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# Design, Synthesis, and Herbicidal Activities of Novel 2-Cyanoacrylates Containing Isoxazole Moieties†

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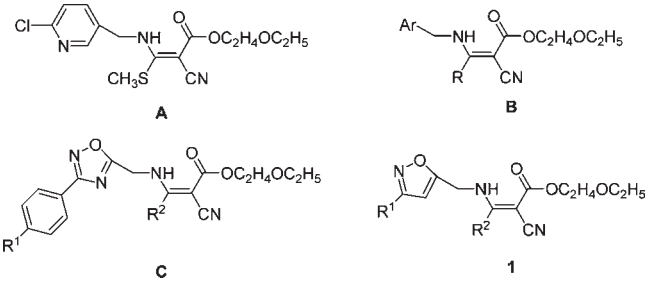
A series of novel 2-cyanoacrylates containing an isoxazole moiety were designed and synthesized. Their structures were characterized by $^1$H NMR and elemental analysis (or high-resolution mass spectrometry). Their herbicidal activities against four species were evaluated, and the results indicated that some of the title compounds showed excellent herbicidal activities against rape and amaranth pigweed in postemergence treatment even at a dose of 75 g/ha.

**KEYWORDS: Cyanoacrylates; isoxazole; herbicidal activity; PSII electron transfer inhibitor**

## INTRODUCTION

2-Cyanoacrylates are inhibitors of photosystem II (PSII) electron transport, which inhibits the growth of weeds by disrupting photosynthetic electron transport at the PSII reaction center (*1*). Therefore, this kind of compound can be used as a potential herbicide. In previous works, we have reported the syntheses of cyanoacrylates containing a pyridine group (*2*, *3*), of which compound **A** gave excellent herbicidal activities especially against dicotyledon species. A series of heterocycles such as thiazole, furan, tetrahydrofuran, pyridazine, and pyrimidine groups were then introduced to cyanoacrylates (structure **B**), and the groups showed notable influence on the herbicidal activities of corresponding compounds (*4*−*6*) The quantitive structure−activity relationship research by comparative molecular field analysis (CoMFA) indicated that a bulky and electronegative group around the para position of proper aromatic rings would have the potential for higher activity (*6*). Moreover, the binding model of compound **A** with the D1 protein of PSII was built, and it was proved that the N atom on the pyridine ring could form an H-bond with the backbone amide of Phe265 on the D1 protein (*7*). Therefore, a series of new 2-cyanoacrylates bearing an N-containing heterocycle such as an oxazole, oxadiazole, or quinoline group (structure **B**) were designed, and some of them indeed exhibited good herbicidal activities (*8*). Among those compounds, the 3-phenyl-1,2,4-oxadiazol-5-yl moieties (structure **C**) seemed to have helped with their herbicidal activities, because most of them exhibited higher activities against all four tested species than oxazole-containing compounds (*8*). 1,2-Isoxazole, a structure very similar to 1,2,4-oxadiazole and also the important moiety in many activity compounds (*9*, *10*), was then considered as a bioisosteric analogue to introduce the 2-cyanoacrylates. In this paper, we focus on the isoxazole-containing 2-cyanoacrylates bearing different substituents at the 3-position of the 1,2-isoxazole ring (compound **1** and **Table 1**) and report the exciting results.




## MATERIALS AND METHODS

**Instruments.** $^1$H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values ($\delta$) are given in parts per million. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. High-resolution mass spectrometry (HRMS) data were obtained on a FTICR-MS instrument (Ionspec 7.0T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Technical Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized.

Oximes **3a**−**3h** were prepared from corresponding aldehyde according to a classical procedure (*11*). Dibromoformaloxime was prepared according to a published procedure (*12*). Compounds **7a** and **7b** were prepared according to our previous work (*2*, *4*). All of the anhydrous solvents were dried and distilled by using standard techniques.

**General Synthetic Procedure for 4a−4h (*13*).** To a cooled (below 0 °C) solution of aldehyde oxime **3** (10 mmol), propargyl bromide (12 mmol), and triethylamine (10 mmol) in dichloromathane (20 mL) was dropwise added 8% aqueous sodium hypochlorite (30 mL). After 8 h of stirring at room temperature, the reaction phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel to afford compound **4**.

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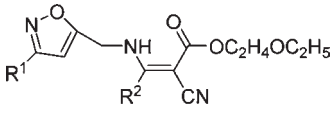
**Table 1.** Title Compounds **1a**−**1q**



**1**

| compd | $R^1$ | $R^2$ | compd | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **1a** | phenyl | MeS | **1j** | 4-t-Bu-phenyl | MeS |
| **1b** | phenyl | i-Pr | **1k** | 4-t-Bu-phenyl | i-Pr |
| **1c** | 2-Cl-phenyl | i-Pr | **1l** | 2,4-$Cl_2$-phenyl | MeS |
| **1d** | 4-Cl-phenyl | MeS | **1m** | 2,4-$Cl_2$-phenyl | i-Pr |
| **1e** | 4-Cl-phenyl | i-Pr | **1n** | i-Pr | MeS |
| **1f** | 2-$OCH_3$-phenyl | MeS | **1o** | i-Pr | i-Pr |
| **1g** | 2-$OCH_3$-phenyl | i-Pr | **1p** | Br | MeS |
| **1h** | 4-$OCH_3$-phenyl | MeS | **1q** | Br | i-Pr |
| **1i** | 4-$OCH_3$-phenyl | i-Pr | | | |

*Data for **4a**:* yield, 73.1%; mp, 87−89 °C (88 °C (*14*)); $^1$H NMR ($CDCl_3$) $\delta$ 4.51 (s, 2H), 6.63 (s, 1H), 7.42−7.47 (m, 3H), 7.78−7.81 (m, 2H).

*Data for **4b**:* yield, 84.3%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 4.53 (s, 2H), 6.80 (s, 1H), 7.32−7.40 (m, 2H), 7.46−7.50 (m, 1H), 7.74 (dd, $J$ = 7.2 Hz, 2.1 Hz, 1H).

*Data for **4c**:* yield, 60.7%; mp, 117−119 °C (118−120 °C (*15*)); $^1$H NMR ($CDCl_3$) $\delta$ 4.51 (s, 2H), 6.61 (s, 1H), 7.44 (d, $J$ = 8.4 Hz, 2H), 7.73 (d, $J$ = 8.4 Hz, 2H).

*Data for **4d**:* yield, 95.1%; $^1$H NMR ($CDCl_3$) $\delta$ 3.90 (s, 3H), 4.52 (s, 2H), 6.84 (s, 1H), 6.98−7.08 (m, 2H), 7.43 (td, $J$ = 7.8 Hz, 1.8 Hz, 1H), 7.89 (dd, $J$ = 7.8 Hz, 1.8 Hz, 1H).

*Data for **4e**:* yield, 60.0%; mp, 86−87 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.86 (s, 3H), 4.50 (s, 2H), 5.58 (s, 1H), 6.97 (d, $J$ = 8.7 Hz, 2H), 7.73 (d, $J$ = 8.7 Hz, 2H).

*Data for **4f**:* yield, 62.0%; mp, 75−76 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.35 (s, 9H), 4.50 (s, 2H), 6.61 (s, 1H), 7.47 (d, $J$ = 8.4 Hz, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H).

*Data for **4g**:* yield, 90.1%; mp, 57−59 °C (61−62 °C (*12*)); $^1$H NMR ($CDCl_3$) $\delta$ 4.53 (s, 2H), 6.68 (s, 1H), 7.35 (dd, $J$ = 8.4 Hz, 2.1 Hz, 1H), 7.52 (d, $J$ = 2.1 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 1H).

*Data for **4h**:* yield, 78.4%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.28 (d, $J$ = 6.9 Hz, 6H), 3.01−3.09 (m, 1H), 4.44 (s, 2H), 6.20 (s, 1H).

**Synthetic Procedure for 4i (*16*).** A solution of dibromoformaloxime (4.1 g, 20 mmol) in dichloromathane (20 mL) was added over 5 h to a stirred solution of propargyl bromide (2.86 g, 24 mmol), potassium bicarbonate (2.5 g, 30 mmol), dichloromethane (100 mL), and water (10 mL). After 2 h, water (50 mL) was added. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel to afford compound **4i** as a colorless oil, yield 50.0%: $^1$H NMR ($CDCl_3$) $\delta$ 4.44 (s, 2H), 6.41 (s, 1H).

**General Synthetic Procedures for 5a−5i.** To a solution of **4** (6 mmol) in *N*,*N*-dimethylformamide (10 mL) was added potassium phthalimide (6 mmol) in portions. After the mixture was stirred at room temperature for 5 h, water (50 mL) was added, and the precipitate was collected by filtration and washed with water. After recrystallization from ethanol, N-substituted phthalimide **5** was obtained as a white crystal.

*Data for **5a**:* yield, 98.5%; mp, 162−164 °C; $^1$H NMR ($CDCl_3$) $\delta$ 5.04 (s, 2H), 6.57 (s, 1H), 7.41−7.43 (m, 3H), 7.74−7.77 (m, 4H), 7.88−7.92 (m, 2H).

*Data for **5b**:* yield, 84.0%; mp, 120−121 °C; $^1$H NMR ($CDCl_3$) $\delta$ 5.06 (s, 2H), 6.74 (s, 1H), 7.26−7.48 (m, 3H), 7.68 (d, $J$ = 7.2 Hz, 1H), 7.74−7.78 (m, 2H), 7.88−7.92 (m, 2H).

*Data for **5c**:* yield, 96.3%; mp, 173−175 °C; $^1$H NMR ($CDCl_3$) $\delta$ 5.03 (s, 2H), 6.54 (s, 1H), 7.39 (d, $J$ = 8.4 Hz, 2H), 7.68 (d, $J$ = 8.4 Hz, 2H), 7.74−7.78 (m, 2H), 7.88−7.91 (m, 2H).

*Data for **5d**:* yield, 98.2%; mp, 149−151 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.87 (s, 3H), 5.03 (s, 2H), 6.78 (s, 1H), 6.95−7.02 (m, 2H), 7.38 (t, $J$ = 6.8 Hz, 1H), 7.72−7.76 (m, 2H), 7.81 (dd, $J$ = 6.8 Hz, 4.6 Hz, 1H), 7.87−7.90 (m, 2H).

*Data for **5e**:* yield, 89.0%; mp, 177−178 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.84 (s, 3H), 5.02 (s, 2H), 6.51 (s, 1H), 6.93 (d, $J$ = 8.7 Hz, 2H), 7.69 (d, $J$ = 8.7 Hz, 2H), 7.74−7.78 (m, 2H), 7.88−7.92 (m, 2H).

*Data for **5f**:* yield, 97.0%; mp, 205−206 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (s, 9H), 5.03 (s, 2H), 6.54 (s, 1H), 7.44 (d, $J$ = 8.4 Hz, 2H), 7.69 (d, $J$ = 8.4 Hz, 2H), 7.74−7.78 (m, 2H), 7.88−7.92 (m, 2H).

*Data for **5g**:* yield, 85.2%; mp, 152−154 °C; $^1$H NMR ($CDCl_3$) $\delta$ 5.06 (s, 2H), 6.73 (s, 1H), 7.31 (dd, $J$ = 8.4 Hz, 2.0 Hz, 1H), 7.48 (d, $J$ = 2.0 Hz, 1H), 7.64 (d, $J$ = 8.4 Hz, 1H), 7.75−7.78 (m, 2H), 7.80−7.91 (m, 2H).

*Data for **5h**:* yield, 86.0%; mp, 109−110 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.24 (d, $J$ = 6.9 Hz, 6H), 2.97−3.06 (m, 1H), 4.95 (s, 2H), 6.11 (s, 1H), 7.74−7.77 (m, 2H), 7.78−7.91 (m, 2H).

*Data for **5i**:* yield, 70.0%; mp, 156−157 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.99 (s, 2H), 6.36 (s, 1H), 7.73−7.79 (m, 2H), 7.79−7.92 (m, 2H).

**General Synthetic Procedures for 6a−6i.** To a suspension of N-substituted phthalimide **5** (4 mmol) in ethanol (20 mL) was added hydrazine hydrate (50%, 0.48 g, 4.8 mmol). The reaction mixture was refluxed for 5 h and then cooled. The precipitated phthalylhydrazide was filtered off and washed with ethanol, and then the filtrate was concentrated under reduced pressure to give crude **6**, which was utilized in the next reaction without further purification.

*Data for **6a**:* yield, 94.3%; mp, 61−62 °C (51−52 °C (*17*)); $^1$H NMR ($CDCl_3$) $\delta$ 1.64 (s, 2H), 4.01 (s, 2H), 6.45 (s, 1H), 7.43−7.46 (m, 3H), 7.77−7.80 (m, 2H).

*Data for **6b**:* yield, 98.5%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.75 (s, 2H), 4.04 (s, 2H), 6.60 (s, 1H), 7.34−7.38 (m, 2H), 7.46−7.50 (m, 1H), 7.70−7.78 (m, 1H).

*Data for **6c**:* yield, 82.7%; mp, 79−81 °C (81 °C (*18*)); $^1$H NMR ($CDCl_3$) $\delta$ 1.58 (s, 2H), 4.02 (s, 2H), 6.43 (s, 1H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H).

*Data for **6d**:* yield, 95.0%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.87 (s, 2H), 3.85 (s, 3H), 3.98 (s, 2H), 6.61 (s, 1H), 6.94−7.02 (m, 2H), 7.37 (t, $J$ = 7.6 Hz, 1H), 7.82 (d, $J$ = 7.6 Hz, 1H).

*Data for **6e**:* yield, 92.0%; mp, 111−112 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.58 (s, 2H), 3.85 (s, 3H), 4.01 (s, 2H), 6.40 (s, 1H), 6.97 (d, $J$ = 8.8 Hz, 2H), 7.73 (d, $J$ = 8.8 Hz, 2H).

*Data for **6f**:* yield, 95.7%; mp, 65−67 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.35 (s, 9H), 1.62 (s, 2H), 4.02 (s, 2H), 6.43 (s, 1H), 7.47 (d, $J$ = 8.4 Hz, 2H), 7.73 (d, $J$ = 8.4 Hz, 2H).

*Data for **6g**:* yield, 97.2%;$^1$H NMR ($CDCl_3$) $\delta$ 1.59 (s, 2H), 4.05 (s, 2H), 6.60 (s, 1H), 7.33 (dd, $J$ = 8.4 Hz, 2.0 Hz, 1H), 7.50 (d, $J$ = 2.0 Hz, 1H), 7.67 (d, $J$ = 8.4 Hz, 1H).

*Data for **6h**:* yield, 97.0%; oil;$^1$H NMR ($CDCl_3$) $\delta$ 1.27 (d, $J$ = 6.9 Hz, 6H), 1.60 (s, 2H), 3.01−3.08 (m, 1H), 3.93 (s, 2H), 6.01 (s, 1H).

*Data for **6i**:* yield, 95.6%; oil;$^1$H NMR ($CDCl_3$) $\delta$ 1.57 (s, 2H), 3.94 (s, 2H), 6.21 (s, 1H).

**General Synthetic Procedures for the Title Compounds 1a−1q.** A mixture of **7a** (or **7b**) (1.35 mmol) and crude **6** (1.45 mmol) in ethanol (20 mL) was refluxed for 2 h and then evaporated under reduced pressure to give crude product. The residue was purified by flash chromatography on a silica gel to afford the title compounds.

*Data for **1a**:* yield, 98.3%; mp, 86−88 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 2.72 (s, 3H, $SCH_3$), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.33 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.97 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.51 (s, 1H, isoxazole), 7.46−7.48 (m, 3H, Ph), 7.78−7.80 (m, 2H, Ph), 10.41 (s, 1H, NH). Anal. Calcd for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.88; H, 5.30; N, 10.68.

*Data for **1b**:* yield, 90.5%; mp, 88−89 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.44 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.19−3.22 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.31 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.77 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.53 (s, 1H, isoxazole), 7.47−7.48 (m, 3H, Ph), 7.78−7.80 (m, 2H, Ph), 10.68 (s, 1H, NH). Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.51; H, 6.37; N, 11.09. Found: C, 65.78; H, 6.57; N, 10.96.

*Data for **1c**:* yield, 87.3%; mp, 64−65 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.45 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.19−3.22 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.70 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CH_2O$), 4.30 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CO_2CH_2$), 4.78 (d, $^3J_{HH}$ = 6.4 Hz, 2H, $CH_2N$), 6.69 (s, 1H, isoxazole), 7.35−7.44 (m, 2H,

Ph), 7.50 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ph), 7.71 (d, $^3J_{HH}$ = 7.2 Hz, 1H, Ph), 10.68 (s, 1H, NH). Anal. Calcd for $C_{21}H_{24}ClN_3O_4$: C, 60.36; H, 5.79; N, 10.06. Found: C, 59.96; H, 5.87; N, 10.11.

*Data for* ***1d****:* yield, 92.1%; mp, 108−109 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 2.73 (s, 3H, $SCH_3$), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.33 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.98 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.49 (s, 1H, isoxazole), 7.45 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 7.72 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 10.42 (s, 1H, NH). Anal. Calcd for $C_{19}H_{20}ClN_3O_4S$: C, 54.09; H, 4.78; N, 9.96. Found: C, 54.94; H, 4.81; N, 9.95.

*Data for* ***1e****:* yield, 85.0%; mp, 80−82 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.44 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.20−3.21 (m, 1H, CH), 3.59 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.31 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.77 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.51 (s, 1H, isoxazole), 7.45 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 7.72 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 10.68 (s, 1H, NH). Anal. Calcd for $C_{21}H_{24}ClN_3O_4$: C, 60.36; H, 5.79; N, 10.06. Found: C, 60.48; H, 5.98; N, 10.03.

*Data for* ***1f****:* yield, 98.4%; mp, 80−82 °C;$^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 2.72 (s, 3H, $SCH_3$), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 3.91 (s, 3H, $OCH_3$), 4.32 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.96 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.71 (s, 1H, isoxazole), 7.00−7.07 (m, 2H, Ph), 7.44 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ph), 7.86 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ph), 10.39 (s, 1H, NH). Anal. Calcd for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.55; N,10.07. Found: C, 57.35; H, 5.85; N, 9.79.

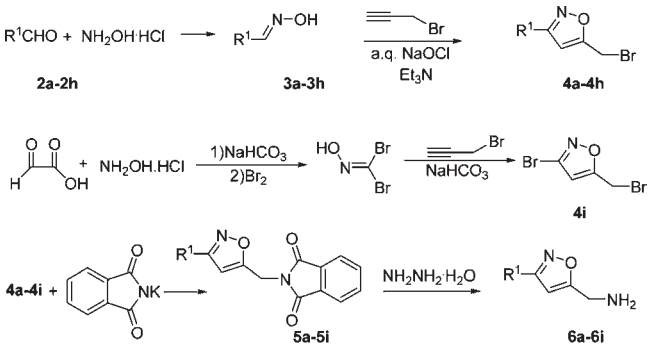
*Data for* ***1g****:* yield, 84.4%; oil;$^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.45 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.18−3.21 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 3.85 (s, 3H, $OCH_3$), 4.30 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.75 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.71 (s, 1H, isoxazole), 7.00−7.07 (m, 2H, Ph), 7.44 (t, $^3J_{HH}$ = 7.6 Hz, 1H, Ph), 7.85 (d, $^3J_{HH}$ = 6.8 Hz, 1H, Ph), 10.67 (s, 1H, NH). HRMS for $C_{22}H_{27}N_3O_5$ + Na: 436.1843. Found: 436.1840.

*Data for* ***1h****:* yield, 98.0%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (t, $^3J_{HH}$ = 6.8 Hz, 3H, $CH_3$), 2.71 (s, 3H, $SCH_3$), 3.57 (q, $^3J_{HH}$ = 6.8 Hz, 2H, $OCH_2$), 3.70 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CH_2O$), 4.32 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CO_2CH_2$), 4.94 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.44 (s, 1H, isoxazole), 6.97 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 7.72 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 10.39 (s, 1H, NH). Anal. Calcd for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.55; N, 10.07. Found: C, 57.75; H, 5.80; N, 10.01.

*Data for* ***1i****:* yield, 84.1%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.43 (d, $^3J_{HH}$ = 6.8 Hz, 6H, $C(CH_3)_2$), 3.10−3.30 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.70 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CH_2O$), 3.85 (s, 3H), 4.30 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CO_2CH_2$), 4.74 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.46 (s, 1H, isoxazole), 6.97 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ph), 7.72 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ph), 10.66 (s, 1H, NH). Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.77; H, 6.59; N, 10.19.

*Data for* ***1j****:* yield, 92.0%; mp, 94−96 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.35 (s, 9H, $C(CH_3)_3$), 2.72 (s, 3H, $SCH_3$), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.33

**Scheme 1.** General Synthetic Route for Aminomethyl Isoxazoles **6a**−**6i**




| 4,5,6 | $R^1$ | 4,5,6 | $R^1$ |
|---|---|---|---|
| a | Phenyl | f | 4-*t*-Bu-phenyl |
| b | 2-Cl-phenyl | g | 2,4-$Cl_2$-Phenyl |
| c | 4-Cl-phenyl | h | *i*-Pr |
| d | 2-$CH_3O$-phenyl | i | Br |
| e | 4-$CH_3O$-phenyl | | |

**Scheme 2.** General Synthetic Route for the Title Compounds **1a**−**1q**

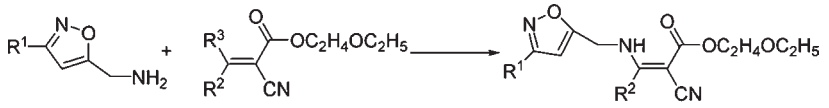



**Table 2.** Herbicidal Activities of Compounds**1a**−**1q** (1.5 kg/ha, Percent Inhibition)

| | postemergence treatment | | | | preemergence treatment | | | |
|---|---|---|---|---|---|---|---|---|
| compd | rape | amaranth pigweed | barnyard grass | hairy crabgrass | rape | amaranth pigweed | barnyard grass | hairy crabgrass |
| **1a** | **100** | **100** | **57.0** | **55.5** | 15.8 | 67.7 | 0 | 0 |
| **1b** | **100** | **100** | 40.0 | **59.4** | 28.7 | 88.6 | 0 | 24.9 |
| **1c** | **100** | **100** | 47.2 | 24.0 | | 0 | 0 | 0 |
| **1d** | **100** | **89.9** | **58.2** | **72.7** | 28.4 | 23.1 | 0 | 14.8 |
| **1e** | **100** | **100** | 33.0 | **64.1** | 10.6 | 68.7 | 0 | 0 |
| **1f** | **100** | **90.6** | **52.0** | **52.3** | 19.0 | 47.8 | 0 | 17.3 |
| **1g** | **100** | **95.1** | **56.4** | **82.0** | 17.4 | 44.9 | 0 | 5.5 |
| **1h** | **100** | **100** | 0 | 32.5 | 10.0 | 0 | 0 | 0 |
| **1i** | **100** | **100** | 0 | 14.3 | 40.9 | 45.2 | 0 | 0 |
| **1j** | **100** | **100** | 0 | **55.8** | 0 | 10.0 | 0 | 0 |
| **1k** | **100** | **100** | 0 | 24.7 | 0 | 0 | 0 | 0 |
| **1l** | **100** | **89.9** | 45.2 | **64.1** | 45.0 | 65.8 | 0 | 15.6 |
| **1m** | **100** | **100** | **56.7** | **63.3** | 21.3 | 50.2 | 0 | 18.1 |
| **1n** | **100** | **94.0** | 32.6 | 48.4 | | 25.0 | 0 | 0 |
| **1o** | **100** | **100** | 12.5 | 48.4 | | 100 | 5.0 | 0 |
| **1p** | **100** | **99.1** | 36.8 | 55.3 | | 0 | 2.4 | 0 |
| **1q** | **100** | **100** | **66.5** | 42.1 | | 60.0 | 22.6 | 0 |
| **A** | **100** | **100** | **55.3** | **54.1** | 47.6 | 32.4 | 3.6 | 18.8 |

(t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.97 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.48 (s, 1H, isoxazole), 7.27 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 7.48 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 10.40 (s, 1H, NH). Anal. Calcd for $C_{23}H_{29}N_3O_4S$: C, 62.28; H, 6.59; N, 9.47. Found: C, 62.18; H, 6.56; N, 9.50.

*Data for* ***1k****:* yield, 51.0%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_3$), 1.35 (s, 9H, $C(CH_3)_3$), 1.44 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.14−3.26 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 6.9 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.31 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.75 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.50 (s, 1H, isoxazole), 7.48 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 7.72 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 10.67 (s, 1H, NH). HRMS for $C_{25}H_{33}N_3O_4$ + Na: 462.2363. Found: 462.2357.

*Data for* ***1l****:* yield, 91.2%; mp, 85−86 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_3$), 2.73 (s, 3H, $SCH_3$), 3.58 (q, $^3J_{HH}$ = 6.9 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.33 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 5.00 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.68 (s, 1H, isoxazole), 7.34−7.36 (m, 1H, Ph), 7.50−7.54 (m, 1H, Ph), 7.66−7.69 (m, 1H, Ph), 10.41 (s, 1H, NH). Anal. Calcd for $C_{19}H_{19}Cl_2N_3O_4S$: C, 50.01; H, 4.20; N, 9.21. Found: C, 50.08; H, 4.31; N, 9.16.

*Data for* ***1m****:* yield, 70.6%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_3$), 1.45 (d, $^3J_{HH}$ = 6.9 Hz, 6H, $C(CH_3)_2$), 3.17−3.23 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 6.9 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.31 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.79 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.68 (s, 1H, isoxazole), 7.34−7.37 (m, 1H, Ph), 7.51−7.55 (m, 1H, Ph), 7.65−7.68 (m, 1H, Ph), 10.68 (s, 1H, NH). HRMS for $C_{21}H_{23}Cl_2N_3O_4$ + Na: 474.0958. Found: 474.0954.

*Data for* ***1n****:* yield, 90.6%; mp, 49−50 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.28 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 2.70 (s, 3H, $SCH_3$), 3.02−3.09 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CH_2O$), 4.32 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CO_2CH_2$), 4.88 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.06 (s, 1H, isoxazole), 10.34 (s, 1H, NH). Anal. Calcd for $C_{16}H_{23}N_3O_4S$: C, 54.37; H, 6.56; N, 11.89. Found: C, 54.23; H, 6.54; N, 11.86.

*Data for* ***1o****:* yield, 89.5%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.28 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 1.42 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.01−3.11 (m, 1H, CH), 3.12−3.22 (m, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.71 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CH_2O$), 4.30 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CO_2CH_2$), 4.67 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.07 (s, 1H, isoxazole), 10.61 (s, 1H, NH). HRMS for $C_{18}H_{27}N_3O_4$ + Na: 372.1894. Found: 372.1887.

*Data for* ***1p****:* yield, 87.6%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 6.9 Hz, 3H, $CH_3$), 2.71 (s, 3H, $SCH_3$), 3.57 (t, $^3J_{HH}$ = 6.9 Hz, 2H, $OCH_2$), 3.70 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CH_2O$), 4.32 (t, $^3J_{HH}$ = 5.1 Hz, 2H, $CO_2CH_2$), 4.92 (d, $^3J_{HH}$ = 6.3 Hz, 2H, $CH_2N$), 6.30 (s, 1H, isoxazole), 10.34 (s, 1H, NH). HRMS for $C_{13}H_{16}BrN_3O_4S$ + Na: 411.9937. Found: 411.9935.

*Data for* ***1q****:* yield, 80.0%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_3$), 1.42 (d, $^3J_{HH}$ = 7.2 Hz, 6H, $C(CH_3)_2$), 3.10−3.20 (br s, 1H, CH), 3.58 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $OCH_2$), 3.70 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CH_2O$), 4.30 (t, $^3J_{HH}$ = 4.8 Hz, 2H, $CO_2CH_2$), 4.74 (d, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2N$), 6.34 (s, 1H, isoxazole), 10.61 (s, 1H, NH). HRMS for $C_{15}H_{20}BrN_3O_4$ + Na: 408.0529. Found: 408.0525.

**Herbicidal Activity.** Two dicotyledon species, rape (*Brassica napus* L.) and amaranth pigweed (*Amaranthus retroflexus*), and two monocotyledon weeds, barnyard grass (*Echinochloa crusgalli* (L.) Beauv) and hairy crabgrass (*Digitaria sanguinalis* L. Scop.), were used to test the herbicidal activities of compounds **1a**−**1q** using a previously reported procedure (*2*).

## RESULTS AND DISCUSSION

**Synthesis.** Oximes **3a**−**3h** were prepared from corresponding aldehydes (**2a**−**2h**) according to a classical procedure. In the presence of sodium hypochlorite, compounds **3a**−**3h** first generated nitrile oxide and subsequently reacted with propargyl bromide to give isoxazoles **4a**−**4h** via 1,3-dipolar cycloaddition. **4i** was similarly prepared by reacting dibromoformaloxime with propargyl bromide in the presence of potassium bicarbonate. Bromomethyl compounds **4a**−**4i** were converted to corresponding aminomethyl isoxazoles **6a**−**6i** by Gabriel reaction (**Scheme 1**).

Alkyoxy- or methylthio-substituted cyanoacrylate **7a** and **7b** were prepared according to our previous work (*2*, *4*). The title compounds **1a**−**1q** were synthesized from **6** and **7** with good yields (**Scheme 2** and **Table 1**).

**Table 3.** Herbicidal Activities of Compounds **1a**−**1q** in Postemergence Treatment (Percent Inhibition)

| compd | dose (kg/ha) | rape | amaranth pigweed |
|---|---|---|---|
| **1a** | 750 | 100 | 34.0 |
| | 375 | 17.8 | 7.0 |
| **1b** | 750 | **100** | **100** |
| | 375 | **100** | **100** |
| | 150 | 97.3 | **78.3** |
| | 75 | 54.2 | **17.4** |
| **1c** | 750 | **100** | **98.3** |
| | 375 | **100** | **96.0** |
| | 150 | **100** | **94.4** |
| | 75 | **100** | **77.0** |
| **1d** | 750 | 0 | 22.0 |
| | 375 | 0 | 4.0 |
| **1e** | 750 | **100** | **100** |
| | 375 | **100** | **100** |
| | 150 | 36.3 | **26.1** |
| | 75 | 29.6 | **8.7** |
| **1f** | 750 | 43.8 | 16.0 |
| | 375 | 15.8 | 0 |
| **1g** | 750 | **100** | **100** |
| | 375 | **100** | **100** |
| | 150 | 27.0 | **23.9** |
| | 75 | 17.1 | **17.4** |
| **1h** | 750 | 94.6 | 87.0 |
| | 375 | 57.5 | 34.8 |
| **1i** | 750 | **100** | **100** |
| | 375 | **100** | **100** |
| | 150 | **100** | **93.5** |
| | 75 | **82.5** | **65.2** |
| **1j** | 750 | 22.2 | 45.7 |
| | 375 | 9.8 | 28.3 |
| **1k** | 750 | 85.8 | 89.1 |
| | 375 | 41.7 | 54.3 |
| **1l** | 750 | 0 | 46.0 |
| | 375 | 0 | 0 |
| **1m** | 750 | **100** | **100** |
| | 375 | **100** | **100** |
| | 150 | 21.8 | **19.6** |
| | 75 | 11.4 | **10.9** |
| **1n** | 750 | 76.9 | 37.6 |
| | 375 | 52.3 | 0 |
| **1o** | 750 | 100 | 100 |
| | 375 | 97.7 | 54.6 |
| | 150 | 92.8 | 0 |
| | 75 | 52.0 | 0 |
| **1p** | 750 | 93.0 | 0 |
| | 375 | 87.0 | 0 |
| **1q** | 750 | **100** | **100** |
| | 375 | **100** | **100** |
| | 150 | **100** | **90.0** |
| | 75 | **100** | **46.5** |
| **A** | 750 | **100** | **87.9** |
| | 375 | **100** | **18.7** |
| | 150 | **100** | **0** |
| | 75 | **80.9** | **0** |

**Herbicidal Activity Bioassay.** Herbicidal activities of the title compounds **1a**−**1q** and control compound **A**, a previously prepared pyridiyl analogue, are listed in **Table 2**. Like other 2-cyanoacrylates in our previous work (*2*−*7*), all of the title compounds showed higher herbicidal activities in postemergence treatment as compared to preemergence treatment. To our pleasure, most of the compounds exhibited 100% inhibition against dicotyledon species (rape and amaranth pigweed) at 1.5 kg/ha, and half of them showed >50% inhibition against

monocotyledon weeds (barnyard grass and hairy crabgrass), which indicated that the introduction of the isoxazole ring to 2-cyanoarylate effectively enhanced their herbicidal activities.

Their herbicidal activities at lower doses against rape and amaranth pigweed in postemergence treatment revealed the influence of substituents on their reactivity (**Table 3**). 3-Isopropylacrylate compounds exhibited much higher activities than 3-methylthio analogues; whereas **1b**, **1c**, **1e**, **1g**, **1i**, **1m**, and **1q** maintained 100% inhibition at a dose of 375 g/ha, most of 3-methylthio analogues gave only 20% control at the same dose. When substituents at the 3-position of the isoxazole were tested, bromo-substituted compounds (**1p** and **1q**) gave better herbicidal activities than isopropyl and phenyl analogues (**1n**, **1o**, **1a**, and **1b**), which can be explained as higher electron negativity. The activities of substituted-phenyl-containing compounds varied largely with the groups on the phenyl group. For instance, from data of herbicidal activities against rape, the percent inhibition of **1c** ($R^1$ = 2-Cl-phenyl) was higher than that of **1b** ($R^1$ = phenyl) and **1e** ($R^1$ = 4-Cl-phenyl), whereas **1g** ($R^1$ = 2-$OCH_3$-phenyl) was showed less inhibition than **1b** ($R^1$ = phenyl) and **1i** ($R^1$ = 4-$OCH_3$-phenyl). Therefore, both the electrostatic and steric effects dominated their activities, but 4-*tert*-butylphenyl compounds (**1k**) gave the least herbicidal activity, which indicated a bulky group at the para position of phenyl to be not suitable.

Among all of the compounds, **1c** ($R^1$ = 2-Cl-phenyl, $R^2$ = i-Pr), **1i** ($R^1$ = 4-$OCH_3$-phenyl, $R^2$ = i-Pr), and **1q** ($R^1$ = Br, $R^2$ = i-Pr) exhibited excellent activities against rape and good activities against amaranth pigweed even at a dose of 75 g/ha, which was better than compound **A**. However, the activities of their methylthio analogues (**1a** and **1p**) were still lower than that of compound **A**. Comprehensive QSAR will be carried out with other types of compounds.

In summary, 2-cyanoacrylates containing an isoxazole moiety were synthesized and their herbicidal activities against four species were evaluated. Most of the compounds exhibited good inhibition against dicotyledon species (rape and amaranth pigweed) in postemergence treatment, of which 3-isopropylacrylate compounds gave much higher activities than 3-methylthio analogues. The substituents on the 3-position of the isoxazole ring varied the activities to some extent. Compounds **1c**, **1i**, and **1q** exhibited excellent herbicidal activities against rape and good activities against amaranth pigweed even at a dose of 75 g/ha. These compounds deserved further investigation, which we will report in the future.

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