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Studies of the New Herbicide KIH-6127. Part II.* Synthesis and Herbicidal Activity of 6-Acyl Pyrimidin-2-yl Salicylates and Analogues against Barnyard Grass

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Abstract: The method reported previously (Part I) was employed to prepare a variety of novel 6-acylsalicylates as key intermediates. 6-Acylpyrimidin-2-yl salicylates (2-acyl-6-[(4,6-disubstituted pyrimidin-2-yl)oxy]benzoate derivatives: Type 1), the closely related phthalide compounds (3-alkyl-7-[(4,6-dimethoxypyrimidin-2-yl)oxy]phthalide derivatives: Type 2) and the ketal derivatives of 2-acyl-6-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoates (Type 3) were synthesized and their herbicidal activities measured. Methyl 2-acetyl-6-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate gave excellent control of barnyard grass with a promising profile as a prototype rice herbicide.

Key words: herbicide, barnyard grass, PS compound, 6-acylsalicylate, structure–activity, phthalide, KIH-6127, paddy rice, pyrimidine, triazine

1 INTRODUCTION

Sulfonylurea herbicides, such as bensulfuron-methyl and pyrazosulfuron-ethyl, control sedge and broad-leaf weeds at very low application rates in transplanted rice. These herbicides have only a moderate activity against barnyard grass (*Echinochloa* spp.), the most problematic weed in paddy fields, at practical application rates. Barnyard grass thus frequently escapes from the application of existing commercial herbicides, which usually still require relatively high rates of application.

From both the agricultural and environmental points of view, new low-dose herbicides are required which exhibit excellent efficacy against paddy field weeds, especially barnyard grass, over a wide range of growth stages including pre-emergence. Thus, the objective of our study was to focus on evaluation of new paddy rice herbicides, particularly against barnyard grass.

The primary target site of the sulfonylureas and pyrimidin-2-yl salicylates (Fig. 1; **2**), has been reported to be acetolactate synthase (ALS).[1,2] These ALS inhibitors block branched-chain amino acid biosynthesis in the plant, resulting in phytotoxicity at low concentrations. The corresponding biosynthetic pathway in mammals is absent.[3,4] However, ALS inhibitory herbicides are not yet commercially available for use against barnyard grass. We therefore sought a novel series of pyrimidin-2-yl salicylate compounds for evaluation against this target.

A novel synthesis of methyl 6-acetylsalicylates, the key intermediates for the chemistry reported in this study, was reported in an earlier paper.[5] A novel series of 6-acylpyrimidin-2-yl salicylates (see Table 1), were

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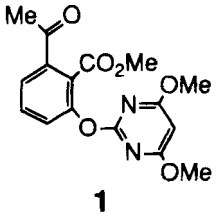

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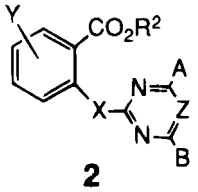

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Fig. 1. Structures of pyrimidin-2-yl salicylates and related compounds.

synthesized and screened for their herbicidal activity against weeds in rice. We found that several of these compounds gave good control of barnyard grass (*Echinochloa oryzicola* Frit.) in preliminary pot-tests.

We then prepared the analogous phthalides (3-alkyl-7-[(4,6-dimethoxypyrimidin-2-yl)oxy]phthalides; see Table 2), and the ketal derivatives of 2-acyl-6-[(4,6-disubstituted-pyrimidin-2-yl)oxy]benzoates (see Table 3).

The herbicidal profile of **1** (Fig. 1) satisfied our requirement as a prototype for a barnyard grass herbicide. The present study describes the synthesis and herbicidal activity of the 6-acylpyrimidin-2-yl salicylates and analogues.

2 MATERIALS AND METHODS

2.1 General

[^{1}H]NMR spectra were recorded in δ (ppm) on a JEOL JMN-PMX-60Si using tetramethylsilane as an internal standard, while IR spectra were measured on a Shimadzu IR-240. All melting points were uncorrected. The structures of compounds were confirmed by NMR and IR spectroscopies.

The physical properties and herbicidal activities of the test compounds are listed in Tables 1–3.

2.2 Application of the ortho-lithiation method to the syntheses of 6-acylsalicylates

Several novel 6-acylsalicylates (**43**) [R^1: C_2H_5, C_3H_7, $CH(CH_3)_2$, $CH_2C_6H_5$] were prepared by the previously reported method (Fig. 2).[5] Grignard reaction of commercially available 3-benzyloxybenzaldehyde (**37**) (0·1 mol) with the corresponding R^1MgBr (prepared from 0·16 mol of R^1Br and 6 g of Mg) was performed, according to the conventional method,[6] to give the corresponding alcohols (**38**) in 76–83% yields. The alcohols (**38**) were oxidized to the corresponding ketones (**39**) using Swern's method.[7]

In a typical run, dichloromethane (50 ml) and dimethyl sulfoxide (DMSO; 0.1 mol) were cooled below −50°C, and trifluoroacetic anhydride (0·075 mol) in dichloromethane (25 ml) was added dropwise to the stirred cold solution during 10 min. A solution of the alcohol (**38**) (0·05 mol) in dichloromethane (50 ml) was added dropwise during 10 min to the mixture maintained at −50°C. Stirring was continued at −50°C for 30 min, followed by addition of triethylamine (20 ml) during 10 min, maintaining the temperature below −50°C. The mixture was allowed to warm to room temperature and finally washed successively with dilute sulfuric acid, aqueous sodium hydrogen carbonate, and water. The organic layer was dried and concentrated to give a residue, which was chromatographed on a silica-gel column to afford the corresponding ketone (**39**) in 75–92% yield.

A mixture of **39**, triethoxymethane (91 g, 0·6 mol) *p*-toluenesulfonic acid monohydrate (1 g) in ethylene glycol (150 ml) was stirred at 120°C for 1·5 h. The resulting mixture was extracted with toluene, then washed with saturated sodium hydrogen carbonate solution and water, dried and concentrated to give the corresponding ketal (**40**) in 87–95% yield.

Application of the *ortho*-lithiation method, as described in the preceding report,[5] then led to the corresponding **41** in 75–83% yield.

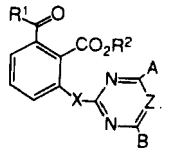
A mixture of **41** (0·07 mol) and 10% Pd/C (1·5 g) in ethyl acetate (200 ml) was stirred until the theoretical amount of hydrogen had been consumed. Filtration and concentration gave **42** in 95–98% yield. A methanol solution of **42** (0·06 mol; 30 ml) was then treated with 0·5% hydrochloric acid (2·1 g, 0·3 mmol) at 35°C for 18 h or with 5% hydrochloric acid (0·5 g, 0·7 mmol) at room temperature for 24 h and neutralized with aqueous sodium hydrogen carbonate. After extraction with ethyl acetate, the organic layer was washed with water, dried and concentrated. The residue was chromatographed on a silica-gel column to give the corresponding 6-acylsalicylates (**43**) in 65–75% yield.

Table 4 summarizes the physical and spectroscopic data for compounds **40**–**43**. These 6-acylsalicylate intermediates were then converted into the test compounds as described in the next section.

2.3 Synthesis of test compounds

The pyrimidin-2-yl salicylate compounds in Tables 1–3 were obtained by the reaction of the corresponding starting materials such as 6-acylsalicylates, 2-acyl-6-mercaptobenzoates and *N*-formyl-6-acylanthranilates,

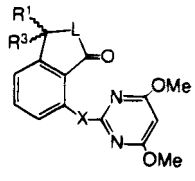
TABLE 1
Melting Points and Herbicidal Activities of 6-Acyl-2-(Pyrimidin-2-yl) Benzoates



Compound number	Substituents						m.p. (°C)	Herbicidal activity[a,b,c] (63 g AI ha^{-1})				(16 g AI ha^{-1})			
	R^1	R^2	A	B	X	Z		Ec	Mo	Sc	Or	Ec	Mo	Sc	Or
1	Me	Me	OMe	OMe	O	CH	164–166	10	10	10	3	10	2	4	0
3	Me	H	OMe	OMe	O	CH	169–171	10	9	10	9	10	6	10	6
4	Me	Et	OMe	OMe	O	CH	130–133	8	0	4	1	8	0	0	0
5	Me	Bn	OMe	OMe	O	CH	141–143	10	2	6	10	4	0	0	2
6	H	Me	OMe	OMe	O	CH	91–93	0	0	0	0	N	N	N	N
7	Et	Me	OMe	OMe	O	CH	120–122	10	10	10	10	9	9	10	9
8	Pr	Me	OMe	OMe	O	CH	84·5–86	9	8	9	8	4	8	9	4
9	Ph	Me	OMe	OMe	O	CH	121–122	0	0	0	0	N	N	N	N
10	Me	Me	OMe	OMe	S	CH	149–151	9	2	1	0	6	0	0	0
11	Me	H	OMe	OMe	S	CH	177–180	9	9	10	0	5	9	0	0
12	Me	Me	OMe	OMe	NCHO	CH	144–148	9	6	10	9	9	0	9	3
13	Me	Me	OMe	OMe	NH	CH	108–110	0	0	0	0	N	N	N	N
14	Me	Me	OMe	$OCHF_2$	O	CH	70–73	10	8	8	8	7	4	6	3
15	Me	Me	OMe	Cl	O	CH	117–120	0	0	0	0	N	N	N	N
16	Me	Me	Me	Cl	O	CH	109–112	0	0	0	0	N	N	N	N
17	Me	Me	OMe	Me	O	CH	127–130	0	0	0	0	N	N	N	N
18	Me	Me	Me	Me	O	CH	138–140	0	0	0	0	N	N	N	N
19	Me	Me	OMe	OMe	O	N	151–156	0	0	0	0	N	N	N	N
20	Me	Me	OMe	$N(Me)_2$	O	N	145–149	0	0	0	0	N	N	N	N
Bensulfuron[d]	—	—	—	—	—	—	—	9	10	10	2	6	10	9	0

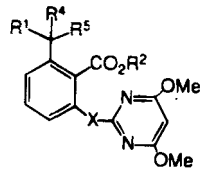
[a] Pre-emergence.
[b] *Ec*: *Echinochloa oryzicola*: *Mo*: *Monochoria veginalis*: *Sc*: *Scirpus juncoides*: *Or*: *Oryza sativa*. N: Not Tested.
[c] Visually evaluated 0–10 rating scale: 10 (complete control and injury)–0 (no effect and no injury).
[d] Standard compound.

TABLE 2
Physical Properties of Phthalide Compound



Compound number	Substituents				m.p. (°C)
	R^1	R^3	L	X	
21	Me	OMe	O	O	113–115 (114–115, lit.[15])
22	Me	OEt	O	O	99–103
23	H	H	S	O	199–202
24	Me	H	S	O	159–162
25	Me	H	O	NCHO	159–164
26	Me	H	O	NH	108–110
27	Me	OMe	O	NH	183–185

TABLE 3
Physical Properties of 6-Ketal Pyrimidin-2-yl Salicylates



Compound number	*Substituents*				*m.p. (°C)* *nD²⁰*
	R¹	*R²*	*R⁴*	*R⁵*	
28	H	Me	OMe	OMe	83–85
29	Me	Me	OMe	OMe	78–81
30	Me	Me	—OCH_2CH_2O—		123–126
31	Me	H	—OCH_2CH_2O—		142–146
32	Me	Me	—$OCH_2CH(Me)O$—		1.5173
33	Me	Me	—$OCH(Me)CH(Me)O$—		1.5123
34	Me	Me	—$OCH_2CH_2CH_2O$—		148–156
35	Me	Me	—SCH_2CH_3S—		113–115
36	H	Me	—SCH_2CH_2S—		86–87

with the corresponding 4,6-disubstituted-2-methanesulfonyl (or -2-halo)-pyrimidine (or triazine) in the presence of potassium carbonate at 80–100°C, or sodium hydride below room temperature in *N,N*-dimethylformamide (DMF) for 1–3 h. Compound **3** was prepared by the hydrolysis of **1**. General synthetic methods for the test compounds are summarized in Fig. 3.

Some of the intermediates were prepared in our previous studies,[5] or by literature methods.[8–15]

Typical examples of synthetic procedures are given below.

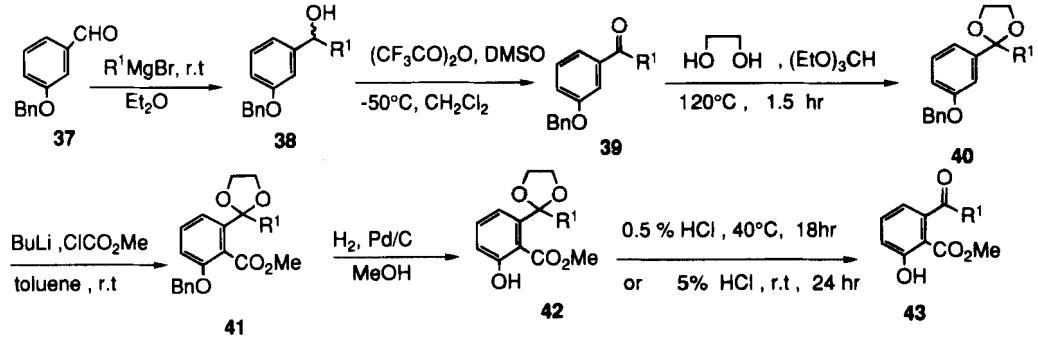


Fig. 2. Synthesis of methyl 6-acylsalicylates.

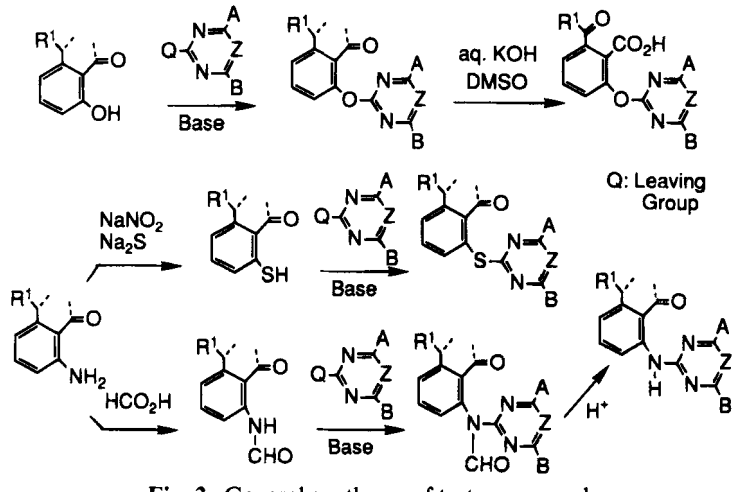


Fig. 3. General syntheses of test compounds.

TABLE 4
Physical and Spectroscopic Data for Compounds **40–43** (Fig. 2)

Compd. No.	R^1	*mp/nD*^{20}	[^{1}*H*]*NMR δ (ppm)*
40	Et	54–56°C	0·87 (t J = 7 Hz 3H), 1·90 (q J = 7 Hz 2H), 3·50–4·17 (m 4H), 5·0 (s 2H), 6·70–7·50 (m 9H)
	Pr	76–78°C	0·87 (t J = 6 Hz 3H), 1·10–1·60 (m 2H), 1·60–2·10 (m 2H), 3·50–4·16 (m 4H), 5·00 (s 2H), 6·67–7·50 (m 9H)
	Pr-i	53–55°C	0·86 (d J = 7 Hz 6H), 2·06 (hept.J = 7 Hz 1H), 3·50–4·10 (m, 4H), 5·03 (s 2H), 6·67–7·50 (m 9H)
	Bn	76–77°C	3·10 (s 2H), 3·73 (s 4H), 5·00 (s 2H), 6·60–7·17 (m 14H)
41	Et	99–100°C	0·91 (t J = 8 Hz 3H), 2·00 (q J = 8 Hz 2H), 3·66–4·30 (m 4H), 3·86 (s 3H), 5·10 (s 2H), 6·79–7·67 (m 8H)
	Pr	77–78°C	0·83 (t J = 6 Hz 3H), 1·07–1·67 (m 2H), 1·67–2·20 (m 2H), 3·83 (s 3H), 3·50–4·20 (m 4H), 5·03 (s 2H), 6·63–7·50 (m 8H)
	Pr-i	66–67°C	0·93 (d J = 7 Hz 6H), 2·00–2·60 (m 1H), 3·57–4·07 (m 4H), 3·80 (s 3H), 5·07 (s 2H), 6·67–7·50 (m 8H)
	Bn	104–105°C	3·26 (s 2H), 3·70 (s 4H), 3·86 (s 3H), 5·03 (s 2H), 6·67–7·50 (m 13H)
42	Et	131–132°C	1·00 (t J = 7 Hz 3H), 2·17 (q J = 7 Hz 2H), 3·92 (s 3H), 3·36–4·13 (m 4H), 6·66–7·50 (m 3H)
	Pr	137–138°C	0·91 (t J = 7 Hz 3H), 1·17–1·83 (m 2H), 1·83–2·33 (m 2H), 3·86 (s 2H), 3·40–4·15 (m 4H), 6·67–7·50 (m 3H)
	Pr-i	126–127°C	1·00 (d J = 7 Hz 6H), 2·59 (hept.J = 7 Hz 1H), 3·40–4·20 (m 4H), 3·90 (s 3H), 6·67–7·50 (m 3H)
	Bn	144–145°C	3·36 (s 2H), 3·33–3·79 (m 4H), 3·96 (s 3H), 6·69–7·50 (m 3H), 7·20 (s 5H)
43	Et	1·5309	1·18 (t J = 6 Hz 3H), 2·73 (q J = 6 Hz 2H), 3·68 (s 3H), 6·59 (d J = 7 Hz 1 H), 6·96 (d J = 7 Hz 1H), 7·40 (t J = 7 Hz 1H), 10·6 (s 1H)
	Pr	1·5581	1·00 (t J = 7 Hz 3H), 1·70 (hept.J = 7 Hz 2H), 2·69 (t J = 7 Hz 2H), 3·83 (s 3H), 6·63 (d J = 7 Hz 1H), 6·96 (d J = 7 Hz 1H), 7·40 (t J = 7 Hz 1H), 10·00–11·50 (brs 1H)
	Pr-i	1·5462	1·13 (d J = 8 Hz 6H), 2·80 (hept.J = 7 Hz 1H), 3·87 (s 3H), 6·56 (d J = 8 Hz 1H), 6·93 (d J = 8 Hz 1H), 7·38 (t J = 8 Hz 1H), 10·00–11·50 (brs 1H)
	Bn	1·5828	3·83 (s 3H), 4·03 (s 2H), 6·37–7·66 (m 3H), 7·27 (s 5H), 10·00–12·00 (brs 1H)

2.3.1 Synthesis of methyl 2-acetyl-6-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate (1)
A mixture of methyl 6-acetylsalicylate (194 g, 1 mol), 4,6-dimethoxy-2-methanesulfonylpyrimidine (DMSP; 218 g, 1 mol), potassium carbonate (79 g, 0·57 mol) in DMF (1 litre) was stirred at 80–100°C for 3 h. The resulting mixture was poured into ice-water (4 litre), and the precipitate was collected by filtration, washed successively with water, isopropyl ether + hexane (1 + 1 by volume; 1·5 litre) and ethyl acetate (0·5 litre), and dried under vacuum to give **1** (278·9 g; 84%); m.p. 164–166°C, [^{1}H]NMR (deuterochloroform) δ: 2.53 (s, 3H), 3.72 (s, 9H), 5.85 (s, 1H), 7·3–7·7 (m, 3H) ppm; IR (potassium bromide): 1750, 1690, 1600, 1570, 1360, 1270, 1240, 1200 cm^{-1}.

2.3.2 Synthesis of 2-acetyl-6-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoic acid (3)
Aqueous potassium hydroxide (4·2 g, 75 mmol in 15 ml water) was added dropwise to a solution of **1** (8·2 g, 24·7 mmol) in DMSO (50 ml) at room temperature, then stirred for 4 h. The resulting mixture was poured into aqueous citric acid, the precipitate collected by filtration, washed with water and dried to give **3** (5·8 g; 74%); m.p. 169–171°C, [^{1}H]NMR (hexadeutero dimethyl sulfoxide) δ: 1·82 (s, 3H), 3·76 (s, 6H), 5·79 (s, 1H), 7·15–7·9 (m, 4H) ppm; IR (potassium bromide): 3300, 3000, 1780, 1600, 1560, 1360, 1240, 1200 cm^{-1}.

2.3.3 Synthesis of benzyl 2-acetyl-6-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate (5)
Aqueous potassium hydroxide (1·3 g, 23 mmol in 5 ml water) was added dropwise to a solution of **1** (5·7 g, 17 mmol) in DMSO (20 ml) and stirred at room temperature for 4 h, then benzyl bromide (3·15 g, 0·018 mol) was added dropwise. The mixture was stirred at room temperature for 4 h to give **5** which was purified by silica-gel column chromatography using hexane + ethyl acetate (4 + 1 by volume) as eluent; (4·02 g; 58·6%); m.p. 141–143°C, [^{1}H]NMR (deuterochloroform): δ: 2·53 (s, 3H), 3·66 (s, 6H), 5·16 (s, 2H), 5·66 (s, 1H), 7·16 (s, 5H), 7·16–7·60 (m, 3H) ppm;

IR (potassium bromide): 3200, 3000, 1740, 1690, 1600, 1560, 1600, 1560, 1470, 1400, 1270, 1240, 1200 cm^{-1}.

2.3.4 Synthesis of methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-propionylbenzoate (7)

Sodium hydride (60% oil dispersion, 0·15 g, 6·7 mmol) was added to a solution of 3-hydroxy-2-methoxycarbonyl propiophenone (0·83 g, 4 mmol) in DMF (60 ml) below 15°C, then DMSP (0·83 g, 4 mmol) was added at room temperature and the mixture stirred for 3 h. It was then extracted with ethyl acetate and washed with water. The organic layer was concentrated to give **7**, which was purified by silica-gel column chromatography using hexane + diethyl ether (1 + 1 by volume) as eluent, (0·97 g; 71%); m.p. 120–122°C, [^{1}H]NMR (deuterochloroform) δ: 1·15 (t, J = 7 Hz, 3H), 2·92 (q, J = 7 Hz, 6H), 3·35 (s, 6H), 5·65 (s, 1H), 7·12–7·6 (m, 3H) ppm; IR (potassium bromide): 2950, 1740, 1680, 1600, 1560, 1400, 1360, 1240, 1200 cm^{-1}.

2.3.5 Synthesis of 2-acetyl-6-[(4,6-dimethoxypyrimidin-2-yl)thio]benzoic acid (11)

2-Amino-6-acetylbenzoic acid (10·2 g, 0·053 mol) was converted to the diazonium salt using a mixture of concentrated hydrochloric acid (14·2 ml), water (40 ml) and sodium nitrite (4·3 g, 0·062 mol). The diazonium salt was gradually added at 0–5°C to an aqueous disodium sulfide solution [prepared from $Na_2S \cdot 9H_2O$ (14·3 g, 0·060 mol), sulfur (1·9 g, 0·06 mol), sodium hydroxide (4·6 g, 0·115 mol) and water (30 ml)]. The resultant mixture was stirred for 2 h at room temperature to complete the reaction. The reaction liquor was poured into a large volume of water. After adding concentrated hydrochloric acid (5 ml), the product was extracted with ethyl acetate, and the organic solution then extracted with aqueous sodium hydrogen carbonate. Sodium metabisulphite ($Na_2S_2O_5$; 14·8 g, 0·078 mol) was added to the resulting aqueous solution, and the mixture was heated at reflux for 30 min. After cooling, concentrated hydrochloric acid (5 ml) was added to the reaction mixture, and the product was extracted with ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and concentrated to obtain crude 2-acetyl-6-mercaptobenzoic acid (10·1 g; 96%).

The crude product (10·1 g, 0·05 mol) and sodium hydroxide (7·6 g, 0·19 mol) were then dissolved in a mixture of water (20 ml) and DMF (30 ml). DMSP (13·5 g, 0·062 mol) was then added to the solution, and the resulting mixture was stirred at room temperature for 2 h and then at 60°C for 0·5 h. The reaction mixture was then poured into water, and extracted with chloroform. Concentrated hydrochloric acid (10 ml) was added to the aqueous layer, and the oily product was extracted with diethyl ether and dried. The ether solution was passed through a short column of Florisil, and the ether evaporated to give 11 (6·1 g; 34%); m.p. 177–180°C, [^{1}H]NMR (deuterochloroform/hexadeuterodimethyl sulfoxide) δ: 1·83 (s, 3H), 3·70 (s, 6H), 5·76 (s, 1H), 6·70–7·30 (brs, 1H), 7·30–8·00 (m, 3H) ppm; IR (potassium bromide): 3400, 1730, 1570, 1540, 1450, 1380, 1360, 1320, 1290, 1250, 1180, 1160, 1030 cm^{-1}.

2.3.6 Synthesis of methyl 2-acetyl-6-[(4,6-dimethoxypyrimidin-2-yl)thio]benzoate (10)

Compound **11** (2·5 g, 6·9 mmol) was added to a mixture of 60% aqueous sodium hydroxide (0·3 g, 7·5 mmol), tetrahydrofuran (20 ml) and DMF (20 ml). The mixture was stirred for 30 min, and methyliodide (1·3 g, 9·3 mmol) then added dropwise at room temperature. After heating under reflux for 2 h, the mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and concentrated. The residue was purified by silica-gel column chromatography to give **10** (5·8 g; 32%) m.p. 149–151°C, [^{1}H]NMR (deuterochloroform) δ: 2·54 (s, 3H), 3·94 (s, 3H), 4·00 (s, 6H), 5·86 (s, 1H), 7·15–8·00 (m, 3H) ppm; IR (potassium bromide): 3100, 2950, 1740, 1680, 1590, 1560, 1480, 1440, 1420, 1380, 1360, 1300, 1270, 1230, 1180, 1140, 1120, 1080, 1060, 640 cm^{-1}.

2.3.7 Synthesis of methyl 2-acetyl-6-[(4,6-dimethoxytriazin-2-yl)oxy]benzoate (19)

Methyl 6-acetylsalicylate (1·0 g, 5·15 mmol) was added to a suspension of sodium hydride (0·14 g, 5·83 mmol) in benzene (30 ml), and the resulting mixture stirred for 10 min at room temperature. 2-Chloro-4,6-dimethoxytriazine (0·95 g, 6·64 mmol) was added and the mixture stirred for 16 h at room temperature.

The reaction mixture was poured into water, extracted with ethyl acetate, and the extract washed with water, dried and concentrated to give a residue which was purified by silica-gel column chromatography to give **19** (1·15 g; 67%) yield; m.p. 151–156°C, [^{1}H]NMR (deuterochloroform) δ: 2·53 (s, 3H), 3·83 (s, 3H), 3·90 (s, 6H), 7·15–7·66 (m, 3H) ppm; IR (potassium bromide): 3200, 3100, 2950, 1740, 1690, 1600, 1560, 1480, 1460, 1440, 1420, 1360, 1260, 1240, 1210, 1200, 1140, 1120, 1100, 1080, 960, 940, 880, 820, 790 cm^{-1}

2.2 Biological test

Each test compound was formulated as a 100 g kg^{-1} wettable powder, containing 'Emalgen' 810 (5·0 g kg^{-1}) 'Demoln' (5·0 g kg^{-1}) Kunilite 250 (diatomaceous earth; 180 g kg^{-1}), Carplex No/80 (white carbon; 60 g kg^{-1}) and Zeeklite (clay). The wettable powder was diluted with water to the desired concentration. Plastic pots (square: 100 cm^2 in surface area) were packed with clay loam soil (Organic matter 1·44%, pH 5·6) and water

was added up to 3 cm in depth. The water depth was managed during the test period. *E. oryzicola* (Ec), *Scirpus juncoides* L. (Sc) and *Monochoria veginalis* Presl. (Mo) were seeded at a depth of 0·5 cm on one day after puddling and fertilization. Rice seedlings (*Oryza sativa* L., two-leaf growth stage) (Or) were transplanted at a depth of 3 cm in the same pot. One day after seeding, a diluted suspension of wettable powder was applied to the pots. Three weeks later, the herbicidal activities and crop injury were visually evaluated by the 0–10 rating scale: 10 (complete control and injury), 9 (90–99%), 8 (80–89%), 7 (70–79%), 6 (60–69%), 5 (50–59%), 4 (40–49%), 3 (30–39%), 2 (20–29%), 1 (<19%), 0 (no effect and no injury), respectively.

Bensulfuron-methyl was used as a reference compound in all greenhouse tests.

3 RESULTS AND DISCUSSION

3.1 Synthesis of test compounds

In our previous research, attempted mild alkaline hydrolysis of the carboxylate group in pyrimidin-2-yl salicylate esters incorporating 6-halo, 6-alkyl, 6-alkoxy and 6-phenyl groups was unsuccessful, presumably as a result of the steric hindrance of the *ortho*-disubstitution. More forcing base hydrolysis still failed to give any desired compounds. Under these conditions, a bond cleavage of the ether (—O—) linkage between the benzene ring and pyrimidine ring occurred instead.[16]

Compound **1**, which incorporates a γ-keto carboxylate group would also be expected to undergo alkaline hydrolysis.[14,17] We therefore attempted the hydrolysis of **1** in the presence of aqueous potassium hydroxide at room temperature in DMSO. The desired transformation was accomplished to afford **3** as shown in Fig. 4.

The chemistry of the esterified 6-acyl pyrimidin-2-yl salicylates therefore seems to be quite different from that of the other esterified 6-substituted compounds and may affect their biological behaviour as discussed in Section 3.2.

The esterification of **3** was then attempted as shown in Fig. 4. Using sodium hydride at room temperature in DMSO or with potassium carbonate at 80°C in DMF the undesired phthalide derivatives **21** and **22** were obtained, along with a small amount of the desired 6-acyl derivatives **1** and **4**. The undesired cyclization reaction was observed even under mild conditions (potassium carbonate, DMSO, room temperature overnight). When the hydrolysis and subsequent alkylation of **1** were carried out in a single flask without isolation of an intermediate, however, the desired esters were obtained. Thus, when **1** was hydrolyzed with aqueous potassium hydroxide at room temperature in DMSO, and subsequently alkylated with the corresponding alkyl halides at room temperature for 4 h, **4** and **5** were obtained as the sole products.

Reaction of methyl 6-propionyl (or butyryl)salicylate with DMSP in the presence of potassium carbonate in DMF at 80–90°C led to the corresponding indandione derivatives as shown in Fig. 5. In order to obtain the desired products **7** and **8**, 6-propionyl or 6-butyrylsalicylate was treated with DMSP in the presence of sodium hydride in DMF below room temperature. Reaction of other 6-acyl salicylates incorporating the bulkier 6-isobutyryl and 6-phenylacetyl groups, with DMSP and sodium hydride in DMF gave only the indandione derivatives even at below room temperature.

The other test compounds (**21–36**) were obtained according to published procedures.[8–15]

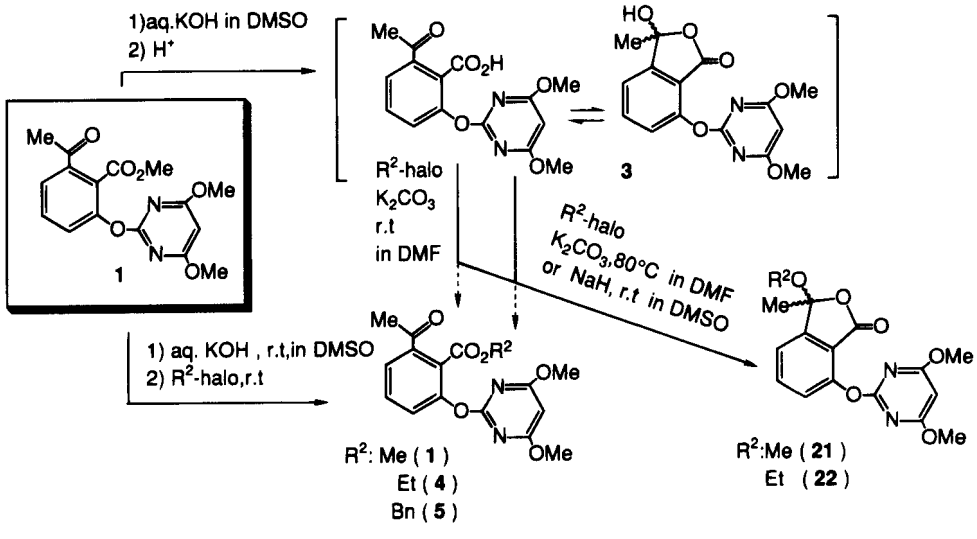


Fig. 4. Synthesis of phthalide related analogues.

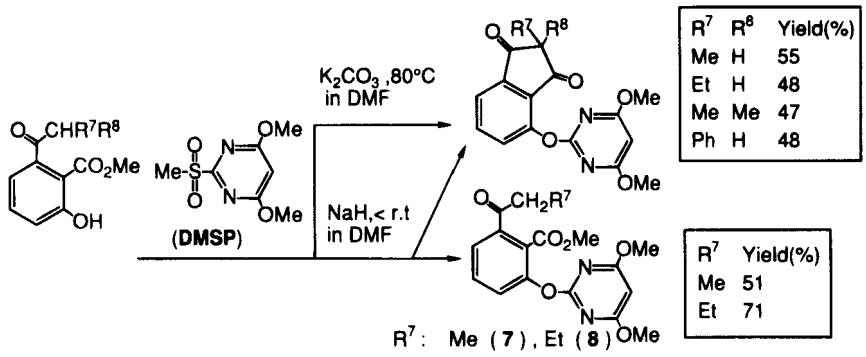


Fig. 5. Condensation of DMSP with 6-propionyl and 6-butyryl salicylate.

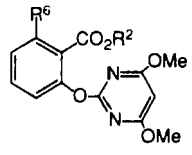
3.2 Herbicidal activity of test compounds

As shown in Table 1, most of the compounds bearing the 4,6-dimethoxypyrimidin-2-yl group gave good control of barnyard grass at a 63 g AI ha^{-1}. The triazines and other pyrimidines except for the difluoromethoxy compound (**14**) did not show any herbicidal activity even at higher rate (250 g AI ha^{-1}).

Focusing on the R^1 moiety, the herbicidal effects against barnyard grass of compounds **1** and **6–9** were as

TABLE 5

Typical Example of Decreasing Herbicidal and ALS Inhibitory Activities with Introduction of Esters into the R^2 Moiety of 6-substituted Pyrimidin-2-yl Salicylate Compounds



R^6	R^2	*ALS*[a] *Inhibitory effect* pI_{50}	*Herbicidal activity*[b] (63 g AI ha^{-1}) Ec	Mo	Sc	Or	(16 g AI ha^{-1}) Ec	Mo	Sc	Or
Cl	H	7.62	10	10	10	10	10	10	8	10
	Me	<5	7	9	0	0	N	N	N	N
	Et	<5	6	6	3	5	N	N	N	N
	Pr	<5	7	6	3	4	N	N	N	N
Br	H	7.82	10	10	10	10	10	10	10	10
	Me	<5	7	2	3	0	N	N	N	N
Me	H	6.89	10	10	10	10	10	10	8	10
	Me	<5	2	7	4	0	N	N	N	N
OMe	H	7.36	10	10	10	10	9	10	10	10
	Me	<5	7	0	8	2	N	N	N	N
OEt	H	7.05	10	10	10	10	10	10	10	10
	Me	<5	7	2	3	0	N	N	N	N
NO_2	H	6.68	4	7	2	0	N	N	N	N
	Me	<5	0	0	0	0	N	N	N	N
CF_3	H	6.96	10	10	10	10	10	10	7	7
	Me	<5	0	0	0	0	N	N	N	N
C_6H_5	H	7.80	10	10	10	10	10	10	10	10
	Me	<5	0	0	0	0	N	N	N	N

[a] The activity expressed as pI_{50}, where I_{50} value is defined as the molar concentration required for 50% inhibition according to the method previously reported.[2]

[b] See footnotes *a–c* to Table 1.

follows: H (**6**) ≪ CH_3 (**1**) > C_2H_5 (**7**) > C_3H_7 (**8**) ≫ C_6H_5 (**9**). The H compound (**6**) and the phenyl compound (**9**) were inactive. This relationship seems to indicate that an optimum number of carbon atoms or bulkiness of R^1 is required for high activity, particularly against barnyard grass.

Although the ethyl compound (**7**) appeared to have a broader spectrum of activity than **1**, the methyl compound (**1**) was much less damaging against rice than **7**.

Comparison of the R^2 moiety of compounds **1** and **3–5** showed that only compound **1** and the carboxylic acid derivative (**3**) had a wide spectrum of activity. Only **1**, however, was comparatively safe to rice.

According to our previous study, the esterification of the 6-substituted pyrimidin-2-yl salicylic acid compounds diminished their ALS inhibitory activities and herbicidal activities as shown in Table 5, and the free carboxylic acid was essential for ALS inhibitory activities.[18] Therefore, these esterified compounds appeared to be resistant to biological hydrolysis as well as to chemical hydrolysis as discussed in Section 3.1.

Nevertheless, even the esterified 6-acyl derivatives (**1**, **4**, **5**, **7**, **8**, **10–12** and **14**) retained herbicidal activity against barnyard grass. It is proposed that those esterified 6-acyl primidin-2-yl salicylate compounds might be metabolically hydrolyzed and converted to the activated acid form[18] more easily than the weakly active 6-substituted esters, in a similar fashion to their chemical hydrolysis as discussed in Section 3.1.

Thus, the biological behaviour as well as the chemical reactivity of esterified 6-acyl pyrimidin-2-yl salicylates was quite different from that of the rest of the esterified 6-substituted compounds.

Concerning the bridge moiety, the sulfur-bridged analogues (**10**, **11**) proved to be less active than their oxygen counterparts (**1**, **3**). Furthermore, it is interesting to note that the *N*-formylated compound (**12**) retained good activity, in contrast with the deformylated amine (**13**) which was inactive.

Considering both weed control activity and rice injury, compound **1** (Fig. 1) exhibited the best profile as a lead for a barnyard grass herbicide. However, in advanced tests, compound **1** caused considerable damage to rice.

Surprisingly, all the phthalide (Type 2) and ketal (Type 3) compounds were inactive even at 63 g AI ha^{-1}.

In conclusion, 6-acylsalicylates were prepared via a novel synthetic route,[5,8–10] and converted into the 6-acyl pyrimidin-2-yl salicylate compounds (Type 1) and their analogues (Type 2 and Type 3). Herbicidal evaluation showed that compound **1** exhibited the optimum performance.

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REFERENCES

1. Subramanian, M. V., Loney, V. & Pao, L., BCPC Monograph, No 42. ed. L. G. Copping, J. Dalziel & A. D. Dodge. Lavenham Press Limited, Lavenham, Suffolk, 1989, pp. 97–100.
2. Shimizu, T., Nakayama, I., Nakao, T., Nezu, Y. & Abe, H., *Nippon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **19** (1994) 59–67.
3. Rose, W. C., Johnson, J. E. & Haines, W. J., *J. Biol. Chem.*, **182** (1950) 541–56.
4. Wissler, R. W., *J. Nutr.*, **36** (1948) 245–62.
5. Tamaru, M. & Saito, Y., Studies of the New Herbicide KIH-6127. Part I. Novel Synthesis of Methyl 6-Acetylsalicylate as a Key Synthetic Intermediate for the Preparation of 6-Acetyl Pyrimidin-2-yl Salicylates and Analogues. *Pestic Sci.*, **47** (1996) 125–30.
6. Rastogi, S. N., Anand, N., Gupta, P. P. & Sharma, J. N., *J. Med. Chem.*, **16** (1973) 797–804.
7. Omura, K., Sharma, K. A. & Swern, D., *J. Org. Chem.*, **41** (1976) 957–62.
8. Tamaru, M., Kawamura, N., Sato, M., Takabe, F., Tachikawa, S. & Yoshida, R., Kumiai Chemical Ind., Co., Ltd. & Ihara Chemical Ind., Co., Ltd., Jpn. Kokai Tokkyo Koho, JP. 4-134080 (1993).
9. Umezu, K., Isozumi, K., Miyazaki, T., Tamaru, M., Takabe, F., Masuyama, N. & Kimura, Y., *Synlett.* (1) (1994) 61–2.
10. Tamaru, M., Umezu, K., Isozumi, K., Maejima, C., Kageyama, H. & Kimura, Y., *Synth. Commun.*, **24** (1994) 2749–56.
11. Buehler, C. A., Powers, T. A. & Michels, J. G., *J. Am. Chem. Soc.*, **66** (1944) 417–18.
12. Uemura, M., Tokuyama, S. & Sakan, T., *Chem. Lett.* (1975) 1195–8.
13. Chase, B. H. & Hey, D. H., *J. Chem. Soc.* (1957) 553–72.
14. Bhatt, M. V., Rao, G. V. & Rao, K. S., *J. Org. Chem.*, **44** (1979) 984–9.
15. Luethy, C. & Obrecht, J. P., Dr. R. Maag AG WO-91-05781 (1991).
16. Wada, S., Saito, Y., Kaku, K., Neuz, M. & Shigematsu, S., *Annual Meeting of Pesticide Society of Japan* (1992) 15 (in Japanese).
17. Bender, M. L. & Silver, M. S., *J. Am. Chem. Soc.*, **84** (1962) 4589–90.
18. Shimizu, M., Nakayama, I., Nakao, T., Takahashi, S., Tamaru, M., Wada, N., Nezu, Y. & Abe, H., *Eighth Internat. Congr. Pestic. Chem.*, Washington, DC, 1994, 9B-669.