **3'**.

For the herbicidal evaluation, plant species were grown to the two to three leaf stages. Seeds of pre-germinated *Oryza sativa L.* and dry seeds of various plants were sown in white plastic pots having surface area of 350 cm^2 filled with sandy loam with 1.2 % of organic matter and pH 6.0 in the green

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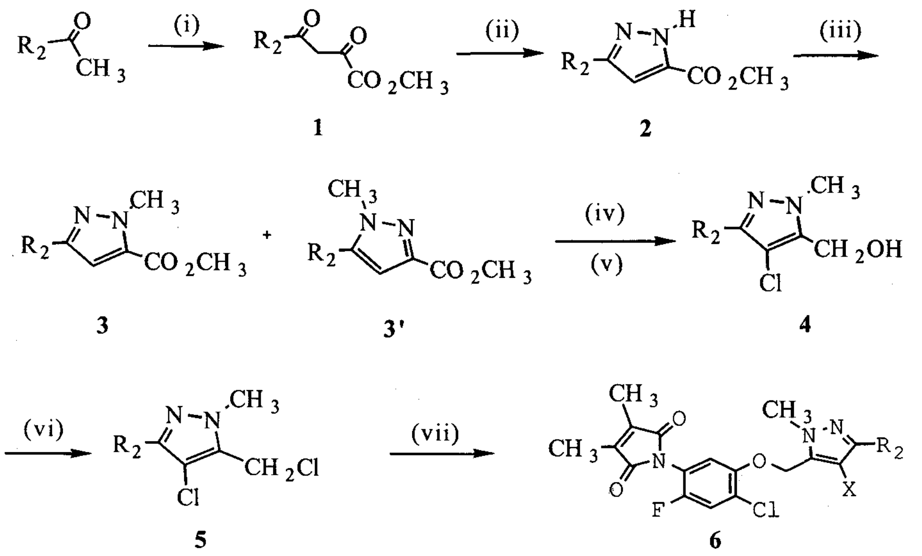


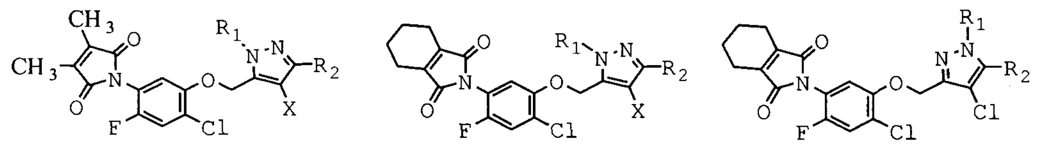
R_2 = 2,4-dichloro-5-nitrophenyl, t-butyl, 2-chlorophenyl, 3-methylphenyl, 2,4-dichlorophenyl

(i) $(CO_2Et)_2$, NaOMe in MeOH (ii) H_2NNH_2, AcOH (iii) Me_2SO_4 (4 eq.), CH_3CN (80 °C) (iv) NCS, DMF (80 °C) (v) $LiAlH_4$ or $NaBH_4$ - THF (vi) $MeSO_2Cl$, Et_3N (vii) DMF, NaH, n-Bu_4NI (cat.), 3,4-dimethyl *N*-(4-chloro-2-fluoro-5-hydroxyphenyl)maleimide

Scheme 1

stages, treatments were made at various growth stages. A solution containing the target herbicide solution was prepared by dissolving the compound in 50% of acetone containing 0.2% of Tween-20 and applied in a spray volume of 4,000 L/ha at 8~12 days after seeding. Herbicidal activities were determined fourteen days after treatment and recorded as percent control on a scale 0 to 100, where 0 indicated no visible effect and 100 indicated complete killing of plants. The results of the herbicidal activities are summarized in **Table 1.**

Interestingly, *N*-alkyl group on pyrazolyl moiety showed high effect on herbicidal activity. Without *N*-alkyl group on pyrazoyl moiety, no herbicidal



6 7 8

6a: R_1= H, R_2= 2,4-dichloro-5-nitrophenyl, X = H

6b: R_1= CH_3, R_2= 2,4-dichloro-5-nitrophenyl, X = Cl

6c: R_1= CH_3, R_2= t-butyl, X = H

6d: R_1= ethyl, R_2= 2-chlorophenyl, X = Cl

6e: R_1= CH_3, R_2= 2-chlorophenyl, X = Cl

6f: R_1= CH_3, R_2= 3-methylphenyl, X = Cl

6g: R_1= CH_3, R_2= 2,4-dichlorophenyl, X = Cl

7: R_1= CH_3, R_2= 2,4-dichloro-5-nitrophenyl, X = H

8: R_1= CH_3, R_2= 2,4-dichloro-5-nitrophenyl, X = H

Scheme 2

Table 1. Herbicidal activities of N-{5-[(pyrazolylmethyl)oxy]phenyl}imides under paddy condition

Compound	Rate (g/ha)	ORYSA[a)] (3-leaf)	ORYSA (seed)	% control of				
				ECHOR	SCPJU	MOOVA	CYPSE	SAGPY
6a	1000	0	0	0	0	0	0	0
6b	1000	0	70	100	0	70	×	0
	250	0	0	70	0	40	×	0
	63	0	0	30	0	0	×	0
6c	1000	0	100	100	0	100	100	50
	250	0	100	100	0	90	100	20
	63	0	70	100	0	80	100	20
6d	1000	0	100	100	0	100	100	50
	250	0	100	100	0	100	100	20
	63	0	30	70	0	50	100	20
	16	0	0	20	0	0	100	0
6e	1000	0	100	100	0	100	100	50
	25	0	100	100	0	100	100	0
	63	0	100	90	0	100	100	0
	16	0	50	70	0	60	0	0
6f	1000	0	100	100	0	100	100	0
	250	0	100	100	0	100	100	0
	63	0	100	100	0	100	100	0
	16	0	100	90	0	60	100	0
6g	1000	0	100	70	0	40	100	0
7	1000	0	100	100	0	100	×	0
	250	0	100	90	0	100	×	0
	63	0	100	90	0	100	×	0
	16	0	100	30	0	50	×	0
8	1000	0	100	100	0	100	100	0
	250	0	40	100	0	100	100	0
	63	0	40	70	0	40	100	0
	16	0	0	0	0	0	0	0

[a)]ORYSA:*Oryza sativa* L.(rice), ECHOR:*Echinochloa crus-galli*(barnyardgrass), SCPJU:*Scirpus juncoides* ROXB.(bulrush), MOOVA:*Monochoria vaginalis* PRESL.(monochria), CYPSE:*Cyperus serotinus* ROTTB.(flat-sedge), SAGPY:*Sagittaria pygmaea* MTQ.(arrow head).

activity was observed. The compound **8** derived from pyrazol isomer **3'** showed less herbicidal activity than the compound **7** derived from pyrazol isomer **3**(Entry 8 and 9). It was noted that the compounds which have *N*-methyl-5-pyrazolylmethyloxy moiety showed strong tolerance in transplanted rice and 100 % control against barnyardgrass at below 60 g/ha although they had strong damage on seeded rice. The compound **6f** had strong tolerance in transplanted rice with good herbicidal activity on barnyardgrass, monochoria (MOOVA) and flat-sedge(CYPSE). When herbicide **6f** was applied at rate of 63~125 g/ha, the growth of 3-leaved rice was inhibited by slight chlorosis through the rice leaf. The inhibition appeared severely after seven days of application, but it was gradually recovered after 2 weeks. Evaluation of herbicidal activity in green house indicated that the compound **6f** has potential post-emergent herbicide at rice field in 5~15 days after transplantation at rate of 60~125 g/ha. In conclusion, we had synthesized new *N*-{5-[(pyrazolylmethyl)oxy]phenyl} imides and evaluated their herbicidal activities under paddy conditions.

Among them, compound **6f** showed promising herbicidal activities against barnyardgrass with excellent 3-leaf rice tolerance at a rate of 60 g/ha.

Spectral Data (1H NMR, 200 MHz, CDCl3)

N-Methyl-3-(2,4-dichlorophenyl)-5-methoxycarbonylpyrazole (3): δ 3.92 (t, 3H, OCH3), 4.24 (s, 3H, NCH3), 7.26-7.32 (dd, 1H, J=2.2 and 8.6), 7.35 (s, 1H, CH), 7.78 (d, 1H, J=8.6, Ph).

N-Methyl-5-(2,4-dichlorophenyl)-3-ethoxycarbonyl-pyrazole (3′): δ 1.43 (t, 3H, OCH2CH3), 3.81 (s, 3H, NCH3), 4.44 (q, 2H, OCH2CH3), 6.85 (s, 1H, pyrazole C=CH), 7.27-7.57 (m, 3H, Ph)

6a: δ 2.06 (s, 6H, 2CH3), 4.02 (s, 3H, NCH3), 5.11 (s, 2H OCH2), 6.83 (s, 1H), 6.94 (d, 1H, Ph), 7.31 (d, 1H, Ph), 7.70 (s, 1H, Ph), 8.13 (s, 1H, Ph)

6b: δ 2.07 (s, 6H, 2CH3), 4.06 (s, 3H, NCH3), 5.17 (s, 2H, OCH2), 6.94 (d, 1H, Ph), 7.31 (d, 1H, Ph), 7.70 (s, 1H, Ph), 8.13 (s, 1H, Ph)

6c: δ 1.23 (s, 9H, tBu), 2.13 (s, 6H, 2CH3), 3.85 (s, 3H, NCH3), 6.67 (s, 1H, pyrazole), 6.84 (d, 1H, Ph), 7.30 (d, 1H, Ph)

6d: δ 2.06 (s, 6H, 2CH3), 2.38 (s, 3H, CH3), 3.99 (s, 3H, NCH3), 5.07 (s, 2H, CH2), 6.60 (s, 1H, CH=), 6.90-7.63 (m, 6H, Ph)

6e: δ 2.06 (s, 6H, 2CH3), 4.05 (s, 3H, NCH3), 5.11 (s, 2H, CH2), 6.82 (s, 1H, CH=), 6.94 (m, 1H, Ph), 7.20-7.49 (m, 4H, Ph), 7.76-7.91 (m, 1H, Ph)

6f: δ 1.21 (t, 3H, NCH2CH3), 2.06 (s, 6H, 2CH3), 3.92 (q, 2H, NCH2CH3), 5.09 (s, 2H, OCH2), 6.38 (s, 1H, CH=), 7.17-7.84 (m, 6H, Ph)

6g: δ 2.07 (s, 6H, 2CH3), 4.04 (s, 3H, NCH3), 5.12 (s, 2H, OCH2), 6.87 -6.95 (m, 2H, ph), 7.26-7.29 (m, 1H, Ph), 7.32 (s, 1H, CH=), 7.62 (d, 1H, Ph)

7: δ 1.83 (m, 4H, 2CH2), 2.42 (m, 4H, 2CH2), 4.02 (s, 3H, NCH3), 5.11 (s, 2H, OCH2), 6.94 (d, 1H, Ph), 7.31 (d, 1H, Ph), 7.70 (s, 1H, Ph), 8.13 (s, 1H, Ph)

8: δ 1.83 (m, 4H, 2CH2), 2.43 (m, 4H, 2CH2), 4.16 (s, 3H, NCH3), 5.66 (s, 2H, OCH2), 7.02 (d, 1H, Ph), 7.35 (d, 1H, Ph), 7.71 (s, 1H, Ph), 8.16 (s, 1H, Ph)

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새로운 *N*-{5-[(Pyrazolylmethyl)oxy]phenyl}imide 유도체들의 합성 및 제초활성

김경만, 송종환, 전동주, 김형래, 최정섭, 오도연, 유응걸*(한국화학연구소, 대전, 유성사서함 107, 305-606)

요약 : 제초제 후부물질로서 3,4-dimethyl-N-[4-chloro-2-fluoro-5-{(pyrazolylmethyl)oxy}phenyl]maleimide 유도체들과 또는 3,4,5,6-tetrahydro-N-[4-chloro-2-fluoro-5-{(pyrazolylmethyl)oxy}phenyl]phthalimide 유도체들을 합성하여 제초활성을 온실조건에서 평가하였다. 이들 중 N-methyl-5-pyrazolylmethyloxy를 갖는 화합물들이 처리량 60 g/ha이하에서 이앙벼에 안전하면서 논피에 강한 제초활성을 나타내었다.

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