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Original Article

Synthesis and herbicidal activity of 2-acylimino-3-phenyl-1,3-thiazolines—A new family of bleaching herbicides—

Yuzuru SANEMITSU,* Shinichi KAWAMURA, Junichi SATOH, Tadasi KATAYAMA and Shunichi HASHIMOTO

Sumitomo Chemical Co. Ltd., Agricultural Chemicals Research Laboratory, 2–1 Takatsukasa 4-Chome, Takarazuka, Hyogo 665–8555, Japan

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A novel series of substituted 2-acylimino-1,3-thiazolines was synthesized and their herbicidal activity against upland weeds and selectivity against crops was assessed. The structure–activity relationships were probed by substitution of the thiazoline nucleus and/or an imino group. Highest activity was seen with compounds which contain two substituents: a methyl group at the 5-position of the thiazoline nucleus and a trifluoroacetyl or a difluoroacetyl group on an imino moiety. Among the compounds examined, 2-(*N*-difluoroacetylimino)-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline applied at rates between 62.5 and 125 g a.i./ha, showed excellent broad-spectrum pre-emergence herbicidal activity against grass and broadleaf weeds without injury to cotton. © Pesticide Science Society of Japan

Keywords: 1,3-thiazoline, bleaching herbicidal activity, structure–activity relationship, pre-emergent herbicide.

Introduction

Recently, a variety of heterocyclic compounds containing nitrogen and sulfur atoms have contributed significantly to many current commercial agrochemicals. Our attention was directed to these heterocycles as a screening target to create novel bioactive compounds.[1–3] In spite of the recent progress in biorational research to directly lead discovery, we selected the chemical approach to *N*- and *N,S*-heterocyclic compounds with the expectation of a new chemical class with biological activity.[2–6] Until now, this method has served as a rich lead source to find a number of various heterocycles with bleaching herbicidal activity.[7–10]

While exploring the synthetic development of *N,S*-heterocycles using heterocumlenes,[11] such as acyl isothiocyanates,[12] we discovered novel cyclization reactions affording 2-(*N*-acylimino)-5-methylene-1,3-thiazolidines (**V**; $\mathbf{R^3}$=H). Compounds **V** thus obtained can be easily interconverted to 2-(*N*-acylimino)-5-methyl-1,3-thiazolines (**VI**; $\mathbf{R^3}$=H). This prompted us to synthesize a series of compounds **VI**, resulting in the generation of 2-(*N*-acylimino)-3-(3-trifluoromethylphenyl)-1,3-thiazolines, which showed potent bleaching herbicidal activity.[13]

Our interest in the structure and herbicidal activities of these novel heterocycles encouraged us to perform a systematic screening study around a thiazoline herbicide. Here, the synthesis, structure–activity relationships and structural optimization of these 1,3-thaizoline heterocycles are reported (Fig. 1).

Materials and Methods

1. *Instrumental analysis*

All melting points were determined on a Yazawa BY-2 micro melting point apparatus and are uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 spectrometer at 400 MHz using tetramethylsilane (TMS) as an internal standard.

2. *Synthesis of compounds*

First, the general synthetic route of 2-(*N*-acylimino)-5-alkyl-

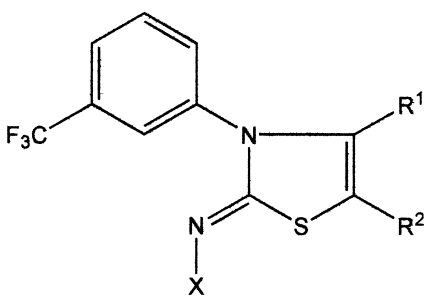

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Fig. 1. General structure of 2-(*N*-substituted imino)-3-(3-trifluoromethylphenyl)-1,3-thiazolines (**I**).

* To whom correspondence should be addressed.
E-mail: y3sanemi@nodai.ac.jp

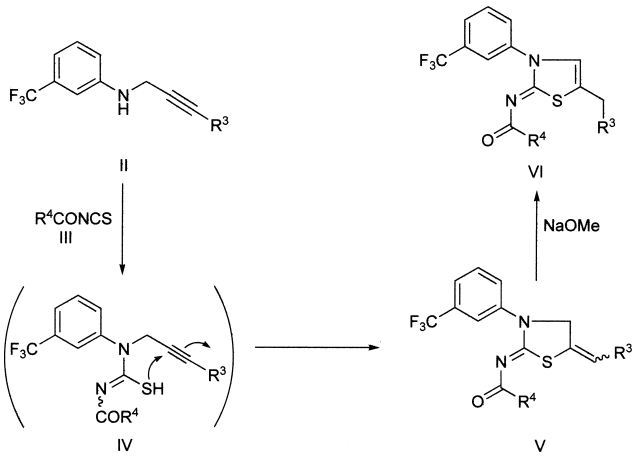


Fig. 2. Synthesis of 2-(*N*-acylimino)-5-alkyl-3-(trifluoromethylphenyl)-1,3-thiazolines (**VI**).

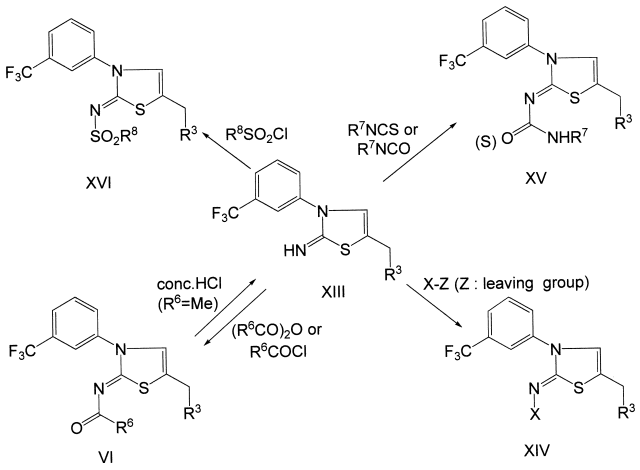


Fig. 4. Synthesis of 2-(*N*-substituted imino)-3-(3-trifluoromethylphenyl)-1,3-thiazolines (**VI** and **XIV**—**XVI**).

3-(3-trifluoromethylphenyl)-1,3-thiazolines (**VI**) is shown in Fig. 2. The desired compounds **VI** were prepared in two steps. Treatment of *N*-propargylanilines with acyl isothiocyanates (**III**) furnished 2-(*N*-acylimino)-1,3-thiazolidines (**V**) after stirring at room temperature for 8 hr in tetrahydrofuran. This novel cyclization reaction probably proceeds through the formation of a thiourea (**IV**), followed by the nucleophilic attachment of a sulfur atom onto the electrophilic carbon atom of the triple bond. Conversion of 5-alkylidene-1,3-thiazolidines (**V**) into 5-alkyl-1,3-thiazolines (**VI**) was achieved by treatment with sodium methoxide in ethanol.

Successful routes for preparing a variety of 2-(*N*-acylimino)-1,3-thiazolines are summarized in Fig. 3. The reaction of 1-acyl-3-(3-trifluoromethylphenyl)thioureas (**VII**) with 1,2-dibromoethane in acetone in the presence of excess K_2CO_3 afforded 2-(*N*-acylimino)-3-(3-trifluoromethylphenyl)-1,3-thiazolidines (**VIII**) in yields of 70～82% after heating for 5 hr under reflux. When 1,3-thiazolidines (**VIII**) were treated with *N*-halogenated succinimide in chloroform under reflux for 10 hr, the corresponding 5-halogenated 2-(*N*-acylimino)-1,3-thiazolines (**IX**) were obtained in yields of 34～67%.

5-Unsubstituted 2-(*N*-acylimino)-1,3-thiazoline (**X**) was easily prepared from 5-halogenated 2-(*N*-acylimino)-1,3-thiazolines (**IX**) by reduction with an excess of tributyltin hydride in tetrahydrofuran under reflux for 10 hr.

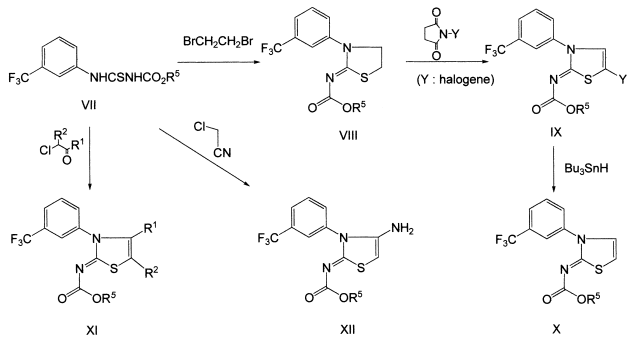


Fig. 3. Synthesis of 2-(*N*-alkoxycarbonylimino)-3-(3-trifluoromethylphenyl)-1,3-thiazolines (**IX**—**XII**).

Treatment of compound **VII** with various α-chloroketones afforded the corresponding 1,3-thiazolines (**XI**).[14] Similarly, the reaction of compound (**VII**) with α-chloroacetonitrile gave 4-amino derivatives (**XII**).

To prepare a variety of *N*-substituted 1,3-thiazolines, 2-imino-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazolines (**XIII**) were chosen as key intermediates. The novel synthesis of compounds **XIII** was accomplished by acid hydrolysis of 2-(*N*-acetylimino)-1,3-thiazolines (**VI**; $\mathbf{R^6}$=Me). Successively, the reaction of **XIII** with various electrophiles such as acyl halides, alkyl isocyanates, alkyl halides and alkyl sulfonylhalides resulted in the formation of *N*-acylimino-(**VI**), *N*-alkylimino-(**XIV**), *N*-carbamoylimino-(**XV**) and *N*-alkylsulfonylimino-(**XVI**)1,3-thiazolines, respectively (Fig. 4). Typical synthetic procedures are described below.

*2.1. 2-(N-Ethoxycarbonylimino)-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline (**5**)*

A mixture of 3-trifluoromethylaniline (30 g, 150.6 mmol) and propargyl bromide (12 g, 99.2 mmol) was heated at 80°C with stirring for 3 hr, followed by filtration of the reaction mixture. The filtrate was subjected to column chromatography (ethyl acetate/hexane) to give 7.0 g of crude *N*-propargyl-3-trifluoromethylaniline (**II**; $\mathbf{R^3}$=H). It was used in the next reaction without further purification.

The mixture of *N*-propargyl-3-trifluoromethylaniline thus obtained (5.1 g, 25.6 mmol) and ethoxycarbonyl isothiocyanate (3.7 g, 28.2 mmol) in tetrahydrofuran (100 ml) was stirred at room temperature for 8 hr. After cooling, the mixture was poured into ice-cold water (200 ml) and saturated aqueous ammonium chloride solution (100 ml), followed by extraction with chloroform (200 ml). The organic layer was washed with brine (100 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 5.7g (67%) of 2-(*N*-ethoxycarbonylim-

ino)-5-methylene-3-(3-trifluoromethylphenyl)-1,3-thiazolidine (**V**; $\mathbf{R}^3$=H, $\mathbf{R}^4$=OEt) as colorless crystals, mp 97.2°C. ^{1}H NMR δ ($CDCl_3$): 1.28 (3H, t, J=7.2 Hz, CH_3), 4.19 (2H, q, J=7.2 Hz, CH_2), 4.77 (2H, t, J=2.6 Hz, NCH_2), 5.32 (1H, dd, J=2.4, 2.6 Hz, CH), 5.36 (1H, dd, J=2.4, 2.6 Hz, CH), 7.54–7.73 (4H, m, phenyl).

To a stirred solution of **V** ($\mathbf{R}^3$=H, $\mathbf{R}^4$=OEt; 2.0 g, 6.0 mmol) in ethanol (50 ml) was added sodium methoxide (0.6 g, 11 mmol), and the reaction was refluxed for 30 min. Subsequently, the reaction mixture was poured into ice-cold water (100 ml), acidified with 35% hydrochloric acid, and extracted with ethyl acetate (100 ml). The organic layer was washed with brine, dried over anhydrous magnesium and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1.6 g (80%) of compound **5**. The product was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles, mp 115.5 °C. Anal. Found: C, 50.92; H, 4.02; F, 17.40; N, 8.49, Calcd. for $C_{14}H_{13}F_3N_2O_2S$: C, 50.90; H, 3.97; F, 17.25; N, 8.48%. ^{1}H NMR δ ($CDCl_3$): 1.30 (3H, t, J=7.2 Hz, CH_3), 2.32 (1H, s, CH_3), 4.22 (2H, q, J=7.2 Hz, CH_2), 6.73 (1H, s, 4-H), 7.60–7.75 (4H, m, phenyl).

*2.2. 2-(N-Ethoxycarbonylimino)-5-iodo-3-(3-trifluoromethylphenyl)-1,3-thiazoline(**11**)*

1-Ethoxycarbonyl-3-(3-trifluoromethylphenyl)thiourea (1.8 g, 6.1 mmol) was added to a mixture of 1,2-dibromoethane (1.29 g, 6.8 mmol) and anhydrous potassium carbonate (2.6 g, 14.2 mmol) in acetone (20 ml), and the mixture was refluxed for 5 hr. The reaction mixture was poured into ethyl ether (100 ml) and washed with brine (50 ml×2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from a mixture of hexane and ethanol to give 1.63 g (83%) of 2-(*N*-ethoxycarbonylimino)-3-(3-trifluoromethylphenyl)-1,3-thiazolidine (**VIII**; $\mathbf{R}^5$=Et) as colorless needles, mp 75.8°C. ^{1}H NMR δ ($CDCl_3$): 1.31 (3H, t, J=7.2 Hz, CH_3), 3.29 (2H, t, J=8.0 Hz, 5-CH_2), 4.12 (2H, t, J=8.0 Hz, 4-CH_2), 4.23 (2H, q, J=7.2 Hz, CH_2), 7.47–7.70 (5H, m, phenyl).

A mixture of **VIII** ($\mathbf{R}^5$=Et; 0.5 g, 1.57 mmol), *N*-iodosuccimide (0.4 g, 2.22 mmol) and 2,2′-azobis(isobutyronitrile) (0.03 g, 0.18 mmol) in chloroform (50 ml) was heated under reflux with stirring for 10 hr. After cooling, the reaction mixture was poured into ice-cold water (100 ml) and washed with brine (100 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.1 g (15%) of compound **11**. The product was recrystallized from a mixture of ethyl acetate and hexane to give colorless prisms, mp 121.6°C. Anal. Found: C, 35.43; H, 2.32; N, 6.45; F, 12.80, Calcd. for $C_{13}H_{10}N_2F_3IO_2S$: C, 35.3; H, 2.28; N, 6.34; F, 12.89%. ^{1}H NMR δ ($CDCl_3$): 1.30 (3H, t, J=7.2 Hz, CH_3), 4.22 (2H, q, J=7.2 Hz, CH_2), 7.12 (1H, s, 4-H), 7.64–7.73 (4H, m, phenyl).

*2.3. 2-(N-Ethoxycarbonylimino)-3-(3-trifluoromethylphenyl)-1,3-thiazoline (**1**)*

A mixture of **11** (4.7 g, 10.6 mmol), tributyltin hydride (6.9 g, 39 mmol), benzoyl peroxide (0.1 g, 0.4 mmol) and tetrahydrofuran (100 ml) was heated under reflux with stirring for 10 hr. After cooling, the reaction mixture was poured into ice-cold water (300 ml) and washed with brine (100 ml×2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from a mixture of hexane and ethanol to give 2.85 g (85%) of **1** as colorless needles, mp 134.5°C. Anal. Found: C, 49.52; H, 3.63; N, 8.80; F, 18.20, Calcd. for $C_{13}H_{11}N_2F_3O_2S$: C, 49.36; H, 3.51; N, 8.86; F, 18.02%. ^{1}H NMR δ ($CDCl_3$): 1.30 (3H, t, J=7.0 Hz, CH_3), 4.23 (2H, q, J=7.0Hz, CH_2), 6.71 (1H, d, J=4.0 Hz, 5-H), 7.03 (1H, d, J=4.0 Hz, 4-H), 7.63–7.78 (4H, m, phenyl).

*2.4. 2-(N-Difluoroacetylimino)-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline (**38**)*

A mixture of 2-(*N*-acetylimino)-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline **22** (3.5 g, 11.6 mmol) prepared from *N*-propargyl-3-trifluoromethylaniline (**II**; R^3=H) and acetyl isothiocyanate (**III**; $\mathbf{R}^4$=Me) according to Fig. 2, 36% hydrochloric acid (3.5 ml) and 20% aq. ethanol (10 ml) was heated under reflux with stirring for 3 hr. After cooling, the reaction mixture was neutralized with 0.1 *N* sodium hydroxide and extracted with ethyl acetate (50 ml×3). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 2.7 g (90%) of 2-imino-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline (**XIII**; $\mathbf{R}^3$=H) as a colorless oil. ^{1}H NMR δ ($CDCl_3$): 2.10 (3H, s, CH_3), 6.40 (1H, s, 4-H), 7.40–7.94 (4H, m, phenyl).

A mixture of **XIII** ($\mathbf{R}^3$=**H**; 0.42 g, 1.4 mmol), triethylamine (2.2 g, 21 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.8 g, 4.1 mmol), difluoroacetic acid (0.75 g, 7.8 mmol) and chloroform (10 ml) was heated under reflux with stirring for 8 hr. After cooling, the mixture was poured into ice-cold water (100 ml) and washed with 1 *N* hydrochloric acid. The organic layer was washed with brine (100 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 0.4 g (75%) of compound **38**. The product was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles, mp 117.9 °C. Anal. Found: C, 46.53; H, 2.98; N, 8.53; F, 28.25, Calcd. for $C_{13}H_9N_2F_5OS$: C, 46.43; H, 2.70; N, 8.33 ; F, 28.25%. ^{1}H NMR δ ($CDCl_3$): 2.40 (3H, s, CH_3), 5.90 (1H, t, J_{HF}=55 Hz, CHF_2), 6.97 (1H, s, 4-H), 7.65–7.79 (4H, m, phenyl).

3. Biological assay

The test species included in these evaluations were Japanese millet (*Echinochloa frumentacea*), velvetleaf (*Abutilon*

theophrasti), morning glory (*Ipomoea purpurea*), prickly sida (*Sida spinosa*), barnyard grass (*Echnochloa crus-galli*), large crabgrass (*Digitaria sanguinalis*), Johnson grass (*Sorgum jalepense*), amaranth slenderb (*Amaranthus viridus*), and purslaneand common (*Portulaca oleracea*).

For the preemergence herbicidal activity tests, an emulsifiable concentrate was prepared by mixing 10 parts of the compound, 14 parts of polyoxyethylene styrylphenyl ether, 6 parts of calcium dodecylbenzenesulfonate, and 70 parts of xylene. The herbicidal effect and phytotoxicity of the compound were determined by visual observation of the treated plants in comparison with the untreated controls. The herbicidal rating score ranged from 0 to 10; zero represented no significant effect on seedling growth and 10 represented seedling death.

3.1. Preemergence herbicidal activity tests (Tables 1, 2, and 3)

Cylindrical plastic pots (diameter 10 cm, height 10 cm) were filled with upland field soil, and the seeds of Japanese millet, morning glory, and velvetleaf were sowed and covered with soil. A designated amount of the test compound formulated in an emulsifiable concentrate was diluted with water, and the dilution was sprayed onto the soil surface by means of a small hand sprayer at a spray volume of 1000 l/ha. The dosages of the compounds were 500 and 125 g a.i./ha. The test plants were grown in a greenhouse for 20 days, and the herbicidal activity of the compound was determined.

3.2. Preemergence herbicidal activity test (Table 4)

Upland field soil in a vat measuring 33 cm×23 cm×11 cm deep was sown with cotton, barnyard grass, large crabgrass, Johnson grass, amaransh slender, purslaneand common, velvetleaf, morning glory, and prickly sida. Similar treatment was conducted by using a small sprayer with a dilute liquid (230 *l*/ha) containing a prescribed amount of sample emulsifiable concentrates. The dosages of the compounds were 62.5 and 125 g a.i./ha. After thirty days of outdoor treatment, the herbicidal effect and crop injury were determined.

Results and Discussion

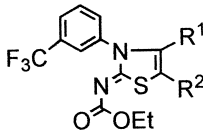
1. Optimization of a new lead compound

In general, the optimum herbicidal activity of this class of herbicides was obtained when a trifluoromethyl group was introduced at the *meta* position of the phenyl ring.[7–10] As a starting point for structural optimization of the new lead, we divided the core structure into two subsections, the thiazoline nucleus (R^1 and R^2) and the imino group (X), while keeping the 3-trifluoromethylphenyl moiety at 3-position on the 1,3-thiazoline ring (Fig.1).

1.1. Effect of 4(R^1)- and 5(R^2)-substituents on the 1,3-thiazoline ring

First, our attention was directed toward the varied activity optimization at the 4- and/or 5-positions on the 1,3-thiazoline ring (Table 1). In the series of 4-substituted derivatives, the introduction of various substituents such as methyl group (**2**), chlorine atom (**3**) and amino group (**4**) resulted in diminished activity relative to an unsubstituted derivative (**1**). Also, all 4,5-disubstituted derivatives (**14**—**17**) showed a complete loss of activity. These results indicated that the introduction of various substituents at the 4-position was not favorable for activity, irrespective of the nature of the substituents. Thus, R^1 should be hydrogen in order to maximize activity.

Table 1. 4 and/or 5-Substituted *N*-ethoxycarbonylimino-1,3-thiazolines with pre-emergence herbicidal activity



Compound No.	R^1	R^2	mp (°C)	Herbicidal activity[a)]		
				Jm	Vl	Mg
1	H	H	134.5	5	2	2
2	Me	H	161.1	0	0	0
3	Cl	H	89.2	0	0	0
4	NH_2	H	128.0	3	0	1
5	H	Me	115.5	9	9	9
6	H	Et	97.1	7	7	7
7	H	*n*-Pr	69.0	6	0	4
8	H	*i*-Pr	75.1	0	0	1
9	H	Cl	138.2	9	7	6
10	H	Br	107.2	9	10	6
11	H	I	121.6	8	6	9
12	H	SMe	129.2	7	4	5
13	H	CN	128.3	2	0	0
14	-$(CH_2)_3$-		204.6	0	0	0
15	-$(CH_2)_4$-		198.9	0	0	0
16	Br	Me	202.6	2	0	4
17	Br	Br	201.1	2	0	4

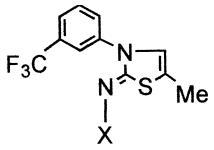
[a)] Dosage: 500 g a.i./ha. Rating scale: 0 (no control)–10 (complete kill). Jm: Japanese millet, Vl: Velvet leaf, Mg: Morning glory.

Turning to the substituents at 5-position on the thiazoline ring, we observed that the nature of the substituent was critical to herbicidal activity. Where R^1 was held constant as hydrogen, moderate activity was seen for electron-withdrawing lipophilic substituents such as halogen atoms (**9**–**11**) and the methylthio group (**12**). When R^2 was a methyl moiety, compound (**5**) showed the highest activity, in spite of lower activity for larger (**6**, **7**) or branched (**8**) alkyl analogs. Hydrogen (**1**) and cyano (**13**) analogs showed reduced herbicidal activity.

1.2. Effect of N-substituents on the 2-imino-1,3-thiazoline ring

Table 2 shows the effects of various substituents (X) on the imino moiety of the thiazoline ring on herbicidal activity.

Table 2. *N*-Substituted 2-imino-1,3-thiazolines with pre-emergence herbicidal activity



Compound No.	X	mp (°C) or (n_D 24°C)	Herbicidal activity[a]		
			Jm	Vl	Mg
18	H	(1.5465)	4	0	0
19	Me	193.0	0	0	0
20	4-ClC_6H_4	170.9	0	0	0
5	CO_2Et	136.8	9	9	8
21	CS_2Me	155.7	5	3	4
22	COMe	127.9	10	9	10
23	CSMe	162.6	1	0	0
24	CONHEt	93.2	8	4	4
25	CSNHEt	203.4	2	0	0
26	$CON(Me)_2$	169.1	7	3	2
27	CONHPh	129.9	6	6	4
28	SO_2Me	129.9	9	8	8
29	CN	168.2	9	6	5

[a] Activity scores and abbreviations, see Table 1.

Among the thiazoline derivatives (**5**, **18**–**29**), the acetyl analog (**22**) was the most active, followed by the ethoxycarbonyl derivative (**5**). Interestingly, introduction of the alkoxylcarbonyl (**24**, **26**, **27**), methanesulfonyl (**28**) or cyano (**29**) group on the imino moiety elicited herbicidal activity, though overall activities were still less than for **5**. The herbicidal activity of 2-imino-1,3-thiazoline derivative (**18**) was poor, and the thiazoline derivatives with a methyl (**19**) or a 4-chlorophenyl (**20**) group were entirely inactive. In general, the thiocarbonyl derivatives (**21**, **23**, **25**) showed reduced herbicidal activity relative to the corresponding carbonyl derivatives (**5**, **22**, **24**), respectively.

From the results shown in Table 2, it was concluded that the incorporation of the substituent, especially a carbonyl, cyano or sulfonyl group on the imino moiety of thiazoline ring, was important for high bleaching herbicidal activity. In particular, the acetyl derivative (**22**) exhibited the highest activity, which prompted us to modify the acetyl moiety of compound **22**.

1.3. Effects of N-alkylcarbonyl groups on the 2-imino-1,3-thiazoline ring

Table 3 shows the effects of various alkanonylimino moieties at the 2-position of the 1,3-thiazoline ring on herbicidal activity. At a lower rate of 125 g a.i./ha, in the series of unsubstituted alkyl groups (**22**, **30**, **31**), moderate activity was observed for the methyl derivative (**22**), and activity decreased gradually on moving to the ethyl (**30**) and *n*-Pr (**31**) substituents, indicating a size constraint at this position. Accordingly, poor activity was also seen for the branched alkyl (**32**, **33**) and cycloalkyl (**34**) derivatives.

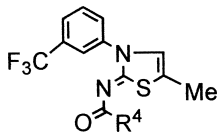
Interestingly, introduction of a halogenated methyl substituent had a dramatic effect on herbicidal activity. A chloromethyl or dichloromethyl substituent such as compounds **35** or **36** provided diminished activity compared to the methyl derivative (**22**). On the other hand, the substitution of fluorinated alkyl groups (**37**–**40**) increased herbicidal activity. Among those fluorinated alkyl analogs, difluoromethyl (**38**) and trifluoromethyl (**39**) derivatives controlled all weeds tested at 125 g a.i./ha, while monofluoromethyl (**37**) and pentafluoroethyl (**40**) analogs exhibited moderate activity.

These results suggested that the presence of electron-withdrawing and hydrophobic properties such as CF_3 and CHF_2 substituents was responsible for increasing herbicidal activity. Based on the overall considerations of herbicidal efficacy and safety to cotton, compounds **38** and **39** were selected for further evaluation.

*2. Herbicidal properties of **38** and **39***

Table 4 summarizes the herbicidal activity and crop safety in cotton for fluorinated alkyl compounds **38** and **39** with pre-emergence application at 62.5 and 125 g a.i./ha. Compound

Table 3. *N*-Alkylcarbonylimino-1,3-thiazolines with pre-emergence herbicidal activities



Compound No.	R^4	mp (°C)	Herbicidal activity[a]		
			Jm	Vl	Mg
22	Me	222.6	9	6	9
30	Et	164.6	7	5	6
31	*n*-Pr	111.0	4	2	4
32	*i*-Pr	139.6	7	6	4
33	*t*-Bu	94.7	5	4	6
34	*cyclo*-Pr	132.6	9	4	6
35	CH_2Cl	129.0	2	0	0
36	$CHCl_2$	129.0	3	0	0
37	CH_2F	135.7	9	7	9
38	CHF_2	117.9	10	10	10
39	CF_3	128.1	10	10	10
40	CF_3CF_2	98.5	8	8	7

[a] Activity scores and abbreviations, see Table 1. Dosage: 125 g a.i./ha.

Table 4. Selected compounds (**38** and **39**) and their herbicidal activity against uplands weeds and selectivity against cotton

Compound No.	Dosage g a.i./ha	Selectivity[a)]	Herbicidal activity[a)]							
		Co	Bg	Cg	Jg	As	Pc	Vl	Mg	Ps
38	125	0	10	9	9	10	10	10	10	10
	62.5	0	9	9	9	10	10	10	10	10
39	125	3	10	9	9	10	9	10	10	10
	62.5	1	8	8	7	9	9	9	8	9

[a)] Co: Cotton, Bg: Baryard grass, Cg: Large crabgrass, Jg: Johnson grass, As: Amaranth slender, Pc:Purslaneand common, Ps: Prickly sida. Activity scores and other abbreviations, see Table 1.

38 showed excellent broad-spectrum activity against both grass and broadleaf at 62.5 g a.i./ha with good cotton selectivity. Compound **39** provided very good levels of activity at 125 g a.i./ha, while causing slight damage to cotton. Moreover, compound **39** was less active than compound **38** at 62.5 g a.i./ha against all weeds tested. In this present study, compound **38** was chosen as a candidate to be developed as a possible cotton herbicide.

On the basis of biochemical studies, novel 1,3-thiazolines have been characterized as new inhibitors of phytoene desaturase.[15)] The manufacturing process of compound **38** and biochemical studies on 1,3-thiazolines will be reported in the near future.

Conclusions

As a methodology to search for a new lead compound as a herbicide, we focused on the chemical approach to *N,S*-heterocycles. This approach led to the evolution of 2-acylimino-3-(3-trifluoromethylphenyl)-1,3-thiazolines as the lead to bleaching herbicides. Further structural modifications resulted in the discovery of a new familiy of bleaching herbicides, represented by 2-(*N*-difluoroacetylimino)-5-methyl-3-(3-trifluoromethylphenyl)-1,3-thiazoline (**38**), which showed potent preemergence herbicidal activity and excellent selectivity for a cotton crop.

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References

1) Y. Sanemitsu: *J. Synth. Org. Chem.* **44**, 939–952 (1986) (in Japanese).
2) Y. Sanemitsu, M. Mizutani, Y. Nakayama and M. Shiroshita: *Sumitomo Kagaku* **1**, 1–4 (1987) (in Japanese).
3) Y. Sanemitsu, M. Mizutani and Y. Nakayama: *J. Synth. Org. Chem.* **50**, 875–886 (1992) (in Japanese).
4) Y. Sanemitsu, Y. Nakayama, T. Yano and Y. Tanabe: *Agric. Biol. Chem.* **53**, 2843–2844 (1989).
5) Y. Sanemitsu and M. Mizutani: *Agric. Biol. Chem.* **51**, 3173–3175 (1987).
6) Y. Sanemitsu, M. Mizutani and R. Yoshida: *Agric. Biol. Chem.* **51**, 3177–3181 (1987).
7) S. Kawamura, T. Hamada, R. Satoh and Y. Sanemitsu: *J. Agric. Food Chem.* **39**, 2279–2282 (1991).
8) S. Kawamura, T. Hamada, R. Satoh, Y. Sanemitsu, G. Sandmann and P. Babczinski: "Synthesis and Chemistry of Agrochemicals III," ed. by D. R. Baker, J. G. Fenyes and J. G. Steffens, ACS Symposium Series No. 504, American Chemical Society, Washington, D. C., pp. 103–108, 1992.
9) S. Kawamura, J. Satoh, T. Hamada, M. Sakaki and Y. Sanemitsu: *J. Agric. Food Chem.* **41**, 288–291 (1993).
10) H. Yamanaka, N. Ohsawa, S. Konno, Y. Sanemitsu and M. Sakaki: *J. Agric. Food Chem.* **43**, 838–842 (1993).
11) H. Ulrich: "Cycloaddition Reactions of Heterocumlenes," Vol. 9, ed. by A. T. Blomquist, Organic Chemistry, A Series of Monographs, Academic Press, New York, pp. 129–219, 1967.
12) S. Kawamura and Y. Sanemitsu: *J. Org. Chem.* **58**, 414–418 (1993).
13) S. Kawamura, K. Izumi, J. Satoh and Y. Sanemitsu (Sumitomo Chmical Co. Ltd.): *Eur. Pat. Appl.* EP446802 (1991).
14) A. V. Krasovskii and I. S. Burmistrov: *Geterotsikl Soedin.*, 1969, 56–62; *Chem. Abstr.* **70**, 115051 (1969).
15) Y. Sanemitsu, S. Kawamura, S. Hashimoto, J. Satoh, T. Katayama and G. Sandmann: "Synthesis and Chemistry of Agrochemicals VIII," ed. by D. R. Baker, J. G. Fenyes, G. P. Lahm, T. Selby and T. M. Stevenson, American Chemical Society, Washington, D. C., 2006 (in press).