# Synthesis and Herbicidal Activity of Some 2,4-Diarylpyrimidines

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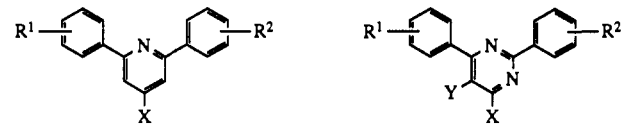
A novel series of substituted 2,4-diarylpyrimidines was synthesized and found to possess bleaching herbicidal activity. These diarylpyrimidines, which incorporate a pyrimidine nucleus substituted by two aryl moieties, are new chemical families of bleaching herbicides. The structure–activity relationships were probed by substitution of the pyrimidine and/or aryl groups. Highest activity was seen with compounds that contain three substituents: a trifluoromethyl group at a meta position of an aryl moiety at the pyrimidine 4-position, a fluorine or trifluoromethyl group at the para position of the other at the 2-position, and a methoxy group at the 5-position.

In our continuing studies in the search for biologically active heterocycles, we have disclosed that a series of 2,6-diarylpyridines I (Figure 1) show potent herbicidal activity (Kawamura et al., 1991). The biochemical studies led to the conclusion that their primary mode of action is direct inhibition of phytoene desaturase (Böger et al., 1989), which results in decreased biosynthesis of colored carotenoids (Babczinski et al., 1992).

In connection with a program directed toward further development of new herbicides, we focused on the diarylpyrimidines II (Figure 1) in relation to the structural similarity of diarylpyridines I. On the basis of the limited structure–activity relationships of 2,6-diarylpyridines I, 6-(3-chlorophenyl)-4-(methylthio)-2-phenylpyrimidine (**5a**) was prepared and tested for herbicidal activity. Compound **5a** exhibited moderate postemergent herbicidal activity. This result encouraged us to examine a systematic screening study on diarylpyrimidine herbicides. The herbicidal activities of diarylpyrimidines were found to be superior to that of diarylpyridines. Here, we now report the syntheses and structure–activity relationships of some diarylpyrimidines.



Diarylpyridines I Diarylpyrimidines II

**Figure 1.**

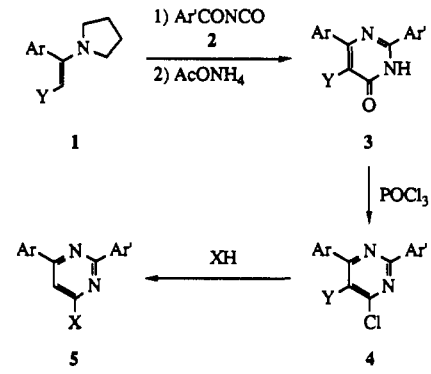
## EXPERIMENTAL PROCEDURES

**Synthesis.** Enamines (Haynes, 1969) and benzoyl isocyanates (Speziale and Smith, 1963) were prepared according to the literature. All melting points were measured by using a Metler FP61 (automatic melting point apparatus) and are uncorrected. $^1$H NMR spectra were recorded on a Hitachi R-24B (60 MHz) spectrometer using TMS as an internal reference; chemical shifts are expressed in $\delta$ values. Mass spectra were obtained on a Hitachi M-80 instrument (EI, 70 eV). Microanalytical data were provided by Sumika Analysis Center (Osaka).

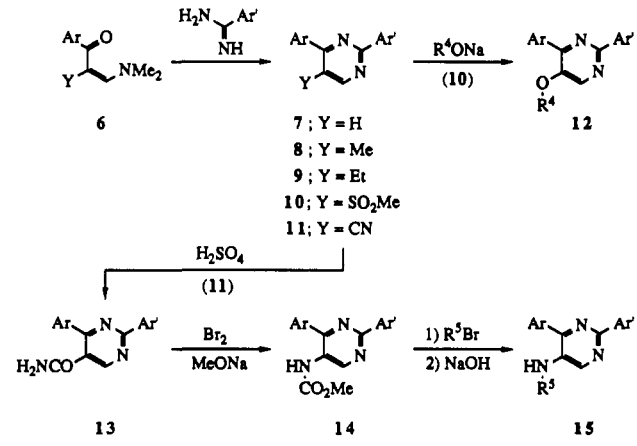
*6-Substituted and 5,6-Disubstituted 2,4-Diarylpyrimidines (Scheme I).* Diarylpyrimidin-4(3*H*)-ones (**3**) were chosen as a key intermediate to prepare 6-substituted and 5,6-disubstituted 2,4-diarylpyrimidines (**5**). A novel synthesis of compounds **3** was accomplished through a one-pot reaction starting from enamines (**1**) (Kawamura and Sanemitsu, 1991). Reaction of enamines (**1**) with benzoyl isocyanates (**2**) followed by treatment with ammonium acetate yielded 2,6-diarylpyrimidin-4(3*H*)-ones (**3**), which were converted into the corresponding 4-chloro derivatives (**4**) in excellent yields upon treatment with phosphorus oxychloride. Nucleophilic displacement of compounds **4** with various nucleophiles, such as alkoxides or amines, afforded 4-alkoxy or 4-amino derivatives (**5**).

*5-Substituted 2,4-Diarylpyrimidines (Scheme II).* 5-Substituted 2,4-diarylpyrimidines (**7**–**11**) were synthesized from the reaction of 3-(dimethylamino)-1-phenylpropenones (**6**) with benzamidines according to the well-known methods (Abdulla et al., 1979; Takahashi et al., 1986). On the other hand, each of

**Scheme I**



**Scheme II**



5-alkoxy (**12**) or 5-amino (**15**) derivatives were derived from the corresponding 5-methylsulfonyl (**10**) or 5-cyano (**11**) derivatives, respectively. Namely, reaction of 5-methylsulfonyl derivatives (**10**) with sodium alkoxides effected the nucleophilic displacement to afford 5-alkoxy derivatives (**12**) in excellent yields. To prepare 5-amino derivatives (**15**), 5-(methoxycarbonyl)amino derivatives (**14**) were prepared via Hofmann rearrangement of amide derivatives (**13**), which were easily prepared from acid hydrolysis of cyano derivatives (**11**). Successively, direct alkylation of

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compounds 14 with alkyl bromides followed by alkaline hydrolysis provided 5-amino derivatives (15) in good yields.

*General Procedure for the Preparation of 2,6-Diarylpyrimidin-4(3H)-ones* (3). To a solution of 1-pyrrolidinylstyrene derivative (1, 10 mmol) in THF (50 mL) was added dropwise benzoyl isocyanate (2, 10 mmol) in THF (10 mL) at 0 °C. After the mixture was stirred for 30 min at 0 °C, ammonium acetate (3.90 g, 50 mmol) in AcOH (10 mL) was added. The reaction mixture was refluxed for 2 h with continuous removal of THF. Then the solution was cooled to room temperature and diluted with water (100 mL). The resultant precipitate was collected and purified by recrystallization to afford the pure product 3.

*6-(3-Chlorophenyl)-2-phenylpyrimidin-4(3H)-one* (3a): yield 87%; mp 260.8 °C (from AcOH–MeOH); $^1$H NMR ($CF_3CO_2D$) δ 7.06 (s, 1 H), 7.50–8.28 (m, 9 H); MS *m/z* 282 ($M^+$).

Anal. Calcd for $C_{16}H_{11}N_2OCl$: C, 68.0; H, 3.9; N, 9.9. Found: C, 67.7; H, 3.8; N, 9.8.

*6-(3-Chlorophenyl)-5-methyl-2-phenylpyrimidin-4(3H)-one* (3b): yield 88%; mp 203.5 °C (from AcOH–MeOH); $^1$H NMR ($CF_3CO_2D$) δ 2.36 (s, 3 H), 7.20–8.20 (m, 9 H); MS *m/z* 296 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2OCl$: C, 68.8; H, 4.4; N, 9.4. Found: C, 68.8; H, 4.4; N, 9.5.

*6-(3-Chlorophenyl)-5-methoxy-2-phenylpyrimidin-4(3H)-one* (3c): yield 87%; mp 240.2 °C (from AcOH–*i*-PrOH); $^1$H NMR ($CF_3CO_2D$) δ 4.03 (s, 3 H), 7.50–8.23 (m, 9 H); MS *m/z* 312 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2O_2Cl$: C, 65.3; H, 4.2; N, 9.0. Found: C, 65.4; H, 4.2; N, 9.0.

*General Procedure for the Preparation of 4-Chloro-2,6-diarylpyrimidines* (4). The appropriate pyrimidin-4(3*H*)-one (3, 5 mmol) was dissolved in phosphorus oxychloride (5 mL), and the mixture was refluxed for 2 h. After removal of an excess of phosphorus oxychloride under reduced pressure, the residue was dissolved in $Et_2O$ (100 mL). The organic phase was washed with water and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by recrystallization to give pure product 4.

*4-Chloro-6-(3-chlorophenyl)-2-phenylpyrimidine* (4a): yield 96%; mp 114.2 °C (from hexane–EtOAc); $^1$H NMR ($CDCl_3$) δ 7.28–7.65 (m, 6 H), 7.71–8.20 (m, 2 H), 8.25–8.66 (m, 2 H); MS *m/z* 300 ($M^+$).

Anal. Calcd for $C_{16}H_{10}N_2Cl_2$: C, 63.8; H, 3.4; N, 9.3. Found: C, 63.9; H, 3.1; N, 9.3.

*4-Chloro-6-(3-chlorophenyl)-5-methyl-2-phenylpyrimidine* (4b): yield 87%; mp 117.5 °C (from hexane–EtOAc); $^1$H NMR ($CDCl_3$) δ 2.37 (s, 3 H), 7.20–7.64 (m, 7 H), 8.20–8.68 (m, 2 H); MS *m/z* 314 ($M^+$).

Anal. Calcd for $C_{17}H_{12}N_2Cl_2$: C, 64.8; H, 3.8; N, 8.9. Found: C, 64.7; H, 4.0; N, 8.9.

*4-Chloro-6-(3-chlorophenyl)-5-methoxy-2-phenylpyrimidine* (4c): yield 92%; mp 92.0 °C (from hexane–EtOAc); $^1$H NMR ($CDCl_3$) δ 3.71 (s, 3 H), 7.30–7.70 (m, 5 H), 7.96 (m, 4 H); MS *m/z* 330 ($M^+$).

Anal. Calcd for $C_{17}H_{12}N_2OCl_2$: C, 61.7; H, 3.7; N, 8.5. Found: C, 61.7; H, 3.8; N, 8.6.

*General Procedure for the Preparation of 4-Substituted 2,6-Diarylpyrimidines* (5). A mixture of appropriate 4-chloro derivative (4, 5 mmol) and sodium alkoxide (sodium methanethiolate or amines) (5.5 mmol) in methanol (100 mL) was heated at 80 °C for 1 h, and then methanol was distilled off. The residue was poured onto ice–water. The resultant precipitate was collected and purified by recrystallization, yielding pure product 5.

*6-(3-Chlorophenyl)-4-(methylthio)-2-phenylpyrimidine* (5a): yield 86%; mp 127.1 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 2.70 (s, 3 H), 7.22–7.58 (m, 6 H), 7.70–8.15 (m, 2 H), 8.42–8.62 (m, 2 H); MS *m/z* 312 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2N_2SCl$: C, 65.3; H, 4.2; N, 9.0. Found: C, 65.4; H, 4.1; N, 8.9.

*6-(3-Chlorophenyl)-4-methoxy-2-phenylpyrimidine* (5b): yield 89%; mp 118.6 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 4.08 (s, 3 H), 6.88 (s, 1 H), 7.25–7.60 (m, 5 H), 7.55–8.21 (m, 2 H), 8.40–8.70 (m, 2 H); MS *m/z* 296 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2OCl$: C, 68.8; H, 4.4; N, 9.4. Found: C, 68.9; H, 4.5; N, 9.5.

*6-(3-Chlorophenyl)-4-(methylamino)-2-phenylpyrimidine* (5c): yield 87%; mp 119.5 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 2.78 (d, *J* = 6 Hz, 3 H), 5.18 (b q, *J* = 6 Hz, 1 H), 6.25 (s, 1 H), 7.05–7.56 (m, 5 H), 7.69–7.96 (m, 1 H), 8.05 (s, 1 H), 8.14–8.62 (m, 2 H); MS *m/z* 295 ($M^+$).

Anal. Calcd for $C_{17}H_{14}N_3Cl$: C, 69.0; H, 4.8; N, 14.2. Found: C, 69.1; H, 4.9; N, 14.1.

*4-(Dimethylamino)-6-(3-chlorophenyl)-2-phenylpyrimidine* (5d): yield 86%; mp 113.6 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 3.18 (s, 6 H), 7.25–7.63 (m, 5 H), 7.26–8.18 (m, 2 H), 8.35–8.68 (m, 2 H); MS *m/z* 309 ($M^+$).

Anal. Calcd for $C_{18}H_{16}N_3Cl$: C, 69.8; H, 5.2; N, 13.6. Found: C, 69.6; H, 5.2; N, 13.5.

*6-(3-Chlorophenyl)-4,5-dimethoxy-2-phenylpyrimidine* (5e): yield 89%; mp 113.1 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 4.14 (s, 3 H), 7.25–7.55 (m, 5 H), 7.90–8.20 (m, 2 H), 8.28–8.56 (m, 2 H); MS *m/z* 326 ($M^+$).

Anal. Calcd for $C_{18}H_{15}N_2O_2Cl$: C, 66.2; H, 4.6; N, 8.6. Found: C, 66.3; H, 4.6; N, 8.6.

*6-(3-Chlorophenyl)-4-methoxy-5-methyl-2-phenylpyrimidine* (5f): yield 93%; mp 110.1 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 2.16 (s, 3 H), 4.05 (s, 3 H), 4.05 (s, 3 H), 7.02–7.68 (m, 7 H), 8.19–8.55 (m, 2 H); MS *m/z* 310 ($M^+$).

Anal. Calcd for $C_{18}H_{15}N_2OCl$: C, 69.6; H, 4.9; N, 9.0; Cl. Found: C, 69.6; H, 4.9; N, 8.9.

*6-(3-Chlorophenyl)-5-methyl-4-(methylamino)-2-phenylpyrimidine* (5g): yield 88%; mp 161.3 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 2.06 (s, 3 H), 3.21 (d, *J* = 6 Hz, 2 H), 4.6 (b s, 1 H), 7.15–7.62 (m, 7 H), 8.26–8.58 (m, 2 H); MS *m/z* 309 ($M^+$).

Anal. Calcd for $C_{18}H_{16}N_3Cl$: C, 69.8; H, 5.2; N, 13.6. Found: C, 69.9; H, 5.3; N, 13.9.

*General Procedure for the Preparation of 5-Substituted 2,6-Diarylpyrimidines* (7–11). A mixture of 3-(dimethylamino)-1-phenyl-2-propen-1-one (6, 10 mmol), benzamidine hydrochloride (10 mmol), and sodium methoxide (0.60 g, 11 mmol) in MeOH (100 mL) was heated at 80 °C for 1–6 h. After removal of MeOH, the residue was poured into water (50 mL). The precipitate was collected and purified by recrystallization to afford pure products 7–11.

*6-(3-Chlorophenyl)-2-phenylpyrimidine* (7a): yield 67%; mp 72.3 °C; $^1$H NMR ($CDCl_3$) δ 7.35–7.65 (m, 6 H), 7.85–8.29 (m, 2 H), 8.45–8.72 (m, 2 H), 8.86 (d, *J* = 5 Hz, 1 H); MS *m/z* 266 ($M^+$).

Anal. Calcd for $C_{16}H_{11}N_2Cl$: C, 72.0; H, 4.2; N, 10.5. Found: C, 72.3; H, 4.4; N, 10.5.

*4-(3-Chlorophenyl)-5-methyl-2-phenylpyrimidine* (8a): yield 62%; mp 94.9 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 7.25–7.72 (m, 7 H), 8.32–8.68 (m, 2 H), 8.84 (s, 1 H); MS *m/z* 280 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2Cl$: C, 72.7; H, 4.7; N, 10.0. Found: C, 72.4; H, 4.7; N, 9.8.

*4-(3-Chlorophenyl)-5-ethyl-2-phenylpyrimidine* (9a): yield 63%; mp 76.1 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 1.18 (t, *J* = 6 Hz, 3 H), 2.72 (q, *J* = 6 Hz, 2 H), 7.15–7.65 (m, 7 H), 8.29–8.55 (s, 1 H); MS *m/z* 294 ($M^+$).

Anal. Calcd for $C_{18}H_{15}N_2Cl$: C, 73.3; H, 5.1; N, 9.5. Found: C, 73.2; H, 5.3; N, 9.6.

*4-(3-Chlorophenyl)-5-(methylsulfonyl)-2-phenylpyrimidine* (10a): yield 92%; mp 170.5 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 2.78 (s, 3 H), 7.31–7.82 (m, 7 H), 8.34–8.69 (m, 2 H), 9.40 (s, 1 H); MS *m/z* 344 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2SO_2Cl$: C, 59.2; H, 3.8; N, 8.1. Found: C, 59.0; H, 3.7; N, 8.1.

*4-(3-Chlorophenyl)-5-cyano-2-phenylpyrimidine* (11a): yield 92%; mp 161.6 °C (from EtOH); $^1$H NMR ($CDCl_3$) δ 7.28–7.68 (m, 5 H), 7.85–8.21 (m, 2 H), 8.40–8.70 (m, 2 H), 8.98 (s, 1 H); MS *m/z* 291 ($M^+$).

Anal. Calcd for $C_{17}H_{10}N_3Cl$: C, 70.0; H, 3.5; N, 14.4. Found: C, 70.0; H, 3.5; N, 14.3.

*General Procedure for the Preparation of 5-Alkoxy-2,6-diarylpyrimidines* (12). A mixture of appropriate 5-methylsulfonyl derivative (10, 5 mmol) and sodium alkoxide (5.5 mmol) in dimethoxyethane (30 mL) was heated at 80 °C for 1 h. The solvent was distilled off, and the residue was poured onto ice–water. The resultant precipitate was collected and purified by recrystallization to yield pure product 12.

*4-(3-Chlorophenyl)-5-methoxy-2-phenylpyrimidine* (12a): yield 89%; mp 99.1 °C (from *i*-PrOH); $^1$H NMR ($CDCl_3$) δ 3.98 (s, 3

H), 7.28–7.68 (m, 5 H), 7.95–8.30 (m, 2 H), 8.30–8.55 (m, 3 H); MS *m/z* 296 ($M^+$).

Anal. Calcd for $C_{17}H_{13}N_2OCl$: C, 68.8; H, 4.4; N, 9.4; Cl. Found: C, 69.0; H, 4.4; N, 9.2.

*5-Ethoxy-4-(3-chlorophenyl)-2-phenylpyrimidine (12b)*: yield 72%; mp 101.0 °C (from EtOH); $^1H$ NMR ($CDCl_3$) $\delta$ 1.48 (t, $J$ = 7 Hz, 3 H), 4.21 (q, $J$ = 7 Hz, 2 H), 7.30–7.59 (m, 5 H), 8.04–8.62 (m, 5 H); MS *m/z* 310 ($M^+$).

Anal. Calcd for $C_{18}H_{15}N_2OCl$: C, 69.6; H, 4.9; N, 9.0. Found: C, 69.4; H, 5.0; N, 9.0.

*4-(3-Chlorophenyl)-2-phenyl-5-propoxypyrimidine (12c)*: yield 83%; mp 94.4 °C (from EtOH); $^1H$ NMR ($CDCl_3$) $\delta$ 1.05 (t, $J$ = 7 Hz, 3 H), 1.79 (td, $J$ = 7, 7 Hz, 2 H), 4.08 (t, $J$ = 7 Hz, 2 H), 7.28–7.58, (m, 5 H) 8.04–8.59 (m, 5 H); MS *m/z* 324 ($M^+$).

Anal. Calcd for $C_{19}H_{17}N_2OCl$: C, 70.3 H, 5.3; N, 8.6. Found: C, 70.0; H, 5.4; N, 8.6.

The general syntheses and other examples of 5-alkoxydiarylpyrimidines were reported in a European patent (Sato et al., 1990).

*4-(3-Chlorophenyl)-5-[(methoxycarbonyl)amino]-2-phenylpyrimidine* (**14a**). A solution of **11a** (2.91 g, 10 mmol) in $H_2SO_4$ (5 mL) was heated for 2 h at 100 °C. The mixture was poured into ice–water and cautiously neutralized with aqueous NaOH. The resultant precipitate (**13**) was collected. To a solution of crude product (**13**) and sodium methoxide (2.89 g of 28% methanol solution, 30 mmol) in MeOH (20 mL) was added bromine (2.40 g, 15 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature. After removal of MeOH in vacuo, the residue was extracted with EtOAc. The organic phase was washed with aqueous $Na_2S_2O_3$ and dried over anhydrous $MgSO_4$. The residue obtained by removal of the solvent was purified by column chromatography on silica gel (hexane/EtOAc, 3:1). Recrystallization from *i*-PrOH gave 2.81 g (83%) of **14a** as a white solid: mp 170.4 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.80 (s, 3 H), 6.60–6.80 (b, 1 H), 7.32–7.90 (m, 7 H), 8.28–8.56 (m, 2 H), 9.38 (s, 1 H); MS *m/z* 339 ($M^+$).

Anal. Calcd for $C_{18}H_{14}N_3O_2Cl$: C, 63.6; H, 4.2; N, 12.4. Found: C, 63.6; H, 4.1; N, 12.5.

*General Procedure for the Preparation of 5-Amino-2,6-diarylpyrimidines* (**15**). To an ice-cold solution of **14a** (10 mmol) in DMF (50 mL) was added slowly sodium hydride (0.44 g of a 60% oil dispersion, 11 mmol) while cooling. After 30 min, alkyl bromide (11 mmol) was added dropwise at 0 °C, and the solution was stirred for 2 h at room temperature. The reaction mixture was poured into water. The resultant precipitate was collected and directly added to a mixture of NaOH (2.0 g) in MeOH (50 mL), and the mixture was refluxed for 24 h. After removal of MeOH, the mixture was poured onto ice–water, and the resultant precipitate was collected and purified by recrystallization to give the pure product **15**.

*5-Amino-4-(3-chlorophenyl)-2-phenylpyrimidine (15a)*: prepared without alkylation; yield 78%; mp 146.6 °C (from EtOH); $^1H$ NMR ($CDCl_3$) $\delta$ 3.5–4.2 (b, 2 h), 7.25–7.96 (m, 7 H), 8.22–8.56 (s, 1 H); MS *m/z* 281 ($M^+$).

Anal. Calcd for $C_{16}H_{12}N_3Cl$: C, 68.2; H, 4.3; N, 14.9. Found: C, 68.1; H, 4.5; N, 14.9.

*4-(3-Chlorophenyl)-5-(methylamino)-2-phenylpyrimidine (15b)*: yield 78%; mp 153.2 °C (from EtOH); $^1H$ NMR ($CDCl_3$) $\delta$ 2.89 (d, $J$ = 5 Hz, 3 H), 4.12 (b, 1 H), 7.12–7.82 (m, 7 H), 8.12–8.47 (m, 3 H); MS *m/z* 295 ($M^+$).

Anal. Calcd for $C_{17}H_{14}N_3OCl$: C, 69.0 H, 4.8; N, 14.2. Found: C, 68.9; H, 4.9; N, 14.2.

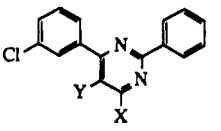
*4-(3-Chlorophenyl)-5-(ethylamino)-2-phenylpyrimidine (15c)*: yield 73%; mp 133.2 °C (from *i*-PrOH); $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (t, $J$ = 6 Hz, 3 H), 3.18 (dt, $J$ = 6 Hz, 2 H), 3.96 (bs, 1 H), 7.24–7.75 (m, 7 H), 8.10–8.40 (m, 3 H); MS *m/z* 309 ($M^+$).

Anal. Calcd for $C_{18}H_{16}N_3Cl$: C, 69.8; H, 5.2; N, 13.6. Found: C, 69.7; H, 5.3; N, 13.6.

*4-(3-Chlorophenyl)-5-(propylamino)-2-phenylpyrimidine (15d)*: yield 73%; mp 108.6 °C (from EtOH); $^1H$ NMR ($CDCl_3$) $\delta$ 0.97 (t, $J$ = 6 Hz, 3 H), 1.66 (q, $J$ = 6 Hz, 2 H), 3.14 (q, $J$ = 6 Hz, 2 H), 4.05 (bs, 1 H), 7.25–7.80 (m, 7 H), 8.15–8.45 (m, 3 H); MS *m/z* 323 ($M^+$).

Anal. Calcd for $C_{19}H_{18}N_3Cl$: C, 70.5; H, 5.6; N, 13.0. Found: C, 70.3; H, 5.6; N, 13.0.

**Table I. Pre- and Postemergence Herbicidal Activities of 4- and/or 5-Substituted Diarylpyrimidines**




| | | | dose giving 70% phytotoxicity, g/are | | | | |
|---|---|---|---|---|---|---|---|
| | | | pre-emergent | | postemergent | | |
| no. | X | Y | Japanese millet | velvetleaf | Japanese millet | garden radish | velvetleaf |
| **7a** | H | H | >80 | >80 | >80 | >80 | >80 |
| **3a** | OH | H | >80 | >80 | >80 | >80 | >80 |
| **4a** | Cl | H | >80 | >80 | >80 | >80 | >80 |
| **5a** | SMe | H | >80 | >80 | 80 | 20 | 20 |
| **5b** | OMe | H | >80 | >80 | 80 | 20 | 20 |
| **5c** | NHMe | H | 40 | >80 | >80 | <5 | 5 |
| **5d** | $NMe_2$ | H | >80 | >80 | >80 | >80 | >80 |
| **8a** | H | Me | >80 | >80 | 20 | <5 | 16 |
| **9a** | H | Et | 80 | >80 | 8 | <5 | <5 |
| **10a** | H | $SO_2Me$ | >80 | >80 | >80 | >80 | >80 |
| **11a** | H | CN | >80 | >80 | >80 | >80 | >80 |
| **12a** | H | OMe | 20 | 35 | <5 | <5 | <5 |
| **12b** | H | OEt | 80 | 80 | 20 | 20 | >80 |
| **12c** | H | O-*n*-Pr | >80 | >80 | >80 | 10 | >80 |
| **14a** | H | $NHCO_2Me$ | >80 | >80 | >80 | >80 | 20 |
| **15a** | H | $NH_2$ | >80 | >80 | >80 | 80 | 20 |
| **15b** | H | NHMe | >80 | >80 | 80 | 50 | 5 |
| **15c** | H | NHEt | 80 | >80 | 10 | <5 | <5 |
| **15d** | H | NH-*n*-Pr | >80 | >80 | 65 | <5 | <5 |
| **3b** | OH | Me | >80 | >80 | >80 | >80 | >80 |
| **3c** | OH | OMe | >80 | >80 | >80 | >80 | >80 |
| **4b** | Cl | Me | >80 | >80 | >80 | >80 | >80 |
| **4c** | Cl | OMe | >80 | >80 | >80 | >80 | >80 |
| **5e** | OMe | OMe | >80 | >80 | >80 | >80 | >80 |
| **5f** | OMe | Me | >80 | >80 | >80 | >80 | >80 |
| **5g** | NHMe | Me | >80 | >80 | >80 | >80 | >80 |

**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*), garden radish (*Raphanus sativus*), and velvetleaf (*Abutilon theophrasti*). An emulsifiable concentrate is prepared by mixing 10 parts of the compound, 14 parts of poly(oxyethylene) 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. The dose giving 70% phytotoxicity was determined by interpolation of control rating plots plotted against the log of the test doses.

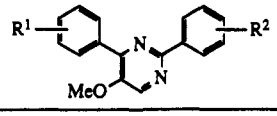
*Preemergent Tests.* Cylindrical plastic pots (diameter 10 cm, height 10 cm) were filled with upland field soil, and the seeds of Japanese millet and velvetleaf were planted. A designed amount of the test compound formulated in an emulsifiable concentrate was diluted with water, and the dilution was 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 Japanese millet, garden radish, and velvetleaf 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.

## RESULTS AND DISCUSSION

In general, a series of diarylpyrimidines exhibits slight to moderate preemergent herbicidal activity and good postemergent herbicidal activity on grass and broadleaf

**Table II. Pre- and Postemergence Herbicidal Activities of 5-Methoxy-2,4-diarylpyrimidines**



| | | | dose giving 70% phytotoxicity, g/are | | | | |
|---|---|---|---|---|---|---|---|
| | | | pre-emergent | | postemergent | | |
| no. | $R^1$ | $R^2$ | Japanese millet | velvet-leaf | Japanese millet | garden radish | velvet-leaf |
| **12c** | H | H | >80 | >80 | >80 | >80 | >80 |
| **12d** | o-$CF_3$ | H | >80 | >80 | >80 | >80 | >80 |
| **12e** | o-$CH_3$ | H | >80 | >80 | >80 | >80 | >80 |
| **12f** | m-F | H | 13 | >80 | <5 | <5 | 5 |
| **12a** | m-Cl | H | 20 | 35 | <5 | <5 | 11 |
| **12g** | m-$CF_3$ | H | 5 | 13 | <5 | <5 | <5 |
| **12h** | p-Cl | H | >80 | >80 | >80 | >80 | >80 |
| **12i** | p-$CH_3$ | H | >80 | >80 | >80 | >80 | >80 |
| **12j** | m-$CF_3$ | o-F | 80 | >80 | 20 | 20 | 80 |
| **12k** | m-$CF_3$ | o-$CF_3$ | >80 | >80 | >80 | >80 | >80 |
| **12l** | m-$CF_3$ | m-F | 10 | 80 | <5 | <5 | <5 |
| **12m** | m-$CF_3$ | m-$CF_3$ | 20 | >80 | <5 | <5 | <5 |
| **12n** | m-$CF_3$ | p-F | <5 | <5 | <5 | <5 | <5 |
| **12o** | m-$CF_3$ | p-Cl | 40 | 35 | <5 | <5 | <5 |
| **12p** | m-$CF_3$ | p-$CF_3$ | <5 | <5 | <5 | <5 | <5 |
| **12q** | m-$CF_3$ | p-$CH_3$ | 10 | 20 | <5 | <5 | <5 |
| Ia[a] | | | >80 | >80 | 38 | <5 | <5 |

[a] Ia, 4-(methylthio)-2-[3-(trifluoromethyl)phenyl]-6-[4-(trifluoromethyl)phenyl]pyridine.

species at 5 g/are. At postemergent application, the chlorotic symptoms cannot be observed in primary leaves, only secondary and later leaves become chlorotic, about 2–3 days after application, resulting in severe necrosis. Similarly, this phenomenon was also observed in 2,6-diarylpyridines.

First, 5- and/or 6-substituted 4-(3-chlorophenyl)-2-phenylpyrimidines were prepared to examine the substituent effect at the pyrimidine nucleus on herbicidal activity. The pre- and postemergence herbicidal activities are summarized in Table I. In the series of 6-substituted derivatives, methylthio (**5a**), methoxy (**5b**), and methylamino (**5c**) derivatives showed higher herbicidal activity than unsubstituted derivative **7a**. On the other hand, the nature of the substituent at the pyrimidine 5-position is critical to the herbicidal activity. Electron-donating substituents such as ethyl (**9a**), methoxy (**12a**), and alkylamino (**15c,d**) groups greatly enhanced the herbicidal activity. The most active analogue in this series was 5-methoxy derivative (**12a**). In alkoxy derivatives (**12a–c**), the activities fell off rapidly with increasing length of the alkyl chain. On the other hand, the introduction of electron-withdrawing substituents such as methylsulfonyl (**10a**) and cyano (**11a**) groups decreased the herbicidal activity. In contrast to these results, all 5,6-disubstituted derivatives (**3b, 4b,c,** and **5e–g**) showed a complete loss of activity, irrespective of the nature of the substituents.

Next, we investigated the effect of varying the nature and position of the substituents in both phenyl rings, using compounds with a methoxy group at the pyrimidine 5-position (Table II). The results show that the substituents in two phenyl rings are very important for activity. For one phenyl ring at the pyrimidine 4-position, a meta substituent (**12a,f,g**) enhanced herbicidal activity, while ortho (**12d,e**) or para (**12h,i**) substituents gave a reduction or complete loss of activity. In the meta-substituted derivatives, a trifluoromethyl derivative (**12g**) showed outstanding activity. The optimization in the other benzene ring ($R^2$) was carried out while keeping the $R^1$ trifluoromethyl group at the meta position. It is evident from Table II that a para-fluoro derivative (**12n**) and a para-(trifluoromethyl) derivative (**12p**) exhibited highest herbicidal activity, while meta substitution appeared to have only a modest effect on herbicidal activity. Also, ortho substitution (**12j,k**) showed decreased herbicidal activity.

The optimized compounds (**12n,p**) showed higher herbicidal activity than Ia ($R^1$ = 3-$CF_3$; $R^2$ = 4-$CF_3$; X = $SCH_3$), which is the most active analogue in diarylpyridines I (Kawamura et al., 1991). Biochemical studies on diarylpyrimidines are under investigation and will be reported in the future.

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