Synthesis and Herbicidal Activities of 4-Substituted 3-Aryl-5-*tert*-butyl-4-oxazolin-2-ones

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A series of novel 3-aryl-5-*tert*-butyl-4-chloro-4-oxazolin-2-ones (**16**) have been prepared and found to show significant herbicidal activity in the grams per are range against broadleaf and narrowleaf weeds. The key step in the introduction of the chlorine atom at the 4-position of the 4-chloro-4-oxazolin-2-one ring is dichlorination using chlorine gas and subsequent dehydrochlorination using diazabicyclo[5.4.0]undecene. 4-Alkylthio- and 4-methyl-4-oxazolin-2-one rings were synthesized from α-substituted α-bromopinacolone by cyclization reaction. Among the synthesized compounds, 5-*tert*-butyl-4-chloro-3-[4-chloro-2-fluoro-5-(2-propynyloxy)phenyl]-4-oxazolin-2-one (**16h**) showed the greatest activity against several weeds without damage to transplanted rice in the paddy field.

Keywords: *4-Oxazolin-2-one; α-bromoketone; cyclization; herbicide; biological isostere*

INTRODUCTION

4-Oxazolin-2-ones have been widely studied (Filler, 1965; Filler and Rao, 1977; Rao and Filler, 1986; Boyd, 1984; Hartner, 1996) since Maselli reported the first synthesis in 1905 (Maselli, 1905). McCombie and co-workers reported the synthesis of 4-oxazolin-2-ones from α-aminoketones and ethyl chloroformate (McCombie and Parkes, 1912; Pain and Slack, 1951). Stoffel and co-workers described the synthesis of 4-oxazolin-2-ones from propargyl alcohol and phenyl isocyanate (Stoffel and Dixon, 1964; Sisido et al., 1962; Cum et al., 1968). Previously, in the course of the study of isoxazole compounds, we discovered a novel synthetic method for 4-oxazolin-2-ones (**4**) from acyl Meldrum's acids (**1**) and *N*-hydroxyaniline derivatives (**2**) via *N*-arylhydroxamic acids (**3**) as shown in Figure 1 (Sato et al., 1986). Compounds **4** obtained in this manner did not show any satisfactory herbicidal activities. However, 4-chloro-4-oxazolin-2-one compounds, which were prepared by similar cyclization from α-chloro-substituted *N*-arylhydroxamic acids, exhibited improved herbicidal activities. The strength of herbicidal activities increased with the bulkiness of the 5-alkyl group (Sugai et al., 1987). This result led us to synthesize compounds having larger substituents, such as the *tert*-butyl group, at the 5-position. Unfortunately, a *tert*-butyl-substituted compound (**7**) could not be obtained using our previous synthetic method. To move beyond unsuccessful cyclizations, other new cyclization methods were surveyed, and, as a result, we discovered the novel preparation reaction of 5-*tert*-butyl-4-oxazolin-2-ones (**7**) as shown in Figure 2 (Kudo et al., 1996). Using this method, 5-*tert*-butyl-4-oxazolin-2-ones were obtained in a single step from *N*-arylcarbamates. To extend the application of this methodology, introduction of substituents at the 4-position was investigated. Herein, we report the first synthesis of 4-substituted 3-aryl-5-*tert*-butyl-4-oxazolin-2-ones and

a comparison of the relative herbicidal activity of compounds in this series.

EXPERIMENTAL PROCEDURES

Chemicals and Reagents. Chlorine was purchased from Sumitomo Seika Chemicals Co., Ltd. 2-Nitrobenzenesulfonyl chloride, *N*,*N*-dimethyaminopyridine (DMAP), *N*,*N*-diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), ethyl mercaptan, bromine, and *N*-bromosuccinimide (NBS) were purchased from Wako Pure Chemical Industries, Ltd. Ethyl chloroformate, sodium hydride, and iodomethane were purchased from Nacalai Tesque, Inc. Methyl mercaptan sodium salt 15% aqueous solution was purchased from Tokyo Chemical Industry Co., Ltd. A 1.0 M solution of LiN(TMS)$_2$ in tetrahydrofuran and diethylaminosulfur trifluoride (DAST) were purchased from Aldrich Chemical Co. A 1.6 M solution of *n*-butyllithium in hexane was purchased from Kanto Chemical Co., Inc. All reagents were used as supplied. Carbon tetrachloride (CCl$_4$), dichloromethane (CH$_2$Cl$_2$), ethyl acetate (AcOEt), dimethyl sulfoxide (DMSO), *N*,*N*-dimethyformamide (DMF), tetrahydrofuran (THF), hexane, methanol, diethyl ether, and benzene were purchased from Wako Pure Chemical Industries, Ltd., and used without further purification.

Synthesis. All melting points (mp) are uncorrected. Infrared (IR) spectra were measured on a Perkin-Elmer 1600 spectrometer. ^{1}H NMR spectra were recorded at 60 MHz on a Varian 360A spectrometer, at 200 MHz on a Varian Gemini 200 spectrometer, and at 270 MHz on a JEOL GX-270 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer and a VG Auto Spec M mass spectrometer.

All new compounds gave acceptable HRMS or elemental analysis results.

*5-tert-Butyl-4-chloro-3-(4-fluorophenyl)-4-oxazolin-2-one (**11a**) (Table 1). Procedure B.* Chlorine gas was bubbled into a suspension of **7a** (Table 1) (1.70 g, 7.23 mmol) in CCl$_4$ (15 mL) at room temperature, and the resulting mixture was stirred for 0.5 h at the same temperature. The reaction mixture was poured into saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (three times). The combined extracts were washed with saturated aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated in vacuo to afford 1.29 g (62.0%) of **13a** (Table 1) as an oil, which was subjected to the next reaction without further purification.

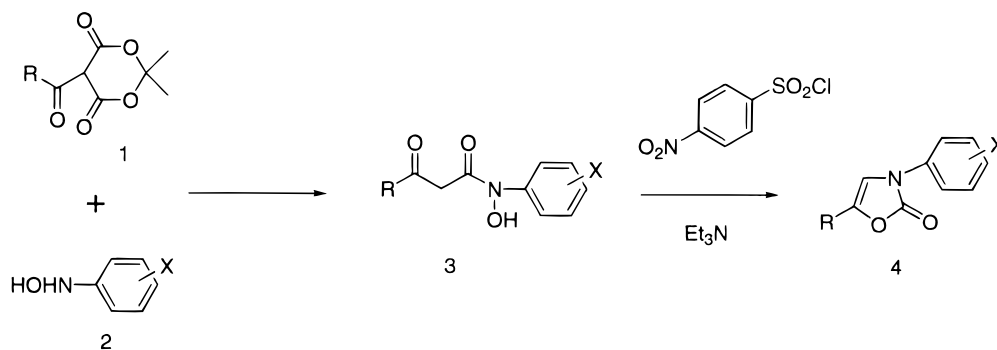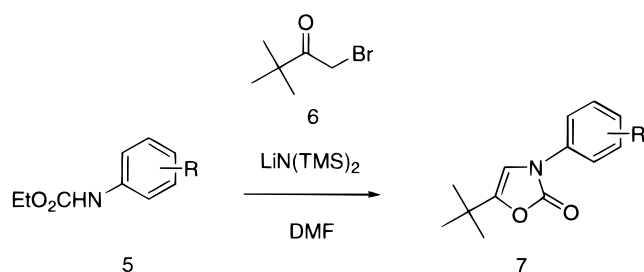**5306** *J. Agric. Food Chem.,* Vol. 46, No. 12, 1998

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Figure 1.

Figure 2.

2-Nitrobenzenesulfonyl chloride (193 mg, 0.87 mmol) was added to a solution of **13a** (50 mg, 0.17 mmol) in CH$_2$Cl$_2$ (2 mL) at room temperature, followed by the addition of DMAP (127 mg, 1.04 mmol) and *N,N*-diisopropylethylamine (0.18 mL, 1.04 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with water, dried over MgSO$_4$, and concentrated in vacuo. The residue was subjected to silica gel column chromatography to give 22.8 mg (48.6%) of **11a** as a light brown powder: ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.34 (2H, dd, *J* = 8.7, 4.8 Hz), 7.17 (2H, t, *J* = 8.7 Hz), 1.37 (9H, s); IR ν_{max} cm^{-1} 1760, 1650, 1605, 1515; MS (*m/z*) 269 (M$^+$), 254 (base), 210, 190, 175, 159.

5-tert-Butyl-4-chloro-3-(2,4-difluorophenyl)-4-oxazolin-2-one (**11b**) *(Table 1). Procedure A.* Chlorine gas was bubbled into a suspension of **7b** (Table 1) (2.49 g, 9.83 mmol) in CCl$_4$ (20 mL) for 30 s at room temperature, and the resulting mixture was stirred for 3 min at the same temperature. The reaction mixture was poured into saturated aqueous NaHCO$_3$ and extracted with AcOEt (three times). The combined extracts were dried over MgSO$_4$ and concentrated in vacuo to afford 3.18 g (99.0%) of **12b** (Table 1) as yellow crystals, which was subjected to the next reaction without further purification.

DBU (13.2 mL, 88.3 mmol) was added to a solution of **12b** (3.18 g, 9.81 mmol) in DMSO (150 mL) at room temperature, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with AcOEt (three times). The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was subjected to silica gel column chromatography to afford 1.60 g (56.6%) of **11b** as a white powder: ^{1}H NMR (60 MHz, CDCl$_3$) δ 7.60−6.85 (3H, s), 1.38 (9H, s); IR ν_{max} cm^{-1} 1780, 1745, 1645, 1605, 1515; MS (*m/z*) 287 (M$^+$), 272 (base), 228, 208, 193, 174, 139, 113.

Compounds **11c**−**11j** were synthesized following procedure A or B as indicated in Table 1.

5-tert-Butyl-3-(4-chloro-2-fluoro-5-hydroxyphenyl)-4-oxazolin-2-one (**20**) *(Figure 6).* To a solution of ethyl *N*-(4-chloro-2-fluoro-5-methoxycarbonylphenyl)carbamate (**19**) (39.0 g, 134 mmol) and 1-bromo-3,3-dimethyl-2-butanone (**6**) (33.0 g, 184 mmol) in DMF (270 mL) was added a 1.0 M solution of LiN(TMS)$_2$ in THF (303 mL, 303 mmol) at room temperature, and the resulting mixture was stirred for 1.5 h at the same temperature. The reaction mixture was diluted with water and washed with a hexane/AcOEt (1:1) mixture. The water layer was acidified with diluted HCl (to pH 1) and extracted with hexane/AcOEt (1:1) mixture (five times). The combined extracts were

washed with water (three times), dried over MgSO$_4$, and concentrated in vacuo to give 23.5 g (61.6%) of **20** as a light brown powder; mp 207−208 °C; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.45 (1H, d, *J* = 7.0 Hz), 7.20 (1H, d, *J* = 10.4 Hz), 7.08 (1H, brs), 6.47 (1H, d, *J* = 3.3 Hz), 1.26 (9H, s); IR ν_{max} cm^{-1} (KBr) 3131, 1732, 1443; MS (*m/z*) 285 (M$^+$), 270 (base), 172. Anal. Calcd for C$_{13}$H$_{13}$ClFNO$_3$: C, 54.65; H, 4.59; N, 4.90. Found: C, 54.54; H, 4.45; N, 4.87.

5-tert-Butyl-4-chloro-3-(4-chloro-2-fluoro-5-hydroxyphenyl)-4-oxazolin-2-one (**23**) *(Figure 6).* Ethyl chloroformate (0.4 mL, 4.18 mmol) was added to a solution of **20** (996 mg, 3.49 mmol) and triethylamine (0.59 mL, 4.23 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into water and extracted with CH$_2$Cl$_2$ (three times). The combined extracts were washed with diluted HCl, dried over MgSO$_4$, and evaporated to afford 1.30 g (quantitative) of **21** as a brown powder.
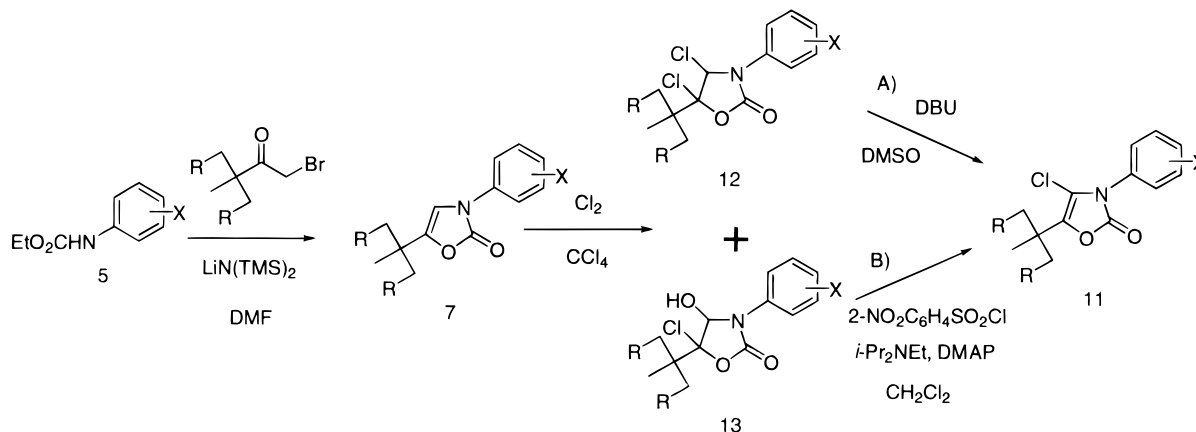
Chlorine gas was bubbled into a suspension of **21** (1.27 g, 3.49 mmol) in CCl$_4$ (15 mL) at room temperature, and the resulting mixture was stirred for 0.5 h. The reaction mixture was poured into saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (three times). The combined extracts were washed with saturated aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated in vacuo to afford 1.63 g (quantitative) of **22** as a yellow oil.

DBU (3.7 mL, 25.0 mmol) was added to a solution of **22** (1.44 g, 3.09 mmol) in DMSO (19 mL) at room temperature, and the resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was poured into water, acidified with diluted HCl (to pH 1), and extracted with AcOEt (five times). The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was subjected to silica gel column chromatography to afford 476 mg (51.5%) of **23** as a white powder: mp 170−171.5 °C; ^{1}H NMR (60 MHz, CDCl$_3$) δ 7.19 (1H, d, *J* = 9.0 Hz), 6.91 (1H, d, *J* = 7.0 Hz), 6.36 (1H, s), 1.37 (9H, s); IR ν_{max} cm^{-1} 3260, 1735, 1650, 1605, 1525; MS (*m/z*) 319 (M$^+$), 304 (base), 260, 240, 225, 206, 171, 117, 107, 89, 81, 57. Anal. Calcd for C$_{13}$H$_{12}$Cl$_2$FNO$_3$: C, 48.77; H, 3.78; N, 4.78. Found: C, 48.78; H, 3.80; N, 4.41.

5-tert-Butyl-4-chloro-3-(4-chloro-2-fluoro-5-methoxyphenyl)-4-oxazolin-2-one (**16a**) *(Table 3).* A solution of **23** (200 mg, 0.62 mmol) in DMF (2 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil) (35 mg, 0.88 mmol) in DMF (5 mL) at 0 °C. After 20 min, iodomethane (55 μL, 0.88 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with AcOEt (three times). The combined extracts were washed with brine, dried over MgSO$_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give 137 mg (65.7%) of **16a** as a white powder: ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.30 (1H, d, *J* = 9.0 Hz), 6.88 (1H, d, *J* = 6.5 Hz), 3.89 (3H, s), 1.35 (9H, s); IR ν_{max} cm^{-1} (KBr) 2973, 1778, 1508, 1201, 1058; MS (*m/z*) 333 (M$^+$), 318 (base), 274, 105, 57; HRMS calcd for C$_{14}$H$_{14}$Cl$_2$FNO$_3$ 333.0335, found 333.0336.

Compounds **16b**−**16m** were synthesized in the same manner.

5-tert-Butyl-4-fluoro-3-(4-fluorophenyl)-5-chloro-1,3-oxazolidin-2-one (**24, 25**) *(Figure 7).* DAST (0.276 mL, 2.09 mmol) was

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Table 1. Structures and Chemical Yields of 3-Aryl-4-oxazolin-2-one Derivatives

entry	X	R	7	12	13	conditions	11
a	4-F	H	85.6		62.0	B	48.6
b	2,4-F$_2$	H	86.5	99.0		A	56.6
c	4-Cl-2-F	H	80.0	46.4		A	86.0
d	4-Cl	H	60.0	60.0	11.0	B	48.3
e	2,4-Cl$_2$	H	97.1	36.2	7.7	A	87.4
f	3,4-Cl$_2$	H	54.5	39.9	35.4	B	55.5
g	3,5-Cl$_2$	H	55.6	17.9	47.1	B	36.2
h	4-OMe	H	89.7	38.9	22.9	A	66.3
I	3-CF$_3$	H	77.5	52.8	25.8	B	48.8
j	4-Cl-2-F	Me	62.7	quant		A	87.4
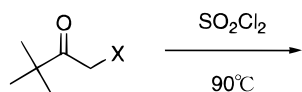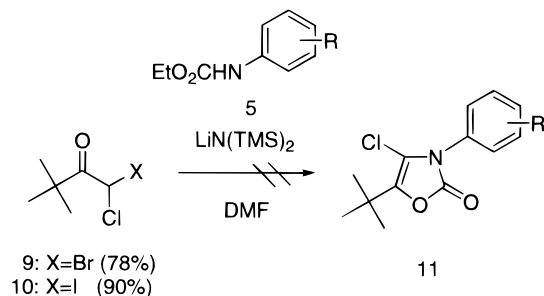
Figure 3.

carefully added to a solution of **13a** (0.5 g, 1.74 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 15 min. The reaction mixture was poured into ice and extracted with CH$_2$Cl$_2$ (three times). The combined extracts were washed with brine, dried over MgSO$_4$, and evaporated in vacuo. The residue was subjected to silica gel column chromatography to afford 302 mg (60.0%) of **24** (less polar isomer) and 81 mg (16%) of **25** (polar isomer): (**24**) mp 113.5−115 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.47 (2H, dd, J = 8.8, 4.6 Hz), 7.16 (2H, t, J = 8.8 Hz), 6.17 (1H, d, J = 68.9 Hz), 1.33 (9H, s); IR ν_{max} cm^{-1} 3050, 1790, 1515, 1410; MS (m/z) 289 (M$^+$), 274, 254, 230, 210, 194, 170, 151, 142 (base). Anal. Calcd for C$_{13}$H$_{14}$ClF$_2$NO$_2$: C, 53.90; H, 4.87; N, 4.83. Found: C, 54.14; H, 4.89; N, 4.85. (**25**) ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.46 (2H, dd, J = 8.7, 4.6 Hz), 7.14 (2H, t, J = 8.7 Hz), 5.93 (1H, d, J = 71.3 Hz), 1.19 (9H, s); IR ν_{max} cm^{-1} 1785, 1605; MS (m/z) 289 (M$^+$), 274, 254, 233, 210, 194, 141 (base), 122, 104, 85, 69, 57 (base). Anal. Calcd for C$_{13}$H$_{14}$ClF$_2$NO$_2$: C, 53.90; H, 4.87; N, 4.83. Found: C, 53.89; H, 4.93; N, 4.87.

*5-tert-Butyl-4-fluoro-3-(4-fluorophenyl)-4-oxazolin-2-one (**26**) (Figure 7).* **26** was also synthesized from **24** with DBU as **11b**: mp 76−79.5 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.45−7.38 (2H, m), 7.16 (2H, t, J = 8.7 Hz), 1.32 (9H, s); IR ν_{max} cm^{-1}

1770, 1740, 1515, 1405; MS (m/z) 253 (M$^+$), 238 (base), 194, 179. Anal. Calcd for C$_{13}$H$_{13}$NO$_2$F$_2$: C, 61.66; H, 5.17; N, 5.53; F, 15.00. Found: C, 61.22; H, 5.37; N, 5.34; F, 14.18.

*5-tert-Butyl-3-(4-chloro-2-fluorophenyl)-4-methy-4-oxazolin-2-one (**33a**) (Table 4).* A 1.0 M solution of LiN(TMS)$_2$ in THF (5.7 mL, 5.7 mmol) was added to a solution of ethyl N-(4-chloro-2-fluorophenyl)carbamate (**5c**) (427 mg, 1.96 mmol) and 4-bromo-2,2-dimethyl-3-pentanone (**32a**) (562 mg, 2.91 mmol) in DMF (3 mL) at room temperature. After being stirred at 90 °C for 1 h, the reaction mixture was diluted with water and extracted with AcOEt (three times). The combined extracts were dried over MgSO$_4$ and concentrated in vacuo. The residue was subjected to silica gel column chromatography to give 149 mg (26.7%) of **33a**: ^{1}H NMR (CDCl$_3$) δ 7.36−7.24 (3H, m), 1.91 (3H, s), 1.32 (9H, s); IR ν_{max} cm^{-1} 2973, 1755, 1505, 1385, 893; MS (m/z) 283 (M$^+$), 268 (base), 170, 129, 94. Anal. Calcd for C$_{14}$H$_{15}$ClFNO$_2$: C, 59.27; H, 5.33; N, 4.94; Cl, 12.50; F, 6.70. Found: C, 59.68; H, 5.41; N, 4.85; Cl, 12.29; F, 6.47.

Compounds **33b**−**33e** were synthesized under the conditions shown in Table 4.

*Alternative Synthesis of 5-tert-Butyl-3-(4-chloro-2-fluorophenyl)-4-(ethylthio)-4-oxazolin-2-one (**33c**) from 12c (Figure 10).* A solution of ethyl mercaptan (0.205 mL, 2.77 mmol) in THF (20 mL) was added to a 1.6 M solution of n-butyllithium in hexane (1.5 mL, 2.43 mmol) at 0 °C under argon atmosphere, and the resulting mixture was stirred at room temperature for 0.5 h. A solution of **12c** (681 mg, 2.00 mmol) in THF (5 mL) was added to the mixture, and the resulting mixture was stirred at room temperature for 3.5 h. The reaction mixture was quenched with water, extracted with AcOEt (three times), dried over MgSO$_4$, and evaporated in vacuo to afford **34** as a yellow oil.

DBU (1.8 mL, 12.0 mmol) was added to a solution of **34** (535 mg, 1.46 mmol) in DMSO (11 mL) at room temperature, and the resulting mixture was stirred for 2 h. The reaction mixture was poured into water and extracted with AcOEt (four times). Combined extracts were washed with brine, dried over MgSO$_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give 231 mg (48.0%) of **33c** as an oil.

Preemergent Herbicide Tests. Plastic pots (surface area = 100 cm^2) were filled with a clay loam soil and kept in a greenhouse. The test plants were five narrowleaf weeds
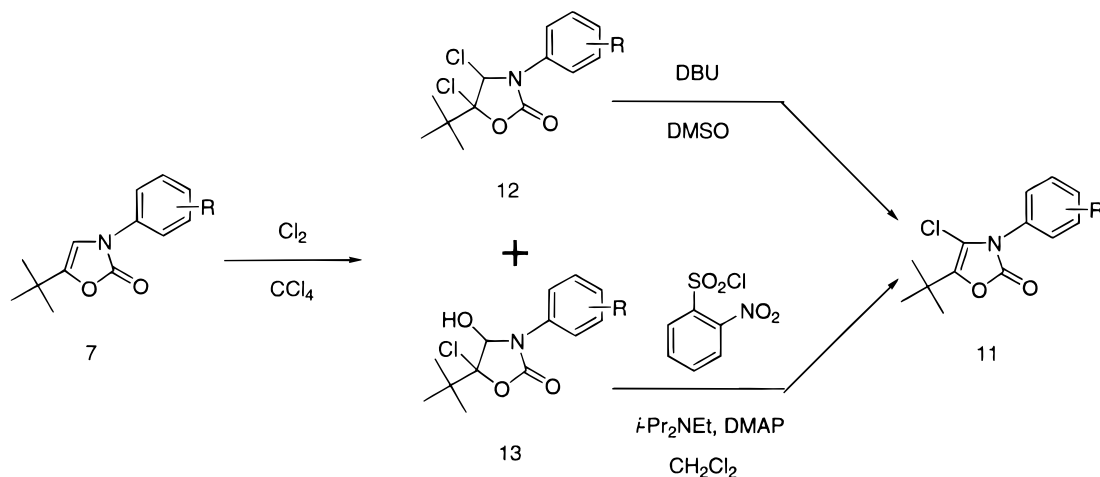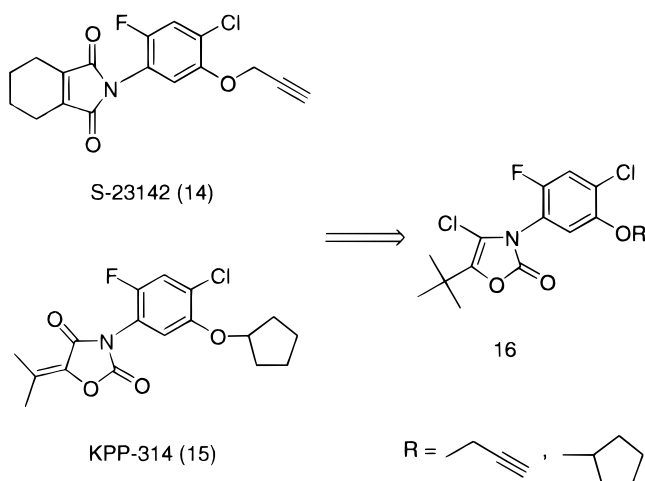
Figure 4.

Figure 5.

[*Echinochloa oryzicola* Vasing., *Scirpus juncoides* Roxb var. *ohwianus* T. Koyama, *Eleocharis acicularis* (L.) Roem. et Schult. var. *longiseta* Sven., *Cyperus serotinus* Rottb., and *Eleocharis kuroguwai* Ohwi] and one broadleaf weed [*Lindernia pyxidaria* L.], *Monochoria vaginalis* Presl var. *plantaginea* (Roxb.) Solms-Laub, *Sagittaria pygmaea* Miq., and *Oryza sativa* L. On the top of the soil were placed a predetermined number of seeds of the weed. The surface of each pot was covered with 1 cm of soil, and then *Oryza sativa* L. that had reached the two-leaf stage was transplanted. For the herbicidal test, wettable powders were prepared by mixing the compounds (10%), Emulgen 810 (surfactant; 0.5%), Demol N (surfactant; 0.5%), Kunilite 210 (diatomaceous earth; 20%), and Dieclite CA (clay; 69%). Each compound, formulated as the wettable powder, was applied 3 days after the seeds had been sown. Approximately 3 weeks after treatment, the herbicidal activity of each compound was judged by visual observation of the symptoms of treated plants in comparison with untreated controls. According to the extent of the injury of plants, the herbicidal potency was scaled from 0 to 5 according to the following criteria: 5, >91% growth inhibition; 4, 71−90% growth inhibition; 3, 51−70% growth inhibition; 2, 31−50% growth inhibition; 1, 11−30% growth inhibition; 0, growth inhibition of <10%.

RESULTS AND DISCUSSION

Synthesis. Previously, acyl Meldrum's acid (**1**) and *N*-hydroxyaniline derivatives (**2**) have been used to form the 4-oxazolin-2-one ring (**4**) (Figure 1), but 5-*tert*-butyl-substituted 4-oxazolin-2-ones were not accessible because of instability of pivaloyl Meldrum's acid (**1**: R =

t-Bu). Therefore, we have developed a novel synthetic method for 3-aryl-5-*tert*-butyl-4-oxazolin-2-ones (**7**) (Figure 2) (Kudo et al., 1996). According to this method, the reaction of 1-chloro-substituted 1-bromo- or iodo-3,3-dimethyl-2-butanone (**9** or **10**) and *N*-arylcarbamate (**5**) was expected to afford the desired 4-chloro-4-oxazolin-2-one (**11**) (Figure 3). Chlorination of 1-bromo- or 1-iodo-3,3-dimethyl-2-butanone (**6** or **8**) with sulfuryl chloride afforded the corresponding chloride (**9** or **10**) in good yields. However, the reaction of the carbamate (**5**) and these chlorides (**9** or **10**) to form 4-chloro-4-oxazolin-2-one (**11**) did not proceed as expected (Figure 3). After further attempts failed, we discovered a two-step conversion of 4-unsubstituted 4-oxazolin-2-one (**7**) to the corresponding 4-chloro-substituted derivatives (Figure 4). Thus, chlorination of **7** with chlorine gas in carbon tetrachloride (CCl₄) usually gave dichloride **12** accompanied by chlorohydrin **13**, which may be the hydrolysis product of an epichloronium intermediate. Despite the completely same reaction conditions, chlorination of **7** gave **12** and/or **13**, depending on the substituents on the benzene ring. There is no clear speculation to account for the result. Dehydrochlorination of **12** using DBU in dimethyl sulfoxide (DMSO) afforded the desired 4-chloro-4-oxazolin-2-one (**11**) in good yields. Alternatively, chlorohydrin **13**, which lacks a chlorine atom at the desired position, was treated with 2-nitrobenzenesulfonyl chloride, *N,N*-diisopropylethylamine, and DMAP to afford the desired 4-chloro-4-oxazolin-2-one derivatives (**11**). This reaction may proceed through the formation of the sulfonate, followed by subsequent chlorine substitution and dehydrochlorination. The results of the present study are compiled in Tables 1 and 2. A variety of 4-oxazolin-2-ones (**7**) were dichlorinated, followed by dehydrochlorination to give the corresponding 4-oxazolin-2-ones (**11**) in satisfactory yields.

Among the synthesized compounds, 4-chloro-2-fluorophenyl compound **11c** has strong herbicidal activity, particularly in preemergent tests on broadleaf weeds, and the other compounds did not show any satisfactory activities. The pattern of herbicidal activities of **11c** is very similar to that of light-dependent herbicides, such as S-23142 (**14**) (Nagano et al., 1983a) or pentoxazone (KPP-314) (**15**) (Hirai et al., 1987). This result let us to synthesize new derivatives (**16**) having propargyloxy or cyclopentyloxy groups in the 5-position of aryl group (Figure 5). Compound **23** seemed to be a useful inter-
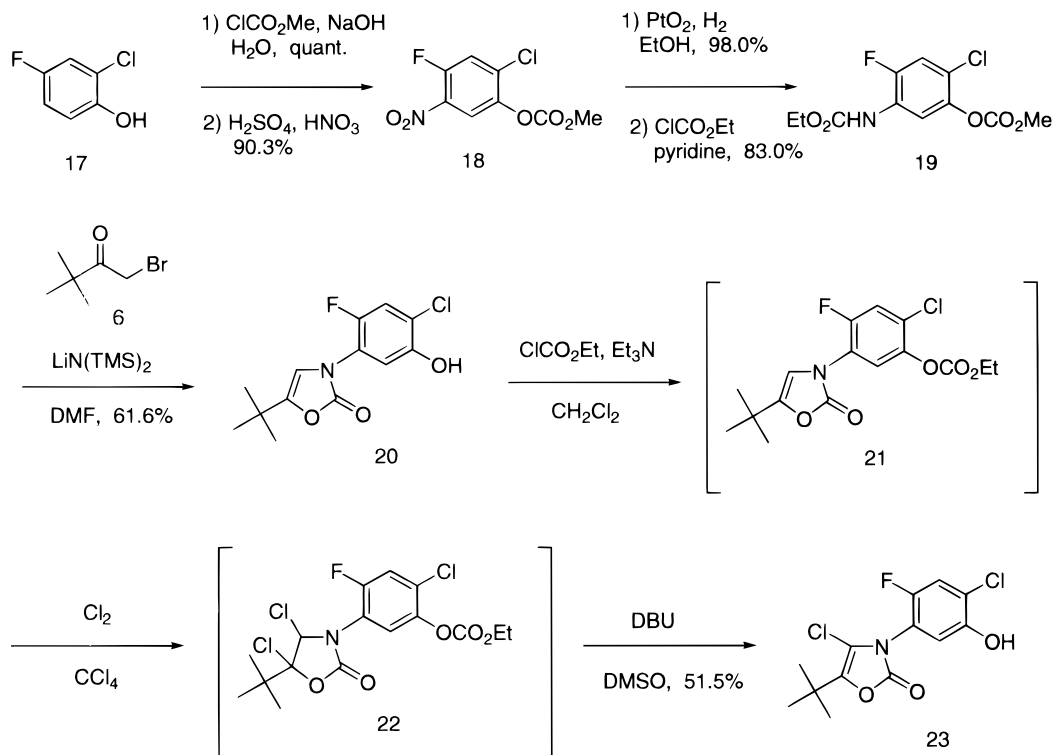
Herbicidal Activity of 4-Substituted 3-Aryl-5-*tert*-butyl-4-oxazolin-2-ones

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Figure 6.

Table 2. Physical Properties of 3-Aryl-4-oxazolin-2-one Derivatives

| | | | analysis (%) | | | | | |
| | | | calcd | | | found | | |
11	mp (°C)	formula	C	H	N	C	H	N
a	94.5−97	$C_{13}H_{13}ClFNO_2$	57.89	4.86	5.19	57.65	5.09	5.06
b	72−74	$C_{13}H_{12}ClF_2NO_2$	54.54	4.42	5.00	54.27	4.20	4.87
c	95−97	$C_{13}H_{12}Cl_2FNO_2$	51.34	3.98	4.61	51.55	4.17	4.61
d	86−87	$C_{13}H_{13}Cl_2NO_2$	54.57	4.58	4.89	54.33	4.64	4.59
e	85−86.5	$C_{13}H_{12}Cl_3NO_2$	48.70	3.77	4.37	48.96	3.96	4.42
f	95.5−97	$C_{13}H_{12}Cl_3NO_2$	48.70	3.77	4.37	48.47	3.92	4.43
g	amorph	$C_{13}H_{12}Cl_3NO_2$	48.70	3.77	4.37	48.65	4.01	4.39
h	113−114	$C_{14}H_{16}ClNO_3$	59.68	5.72	4.97	59.69	5.78	4.91
i	88−89	$C_{14}H_{13}ClF_3NO_2$	52.60	4.10	4.38	52.37	4.23	4.34
j	amorph	$C_{15}H_{16}Cl_2FNO_2$	54.23	4.86	4.22	54.39	4.94	4.25

mediate for the synthesis of **16**. Therefore, the next problem was how to synthesize **23** or its O-protected compound. We chose carbonate groups as protecting groups, and synthesis was performed as shown in Figure 6. According to Sumitomo's method, 2-chloro-4-fluorophenol (**17**) was protected as methyl carbonate (Nagano et al., 1983b) and nitrated (Nagano et al., 1983c) to give **18** in 90.3% yield in two steps. Reduction of **18** (Hirai et al., 1987) followed by carbamate formation afforded **19** (Hirai et al., 1992), which is the precursor of cyclization. Treatment of **19** with 1-bromo-3,3-dimethyl-2-butanone (**6**) and LiN(TMS)$_2$ afforded the deprotected compound (**20**) in 61.6% yield, instead of an O-protected compound, which might result from hydrolysis with ethoxide anion generated from carbamate moiety. Compound **20** was protected as carbonate (**21**) and treated with chlorine gas in CCl$_4$, followed by the addition of DBU in DMSO to give deprotected compound **23** in 51.5% yield in three steps. Compound **23** was alkylated with several alkyl halides or alkyl tosylate to give 3-(5-alkoxy)phenyl compounds as summarized in Table 3. All alkyl halides or alkyl tosylates except cyclohexyl chloride reacted in good yields.

Table 3. Reaction Conditions and Melting Points of 3-Aryl-4-chloro-4-oxazolin-2-ones (16)

16	RX	base	conditions[a]	yield (%)	mp (°C)
a	MeI	NaH	rt,, 2 h	65.7	94−96
b	EtI	NaH	rt, 6 h	62.4	88−90
c	*n*-PrI	NaH	rt, 1 h	75.4	76−76.5
d	*i*-PrI	NaH	rt, 3 h	57.1	78.5−80
e	c-C$_5$H$_9$Cl	K$_2$CO$_3$	110 °C, 1.5 h	94.6	94−96
f	c-C$_6$H$_{11}$Cl	K$_2$CO$_3$	110 °C, 2 h	15.4	122−125
g	CH$_2$=CHCH$_2$Br	NaH	rt, 1.5 h	70.4	82−86
h	HC≡CCH$_2$Br	NaH	rt, 3 h	80.9	83−84
i	HC≡CCH(Me)Br	NaH	50 °C, 1 h	39.0	113−114
j	MeOCH$_2$Br	NaH	rt, 3 h	73.0	98−99
k	MeOCH$_2$CH$_2$Br	NaH	130 °C, 3 h	58.1	58
l	3-tetrahydrofuranyl tosylate	NaH	100 °C, 3 h	36.9	114−115
m	3-tetrahydropyranyl tosylate	K$_2$CO$_3$	100 °C, 5 h	61.7	111−113

[a] rt, room temperature.

To improve the herbicidal activity, a fluorine atom instead of a chlorine atom was introduced into the 4-position of 4-oxazolin-2-one ring according to a procedure illustrated in Figure 7. Chlorohydrin **13a** was treated with DAST to give *syn*-chloro-fluorocompound **24** in 60.0% yield and *anti*-chloro-fluorocompound **25** in 16.0% yield. Treatment of only one of the isomers with DBU provided the desired 4-fluoro-4-oxazolin-2-one (**26**) in 8.1% yield. This result supports that **24** was *syn*-isomer.

Replacement of a chlorine atom by an alkylthio group sometimes brings about drastic changes in biological
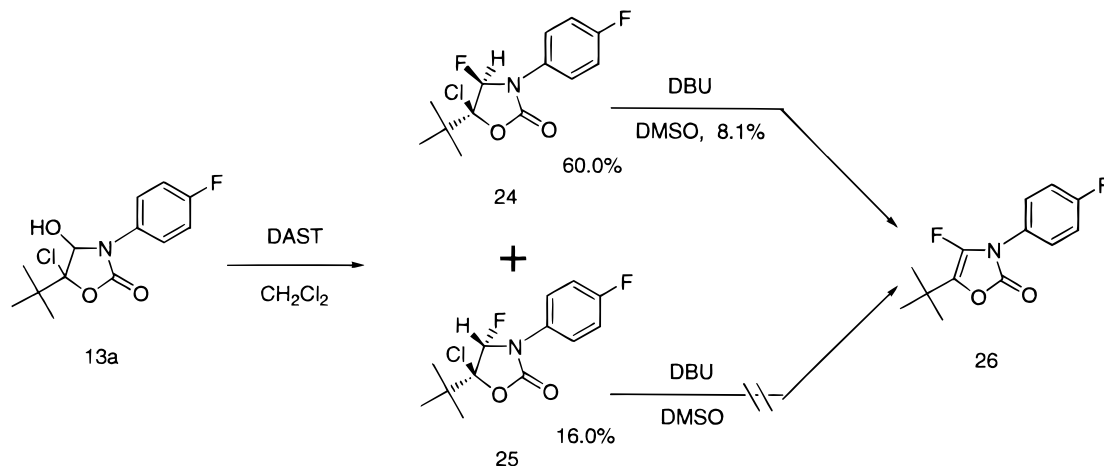
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Figure 7.

Table 4. Reaction Conditions and Physical Properties of 4-Substituted 3-(4-Chloro-2-fluoro)-4-oxazolin-2-ones

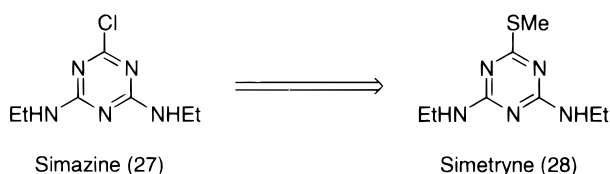|	R	conditions	yield (%)	mp (°C)
7c	H	rt, 0.5 h	80.0	95−97
33a	Me	90 °C, 1 h	26.7	129−132
33b	SMe	60 °C, 2 h	42.9	oil
33c	SEt	rt, 2 h	28.1	oil
33d	S*n*-Pr	90 °C, 1 h	50.4	oil
33e	S*i*-Pr	90 °C, 1 h	46.9	oil

[a] rt, room temperature.

Figure 8.

activities (Sheets and Shaw, 1963). The chlorine atom of *s*-triazine herbicide **27**, named simazine (Pearlman and Banks, 1948), was replaced with a methylthio group, and the resulting compound **28**, named simetryn (Gysin, 1960), showed improved herbicidal activity (Figure 8). In simetryn the methylthio group plays a biologically isosteric role equal to a chlorine atom. This result prompted us to synthesize 4-alkylthio-substituted 4-oxazolin-2-one derivatives. If an alkylthio group can be introduced into the bromopinacolone moiety, 4-alkylthio-substituted 4-oxazolin-2-one could be synthesized in a single step. We also planned to prepare 4-methyl-substituted 4-oxazolin-2-one, because the steric size of the methyl group is considered to be similar to that of the chlorine atom. For the evaluation of the synthetic reaction to 4-oxazolin-2-one ring, α-substituted bromopinacolones were synthesized as illustrated in Figure 9. α-Methyl compound (**32a**) was synthesized through condensation of methyl pivalate (**29**) and propionitrile (Kume et al., 1989; Abdulla, 1983) followed by hydrolysis (Abdulla, 1983) and bromination (Dubois

et al., 1966; Roussel et al., 1971; Katz et al., 1977; Fellmann et al., 1978). On the other hand, synthesis of α-alkylthio compounds was performed as follows. Treatment of 1-bromo-3,3-dimethyl-2-butanone (**6**) with an aqueous solution of alkylmercaptide(Kano et al., 1978) afforded a corresponding thioether (**31b**−**31e**), (Brunet et al., 1984; Norbert et al., 1992) that was subjected to bromination with *N*-bromosuccinimide (NBS) (Tamura et al., 1980) to give α-alkylthio-α-bromopinacolones (**32b**−**32e**). The cyclization reaction between α-substituted bromopinacolones and the carbamate was performed as mentioned before. The results are summarized in Table 4. The low yield of α-methyl compound was probably due to the competitive β-elimination reaction of α-methyl-α-bromopinacolone (**32a**). In the case of α-alkylthio compounds, the cyclization reaction was very slow and, aided by warming, the cyclization reaction proceeded.

α-Alkylthio compounds were also synthesized according to an alternative method as summarized in Figure 10. Dichloro compound (**12c**) obtained by chlorination of **7c** was treated with ethyl mercaptan lithium salt, generated from ethyl mercaptan and *n*-butyllithium to give **34**. Treatment of **34** with DBU afforded **33c**, which was identical to the compound prepared by direct cyclization method as shown in Table 4.

Herbicidal Activity. In general, 3-aryl-*tert*-butyl-4-chloro-4-oxazolin-2-ones (**16**) exhibited moderate to excellent herbicidal activity, particularly in preemergent tests on broadleaf weeds. Tables 5 and 6 show the results of herbicidal evaluations of the synthesized compounds.

Substituents in the 5-position of the 4-oxazolin-2-one ring had the most pronounced effect on activity. As reported previously (Sugai et al., 1987), the activity increased with the size of the substituent at the 5-position of the 4-oxazolin-2-one ring. In the present study the greatest activity was observed for the *tert*-butyl group (**11c**). However, the compound with a 1-ethyl-1-methylpropyl group (**11j**), which is larger than the *tert*-butyl group, was significantly less active in these tests.

4-Unsubstituted 4-oxazolin-2-one compound (**7c**) showed moderate herbicidal activity, but the introduction of a chlorine atom at the 4-position of the 4-oxazolin-2-one ring (**11c**) dramatically improved herbicidal activity against all weeds. The introduction of a methyl group (**33a**), the steric size of which is considered to be similar to that of a chlorine atom, did not provide the same level of herbicidal activity. Alkylthio-substituted
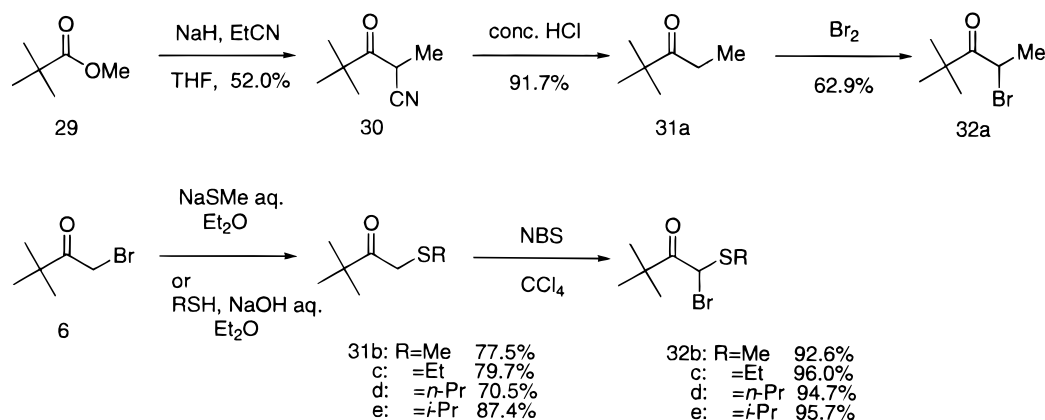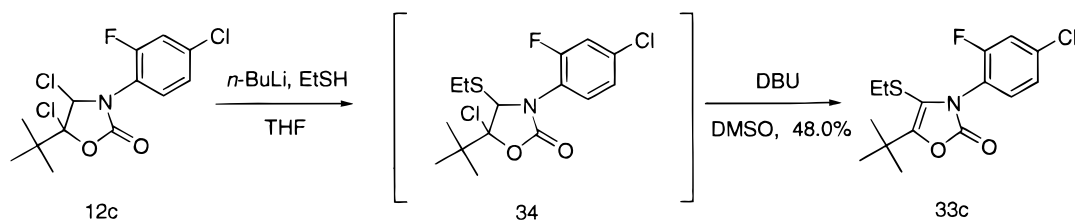
Herbicidal Activity of 4-Substituted 3-Aryl-5-*tert*-butyl-4-oxazolin-2-ones

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Figure 9.

Figure 10.

Table 5. Herbicidal Activity of 3-Aryl-4-chloro-4-oxazolin-2-ones (16)

16	herbicidal activity[a,b]								
	EO	LP	MV	SJ	EA	SP	CS	EK	OS
a	5	5	5	5	4	5	2	5	0
b	5	5	5	4	4	5	3	5	0
c	5	5	5	3	nt[c]	nt	nt	nt	0
d	5	5	5	5	2	2	4	5	0
e	4	5	5	2	nt	nt	nt	nt	0
f	4	5	5	3	nt	nt	nt	nt	0
g	5	5	5	4	1	4	4	5	0
h	5	5	5	5	5	5	5	5	0
i	5	5	5	5	3	5	2	5	0
j	5	5	5	5	5	5	3	5	0
k	5	5	5	5	5	5	4	5	0
l	5	5	5	5	nt	nt	nt	nt	0
m	5	5	5	5	nt	nt	nt	nt	0

[a] Herbicidal activity was evaluated at a dose of 5 g/a. [b] EO, *Echinochloa oryzicola*; LP, *Lindernia procumbens*; MV, *Monochoria vaginalis*; SJ, *Scirpus juncoides*; EA, *Eleocharis acicularis*; SP, *Sagittaria pygmaea*; CS, *Cyperus serotinus*; EK, *Eleocharis kuroguwai*; OS, transplanted rice. [c] nt, not tested.

Table 6. Herbicidal Activity of 4-Substituted 3-(4-Chloro-2-fluoro)-4-oxazolin-2-ones

		herbicidal activity		
	dose (g/a)	EO	LP	SJ
7c	10	5	5	5
	5	3	5	2
11c	10	5	5	5
	5	5	5	5
33a	10	5	5	5
	5	3	5	3
33b	10	0	0	0
	5	0	0	0
33c	10	2	2	1
	5	0	1	0
33d	10	0	0	0
	5	0	0	0
33e	10	2	0	0
	5	0	0	0
11j	10	1	1	1
	5	0	0	0

compounds (**33b**−**33e**), which are considered to be biologically isosteric to 4-chloro-substituted compounds (**11c**), tended to reduce the overall activity. In this series, alkylthio groups did not seem to act as a biological isostere to chlorine atom.

Aromatic phenyl ring substituents also played an important role in activity, and a variety of substituents maintain good herbicidal activity. Alkoxy groups such as the MeO (**16a**) or EtO (**16b**) group on the 5-position of the aromatic phenyl ring showed good herbicidal activity, but substitution of a cycloalkoxy group (**16e**), which KPP-314 has in its phenyl ring, reduced the overall activity. The introduction of the propargyloxy group (**16h**), which S-23142 has in its phenyl ring, exhibited the greatest activity against all weeds. The introduction of an alkoxyalkoxy group (**16j** and **16k**) maintained a high level of activity. The introduction of a cyclic alkoxy group such as the tetrahydrofuran-3-yloxy (**16l**) or tetrahydropyran-3-yloxy group (**16m**) showed a good level of activity with rice selectivity.

In summary, novel 4-oxazolin-2-ones (**16**) presented in this paper showed good to excellent levels of herbicidal activity and showed rice selectivity. Although several compounds were investigated more fully in the greenhouse, none of the compounds was considered to be worthy of detailed field evaluation.

Supporting Information Available: NMR, IR, MS, HRMS, analytical data for **11c**−**11j**, **16b**−**16m**, and **33b**−**33e**; procedures and data for **30**, **31a**−**31e**, and **32a**−**32e** (11 pages). Ordering information is given on any current masthead page.

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