Synthesis and Herbicidal Activities of 2-(5-Isoxazolylloxy)-acetamide Derivatives

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A series of 2-(5-isoxazolylloxy)acetamide derivatives was synthesized and their herbicidal activities against upland field plants were assessed. Studies on the structure-activity relationships revealed that potent herbicidal activity was associated with the compounds carrying a 4-methyl-3-trifluoromethyl-5-isoxazolyl group on the oxyacetamide oxygen. Among the compounds examined, N-(2-chlorophenyl)-N-methyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolylloxy)acetamide (28) showed strong herbicidal activities against upland weeds (barnyard grass, large crabgrass, pale smartweed and slender amaranth) without affecting cotton at 0.25-0.5 kg a.i./ha.

INTRODUCTION

Some oxyacetamide derivatives were reported to show potent herbicidal activities against grass weeds and selectivity to crops.1-4) For example, 2-(2-benzothiazolylloxy)-N-methyl-N-phenylacetamide (mefenacet, in Fig. 1) is a good paddy herbicide.3) In our previous study, we synthesized the oxyacetamides with benzene, pyridine, pyrimidine, pyrazine, benzisoxazole, isoxazole and pyrazole rings instead of the benzothiazole ring of mefenacet and assessed their herbicidal activities. As a result, the oxyacetamides carrying an isoxazole ring showed potent herbicidal activity against paddy field plants (unpublished). Among the isoxazole derivatives, N-methyl-N-phenyl-2-(4-phenyl-3-trifluoromethyl-5-isoxazolylloxy)acetamide (8, SSH-122) was selected as a good paddy herbicide.5)

In the structure-activity relationship study on compounds with potent herbicidal activity against upland field plants, 2-(5-isoxazolylloxy)acetamide derivatives (I, in Fig. 1) were synthesized and their herbicidal activity was investigated.

MATERIALS AND METHODS

1. Synthesis of Compounds

The synthetic routes for 2-(5-isoxazolylloxy)acetamide derivatives are shown in Fig. 2. 2-(5-Isoxazolylloxy)-acetamides (I) were prepared by the reaction of 5-hydroxyisoxazole sodium salts (II) and 2-bromoacetamides (III) (Method A), 5-chloroisoxazoles (IV) and 2-hydroxyacetamides (V) in the presence of a base (Method B), or 2-(5-isoxazolylloxy)acetic acids (VII) and amines VIII in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Method C). Acids VII were prepared by the reaction of 5-hydroxisoxazole (VI) and methyl bromoacetate in the presence of a base, and subsequent hydrolysis.

Melting points were measured with a Büchi 535 melting point apparatus and are given uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer. 1H-NMR spectra were measured on a JEOL JNM-GSX 270 spectrometer at 270 MHz using tetramethylsilane (TMS) as an internal standard.

I.1 N-Methyl-N-(2-methylphenyl)-2-(4-methyl-3-trifluoromethyl-5-isoxazolylloxy)acetamide (22)

A mixture of 4-methyl-3-trifluoromethyl-5-hydroxyisoxazole sodium salt9) (0.38 g, 2 mmol), 2-bromo-N-methyl-N-(2-methylphenyl)acetamide (0.58 g, 2.4 mmol) and acetonitrile (6 ml) was stirred at 60°C for 24 hr. The reaction mixture was poured into water (80 ml) and extracted with ether (80 ml). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/benzene) to give 0.57 g (86.8%) of compound 22. The product was recrystallized from hexane to give colorless crystals, mp 81-82°C. Anal. Found: C, 54.78; H, 4.66; N, 8.64. Calcd. for C_{15}H_{15}F_{3}N_{2}O_{3}: C, 54.87; H, 4.61; N, 8.53. 1H-NMR (CDCl$_3$) δ ppm: 1.95 (3H, s), 2.32 (3H, s), 3.23 (3H, s), 4.45 (1H, d, J = 14.7 Hz), 4.66 (1H, d, J = 15.3 Hz), 7.18 (1H, d, J = 6.7 Hz), 7.28-7.36 (3H, m).
1.2 N-Methyl-N-phenyl-2-(4-phenyl-3-trifluoromethyl-5-isoxazolyloxy)acetamide (8)

To a solution of 2-hydroxy-N-methyl-N-phenylacetamide\(^7\) (0.99 g, 6 mmol) in tetrahydrofuran (6 ml) was added 90% potassium tert-butoxide (0.75 g, 6 mmol) in an ice bath. After being stirred for 0.5 hr, 5-chloro-4-phenyl-3-trifluoromethylisoxazole\(^8\) (1.24 g, 5 mmol) was added to the mixture with stirring. The mixture was stirred under reflux for 24 hr. The reaction mixture was poured into 5% hydrochloric acid (60 ml) and extracted with dichloromethane (60 ml). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1.15 g (61.1%) of compound 8. The product was recrystallized from hexane to give colorless crystals, mp 93-94°C. Anal. Found: C, 61.01; H, 4.35; N, 7.39, Calcd. for C\(_{19}\)H\(_{15}\)F\(_3\)N\(_2\)O\(_3\): C, 60.64; H, 4.02; N, 7.44%. \(^1\)H-NMR (\(\text{CDC}_3\)) \(\delta\) ppm: 3.31 (3H, s), 4.74 (2H, s), 7.20-7.24 (1H, m), 7.31-7.53 (4H, m).

1.3 N-(3-Fluorophenyl)-N-methyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolyloxy)acetamide (34)

Methyl bromoacetate (1.10 g, 7.2 mmol) was added to a mixture of 4-methyl-3-trifluoromethyl-5-hydroxyisoxazole\(^9\) (1.00 g, 6 mmol), potassium carbonate (1.00 g, 7.2 mmol) and acetone (10 ml) in an ice bath, and the mixture was then stirred under reflux for 30 hr. The reaction mixture was poured into water (80 ml) and extracted with dichloromethane (80 ml \(\times 2\)). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.65 g (96.2%) of 2-(4-methyl-3-trifluoromethyl-5-isoxazolyloxy)acetic acid. The product was recrystallized from ethyl acetate and hexane to give colorless crystals, mp 77-78°C. Anal. Found: C, 37.24; H, 2.80; N, 6.40, Calcd. for C\(_7\)H\(_6\)F\(_3\)NO\(_4\): C, 37.34; H, 2.69; N, 6.22%. \(^1\)H-NMR (\(\text{CDC}_3\)) \(\delta\) ppm: 1.97 (3H, s), 4.99 (2H, s), 6.80 (1H, bs).

To a solution of 2-(4-methyl-3-trifluoromethyl-5-isoxazolyloxy)acetic acid (0.34 g, 1.5 mmol) and 3-fluoro-N-methylaniline (0.21 g, 1.65 mmol) in dichloromethane (6 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.32 g, 1.65 mmol), and the mixture was stirred for 3 hr at room temperature. The reaction mixture was poured into water (80 ml) and extracted with dichloromethane (80 ml \(\times 2\)). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 0.65 g (96.2%) of compound 34 as pale yellow crystals, mp 77-78°C. Anal. Found: C, 50.67; H, 3.74; N, 8.54, Calcd. for C\(_{14}\)H\(_{12}\)F\(_4\)N\(_2\)O\(_3\): C, 50.60; H, 3.65; N, 8.43%. \(^1\)H-NMR (\(\text{CDC}_3\)) \(\delta\) ppm: 1.94 (3H, s), 3.30 (3H, s), 4.73 (2H, s), 6.98-7.18 (3H, m), 7.42-7.51 (1H, m).

2. Herbicidal Tests

Seeds of upland field plants, barnyard grass (Echinochloa crus-galli), large crabgrass (Digitaria ciliaris), pale smartweed (Polygonum lapathifolium), slender amaranth (Amaranthus viridis), wheat (Triticum aestivum cv. Nohrin-61), soybean (Glycine max cv. Tamahomare) and cotton (Gossypium hirsutum cv. Hakushuu), were sown in square plastic pots containing loam. The seeds covered with soil were treated with each test compound after 1000 l/ha dilution of predetermined amount. The dosages of the compounds were 0.25, 0.5, 1.0, 2.0, and 4.0 kg a.i./ha, with Tween 20 (obtained from Nacalai Tesque) at a concentration of 100 ppm as a spreader. The treated pots were maintained at 25°C in a greenhouse. Four weeks later, the herbicidal activities of the com-
pounds against each weed and their selectivity toward the crops were evaluated.

The herbicidal rating score ranged from 0 to 5, and was based on visual observation; zero represented no significant effect on seedling growth and 5 represented seedling death.

RESULTS AND DISCUSSION

The physical properties of the synthesized compounds and their herbicidal activities against upland field plants are listed in Tables 1 through 5.

1. Effects of Substituents (R₁ and R₂) on the Isoxazole Ring

Table 1 shows the effects of substituents (R₁ and R₂) on the isoxazole ring of N-methyl-N-phenyl-2-(5-isoxazolyl)acetamides on herbicidal activity. For the substituent (R₁) at position-3, trifluoromethyl group (5-8) seemed to be preferable for high activity. In contrast, alkyl (1 and 2) and phenyl (3 and 4) derivatives had only weak activities. These results suggested that the presence of a strong electron-withdrawing group like trifluoromethyl group at position-3 may enhance the activity. Among the 4-substituted 3-trifluoromethylisoxazole derivatives (5-8), 4-methyl derivative (6) was most active, whereas an introduction of smaller (H, 5) or larger (Et, 7; phenyl, 8) substituents than the methyl group at position-4 reduced the activity. Compound 8 slightly damaged crops.

2. Effects of Substituents on the Amide Nitrogen Atom of the Isoxazolylacetamides

Since the 4-methyl-3-trifluoromethyl-5-isoxazole moiety was found to be favorable for high activity, we examined the activities of N-substituted 2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)acetamides.

Table 2 shows the effects of one substituent (R₃) on the amide nitrogen atom of N-phenyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)acetamides on herbicidal activity. Non-substituted derivative (9) was inactive, and thus substituents on the amide nitrogen atom seem to be essential for the activity. Among the alkyl derivatives (6, 10-14), methyl derivative (6) was most active, whereas introduction of larger alkyl groups reduced the activity. The activity decreased in the order; methyl (6) > propyl (11) > isopropyl (12) > ethyl (10) > butyl (13) > pentyl (14).

Table 3 shows the effects of the other substituent (R₄) on the amide nitrogen atom of N-methyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)acetamides on herbicidal activity. Among the compounds listed in Table 3, phenyl derivative (6) was more active than those having alkyl groups (Bu, 15; i-Bu, 16; s-Bu, 17; hexyl, 19). Derivatives with the other bulky substituents (t-Bu, 18; cyclohexyl, 20; benzyl, 21) were inactive or less active. On the basis of these results, it is likely that the hydrophobic and steric character of the benzene ring directly attached to the amide nitrogen atom may increase herbicidal activity.

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3. Effects of Substituents (X) on the Benzene Ring

Table 4 shows the effects of substituents (X) on the benzene ring of N-methyl-N-phenyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)acetamides on herbicidal activity. Among the 2-substituted phenyl derivatives (22-30), methyl (22), chloro (28) and bromo (29) derivatives showed higher activities than that of the non-substituted derivative (6). 2-Phenyl derivative (25) was inactive. Among the 3-substituted phenyl derivatives (31-37), fluoro derivative (34) was more active than compound 6. The introduction of substituents larger than fluorine atom (31-33 and 35-37) reduced the activity.

The 4-substituted phenyl derivatives (38-45) showed reduced activities relative to that of compound 6.

Table 5 shows the effects of di-substituents (Xn) on the benzene ring of N-methyl-N-phenyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)acetamides on herbicidal activity. Among the compounds listed in Table 5, 2, 3-di-substituted phenyl derivatives (46 and 53) were most active. Derivatives (48, 49 and 52) with substituents larger than fluorine atom on both the ortho
Table 4  N-(Substituted phenyl)-N-methyl-2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)acetamides and their herbicidal activities against upland field weeds.

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<th>Pre-emergence herbicidal activity</th>
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<th>mp (°C) or n° (°C)</th>
<th>Dosage (kg a.i./ha)</th>
<th>Pre-emergence herbicidal activity</th>
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Abbreviation, see Table 1.
positions were inactive or less active. One possible explanation for this is that the benzene ring moiety could not take a suitable conformation for the activity because of the steric influence of the substituents at ortho positions. These results showed differences in the effects of substituents on the herbicidal activity from those reported for chloroacetanilide herbicides. The introduction of larger substituents (2, 6-Et₂) on both the ortho positions of the benzene ring on the amide nitrogen atom of chloroacetanilides resulted in potent herbicidal activities.

4. Herbicidal Activity of Selected Compounds

Based on the above results, compounds 28, 29 and 34 were chosen for the second step of evaluation (Table 6). Compound 28 showed the most potent activity in this series of derivatives. This compound was effective against weeds at 0.25–0.5 kg a.i./ha without damaging cotton, and more active than the oxacacetamides derivatives, mfenacet and N-methyl-N-phenyl-2-(5-trifluoro-methyl-1,3,4-thiadiazol-2-yl)oxyacacetamide. These results indicate that the 4-methyl-3-trifluoromethyl-5-isoxazolyl group on the oxacacetamide oxygen may play an important role in exhibiting herbicidal activity.

Similarly to chloroacetanilide herbicides, isoxazoloyoxacacetamide derivatives showed pre-emergence herbicidal activities and were more effective in controlling grass than broad-leaved weeds. They also suppressed the emergence and shoot elongation of weeds, and occasionally induced malformation and hyperchromic effects against broad-leaved weeds when applied in a pre-emergence. The phytotoxic symptoms by the isoxazoloyoxacacetamides were also similar to those of chloroacetanilide herbicides (data not shown).

Our studies indicated that some of the N-methyl-N-(substituted phenyl)-2-(4-methyl-3-trifluoromethyl-5-isoxazolyl)oxacacetamide derivatives, a new class of herbicides, are highly effective against upland field weeds (barnyard grass, large crabgrass, pale smartweed and slender amaranth) without causing damage to cotton.

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要　約

2-(5-イソオキサソリルオキシ)アセトアミド誘導体の合成と除草活性

甲斐浩幸, 場田幸夫, 三木信夫, 井手重也, 高瀬 克
優れた除草活性を有する化合物の探索を目的として、種々の 2-(5-イソオキサソリルオキシ)アセトアミド誘導体を合成し、畑地雑草に対する除草活性と作物への安全性を評価した。その結果、イソオキサソール環の3位にトリフルオロメチル基、4位にメチル基を有する 2-(5-イソオキサソリルオキシ)アセトアミド誘導体が高い除草活性を示した。合成した誘導体の中で、N-(2-クロロフェニル)-N-メチル-2-(4-メチル-3-トリフルオロメチル-5-イソオキサソリルオキシ)アセトアミド(28) は、イヌピエ、メヒンバ、オオイヌクタデおよびアオピクに対して高い除草活性を有するとともにワクに選択的安全性を示した。