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Synthesis and Herbicidal Activity of 2-Cyano-3-substituted-pyridinemethylaminoacrylates

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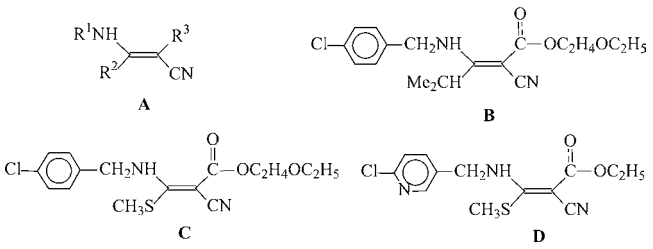
Two series of 2-cyano-3-substituted-pyridinemethylaminoacrylates, namely 12 new (*Z*)-2-cyano-3-methylthio-3-substituted-pyridinemethaneaminoacrylates and 10 new (*Z*)-2-cyano-3-alkyl-3-substituted-pyridinemethaneaminoacrylates, were synthesized as herbicidal inhibitors of photosystem II (PSII) electron transport. All of these compounds were confirmed by ^{1}H NMR, elemental, IR, and mass spectrum analyses. Their herbicidal activities were evaluated. Some compounds exhibited excellent herbicidal activities, even at a dose of 75 g/ha. A suitable substituent at the 2-position of the pyridine ring and the well-fit group at the 3-position of acrylate were essential for high herbicidal activity. 2-Cyanoacrylates containing a substituted pyridine ring provide higher herbicidal activities than parent compounds containing phenyl. These PSII inhibitor herbicides are safe to corn, which is a major crop in China.

KEYWORDS: 2-Cyanoacrylates; substituted pyridinemethaneamino; herbicidal activity; inhibitors of PSII electron transport

INTRODUCTION

The herbicidal activity of cyanoacrylates has been the subject of intense interest for past decades (*1*−*3*). A detailed study of compounds with general structure **A** revealed that cyanoacrylates are inhibitors of photosystem II (PSII) electron transport, which inhibits the growth of weeds by disrupting photosynthetic electron transport at a common binding domain on the 32 kD polypeptide of the PSII reaction center. Among these cyanoacrylates, the compund **B** exhibits the highest inhibitory activity of the Hill reaction yet reported (*4*−*6*). Bayer AG reported compound **C**, but little information was given on herbicidal activity (*7*). It has been reported that the D1 protein of PSII is the herbicide binding site, and the benzyl group of cyanoacrylate fits into the hydrophobic domain of the site maximizing van der Waals ring-stacking interactions with aromatic amino acids (Phe 211, Phe 255, and Tyr 262) flanking this part of the binding domain (*8*−*10*). However, the complete nature and topography of this hydrophobic domain of the D1 protein are unknown, and cyanoacrylates have not commercialized as herbicides because of their high dose rates.

In our previous work on the synthesis of **D**, we reported that **D** (*11*, *12*) showed some insecticidal activity and excellent herbicidal activity, controlling more than 90% of rape (*Brassica napus*) at 150 g/ha. At the same time, we noticed that the compound **D** was also one analogue of structure **A**, which encouraged us to introduce substituted pyridine heterocycles into 2-cyanoacrylates and further study the relationship of structure−herbicidal activity. We are reporting the synthesis of two series of new 2-cyanoacrylates by the replacement of the phenylmethylamino with substituted pyridine methylamino and testing of them for herbicidal activity.



MATERIALS AND METHODS

Synthetic Procedures. All reactions were carried out under a nitrogen atmosphere with the exclusion of moisture. Proton NMR spectra were obtained at 200 MHz using a Bruker AC-P 200 spectrometer. Chemical shift values (δ) are given in ppm and downfield from internal tetramethylsilane. Infrared spectra were recorded on a Shimadzu-435 spectrometer. Elemental analyses were determined on an MT-3 elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and were uncorrected. Mass spectra were recorded with HP 5988A spectrometer using the EI method. Column chromatographic purification was carried out by using silica gel.

Structure Determination. A colorless crystal of approximate dimensions of 0.15 mm × 0.20 mm × 0.25 mm of the target compound **7e** was mounted on a glass fiber in a random orientation. The

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preliminary examination and data collection were performed on an ENRAF-NONIUS CAD-4 diffractometer with Mo Kα radiation (λ = 0.71073 Å) using the $\omega/2\theta$ scan technique at 25 ± 2 °C. A total of 3200 independent reflections were collected in the range of $1.58° \leq \theta \leq 25.03°$, of which 2168 reflections with $I \geq 3\sigma(I)$ were considered to be observed. The multiscan absorption correction was applied. The correction for Lp factors was made by the SADABS program. Final *R* and *Rw* values are 0.0516 and 0.1594, respectively ($\omega = 1/(\sigma 2(F) + 99.0000F^2)$), and S =1.024, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.368$e/Å^3, and $\Delta\rho_{min} = -0.318$e/Å^3. All calculations were performed on a PDP11/44 and Pentium MMX/166 computer using the SDP PLUS program system.

General Synthetic Procedure for 2-Alkoxy-5-pyridinemethaneamines (2a−d). To absolute alcohol (30 mL) cooled with an ice water bath was added metal sodium (1.12 g, 49 mmol). After the sodium disappeared, 2-chloro-5-pyridinemethaneamine (**1**; 2.5 g, 17.5 mmol) was added, and then, the solution was heated under reflux for 16−48 h. Excessive alcohol was evaporated in a vacuum. Water was then added to the residue, and the products were extracted with chloroform. The combined organic layer was dried over anhydrous sodium sulfate. Thereafter, the drying agent was removed by filtration and the solvent was evaporated in a vacuum to afford **2a**−**d**, which were used directly without further purification.

General Synthetic Prodedure for 3a−d. *(Z + E)-2-Cyano-3-methoxyacrylates (**3a**,**b**).* To a mixture of ethoxylethyl 2-cyanoacetate (3.93 g, 0.025 mol), triethylamine (5.05 g, 0.05 mol), magnesium chloride (2.37 g, 0.025 mol), and anhydrous acetonitrile (25 mL) was added acid chloride (0.025 mol) under an ice salt bath. The reaction was continued for 5 h, and the solvent was evaporated. To the residue was added 5 N aqueous hydrochloric acid solution (20 mL) and ether (50 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and distilled under reduced pressure to give a colorless liquid (without further purification).

The gas of diazomethane (0.013 mol) synthesized from 1.32 g of α-nitroso-α-methylurea according to the reported method (*13*) was dissolved in a solution of ethoxylethyl 2-propionyl-2-cyanoacetate (1.07 g, 0.005 mol) in anhydrous ether (10 mL). The reaction mixture was stirred for 12 h. Evaporation of the solvent afforded a yellow oil (without further purification).

*(Z + E)-2-Cyano-3-alkoxyacrylates (**3c**,**d**).* The mixture of ethoxylethyl 2-cyanoacetate (8.0 g, 48.4 mmol), triethyl orthoacetate or orthoformate (61.6 mmol), and acetic acid (0.15 g, 2.5 mmol) was heated under reflux for 2.5 h. The solvent was evaporated under reduced pressure to afford a yellow oil, which was purified by column chromatography using a silica gel. A colorless liquid was obtained.

General Synthetic Procedure for Esters 4a−d. A mixture of cyanoacetic acid (25.5 g, 23.8 mmol), alkanol (31.5 mmol), sodium bisulfate monohydrate (0.7 g, 5.1 mmol), and toluene (15 mL) was placed in a flask equipped with a Dean Stark trap carrying a reflux condenser at its upper end and then heated under reflux. The reaction was not stopped until no more water was collected in appreciable amounts in the water separator. The mixture was filtered, and the filtration was washed with 10% sodium dicarbonate and brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to afford the corresponding esters.

Synthesis of Amide 4e. To the solution of cyanoacetic acid (8.51 g, 0.1 mol) in anhydrous ether (100 mL), phosphorus pentachloride (20.9 g, 0.1 mol) was added gradually. After the addition was completed, the reaction was continued for 0.5 h. The ether and phosphorus oxychloride were evaporated under vacuum, and the residue was cooled for immediate use in the following step.

Dry morpholine (17.4 g, 0.2 mol) was placed in a flask containing anhydrous ether (100 mL). The acid chloride was added dropwise to the stirred solution cooled on an ice bath. The reaction mixture was stirred gently at room temperature for 3 h and filtered. The solvent was evaporated in a vacuum, and the residual solid was recrystallized from ethanol to give pure product.

General Synthetic Procedure for Esters 4f,g. A mixture of sodium cyanoacetate (8.50 g, 80 mmol) and an equivalent amount of ethyl 2-bromide acetate (80 mmol) in *N*,*N*-dimethylformamide (100 mL) was heated to 90 °C for 4 h. *N*,*N*-Dimethylformamide was evaporated in a vacuum, and ethyl acetate (100 mL) was added to the residue. The solid was filtered, and the filtrate was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated in a vacuum, and the residual liquid was distilled to afford the corresponding esters.

General Synthetic Procedures for 2-Cyano-3,3-dimethylthioacrylates (5a−g). Compound **4** (20 mmol) was added dropwise to a mixture of potassium hydroxide powder (2.24 g, 40 mmol) and anhydrous acetonitrile (30 mL) at 5 °C. The mixture was stirred for 0.5 h, and then, a solution of carbon disulfide (1.50 g, 20 mmol) in anhydrous acetonitrile (5 mL) was added over about 10 min. The reaction mixture was stirred for 3 h at room temperature. After the solution was cooled to 4 °C, dimethyl sulfate (5.04 g, 40 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure, and then, water (25 mL) and ethyl acetate (50 mL) were added to the residue. The organic layer was separated and dried with anhydrous magnesium sulfate. Ethyl acetate was evaporated to afford corresponding **5a**−**g**.

General Synthetic Procedure for Target Compounds 6a−l. The mixture of intermediate **5** (5 mmol), substituted pyridinemethaneamine **2** (6 mmol), and ethanol (12 mL) was refluxed for 3 h and then evaporated under reduced pressure to give crude product. The product was purified by vacuum column chromatography on a silica gel.

Data for 6a. Yield, 77.3%; mp, 74−75 °C. ^{1}H NMR ($CDCl_3$): δ 2.67 (s, 3H, SCH_3), 4.64 (d, 2H, CO_2CH_2), 4.76 (d, 2H, CH_2N), 5.32 (q, 2H, C=CH_2), 5.98 (m, 1H, CH=C), 7.34−8.32 (m, 3H, C_5H_3N), 10.4 (w, 1H, NH). Anal. found: C, 51.73; H, 4.34; N, 12.92. Calcd for $C_{14}H_{14}ClN_3O_2S$: C, 51.93; H, 4.36; N, 12.98.

Data for 6b. Yield, 81.5%; mp, 53.5−55 °C. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, CH_3), 3.22 (q, 2H, SCH_2), 4.64 (d, 2H, CO_2CH_2), 4.78 (d, 2H, CH_2N), 5.32 (q, 2H, C=CH_2), 5.98 (m, 1H, CH=C), 7.31−8.32 (m, 1H, CH=C), 10.4 (w, 1H, NH). Anal. found: C, 52.97; H, 4.62; N, 12.18. Calcd for $C_{15}H_{16}ClN_3O_2S$: C, 53.33; H, 4.78; N, 12.44.

Data for 6c. Yield, 74.3%. ^{1}H NMR ($CDCl_3$): δ 1.99 (m, 4H, CH_2), 2.66 (s, 3H, SCH_3), 3.82 (m, 3H, OCH, OCH_2), 4.16 (d, 2H, CO_2-CH_2), 4.76 (d, 2H, CH_2N), 7.34−8.32 (m, 3H, C_5H_3N), 10.4 (w, 1H, NH). Anal. found: C, 51.98; H, 5.21; N, 11.56. Calcd for $C_{16}H_{18}$-ClN_3O_3S: C, 52.24; H, 4.93; N, 11.43.

Data for 6d. Yield, 80.3%; mp, 92−93 °C. ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 3H, SCH_3), 3.59−3.72 (m, 8H, $2OCH_2$, $2NCH_2$), 4.70 (d, 2H, CH_2N), 7.31−8.30 (m, 3H, C_5H_3N), 10.9 (w, 1H, NH). Anal. found: C, 50.88; H, 4.75; N, 15.63. Calcd for $C_{15}H_{17}ClN_4O_2S$: C, 51.08; H, 4.86; N, 15.89.

Data for 6e. Yield, 66.1%; mp, 109−110 °C. ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, SCH_3), 3.75 (s, 3H, CO_2CH_3), 4.67 (s, 2H, $CO_2CH_2CO_2$), 4.75 (d, 2H, CH_2N), 7.34−8.33 (m, 3H, C_5H_3N), 10.3 (w, 1H, NH). Anal. found: C, 46.98; H, 3.77; N, 11.72. Calcd for $C_{16}H_{18}ClN_3O_3S$: C, 47.26; H, 3.97; N, 11.81.

Data for 6f. Yield, 49.6%; mp, 87−89 °C. ^{1}H NMR ($CDCl_3$): δ 1.46 (t, 3H, CH_3), 2.71 (s, 3H, SCH_3), 4.20 (q, 2H, CO_2CH_2), 4.65 (s, 2H, $CO_2CH_2CO_2$), 4.75 (d, 2H, CH_2N), 7.31−8.30 (m, 3H, C_5H_3N), 10.2 (w, 1H, NH). Anal. found: C, 48.82; H, 4.30; N, 11.26. Calcd for $C_{17}H_{20}ClN_3O_3S$: C, 48.71; H, 4.33; N, 11.37.

Data for 6g. Yield, 78.6%; mp, 66−67.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H, CH_2CH_3), 2.67 (s, 3H, SCH_3), 3.53 (q, 2H, OCH_2), 3.66 (t, 2H, CH_2O), 3.93 (s, 3H, OCH_3), 4.25 (t, 2H, CO_2CH_2), 4.68 (d, 2H, CH_2N), 6.74−8.07 (m, 3H, C_5H_3N), 10.2 (w, 1H, NH). Anal. found: C, 54.54; H, 5.77; N, 11.71. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.70; H, 6.03; N, 11.97.

Data for 6h. Yield, 73.3%; mp, 63.5−65 °C. ^{1}H NMR ($CDCl_3$): δ 1.11−1.37 (m, 6H, $2CH_3$), 2.63 (s, 3H, SCH_3), 3.49−3.65 (m, 4H, OCH_2, CH_2O), 4.20−4.32 (m, 4H, $PrOCH_2$, CO_2CH_2), 4.63 (d, 2H, CH_2N), 6.66−8.02 (m, 3H, C_5H_3N), 10.2 (w, 1H, NH). Anal. found: C, 55.72; H, 6.49; N, 11.73. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.89; H, 6.35; N, 11.51.

Data for 6i. Yield, 91.3%; yellow liquid. ^{1}H NMR ($CDCl_3$): δ 0.96 (t, 3H, $C_2H_4CH_3$), 1.14 (t, 3H, CH_2CH_3), 1.74 (m, 2H, $CH_2CH_2CH_3$), 2.63 (s, 3H, SCH_3), 3.50 (q, 2H, OCH_2), 3.63 (t, 2H, CH_2O), 4.16−4.24 (m, 4H, $PrOCH_2$, CO_2CH_2), 4.64 (d, 2H, CH_2N), 6.72−8.02 (m, 3H, C_5H_3N), 10.2 (s, 1H, NH). Anal. found: C, 56.82; H, 6.59; N, 11.07. Calcd for $C_{18}H_{25}N_3O_4S$: C, 56.96; H, 6.65; N, 11.07.

Data for 6j. Yield, 82.3%; yellow liquid. ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H, SCH_3), 3.37 (s, 3H, OCH_3), 3.62 (t, 2H, CH_2O), 4.30 (t, 2H, CO_2CH_2), 5.04 (d, 2H, CH_2N), 7.32−8.63 (m, 4H, C_5H_4N), 10.7 (w, 1H, NH). Anal. found: C, 54.44; H, 5.58; N, 13.44. Calcd for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.58; N, 13.68.

Data for 6k. Yield, 74.6%; mp, 70−71 °C. ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 3H, SCH_3), 3.65 (t, 2H, CH_2O), 4.04 (s, 3H, OCH_3), 4.28 (t, 2H, CO_2CH_2), 4.66 (d, 2H, CH_2N), 7.32−8.42 (m, 3H, C_5H_3N), 10.7 (w, 1H, NH). Anal. found: C, 53.41; H, 5.74; N, 12.58. Calcd for $C_{15}H_{19}N_3O_4S$: C, 53.41; H, 5.68; N, 12.46.

Data for 6l. Yield, 70.7%; mp, 83−84 °C. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_3), 2.67 (s, 3H, SCH_3), 3.38 (s, 3H, OCH_3), 3.61 (t, 2H, CH_2O), 4.30 (m, 4H, OCH_2), 4.67 (d, 2H, CH_2N), 6.70−8.11 (m, 3H, C_5H_3N), 10.2 (w, 1H, NH). Anal. found: C, 54.79; H, 6.11; N, 12.23. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.67; H, 6.03; N, 11.97.

General Synthetic Procedure for Target Compounds 7a−j. The mixture of intermediate **3** (6 mmol), substituted pyridinemethaneamine **2** (6 mmol), and ethanol (15 mL) was heated under reflux for 2 h. The solvent was evaporated under reduced pressure to afford crude product. The product was purified by recrystalliztion or vacuum column chromatography on a silica gel.

Data for 7a. Yield, 82.3%; mp, 92−93 °C. IR (KBr, cm^{-1}): 3379, 1661, 1270, 1106, 1590, 1491, 1459, 2198, 1259, 1055. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H, CH_2CH_3), 1.37 (d, 6H, $C(CH_3)_2$), 3.20 (m, 1H, CH), 3.54 (q, 2H, OCH_2), 3.66 (t, 2H, CH_2O), 3.93 (s, 3H, $PrOCH_3$), 4.24 (t, 2H, CO_2CH_2), 4.51 (d, 2H, CH_2N), 6.74−8.05 (m, 3H, C_5H_3N), 10.6 (s, 1H, NH). EI MS: *m*/*z* (%) 347 (M^+, 8.5), 122 (100). Anal. found: C, 62.27; H, 7.11; N, 12.15. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.27; H, 7.20; N, 12.10.

Data for 7b. Yield, 86.7%; mp, 47−49 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, OCH_2CH_3), 1.36−1.43 (m, 9H, $C(CH_3)_2$, $PrOCH_2$), 3.15 (m, 1H, CH), 3.60 (q, 2H, OCH_2), 3.68 (t, 2H, CH_2O), 4.26 (t, 2H, CO_2CH_2), 4.35 (q, 2H, $PrOCH_2$), 4.52 (d, 2H, CH_2N), 6.74−8.07 (m, 3H, C_5H_3N), 10.6 (s, 1H, NH). Anal. found: C, 63.17; H, 7.69; N, 11.74. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.12; H, 7.54; N, 11.63.

Data for 7c. Yield, 85.7%; mp, 55−56 °C. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, $C_2H_4CH_3$), 1.17 (t, 3H, OCH_2CH_3), 1.37 (d, 6H, $C(CH_3)_2$), 1.78 (m, 2H, $CH_2CH_2CH_3$), 3.15 (m, 1H, CH), 3.54 (q, 2H, OCH_2), 3.65 (t, 2H, CH_2O), 4.20−4.27 (m, 4H, $PrOCH_2$, CO_2CH_2), 4.49 (d, 2H, CH_2N), 6.73−8.04 (m, 3H, C_5H_3N), 10.5 (s, 1H, NH). Anal. found: C, 63.69; H, 7.87; N, 11.18. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.96; H, 7.80; N, 11.19.

Data for 7d. Yield, 83.2%; yellow liquid. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, $C_2H_4CH_3$), 1.14 (t, 3H, CH_2CH_3), 1.34 (d, 6H, $C(CH_3)_2$), 1.42 (m, 2H, $CH_2C_2H_4$), 1.78 (m, 2H, $CH_2C_2H_5$), 3.15 (m, 1H, CH), 3.51 (q, 2H, OCH_2), 3.62 (t, 2H, CH_2O), 4.17−4.24 (m, 4H, $PrOCH_2$, CO_2CH_2), 4.47 (d, 2H, CH_2N), 6.69−8.05 (m, 3H, C_5H_3N), 10.4 (s, 1H, NH). Anal. found: C, 64.77; H, 7.90; N, 11.06. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.77; H, 7.96; N, 10.79.

Data for 7e. Yield, 90.3%; mp, 111−112 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H, CH_3), 1.33 (d, 6H, $C(CH_3)_2$), 3.13 (m, 1H, CH), 3.54 (q, 2H, OCH_2), 3.67 (t, 2H, CH_2O), 4.24 (t, 2H, CO_2CH_2), 4.59 (d, 2H, CH_2N), 7.24−8.30 (m, 3H, C_5H_3N), 10.6 (s, 1H, NH). Anal. found: C, 57.83; H, 6.27; N, 11.77. Calcd for $C_{17}H_{22}N_3O_3Cl$: C, 58.04; H, 6.31; N, 11.95.

Data for 7f. Yield, 83.1%; mp, 78−79 °C. ^{1}H NMR ($CDCl_3$): δ 1.13−1.27 (m, 6H, $2CH_3$), 2.60 (q, 2H, CH_3), 3.54 (q, 2H, OCH_2), 3.64 (t, 2H, CH_2O), 4.22 (t, 2H, CO_2CH_2), 4.53 (d, 2H, CH_2N), 7.30−8.30 (m, 3H, C_5H_3N), 10.2 (w, 1H, NH). Anal. found: C, 56.82; H, 5.64; N, 12.44. Calcd for $C_{16}H_{20}N_3O_3Cl$: C, 56.88; H, 5.92; N, 12.44.

Data for 7g. Yield, 80.7%; mp, 85−86 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, CH_3), 2.31 (s, 3H, $=CCH_3$), 3.56 (q, 2H, OCH_2), 3.60 (t, 2H, CH_2O), 4.28 (t, 2H, CO_2CH_2), 4.55 (d, 2H, CH_2N), 7.26−8.33 (m, 3H, C_5H_3N), 10.3 (s, 1H, NH). Anal. found: C, 55.55; H, 5.41; N, 12.95. Calcd for $C_{15}H_{18}N_3O_3Cl$: C, 55.61; H, 5.62; N, 12.99. IR (KBr, cm^{-1}): 1671, 1274, 1102, 1599, 1562, 1457, 2198, 3381, 810, 772. EI MS: *m*/*z* (%) 323 (M^+, 10.5), 126 (100).

Data for 7h. Yellow liquid. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H, CH_3), 3.53 (q, 2H, OCH_2), 3.67 (t, 2H, CH_2O), 4.28 (t, 2H, CO_2CH_2), 4.50 (d, 2H, CH_2N), 7.90 (s, 1H, $=CH$), 7.34−8.32 (m, 3H, C_5H_3N), 9.2 (s, 1H, NH). Anal. found: C, 54.27; H, 5.13; N, 13.58. Calcd for $C_{14}H_{16}N_3O_3Cl$: C, 54.28; H, 5.22; N, 13.57.

Data for 7i. Yield, 88.6%; mp, 82−84 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H, CH_2CH_3), 2.30 (s, 3H, $=CH_3$), 3.58 (q, 2H, OCH_2), 3.65 (t, 2H, CH_2O), 3.93 (s, 3H, $PrOCH_3$), 4.24 (t, 2H, CO_2CH_2), 4.44 (d, 2H, CH_2N), 6.74−8.05 (m, 3H, C_5H_3N), 10.1 (s, 1H, NH). Anal. found: C, 60.04; H, 6.39; N, 13.31. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.16; H, 6.64; N, 13.16.

Data for 7j. Yield, 91.3%; yellow liquid. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H, $C_2H_4CH_3$), 1.14 (t, 3H, CH_2CH_3), 2.28 (s, 3H, $=CH_3$), 1.74 (m, 2H, $CH_2CH_2CH_3$), 3.50 (q, 2H, OCH_2), 3.60 (t, 2H, CH_2O), 4.17−4.24 (m, 4H, $PrOCH_2$, CO_2CH_2), 4.41 (d, 2H, CH_2N), 6.75−8.00 (m, 3H, C_5H_3N), 10.1 (s, 1H, NH). Anal. found: C, 62.27; H, 7.38; N, 12.23. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.22; H, 7.27; N, 12.10.

Biological Assay. The herbicidal activities of the compounds **6a−l** and **7a−j** and the reported compounds **B** and **C** were evaluated using a previously reported procedure (*7*, *14*).

Plant Material. The three broadleaf species used to test the herbicidal activity of compounds were alfalfa (*Medicago sativa* L.), rape (*B. napus*), and amaranth pigweed (*Amaranthus retroflexus*). Seeds of *A. retroflexus* were reproduced outdoors and stored at room temperature. Seeds of alfalfa and rape were bought from the Institute of Crop, Tianjin Agriculture Science Academy.

Culture Method. Seeds were planted in 6 cm diameter plastic boxes containing artificial mixed soil. Before plant emergence, the boxes were covered with plastic film to keep moist. Plants were grown in the green house. Fresh weight of the above ground tissues was measured 10 days after treatment. The inhibition percent was used to describe the control efficiency of the compounds.

Treatment. The dosage (activity ingredient) for each compound was 1.5 kg/ha. Purified compounds were dissolved in 100 μL of *N*,*N*-dimethylformamide with the addition of a little Tween 20 and were then sprayed using a laboratory belt sprayer delivering a 750 L/ha spray volume. The mixture of the same amount of water, *N*,*N*-dimethylformamide, and Tween 20 was sprayed as control.

Preemergence Treatment. Compounds were sprayed immediately after seed plantings. There were two replicates for each treatment.

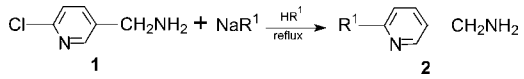
Postemergence Treatment. Compounds were sprayed after the first true leaf expanded.

RESULTS AND DISCUSSION

Synthesis. The intermediate 2-chloro-5-pyridinemethaneamine (**1**) was prepared readily from 2-chloro-5-chloromethylpyridine according to Cheng et al. (*15*). The substitution reaction of **1** by sodium alkoxide under reflux afforded 2-alkoxy-5-pyridinemethaneamine (**2**) in good yield (**Scheme 1**). When R^1 was propoxy or butoxy, the reaction was completed quantitatively.

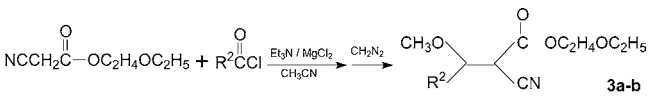
The synthesis of intermediate (*Z* + *E*)-2-cyano-3-alkoxyacrylates **3** using two methods (*16*, *17*) has been reported (**Schemes 2** and **3**). Compounds **3a**,**b** were synthesized by treating ester **4** with acid chloride followed by methylation with diazomethane in good yields. As for the preparation of **3c**,**d**, we adopted the reaction of ester **4** with triethyl orthoacetate or

Scheme 1[a]



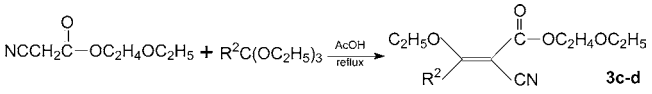
[a] Compounds **2a**–**d**: R^1 = CH_3O, CH_3CH_2O, $CH_3CH_2CH_2O$, and $CH_3CH_2CH_2CH_2O$.

Scheme 2[a]



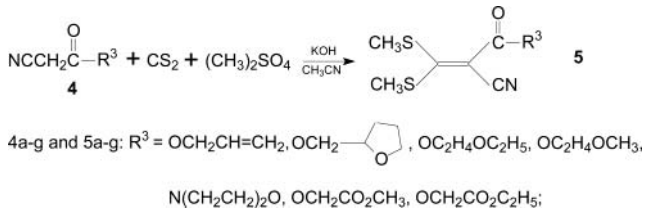
[a] Compounds **3a**,**b**: R^2 = CH_3CH_2 and $(CH_3)_2CH$.

Scheme 3[a]

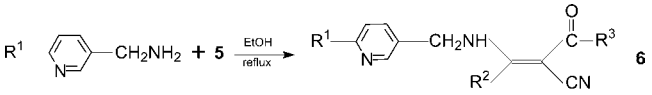


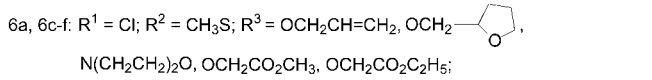
[a] Compounds **3c**,**d**: R^2 = H and CH_3.

Scheme 4

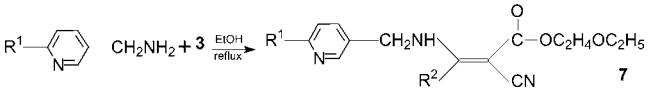


Scheme 5



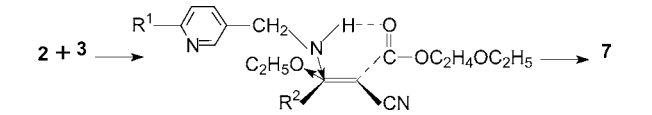


Scheme 6[a]



[a] Compounds **7a**–**d**: R^1 = CH_3O, C_2H_5O, $CH_3CH_2CH_2O$, and $CH_3CH_2CH_2CH_2O$; R^2 = $(CH_3)_2CH$. Compounds **7e**–**h**: R^1 = Cl; R^2 = $(CH_3)_2CH$, C_2H_5, CH_3, and H. Compounds **7i**,**j**: R^1 = CH_3O and $CH_3CH_2CH_2O$; R^2 = CH_3.

Scheme 7



triethyl orthoformate in the presence of acetic acid. It was reported that acetic acid should be added in three separate aliquots, but we found that a better yield was achieved by adding acetic acid at once at 160 °C.

Esters **4** were prepared conveniently from cyanoacetic acid and primary alcohols in the presence of a catalytic amount of sodium bisulfate monohydrate (*18*). Intermediate 2-cyano-3,3-dimethylthioacrylates **5** were achieved by treating corresponding esters **4** with carbon disulfide and 2 mol of dimethyl sulfate in a one pot reaction using potassium hydroxide as alkali in good yield (76−92%) (**Scheme 4**).

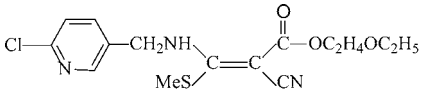
Intermediates **3** or **5** were reacted with substituted pyridinemethanamine **1** or **2** in refluxing absolute ethanol to give the target compounds **6** or **7** in good yields (**Schemes 5** and **6**). This reaction was assumed to go through a nucleophilic addition and elimination reaction (**Scheme 7**). The amine attached the α,β-unsaturated double bond to form a transition state in which the orientation of pyridinemethylamino and ester carbonyl is cis because of the presence of an intramolecular hydrogen bonding. The configuration of target compounds was kept with the loss of a mole of the methylthio group (or methoxy) and was confirmed by the X-ray single-crystal structure of **7e**; the X-ray data confirmed the *Z* sterochemistry of **7e** and demonstrated the presence of a planar core stablized by an intramolecular hydrogen bond between the ester carbonyl oxygen and the pyridinemethylamino hydrogen atom (*19*). All of these target compounds were confirmed by ^{1}H NMR, elemental, IR, and mass spectrum analyses.

Table 1. Herbicidal Activities of Products **6f** and **C** against Alfalfa

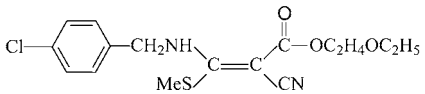
	rate (g/ha)	herbicidal activity (%)	correlation coefficient (*r*)	$y = a + bx$	ED_{50} (g/ha)	ED_{90} (g/ha)
6f	150.00	98.1				
	75.00	95.3	0.99	$y = 5.72 + 1.33x$	4.35	39.3
	37.50	88.9				
	18.75	80.6				
C	150.00	87.0				
	75.00	80.6	0.97	$y = 5.22 + 0.96x$	8.85	193.95
	37.50	76.9				
	18.75	59.3				

Structure−Activity Relationship. In our previous work, the cyanoacrylate structure modified by the replacement of phenyl with ferrocenyl showed higher herbicidal activities than the parent compound (*14*). Introduction of ferrocenyl into cyanoacrylate increased the overall lipophilicity of the molecule.

To further amplify the interaction of these cyanoacrylates with the lipophilic binding domain, phenyl was replaced by pyridine heterocycles in 2-cyanoacrylates, and (*Z*)-ethoxyethyl 2-cyano-3-methylthio-3-(4-chlorophenyl)methaneaminoacrylate (**C**) and (*Z*)-ethoxyethyl 2-cyano-3-methylthio-3-(2-chloro-5-pyridyl)-methaneaminoacrylate (**6f**) were prepared for comparison of herbicidal activity. This comparison (**Table 1**) clearly showed a significant enhanced activity, with compound **6f** having a higher level of herbicidal activity than compound **C**. Moreover, by comparing the herbicidal activity of (*Z*)-ethoxyethyl 2-cyano-3-isopropyl-3-(2-chloro-5-pyridyl)methaneaminoacrylate (**7e**) and (*Z*)-ethoxyethyl 2-cyano-3-isopropyl-3-(4-chlorophenyl)-methaneaminoacrylate (**B**) (**Table 2**), we found that the introduction of pyridine to 2-cyanoacrylate increased the herbicidal activity. These results were in agreement with the above two compounds **6f** and **C**. Thus, subsequent optimization of cyanoacrylate focused on varying the nature of the substitents R^1, R^2, and R^3 while retaining the pyridine heterocycle.



6f

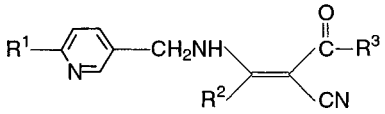


C

From the biological assay results in **Table 2**, which summarized the herbicidal activity of the target compounds, most of the compounds synthesized showed a greater herbicidal activity in postemergence treatment than in preemergence treatment except **7a**,**e**,**g**; so, we herein analyzed the structure−activity relationship according to the data of biological assay in the postemergence treatment.

Compound **6j** with the H-atom at the 2-position of the pyridine ring had little inhibitory effect on weed development as compared with compound **6k** with methoxy at the 2-position, indicating that a suitable group (chlorine or alkoxy) at the 2-position would be essential for herbicidal activity. The

Table 2. Herbicidal Activities of Products **6a**–**l** and **7a**–**j** (1.5 kg/ha)



	R^1	R^2	R^3	Post-emergence treatment			Pre-emergence treatment		
				Alfalfa	Amaranth pigweed	Rape	Alfalfa	Amaranth pigweed	Rape
6a	Cl	MeS	$OCH_2CH{=}CH_2$	100.0	100.0	91.7	0	0	0
6b	Cl	EtS	$OCH_2CH{=}CH_2$	98.8	100.0	100.0	0	0	0
6c	Cl	MeS		64.0	98.8	100.0	16.7	14.3	54.2
6d	Cl	MeS	$N(CH_2CH_2)_2O$	75.0	100.0	99.4	0	0	0
6e	Cl	MeS	$OCH_2CO_2CH_3$	4.8	0	0	0	0	0
6f	Cl	MeS	$OC_2H_4OC_2H_5$	75.0	100.0	80.6	/	/	/
6g	MeO	MeS	$OC_2H_4OC_2H_5$	80.9	100.0	100.0	36.4	56.3	68.3
6h	EtO	MeS	$OC_2H_4OC_2H_5$	91.5	100.0	100.0	0	37.5	22.0
6i	n-PrO	MeS	$OC_2H_4OC_2H_5$	0	93.8	96.8	0	0	16.3
6j	H	MeS	$OC_2H_4OCH_3$	15.9	0	6.4	0	0	9.1
6k	MeO	MeS	$OC_2H_4OCH_3$	72.3	90.0	90.1	10.0	50.0	48.8
6l	EtO	MeS	$OC_2H_4OCH_3$	55.3	70.0	84.5	0	31.3	5.1
7a	MeO	i-Pr	$OC_2H_4OC_2H_5$	53.0	100.0	100.0	32.9	71.0	100.0
7b	EtO	i-Pr	$OC_2H_4OC_2H_5$	45.8	100.0	100.0	10.1	50.7	54.8
7c	n-PrO	i-Pr	$OC_2H_4OC_2H_5$	75.9	100.0	100.0	14.8	30.4	30.7
7d	n-BuO	i-Pr	$OC_2H_4OC_2H_5$	41.0	100.0	100.0	0	10.1	6.3
7e	Cl	i-Pr	$OC_2H_4OC_2H_5$	65.9	93.9	100.0	23.0	97.8	95.5
7f	Cl	Et	$OC_2H_4OC_2H_5$	83.7	100.0	100.0	71.4	71.4	75.0
7g	Cl	Me	$OC_2H_4OC_2H_5$	100.0	100.0	100.0	66.4	93.0	100.0
7h	Cl	H	$OC_2H_4OC_2H_5$	15.8	18.3	7.3	14.8	12.2	21.8
7i	MeO	Me	$OC_2H_4OC_2H_5$	64.0	100.0	69.0	57.1	100.0	92.5
7j	n-PrO	Me	$OC_2H_4OC_2H_5$	34.2	31.0	17.0	17.8	23.4	0
B				28.1	93.9	96.5	0	52.2	0

Table 3. Herbicidal Activities of Products **6a**,**c**,**d**,**f** and **7e**–**g**

		postemergence treatment		
compd	rate (g/ha)	alfalfa	amaranth pigweed	rape
6a	1500	100.0	100.0	91.7
	300	56.1	61.6	82.7
	75	15.9	22.2	33.3
6c	1500	64.0	98.8	100.0
	300	52.3	88.4	97.3
	75	41.9	79.1	94.7
6d	1500	75.0	100.0	99.4
	300	9.7	25.0	0
	75	0	0	0
6f	1500	76.2	100.0	100.0
	300	57.5	96.2	100.0
	75	36.3	52.3	36.8
7e	1500	75.6	100.0	100.0
	300	45.3	93.0	100.0
	75	14.0	72.1	89.4
7f	1500	83.7	100.0	100.0
	300	62.8	100.0	98.4
	75	45.3	88.4	94.1
7g	1500	100.0	100.0	100.0
	75	0	18.3	14.6

replacement of chlorine by an alkoxy group (**6g**−**i**, **7a**−**d**) did not affect the herbicidal activity obviously.

At the rate of 75 g/ha (**Table 3**), compounds **6c** and **7e**,**f** exhibited excellent herbicidal activities. Compound **7g** exhibited excellent herbicidal activity at 1.5 kg/ha; however, its activity decreased remarkably when the dose was reduced to 75 g/ha. Loss of activity was observed when R^2 was replaced by H.

In conclusion, we have demonstrated that 2-cyanoacrylates containing substituted pyridine ring presented excellent herbicidal activity and their structure−activity relationships were studied. Some compounds exhibited excellent herbicidal activities, even at a dose of 75 g/ha. It was found that the suitable substituent at the 2-position of the pyridine ring and the well-fit group at the 3-position of acrylate were essential for high herbicidal activity. These PSII inhibitor herbicides are safe for corn, which is a major crop in China, at the rate of 750 g/ha.

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