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〈단 보〉

Synthesis and Herbicidal Properties of 2-(5-Isoxazolinemethoxyphenyl)-4,5,6,7-tetrahydro-2H-indazole and Their Related Derivatives

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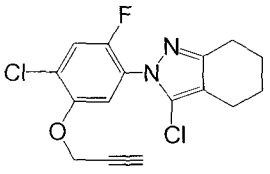
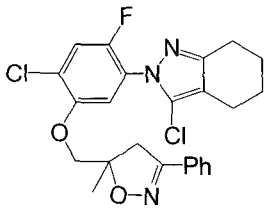
Abstract : A series of bicyclic 4,5,6,7-tetrahydroindazole derivatives **6** have been synthesized, and their herbicidal activities were studied in flooded paddy condition. The compounds **6** showed herbicidal effects to barnyardgrass and Monochoria and good tolerance against rice at a rate of 0.063 kg/ha~0.25 kg/ha.(Received June 4, 2001; accepted September 19, 2001)

Key words : Cyclic imide, Protox inhibitor, bicyclic 4,5,6,7-tetrahydroindazole, herbicide.

Cyclic imide classes of herbicides have been classified as Protox inhibitors, since they have been found to inhibit protoporphyrinogen IX oxidase (Protox) (Hirai, 1999). Most recent cyclic imides consisting of a highly functionalized phenyl group and nitrogen-containing heterocycle moiety exhibit superior efficacy against weeds at low rate of application. 5-Membered cyclic imides were developed practicaly and the compound of this class are under development. Especilly, pyrazole derivatives have been intensively studied and focused on bicyclic 4,5,6,7-tetrahydroindazole derivatives exemplified by S-275 (Nagano et al., 1983).



S-275



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We have extensively studied on the synthesis of diverse types of new compounds containing pyrazole moiety. The compound **1** exhibit a potent herbicidal effect especially to barnyardgrass, and safe to rice in flooded paddy conditions (Ryu *et al.*, 2001; Jeon *et al.*, 1998; Jeon *et al.*, 1999; Lee *et al.*, 2000). Because the starting material in the synthesis of **1**, the fluorine containing aniline derivative was expensive, we were interested in preparing **6** in which chlorine is substituted instead of fluorine. We now report a synthesis of **6** and the herbicidal effect in flooded paddy conditions.

Scheme **1** outlines the synthesis of bicyclic 4,5,6,7-tetrahydroindazole derivatives **6**. The starting material **2** was prepared through nitration of 2,4-dichlorophenol followed by reduction. Compound **2** was dissolved in conc. hydrochloric acid, and treated with a aqueous solution of sodium nitrite at 0 °C. Stirring was continued for 1hr at 5 to -5 °C. The resulting mixture was cooled to -30 °C, and a solution of stannous chloride dissolved in conc. hydrochloric acid was added followed by stirring at -30 °C to 0 °C for 3 hour to give hydrazine derivative **3**. The tetrahydroindazolone **4** was obtained by refluxing with a solution of **3** and ethyl 2-cyclohexanonecarboxylate in acetic acid for 4 hour. The product **4** was added to a 1.5 M solution of phosgene in toluene at room temperature, and the mixture was refluxed for 4 hour to give the tetrahydroindazole **5a**. To a solution of **5a** in acetone was added methallyl chloride, potassium carbonate as a base and catalytic amount of potassium iodide, and the mixture was refluxed for 12 hour to afford **5b**. The cycloaddition reaction between alkene group and nitrile oxides of **5b** was carried out for the following method. To a solution of compound **5b** and various hydroximoyl chlorides dissolved in methylene chloride was added dropwise a solution of triethylamine in methylene chloride. The mixture was stirred at room temperature for 12 hour to give the isoxazolines **6a-h**.

The herbicidal activity of **6a-h** were evaluated under paddy submerged conditions according to the following methods. The sterilized paddy soil was filled in a test pot having a surface area of 140 cm^2 and

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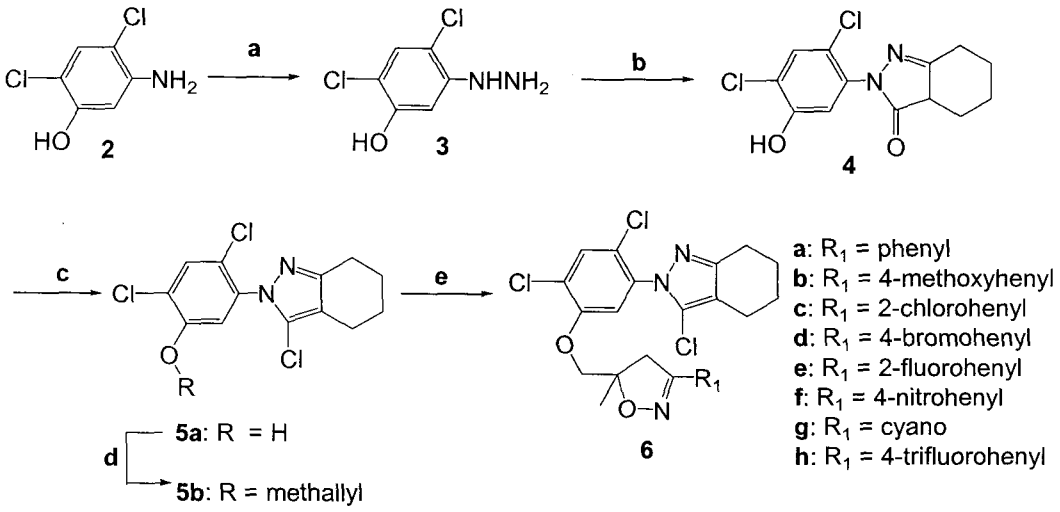

a. 1) $NaNO_2$, C-HCl, 0 °C 2) $SnCl_2.2H_2O$, -30°C **b**. ethyl 2-cyclohexaonecarboxylate, AcOH, reflux **c**. phosgene, toluene, reflux **d**. Methallyl chloride, K_2CO_3, KI, acetone, reflux **e**. R-CHCl=NOH, triethylamine, CH_2Cl_2, rt

Scheme 1

test species were planted. The test compounds dissolved in acetone were added on the surface as an acetone solutions by proper rate. The pots were placed in a greenhouse and watered for 3 weeks. The herbicidal activity data were taken visually by percent control, wherein 0 signifies no herbicidal effect and 100 signifies complete kill. The results are summarized in Table 1.

While compounds in which electron-withdrawing group was substituted in phenyl group at para position such as **6f** and **6h** exhibited no herbicidal effects, the majority of compounds **6** showed herbicidal effects to barnyardgrass and monochoria and good tolerance against rice at a rate of 0.063 kg/ha ~ 0.25 kg/ha. However, they exhibited little advantageous in herbicidal effects or selectivity in comparison with the compound **1** in all their aspects.

Spectral Data:

3-Chloro-2-{4-chloro-5-(3-phenyl-5-methylisoxazolin-5-yl) methoxy-2-chlorophenyl}-4,5,6,7-tetrahydro-2H-indazole (**6a**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.69~7.38 (5H, m), 7.26 (1H, s), 6.96 (1H, s), 4.08 (1H, d, J=9.2 Hz), 3.98(2H, d, J=9.2 Hz), 3.59 (1H, d, J=16.9 Hz), 3.17 (1H, d, J=16.9 Hz), 1.64 (3H, s), 2.72~1.26 (8H, m). MS (70eV) m/z (rel. intensity) 491 (M^+, 6.9), 489 (6.4), 333 (10.9), 331 (35.0), 329 (31.3), 174 (10.6), 160 (19.9), 118 (94.9), 43 (100).

3-Chloro-2-[4-chloro-5-{3-(4-methoxyphenyl)-5-methylisoxazolin-5-yl}methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6b**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.69~7.38 (5H, m), 7.26 (1H, s), 6.96 (1H, s), 4.08 (1H, d, J=9.2 Hz), 4.08 (1H, d, J=9.2 Hz), 3.98 (2H, d, J=9.2 Hz), 3.54 (1H, d, J=16.9 Hz), 3.17 (1H, d, J=16.9 Hz), 1.64 (3H, s), 2.72~1.26 (8H, m). MS (70eV) m/z (rel. intensity) 520 (M^+, 3.2), 519 (8.5), 333 (23.0), 331 (66.2), 329 (69.5), 303 (12.6), 302(10.2), 301 (14.2), 190 (34.9), 148 (100).

3-Chloro-2-[4-chloro-5-{3-(2-chlorophenyl)-5-methylisoxazolin-5-yl}methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6c**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.67~7.38 (4H, m), 7.26 (1H, s), 6.95 (1H, s), 4.07 (1H, d, J=9.2 Hz), 3.98 (2H, d, J=9.2 Hz), 3.58 (1H, d, J=16.9 Hz), 3.16 (1H, d, J=16.9 Hz), 1.69 (3H, s), 2.72~1.26 (8H, m). MS (70 eV) m/z (rel. intensity) 525 (M^+, 2.2), 491 (28.6), 489 (29.5), 454 (6.2), 409 (11.8), 407 (17.4), 333 (32.8), 332 (30.9), 330 (33.6), 329 (100), 227 (2.3).

3-Chloro-2-[4-chloro-5-{3-(4-bromophenyl)-5-methylisoxazolin-5-yl}methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6d**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.80~7.23 (5H, m), 6.96 (1H, s), 4.08 (1H, d, J=9.2 Hz), 3.98 (1H, d, J=9.2 Hz), 3.57 (1H, d, J=16.9 Hz), 3.13 (1H, d, J=16.9 Hz), 1.62 (3H, s), 2.69~1.22 (8H, m). MS (70eV) m/z (rel. intensity) 569 (M^+, 0.7), 333 (1.2), 331 (3.6), 294 (2.2), 238 (2.0), 43 (100).

3-Chloro-2-[4-chloro-5-{3-(2-fluorophenyl)-5-methylisoxazolin-5-yl}methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6e**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82~6.91 (4H, m), 7.43 (1H, s), 6.89 (1H, s), 4.02 (1H, d, J=9.2 Hz), 3.96 (2H, d, J=9.2 Hz), 3.58 (1H,

Table 1. Herbicidal activity of 6a~g in flooded paddy condition

Comp.	rate kg/ha)	ORYSA[a] (3leaf)	ORYSA (seed)	ECHOR[b]	SCPJU[c]	MOOVA[d]	CYPSE[e]	SAGPY[f]
6a	4.000	0	100	100	50	100	100	100
	1.000	0	50	100	30	100	50	40
	0.250	0	50	100	0	100	0	30
	0.063	0	40	80	0	100	0	0
6b	4.000	0	60	100	50	100	0	0
	1.000	0	0	100	40	100	0	0
	0.250	0	30	80	40	100	0	0
	0.063	0	0	60	0	70	0	0
6c	4.000	0	100	100	60	100	90	40
	1.000	0	70	100	50	100	20	0
	0.250	0	40	95	30	100	0	0
	0.063	0	0	50	0	100	0	0
6d	4.000	0	40	100	90	100	70	50
	1.000	0	40	80	20	100	20	0
	0.250	0	40	80	20	100	0	0
	0.063	0	0	0	0	20	0	0
6e	4.000	20	60	100	50	100	0	90
	1.000	10	50	100	40	100	0	30
	0.250	0	30	100	30	100	0	0
	0.063	0	20	60	0	50	0	0
6f	4.000	0	0	0	0	0	0	0
6g	4.000	20	60	100	70	100	0	100
	1.000	10	40	100	30	100	0	70
	0.250	0	10	100	20	100	0	50
	0.063	0	10	80	20	100	0	50
6h	4.000	0	0	0	0	0	0	0

[a]Rice, [b]Barnyardgrass, [c]Bulrush, [d]Monochoria, [e]Flat-sedge, [f]Arrow head.

d, J=16.9 Hz), 3.19 (1H, d, J=16.9 Hz), 1.55 (3H, s), 2.83~1.4 (8H, m). MS (70eV) m/z (rel. intensity) 509 (M^+, 8.4), 507 (8.2), 474 (1.2), 333 (10.3), 331 (31.1), 329 (32.7), 301 (7.2), 295 (4.0), 136 (100).

3-Chloro-2-[4-chloro-5-{3-(4-nitrophenyl)-5-methylisoxazolin-5-yl}methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6f**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.28 (2H, d, J=9.0 Hz), 7.85 (2H, d, J=9.0 Hz), 7.52 (1H, s), 6.99 (1H, s), 4.15 (1H, d, J=9.5 Hz), 4.03 (1H, d, J=9.5 Hz), 3.67 (1H, d, J=16.9 Hz), 3.21 (1H, d, J=16.9 Hz), 1.68 (3H, s), 2.72~1.39 (8H, m). MS (70eV) m/z (rel. intensity) 535 (M^+, 2.1), 534 (4.8), 374 (2.2), 371 (2.4), 369 (2.3), 330 (12.7), 328 (12.6), 315 (4.6), 290 (3.2), 163 (13,6), 43 (100).

3-Chloro-2-[4-chloro-5-(3-cyano-5-methylisoxazolin-5-yl)methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6g**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.51 (1H, s), 6.86 (1H, s), 4.05 (1H, d, J=9.2 Hz), 3.91 (1H, d, J=9.2 Hz), 3.45 (1H, d, J=17.3 Hz), 2.95 (1H, d, J=17.3 Hz), 1.53 (3H, s), 2.66~1.16 (8H, m). MS (70eV) m/z (rel. intensity) 440 (M^+, 100), 438 (81.2), 422 (10.4), 405 (33.7), 403 (38.1), 331 (21.8), 329 (20.4), 318 (24.9), 316 (24.8), 290 (11.2), 288 (11.1), 283 (21.8), 281 (39.8).

3-Chloro-2-[4-chloro-5-{3-(4-trifluoromethylphenyl)-5-methylisoxazolin-5-yl}methoxy-2-chlorophenyl]-4,5,6,7-tetrahydro-2H-indazole (**6h**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.79 (2H, d, J=8.5 Hz), 7.66 (2H, d, J=8.5 Hz), 7.51 (1H, s), 6.97 (1H, s), 4.12 (1H, d, J=9.4 Hz), 4.00 (1H, d, J=9.4 Hz), 3.63 (1H, d, J=16.9 Hz), 3.18 (1H, d, J=16.9 Hz), 1.56 (3H, s), 2.70~1.54 (8H, m). MS (70eV) m/z (rel. intensity) 559 (M^+, 14.6), 557 (14.7), 333 (12.2), 331 (33.1), 329 (34.6), 242 (8.4), 186 (25.7), 43 (100).

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새로운 2-(5-Isoxazolinemethoxyphenyl)-4,5,6,7- tetrahydro-2-indazole의 합성과 제초활성

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요약 : 새로운 bicyclic 4,5,6,7-tetrahydroindazole 유도체들을 합성하여 논 조건에서 제초활성을 시험하였다. 이 화합물들은 0.063~0.25 kg/ha 범위의 처리에서 벼에는 안전하면서도 피와 물달개비 등을 효과적으로 방제하였다.

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