Synthesis and Herbicidal Activity of 2-Difluoromethylthio-1,3,5-triazines

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Forty-one 2-difluoromethylthio-1,3,5-triazines were synthesized and their herbicidal activities were evaluated under pot conditions. Some of them showed high potential as useful herbicides against weeds with little phytotoxicity toward crops. 2-Difluoromethylthio-4,6-bis(isopropylamino)-1,3,5-triazine (exp. code No. SSH-108) showed a particularly high specific pre-emergence herbicidal activity. Their activities and selectivities were compared with those of prometryn.

In the course of studies for the development of new herbicidal compounds, we found excellent herbicides in a series of 2-difluoromethylthio-1,3,5-triazine derivatives. Methylthio-1,3,5-triazine derivatives, such as 2-methylthio-4,6-bis(isopropylamino)-1,3,5-triazine (prometryn), display high herbicidal activity with little injury to soybean, corn, wheat and rice.¹⁾ Their action is exerted *via* inhibition of photosynthesis.¹⁾ In recent years, some pesticides containing fluorine atoms have been found to exhibit interesting activities.^{2~4)} Although a few 1,3,5-triazine derivatives containing fluorine atoms have been reported,^{5,6)} none of them have a difluoromethylthio group substituted on the triazine ring. In this paper, we describe the synthesis and herbicidal activities of a number of 2-difluoromethylthio-1,3,5-triazine derivatives with different alkylamino groups.

MATERIALS AND METHODS

Synthesis. The compounds mentioned here were prepared as outlined in Scheme 1. The reaction of cyanuric chloride (I) with amines followed by the formation of thiol (III) with thiourea was carried out according to in the literature.¹⁾ The melting points and yields of the compounds synthesized for this study are shown in Tables I, II and III. Their analytical data, proton nuclear magnetic resonance spectra (JNM, PMX-60, Nihondenshi, Japan) and infrared spectra (Hitachi 260-10, Japan) were consistent with the proposed structures. A typical procedure, *i.e.*, that for 2-difluoromethylthio-4,6-bis(isopropylamino)-1,3,5-triazine (27), is described below.

General method. According to the procedure reported by Moore,⁷⁾ to a mixture of 4.55 g (20 mmol) of 2,4-bis(isopropylamino)-6-mercapto-1,3,5-triazine, 20 ml of dioxane and 20 ml of water was added 4.2 g (100 mmol) of sodium hydroxide at 0~10°C. The mixture was stirred for 30 min and then at 55~56°C for 30 min, after which chlorodifluoromethane gas was introduced by bubbling over a period of 4 hr. The mixture was extracted with

SCHEME 1. Synthetic Route for 2-Difluoromethylthio-1,3,5-triazines.

dichloromethane, and the extract was dried over anhydrous sodium sulfate and then evaporated to obtain the residue. Purification of the residue by silica gel column chromatography gave 3.25 g (58.6%) of a crystalline product (**27**), mp 56–57°C. IR $\nu_{\max}$ (CDCl₃) cm⁻¹: 3430 (NH), 1560; NMR δ_{H} (CDCl₃): 1.20 (12H, d), 4.10 (2H, m), 5.00 (2H, s), 7.67 (1H, t, $J=56$ Hz); *Anal.* Found: C, 43.27; H, 6.22; N, 25.23; S, 11.79; F, 13.70. Calcd. for C₁₀H₁₇F₂N₃S: C, 43.31; H, 6.18; N, 25.25; S, 11.56; F, 13.70%.

Improved method. (Table I, run 6) To a mixture of 11.37 g (50 mmol) of 2,4-bis(isopropylamino)-6-mercapto-1,3,5-triazine, 34 ml of isopropanol and 11 ml of water was added 8.4 g (200 mmol) of sodium hydroxide at room temperature. The mixture was stirred at 56 ± 1°C for 30 min, and then chlorodifluoromethane gas was introduced by bubbling over a period of 3 hr. The reaction mixture, which consisted of 4% of III and 91% of IV, was worked up in the same manner as described above to give 12.00 g (86.5%) of a crystalline product (**27**).

Biological screening method. Seeds of the test plants, *Echinochloa crus-galli* (ECHCG*), *Digitaria ciliaris* (DIGSP*), *Polygonum lapathifolium* (POLLN*), *Amaranthus viridis* (AMAVI*), corn, soybean, wheat and cotton, were planted in loam in square pots. Then the planted seeds were treated with each test compound, after 10l/a dilution of a predetermined amount. The concentrations of the compounds were 2.5, 5, 10 and 20 g/a, with Tween 20 used 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 compounds against each weed and their phytotoxicities toward the crops were evaluated. The herbicidal rating score, that ranged from 0–5, was based on visual observation; zero represents no significant effect on seedling growth and 5 represents seedling death. The total phytotoxicity toward a plant was calculated as a per-

centage of the sum of the rating scores:

$$\text{Plant phytotoxicity (\%)} = \frac{\sum_{n=16} (\text{rating score})_n}{80} \times 100$$

RESULTS AND DISCUSSION

All compounds were prepared by the general method of Moore.⁷⁾ As the biological characteristics of the difluoromethylthio group were of interest, the preparation of IV was further examined. The method of Moore was reinvestigated in our laboratory, and the yield and purity of the product were considered to be inadequate for the production. Consequently, extensive studies on the difluoromethylation were undertaken. The conditions tested for the difluoromethylation of thiol (III) are given in Table I. The reactions (runs 1 and 2) using sodium methoxide or potassium *t*-butoxide in methanol or tetrahydrofuran gave a lower yield of IV than that in aqueous methanol (run 3). When the amount of chlorodifluoromethane was reduced and that of sodium hydroxide increased (run 4), the conversion proceeded more slowly than in run 3. The best yield of IV was obtained with the use of a large excess of sodium hydroxide and chlorodifluoromethane in aqueous methanol (run 5). This experimental result suggested that the reaction is initiated by the α -elimination of hydrogen chloride from chlorodifluoromethane accompanying the formation of difluorocarbene; in a side reaction, some of the car-

TABLE I. DIFLUOROMETHYLATION OF COMPOUND III TO IV (**27**, R¹=R²=iso-Pr)

Run	Substrate III (mmol)	CHClF ₂ (mmol)	Base (mmol)	Solvent	Composition of reaction mix. ^a	
					III	IV
1	4	>40	MeONa, 9	MeOH	44	53
2	4	>40	<i>t</i> -BuOK, 10	THF	59	36
3	4	>40	NaOH, 10	MeOH-H ₂ O	43	54
4	50	150	NaOH, 200	MeOH-H ₂ O	42	41
5	50	300	NaOH, 340	MeOH-H ₂ O	6	87
6	50	150	NaOH, 150	iso-PrOH-H ₂ O	4	91

^a Determined by HPLC; HPLC was performed with a Shimadzu LC-4A, Nucleosil 5 C₁₈ (Chemco Co., Ltd.) and a detector (UV 230 nm).

* Computer codes published by the Agrochemicals Division of Bayer AG.

benzene is consumed for the addition to methanol, giving the methyl difluoromethyl ether. Hence, isopropanol, which has a steric effect, was used (run 6) instead of methanol in order to reduce the amount of sodium hydroxide and chlorodifluoromethane and thus maintain a high yield. It was particularly surprising that this had an effect equal to that in the case of run 5.

As has been pointed out, the introduction of

a monoalkylamino group at the 4 and 6 positions of 2-chloro-1,3,5-triazine is of importance for potent herbicidal activity,¹⁾ this was also true in the case of 2-difluoromethylthio-1,3,5-triazines. These compounds are shown in Tables II~IV. Table II shows the effect of the 6-alkylamino groups in 4-methylaminotriazines on the phytotoxicity toward weeds and crops. With the exception of the *t*-butyl compound, high herbicidal activity was generally

TABLE II. PHYSICAL AND BIOLOGICAL PROPERTIES, AND YIELDS (FROM THIOL)
OF 6-MONOALKYLAMINO-2-DIFLUOROMETHYLTHIO-4-METHYLAMINO-
1,3,5-TRIAZINES (IV: R² = Me)

Comp. No.	R ¹	mp (°C) ^a	Yield (%)	Phytotoxicity (%)	
				Weeds	Crops
1	Me	137~138	7.2	78	6
2	Et	67.5~68.5	29.8	69	8
3	iso-Pr	58~59	46.1	80	13
4	<i>n</i> -Bu	57~58	34.2	51	5
5	<i>sec</i> -Bu	78~79	52.4	83	9
6	<i>tert</i> -Bu	101.5~102.5	38.0	55	6
7	CH(CH ₃)CH(CH ₃) ₂	—	42.7	71	6
8	CH ₂ C≡CH	103~104	32.0	71	10
9	Cyclopropyl	—	32.4	89	10

^a Melting points are uncorrected.

TABLE III. PHYSICAL AND BIOLOGICAL PROPERTIES, AND YIELDS (FROM THIOL)
OF 6-MONOALKYLAMINO-2-DIFLUOROMETHYLTHIO-4-ETHYLAMINO-
1,3,5-TRIAZINES (IV: R² = Et)

Comp. No.	R ¹	mp (°C) ^a	Yield (%)	Phytotoxicity (%)	
				Weeds	Crops
10	H	96~97	19.0	51	5
11	Et	91~92	29.1	48	3
12	iso-Pr	60~61	38.0	84	3
13	<i>n</i> -Bu	—	46.8	66	8
14	<i>sec</i> -Bu	—	54.1	91	6
15	iso-Bu	55~56	46.9	64	3
16	<i>tert</i> -Bu	88~89	55.9	79	5
17	CH(CH ₃)(CH ₂) ₂ CH ₃	—	34.3	69	6
18	(CH ₂) ₂ CH(CH ₃) ₂	39~41	34.3	65	8
19	CH(CH ₃)CH(CH ₃) ₂	—	55.8	63	5
20	(CH ₂) ₃ OCH ₃	77~78	45.0	58	4
21	<i>n</i> -Hex	—	37.7	54	4
22	C(CH ₃) ₂ CN	122~123	16.3	64	13
23	Cyclopropyl	65~66	36.7	84	15
24	Cyclopentyl	72~73	38.2	63	3

^a Melting points are uncorrected.

TABLE IV. PHYSICAL AND BIOLOGICAL PROPERTIES, AND YIELDS (FROM THIOL)
 OF 6-MONOALKYLAMINO-2-DIFLUOROMETHYLTHIO-4-ISOPROPYLAMINO-
 1,3,5-TRIAZINES (IV: R² = iso-Pr)

Comp. No.	R ¹	mp (°C) ^a	Yield (%)	Phytotoxicity (%)	
				Weeds	Crops
25	H	77~78	44.6	89	18
26	<i>n</i> -Pr	—	57.3	55	4
27	iso-Pr	56~57	58.6	94	3
28	<i>n</i> -Bu	—	60.0	70	6
29	<i>sec</i> -Bu	—	59.2	60	0
30	iso-Bu	—	57.8	69	1
31	<i>n</i> -Amyl	—	53.2	43	0
32	CH(CH ₃)(CH ₂) ₂ CH ₃	—	63.1	75	16
33	(CH ₂) ₂ CH(CH ₃) ₂	—	51.2	65	4
34	CH(CH ₃)CH(CH ₃) ₂	—	45.4	46	9
35	(CH ₂) ₂ CN	125.5~126.5	27.6	45	8
36	CH ₂ CH=CH ₂	—	50.8	69	1
37	(CH ₂) ₃ OCH ₃	—	54.2	73	5
38	Cyclopropyl	59~60	31.1	78	10
39	Cyclopentyl	—	49.4	54	3
40	Cyclohexyl	—	56.7	79	9
41	C(CH ₃) ₂ CN	—	7.5	75	1

^a Melting points are uncorrected.

TABLE V. PLANT PHYTOTOXICITIES OF COMPOUND (27) AND PROMETRYN

	Concentration (g/a)	ECHCG	DIGSP	POLLN	AMAVI	Corn	Soybean	Wheat	Cotton
(27)	20	5	5	5	5	0	2	0	0
	10	5	5	5	5	0	0	0	0
	5	3	5	5	5	0	0	0	0
	2.5	2	5	5	5	0	0	0	0
Prometryn	20	5	5	5	5	0	1	0	0
	10	2	5	5	5	0	0	0	0
	5	2	1	3	2	0	0	0	0
	2.5	1	0	3	2	0	0	0	0

associated with derivatives in which the alkyl chain was branched, as in compounds (3), (5), (7) and (9). In contrast, compounds containing an unbranched alkyl, as in (2) and (4), showed low herbicidal activity, except when the methylamino substituent was involved (1). The data for the 4-ethylamino series shown in Table III indicate a similar structural requirement, as in compounds (12), (14), (23) and (24). Table IV for the 4-isopropylamino series suggests that the biological activity in this series is very similar to that found in the

other two series. The compounds with a cyclopropylamino group, (9), (23) and (38), showed high herbicidal activity, but relatively high phytotoxicity toward crops was also observed. The compound containing an unsubstituted amino group (25) exhibited high phytotoxicity. The high herbicidal activity toward weeds and the low phytotoxicity toward crops might require the optimum hydrophobicity and a large size of substituents.

Among the 41 compounds tested, the 4,6-bis(isopropylamino) derivative (27) was the

most favorable compound with respect to both a broad herbicidal spectrum and crop selectivity. All the weed species tested were more susceptible to compound (27) than prometryn, and few effects were seen on crops (Table V). This compound (27, SSH-108) is currently under field evaluation for corn, wheat, soybean and other crops. For a better understanding of the structural requirements of this series of compounds, a study on the quantitative structure-activity relationships was conducted, which will be reported in another paper.

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