Synthesis of 6-Substituted 3,5-Diaryl-1,2,4-triazines as Potential Herbicidal Agents

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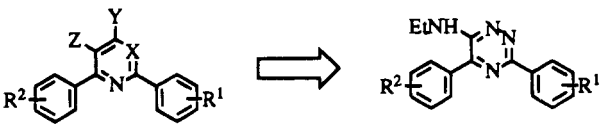
A variety of 6-substituted 3,5-diaryl-1,2,4-triazines were synthesized. These diaryltriazines, which incorporate a triazine nucleus substituted by two aryl moieties, comprise a new class of bleaching herbicides. The structure–activity relationships were proved by introducing a variety of substituents into the triazine and/or two aryl groups. The results indicated very specific structure requirements for herbicidal activity. Highest activity was seen with compounds that contain three substituents: a chlorine group at a meta position of an aryl moiety at the triazine 5-position, a fluorine group at the meta or para position of the other aryl moiety at the 3-position, and an ethylamino group at the 6-position of the triazine nucleus.

Keywords: *Triazines; herbicides; synthesis*

A novel series of 1,2,4-triazine derivatives is one of the most interesting chemical branches for biological activity (Schmidt et al., 1975; Westphal et al., 1976). In our synthetic studies on the 1,2,4-triazine heterocycles (Sanemitsu, 1986; Sagi et al., 1989), we have recently disclosed herbicidal activity in 3-dimethylamino-4*H*-[1,2,4]triazino[5,6-*b*]indoles (Mizutani et al., 1987), fungicidal property of 5-aryl-1,2,4-triazines (Konno et al., 1988) and platelet aggregation inhibitory activity of 3-substituted 5, 6-diaryl-1,2,4-triazines (Konno et al., 1992).

In view of our desire to develop new herbicidal agents of high potency, we required access to 6-substituted 3,5-diaryl-1,2,4-triazines in relation to the structure similarity of herbicidal 2,6-diarylazines (**I**) (Figure 1) (Kawamura et al., 1991, 1993). A search of the literature failed to reveal methodology which would be flexible to allow the rapid introduction of a variety of substituents in the 6-position of this ring system. An effective solution to this synthetic problem led to the discovery of 3,5-diaryl-6-ethylamino-1,2,4-triazine (**II**) as new phytotoxic compounds. In contrast to the numerous reports of 1,3,5-triazine herbicides (Jäger, 1983), little attention has previously been paid to the herbicidal activity of 1,2,4-triazine heterocycles. Here, the synthesis, structure–activity relationships, and structural lead optimization of this novel heterocycle are reported.



I, X = N and/or CH II

Figure 1.

EXPERIMENTAL PROCEDURES

Synthesis. All melting points were determined on a Yazawa BY-2 micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken at 60 MHz with a JOEL JNM-PMX 60 spectrometer. Tetramethylsilane was used as internal standard. Chemical shifts are expressed in d values. The following abbreviations are used: s, singlet; d, doublet; q, quartet; and m, multiplet.

*General Procedure for 3,5-Diaryl-1,2,4-triazines (**4**) and 3,6-Diaryl-1,2,4-triazines (**5**).* To a solution of arylamidrazone (**3**, 20 mmol) in MeOH (20 mL) at 5 °C was added dropwise a solution of arylglyoxal (**2**, 20 mmol) prepared by oxidation (Konno et al., 1988) of substituted acetophenones (**1**, 20 mmol) with selenium oxide in MeOH (10 mL). After the addition, which required about 5 min, the reaction mixture was kept at 5 °C for 24 h and then allowed to remain at room temperature for 24 h. After removal of MeOH in vacuo, the residue was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford the pure products **4** and **5** (Table 1).

*General Procedure for 3,5-Diaryl-1,2,4-triazine 1-Oxides (**6**).* A solution of 3,5-diaryl-1,2,4-triazine (**4**, 10 mmol) in $CHCl_3$ (200 mL) was portionwise added to a solution of *m*-chloroperbenzoic acid (12 mmol) in $CHCl_3$ (100 mL) at room temperature, and the reaction mixture was allowed to stand in the dark at room temperature for 48 h. After addition of $Ca(OH)_2$ (50 mmol) into the reaction mixture, the mixture was stirred at room temperature for 1 h and the precipitate was removed by filtration. The filtrate was washed with H_2O, 10% K_2CO_3 and saturated aqueous NaCl and dried over K_2CO_3. After removal of the solvent, the residue was crystallized from AcOEt giving the pure product (**6**) (Table 2).

*General Procedure for 3,5-Diaryl-6-chloro-1,2,4-triazines (**8**).* A suspension of 3,5-diaryl-1,2,4-triazine 1-oxide (**6**, 5 mmol) in phosphoryl chloride (10 mL) was heated under reflux for 5 h under stirring. The reaction mixture was concentrated to dryness under reduced pressure and a small amount of cold H_2O was added to the residue. The mixture was extracted with $CHCl_3$ and the organic layer was washed successively with H_2O, 5% NH_4OH, and saturated aqueous NaCl solution, and dried over K_2CO_3. After removal of the solvent, the residue was purified by column chromatography on active alumina (Sumitomo KCG) using benzene as an eluent. Recrystallization from *n*-hexane–AcOEt gave pure product (**8**) as pale yellow prisms (Table 3).

*General Procedure for 6-(N-Substituted-amino)-3,5-diaryl-1,2,4-triazines (**9a–u**, **9j$_1$–j$_4$**, **9k**, and **9k$_1$**).* A solution of

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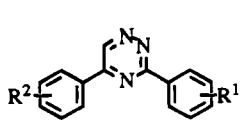
Table 1. Physical Properties of 3,5-Diaryl-1,2,4-triazines (4) and 3,6-Diaryl-1,2,4-triazines (5)



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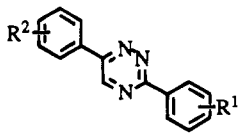

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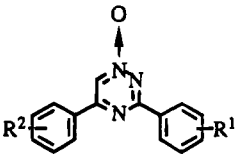
				^{1}H NMR ($CDCl_3$)	
no.	R^1	R^2	mp (°C)	yield (%)	5-H or 6-H
4a	H	H	97–98[a]	51	9.59
5a	H	H	158–160[a]	16	9.04
4b	H	*o*-Me	65–66	64	9.33
5b	H	*o*-Me	93–94	0.7	8.78
4c	H	*o*-Cl	119–120	56	9.65
5c	H	*o*-Cl	89–90	4	9.12
4d	H	*m*-Me	89–90	55	9.58
5d	H	*m*-Me	107–108	7	9.03
4e	H	*m*-Cl	112–113	58	9.60
5e	H	*m*-Cl	161–162	15	9.03
4f	H	*p*-Me	127–128	62	9.57
5f	H	*p*-Me	156–157	4	9.03
4g	H	*p*-Cl	167–168	57	9.57
5g	H	*p*-Cl	197–198	8	9.00
4h	*p*-Br	H	124–125	76	9.57
5h	*p*-Br	H	193–194	9	9.00
4i	*o*-F	*m*-Cl	86–88	44	9.60
5i	*o*-F	*m*-Cl	116–118	13	9.13
4j	*m*-F	*m*-Cl	115–116	48	9.73
5j	*m*-F	*m*-Cl	164–165	7	9.13
4k	*p*-F	*m*-Cl	174–175	52	9.57
5k	*p*-F	*m*-Cl	188–189	12	9.03
4l	*p*-Cl	*m*-Cl	154–155	47	9.57
5l	*p*-Cl	*m*-Cl	200–201	9	9.00
4m	*p*-Br	*m*-Cl	154–155	47	8.89
5m	*p*-Br	*m*-Cl	212–213	8	8.75
4n	*p*-CF_3	*m*-Cl	122–123	39	9.67
5n	*p*-CF_3	*m*-Cl	166–169	11	9.20
4o	*p*-F	*m*-CF_3	177–178	39	9.63
5o	*p*-F	*m*-CF_3	146–147	11	9.10
4p	*p*-Cl	*m*-CF_3	159–169	41	9.63
5p	*p*-Cl	*m*-CF_3	169–170	12	9.06
4q	*p*-Br	*m*-CF_3	178–179	44	9.58
5q	*p*-Br	*m*-CF_3	176–177	13	9.05
4r	*p*-CF_3	*m*-CF_3	172–173	47	9.63
5r	*p*-CF_3	*m*-CF_3	154–155	14	9.20
4s	*p*-F	*o*-Me	75–77	56	9.26
5s	*p*-F	*o*-Me	130–133	1	8.73
4t	*p*-F	*p*-Me	154–155	39	9.53
5t	*p*-F	*p*-Me	182–184	2	8.96
4u	*p*-F	*p*-Cl	189–190	51	9.54
5u	*p*-F	*p*-Cl	190–192	6	8.73

[a] See Neunhoeffer et al. (1969).

6-chloro-3,5-diaryl-1,2,4-triazine (**8**, 4 mmol) and the corresponding amine (4 mmol) in dioxane (2 mL) was heated in a sealed tube at 150 °C for 2 h. After removal of the solvent, a small amount of H_2O was added to the residue. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with H_2O, dried over $MgSO_4$. Removal of the solvent gave the crude product, which was purified by silica gel chromatography (*n*-hexane–ether, 1:1) leaving pure product (**9a–u**, **9j$_1$–j$_4$**, **9k**, and **9k$_1$**) as pale yellow prisms (Table 4).

*General Procedure for 6-Alkoxy-3,5-diaryl-1,2,4-triazines (**9j$_5$**, **9j$_6$**, and **9k$_2$**).* A solution of 6-chloro-3,5-diaryl-1,2,4-triazine (**8**, 3 mmol) in the corresponding alcohol (10 mL) was added to a solution of sodium alkoxide (prepared from metallic sodium (0.08 g, 3.6 mg atom) and corresponding alcohol (5 mL)), and the mixture was refluxed for 2 h. After removal of the solvent, a small amount of H_2O was added to the residue and the reaction mixture was extracted with CH_2Cl_2. The product, isolated from the CH_2Cl_2 extract, was purified by recrystallization from *n*-hexane–AcOEt yielding pure product (**9j$_5$**, **9j$_6$**, and **9k$_2$**) (Table 4).

Table 2. Physical Properties of 3,5-Diaryl-1,2,4-triazine 1-Oxides (6)



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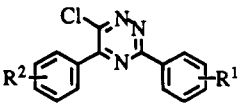
no.	R^1	R^2	mp (°C)	yield (%)
6a	H	H	183–184	97
6b	H	*o*-Me	136–137	96
6c	H	*o*-Cl	145–146	93
6d	H	*m*-Me	142–143	95
6e	H	*m*-Cl	157–158	99
6f	H	*p*-Me	212–213	98
6g	H	*p*-Cl	211–212	99
6h	*p*-Br	H	228–229	94
6i	*o*-F	*m*-Cl	159–161	83
6j	*m*-F	*m*-Cl	164–165	81
6k	*p*-F	*m*-Cl	179–180	70
6l	*p*-Cl	*m*-Cl	169–170	71
6m	*p*-Br	*m*-Cl	188–189	85
6n	*p*-CF_3	*m*-Cl	139–140	85
6o	*p*-F	*m*-CF_3	175–176	88
6p	*p*-Cl	*m*-CF_3	168–169	53
6q	*p*-Br	*m*-CF_3	178–179	97
6r	*p*-CF_3	*m*-CF_3	167–168	99
6s	*p*-F	*o*-Me	158–159	97
6t	*p*-F	*p*-Me	210–211	98
6u	*p*-F	*p*-Cl	250–252	74

Table 3. Physical Properties of 3,5-Diaryl-6-chloro-1,2,4-triazines (8)

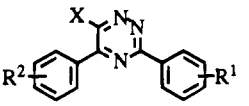


8

no.	R^1	R^2	mp (°C)	yield (%)
8a	H	H	102–103[c]	60
8b	H	*o*-Me	104–105	2
8c	H	*o*-Cl	154–155	17
8d	H	*m*-Me	77–78	65
8e	H	*m*-Cl	116–117	52
8f	H	*p*-Me	121–122	61
8g	H	*p*-Cl	111–112	64
8h	*p*-Br	H	130–131	48
8i	*o*-F	*m*-Cl	89–91	30
8j	*m*-F	*m*-Cl	105–106	41
8k	*p*-F	*m*-Cl	128–129	45
8l	*p*-Cl	*m*-Cl	139–140	55
8m	*p*-Br	*m*-Cl	134–135	33
8n	*p*-CF_3	*m*-Cl	120–121	24
8o	*p*-F	*m*-CF_3	105–106	43
8p	*p*-Cl	*m*-CF_3	109–110	67
8q	*p*-Br	*m*-CF_3	119–120	35
8r	*p*-CF_3	*m*-CF_3	80–81	28
8s	*p*-F	*o*-Me	83–84	37
8t	*p*-F	*p*-Me	145–146	64
8u	*p*-F	*p*-Cl	154–156	58

*Preparation of 6-(Ethylthio)-5-(3-chlorophenyl)-3-(3-fluorophenyl)-1,2,4-triazine (**9j$_7$**).* To a solution of 6-chloro-5-(3-chlorophenyl)-3-(3-fluorophenyl)-1,2,4-triazine (**8**, 4 mmol) and ethanethiol (4.2 mmol) in THF (10 mL) was added portionwise NaH, 60% in oil (0.16 g, 4.2 mmol), and the reaction mixture was refluxed for 1 h. Similar treatment as that of 6-alkoxy-3,5-diaryl-1,2,4-triazine described above resulted in the formation of a crude product which was recrystallized from *n*-hexane–AcOEt yielding pure product (**9j$_7$**) (Table 4).

Table 4. Physical Properties of 6-Substituted 3,5-Diaryl-1,2,4-triazines (9)



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no.	R^1	R^2	X	mp (°C)	yield (%)	^{1}H NMR ($CDCl_3$)[a]
9a	H	H	NHEt	87–89	80	1.27 (3H, t J = 7 Hz), 3.60 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9b	H	*o*-Me	NHEt	158–159	87	1.23 (3H, tg, J = 7 Hz), 2.27 (3H, s), 3.63 (2H, q, J = 7 Hz), 4.3–4.7 (1H, br)
9c	H	*o*-Cl	NHEt	149–150	84	1.28 (3H, t, J = 7 Hz), 3.68 (2H, q, J = 7 Hz), 4.2–4.7 (1H, br)
9d	H	*m*-Me	NHEt	121–122	76	1.32 (3H, t, J = 7 Hz), 2.48 (3H, s), 3.68 (2H, q, J = 7 Hz), 4.8–5.3 (1H, br)
9e	H	*m*-Cl	NHEt	147–148	94	1.32 (3H, t, J = 7 Hz), 3.78 (2H, q, J = 7 Hz), 4.7–5.2 (1H, br)
9f	H	*p*-Me	NHEt	142–143	89	1.30 (3H, t, J = 7 Hz), 2.47 (3H, s), 3.68 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9g	H	*p*-Cl	NHEt	95–96	97	1.30 (3H, t, J = 7 Hz), 3.63 (2H, q, J = 7 Hz), 4.7–5.0 91H, br)
9h	*p*-Br	H	NHEt	103–104	74	1.32 (3H, t, J = 7Hz), 3.65 (2H, q, J = 7 Hz), 4.80–5.20 (1H, br)
9i	*m*-F	*m*-Cl	NHEt	110–111	37	1.33 (3H, t, J = 7 Hz), 3.45 (2H, q, J = 7 Hz), 4.6–5.1 (1H, br)
9j	*m*-F	*m*-Cl	NHEt	147–148	99	1.33 (3H, t, J = 7 Hz), 3.62 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9j$_1$	*m*-F	*m*-Cl	NHMe	152–154	60	3.23 (3H, d, J = 5 Hz), 4.8–5.2 (1H, br)
9j$_2$	*m*-F	*m*-Cl	NH-*n*-Pr	114–115	82	0.9 (3H, t, J = 7 Hz), 1.3–1.6 (2H, m), 3.52 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9j$_3$	*m*-F	*m*-Cl	NH-*i*-Pr	133–134	55	1.33 (3H, d, J = 7 Hz), 4.3–5.0 (1H, m), 5.0–5.2 (1H, br)
9j$_4$	*m*-F	*m*-Cl	NH-*n*-Bu	116–118	86	1.00 (3H, d, J = 7 Hz), 1.2–2.0 (4H, m), 3.63 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9j$_5$	*m*-F	*m*-Cl	OMe	97–98	98	4.31 (3H, s)
9j$_6$	*m*-F	*m*-Cl	OEt	113–114	47	1.60 (3H, t, J = 7 Hz), 4.83 (2H, q, J = 7 Hz)
9j$_7$	*m*-F	*m*-Cl	SEt	141–142	71	1.38 (3H, t, J = 7Hz), 3.18 (2H, q, J = 7 Hz)
9k	*m*-F	*p*-F	NHEt	162–163	82	1.28 (3H, t, J = 7Hz), 3.62 (2H, q, J = 7 Hz), 4.8–5.1 (1H, br)
9k$_1$	*m*-F	*p*-F	NH-*n*-Pr	140–141	82	1.00 (3H, s), 1.50–2.00 (2H, m), 3.62 (2H, q), 4.80–5.10 (1H, br)
9k$_2$	*m*-F	*p*-F	OMe	142–143	82	4.30 (3H, s)
9l	*p*-Cl	*m*-Cl	NHEt	163–164	57	1.30 (3H, t, J = 7 Hz), 3.66 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9m	*p*-Br	*m*-Cl	NHEt	152–153	89	1.30 (3H, t, J = 7 Hz), 3.67 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9n	*p*-CF_3	*m*-Cl	NHEt	98–100	59	1.33 (3H, t, J = 7 Hz), 3.73 (2H, q, J = 7 Hz), 4.9–5.3 (1H, br)
9o	*p*-F	*m*-CF_3	NHEt	158–159	84	1.33 (3H, t, J = 7 Hz), 3.75 (2H, q, J = 7 Hz), 4.8–5.1 (1H, br)
9p	*p*-Cl	*m*-CF_3	NHEt	131–132	75	1.30 (3H, t, J = 7 Hz), 3.68 (2 H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9q	*p*-Br	*m*-CF_3	NHEt	130–131	80	1.30 (3H, t, J = 7 Hz), 3.68 (2H, q, J = 7 Hz), 4.8–5.1 (1H, br)
9r	*p*-CF_3	*m*-CF_3	NHEt	128–130	73	1.31 (3H, t, J = 7 Hz), 3.72 (2H, q, J = 7 Hz), 4.8–5.2 (1H, br)
9s	*p*-F	*o*-Me	NHEt	90–92	29	1.30 (3H, t, J = 7 Hz), 2.28 (3H, s), 3.61 (2H, q, J = 7 Hz), 4.4–4.8 (1H, br)
9t	*p*-F	*p*-Me	NHEt	140–141	84	1.31 (3H, t, J = 7 Hz), 2.47 (3H, s), 3.63 (2H, q, J = 7 Hz), 4.9–5.2 (1H, br)
9u	*p*-F	*p*-Cl	NHEt	114–118	76	1.37 (3H, t, J = 7 Hz), 3.67 (2H, q, J = 7Hz), 4.8–5.2 (1H, br)

[a] All aromatic ring protons are observed at δ 7.00–8.72.

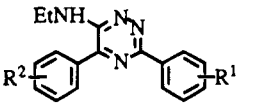
Biological Testing. The pre- and postemergent herbicide evaluations were conducted on all target compounds from the series mentioned above. The test species included in these evaluations were Japanese millet (*Echinochloa frumentacea*), wild oat (*Avena fatua*), garden radish (*Raphanus sativus*), morningglory (*Ipomea hederacea*), and velvetleaf (*Abutilon theophrasti*). An emulsifiable concentrate is 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 activity of the compound was determined by visual observation of the tested plants in comparison with untreated controls. These observations are reported on a scale of 0 (no effect)–10 (death of plants).

Preemergent Tests. Cylindrical plastic pots (diameter 10 cm, height 10 cm) were filled with upland field soil, and the seeds of the above test vegetation. A designed amount of the test compound formulated in an emulsifiable concentrate was diluted with water, and the dilution was sprayed onto the soil surface, by a small hand sprayer at a spray volume of 10 L/are. The plants were grown in a greenhouse for 20 days, and the herbicidal activity of the compound was determined.

Postemergent Tests. Cylindrical plastic pots (diameter 10 cm, height 10 cm) were filled with upland field soil, and the seeds of the above test vegetation were planted. The plants were grown in a greenhouse for 10 days. A designed amount of the test compound formulated in an emulsifiable concentrate, was diluted with water containing Rinoh (purchased from Nihon Noyaku Co., Ltd.) as a spreader (0.1%). The dilution was sprayed over the foliage of the test plants, by a small hand sprayer at a spray volume of 10 L/are. The plants were grown in a greenhouse for 20 days, and the herbicidal activity of the compound was determined.

The herbicidal activities presented in Tables 5–7 are average control ratings for all five species tested at rates of

Table 5. Substitution Effects on 3,5-Diaryl-6-(ethylamino)-1,2,4-triazines for Pre- and Postemergence Herbicidal Activities



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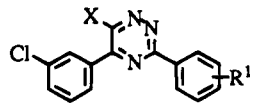
			activity[a]	
no.	R^1	R^2	preemergence	postemergence
9a	H	H	5.0	2.8
9b	H	*o*-Me	0	1.0
9c	H	*o*-Cl	0	1.5
9d	H	*m*-Me	1.0	4.5
9e	H	*m*-Cl	3.7	7.8
9f	H	*p*-Me	0	2.5
9g	H	*p*-Cl	3.5	7.0
9h	*p*-Br	H	0	4.8
9i	*o*-F	*m*-Cl	5.0	8.3
9j	*m*-F	*m*-Cl	6.2	8.5
9k	*p*-F	*m*-Cl	6.8	9.3
9l	*p*-Cl	*m*-Cl	4.2	5.5
9m	*p*-Br	*m*-Cl	3.0	4.8
9n	*p*-CF_3	*m*-Cl	0.5	4.0
9o	*p*-F	*m*-CF_3	6.9	9.0
9p	*p*-Cl	*m*-CF_3	4.8	6.5
9q	*p*-Br	*m*-CF_3	2.5	4.8
9r	*p*-CF_3	*m*-CF_3	1.0	4.3
9s	*p*-F	*o*-Me	0	3.0
9t	*p*-F	*p*-Me	0	0.3
9u	*p*-F	*p*-Cl	1.7	2.0

[a] Average control at 20 g/are for all species tested.

Table 6. Postemergence Herbicidal Activities of 6-Substituted 5-(3-Chlorophenyl)-3-(3- and 4-fluorophenyl)triazines

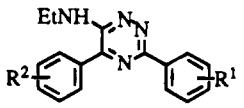


4 and 9

no.	R^1	X	activity[a]
4j	*m*-F	H	4.8
8j	*m*-F	Cl	4.5
9j	*m*-F	NHEt	8.5
9j$_1$	*m*-F	NHMe	6.0
9j$_2$	*m*-F	NH-*n*-Pr	6.3
9j$_3$	*m*-F	NH-*i*-Pr	3.3
9j$_4$	*m*-F	NH-*n*-Bu	1.3
9j$_5$	*m*-F	OMe	2.3
9j$_6$	*m*-F	OEt	2.0
9j$_7$	*m*-F	SEt	5.3
9k	*p*-F	NHEt	9.3
9k$_1$	*p*-F	NH-*n*-Pr	6.3
9k$_2$	*p*-F	OMe	2.6

[a] Average control at 20 g/are for all species tested.

Table 7. Postemergence Herbicidal Activities of 3,5-Diaryl-6-(ethylamino)-1,2,4-triazines (9)



9

			activity[a]		
no.	R^1	R^2	20 g/are	5 g/are	1.25 g/are
9e	H	*m*-Cl	7.8	3.1	1.8
9g	H	*p*-Cl	7.0	2.9	0.8
9i	*o*-F	*m*-Cl	8.3	5.5	4.2
9j	*m*-F	*m*-Cl	8.5	7.9	7.0
9k	*p*-F	*m*-Cl	9.3	8.5	7.9
9o	*p*-F	*m*-CF_3	9.0	5.3	4.0

[a] Average control for all species tested.

20, 5, and 1.25g/are for both the preemergence and postemergence tests.

RESULTS AND DISCUSSION

Chemical Studies. The synthetic approach to the title compounds is outlined in Schemes 1 and 2. Substituted arylgloxals (**2**) were selected as a key material from which to develop the basic methodology. All of the glyoxal species employed in this study were directly prepared through an oxidation of substituted acetophenones (**1**) with selenium(IV) dioxide according to the known method (Konno et al., 1988). Typically the resultant arylglyoxals were used without further purification, and formation of the glyoxals was conveniently monitored by TLC.

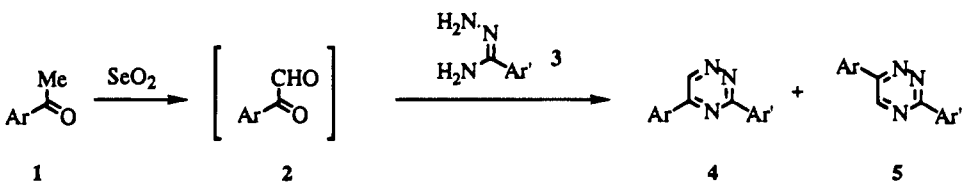
Successively, cyclocondensation of compounds (**2**) with arylamidrazones (**3**) in dry methanol at 5 °C for 24 h afforded mainly the desired 3,5-diaryl-1,2,4-triazines (**4**), accompanied with minor formation of 3,6-diaryl-1,2,4-triazines (**5**) (Neunhoeffer et al., 1969). Their structural assignments for each compound were based on ^{1}H NMR data. The H-6 proton of compounds **4** resonated at δ 9.50–9.67, which is in agreement with literature data (Neunhoeffer et al., 1969), and ~0.6 ppm more upfield from TMS than the H-5 proton of compounds **5**. In the majority of cases examined, the entire sequence from acetophenones to 3,5-diaryl-1,2,4-triazines could be conveniently done in one pot without isolation or purification of intermediates (Scheme 1).

To introduce a variety of substituents at the 6-position in the triazine nucleus, we prepared 3,5-diaryl-6-chloro-1,2,4-triazines (**8**), which afford the title compounds on treatment with various nucleophiles (Scheme 2). Reaction of 3,5-diaryl-1,2,4-triazines (**4**) with *m*-chloroperbenzoic acid in chloroform for 2 days afforded only single products. The compounds (**6**) have the expected molecular formula, indicating the introduction of an oxygen atom in **4**. *A priori* one might expect to get either N-1 or N-2 oxygenated products (**6** or **7**). Distinction between structure (**6**) for the product and the alternative **7** by ^{1}H and ^{13}C NMR spectroscopic analyses was unsuccessful. Therefore, single-crystal X-ray determination was undertaken in order to solve this problem. The result shows the final X-ray model for **6h** confirming the absolute structure to be 3-(4-bromophenyl)-5-phenyl-1,2,4-triazine 1-oxide (vide ante).

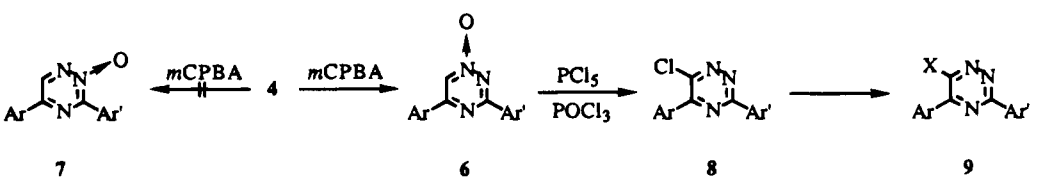
Further transformation of N-1 oxides (**6**) into the requisite 3,5-diaryl-6-chloro-1,2,4-triazines (**8**) was achieved through nucleophilic addition–elimination reactions upon treatment with a mixture of phosphorous pentachloride and phosphoryl chloride in fair yields. Like many other active N-heteroaryl halides, the compounds (**8**) readily reacted with O, N, and S nucleophiles such as alkoxides and amines to give the corresponding 6-alkoxy or 6-N-substituted amino derivatives (**9**) in good yields, respectively.

Biological Evaluations. Compounds of this family were active both postemergence and preemergence producing bleaching symptoms (Table 5). At postemer-

Scheme 1



Scheme 2



gent application, the chlorotic symptoms induced of the affected species can not be observed in primary leaves as usual but only secondary and later leaves become chlorotic, about 2–3 days after application, resulting in severe necrosis. They were generally more effective when foliarly applied, as in postemergence application and demonstrated greater activity against broadleaf weeds than grass weeds. In Tables 5–7 averaged herbicidal data are summarized on the following broadleaf plants and grasses; garden radish (*Raphanus sativus*), velvetleaf (*Abutilon theophrasti*), morning-glory (*Ipomoea hederacea*), Japanese millet (*Echinochloa frumentacea*), and wild oats (*Avena fatua*).

Pre- and postemergence activities at 20 g/are for a number of substituted 3,5-diaryl-6-(ethylamino)-1,2,4-triazines, with substitution varied on both phenyl moieties, are reported in Table 5. Meta-substitution on one phenyl ring (R^2) at the 5-position was preferred over ortho- or para-substitutions, and a chlorine group (**9e**) was found to be an optimum meta substituent. Alkyl substitution was also investigated but these analogs (**9b**, **9d**, and **9f**) were generally less active, irrespective of the substitution position.

Next, the optimization in the other phenyl ring (R^1) was carried out while keeping the R^2 chlorine or trifluoromethyl group at the meta position. It is evident from Table 5 that an introduction of a fluorine group (**9i**, **9j**, **9k**, and **9o**) enhanced the herbicidal activity. Especially the *m*- and the *p*-fluoro derivatives (**9k** and **9o**) showed the highest activity. In a series of para derivatives, an introduction of other halogens (**9l**, **9p**, **9m**, and **9q**) and the trifluoromethyl group (**9n** and **9r**) showed decreased herbicidal activity.

Furthermore, the substitution effect at the triazine 6-position on the herbicidal activity was proved by introducing a variety of substituents in the triazine nucleus of diaryltriazines with optimum substitution in each phenyl ring (where R^1 = *m*-F, R^2 = *m*-Cl and R^1 = *p*-F, R^2 = *m*-Cl). The substitution requirements at the triazine 6-position were quite specific (Table 6). The introduction of an alkylamino group showed higher herbicidal activity than unsubstituted derivative (**4j**). The most active analogues in this series were 6-ethylamino derivatives (**9j** and **9k**). In alkylamino derivatives, the activities fell off rapidly with increasing length of alkyl chain. On the other hand, the introduction of the other substituents such as a chlorine (**8j**), ethoxy ($\mathbf{9j_6}$), or ethylthio ($\mathbf{9j_7}$) groups decreased the herbicidal activity.

Finally, Table 7 shows a comparison of six of the most active compounds at rates of 20, 5, and 1.25 g/are. The highest activity was shown by compounds (**9i** and **9k**) with a chlorine substituent at the meta position of an aryl moiety at triazine 5-position, a fluorine at the meta and/or para of the other, and an ethylamino group at the 6-position.

Biochemical studies on these diaryltriazines are under investigation and will be reported in the future.

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