Synthesis, Crystal Structure, and Herbicidal Activities of 2-Cyanoacrylates Containing 1,3,4-Thiadiazole Moieties

Wang, Tingting(王婷婷) Miao, Wenke(苗文科) Wu, Shanshan(吴姗姗)
Bing, Guifang(邴贵芳) Zhang, Xin(张欣) Qin, Zhenfang(秦振芳)
Yu, Haibo(于海波) Qin, Xue(秦雪) Fang, Jianxin*(方建新)

State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Three series of novel 2-cyanoacrylates **7a**—**7f**, **9a**—**9f**, **10a**—**10f** containing 1,3,4-thiadiazole ring moieties were synthesized as herbicidal inhibitors of photosystem II (PS II) electron transportation. Their structures were clearly verified by ^{1}H NMR, ^{13}C NMR, elemental analysis (or HRMS analysis) and single-crystal X-ray diffraction analysis. Bioassay showed that a suitable group at the 3-position of acrylates was essential for high herbicidal activity. In particular, compound **7e** showed the best herbicidal activities and gave 100% inhibitory activity against rape and amaranth pigweed at a dose of 1.5 kg/ha. Introduction of substituent with higher polarity such as sulfinyl or sulfonyl to the 5-position of 1,3,4-thiadiazole decreased herbicidal activities.

Keywords 2-cyanoacrylate, 1,3,4-thiadiazole, inhibitors of photosystem II electron transportation, herbicidal activity, synthesis

Introduction

Herbicidal activity of cyanoacrylates has been the subject of intense interest for the past decades.[1-3] A detailed study of compounds with general structure **A** (Figure 1) revealed that cyanoacrylates are inhibitors of photosystem II (PS II) electron transportation, which inhibits the growth of weeds by disrupting photosynthetic electron transportation at a common binding domain on the 32 kDa polypeptide (D1 protein) of the PS II reaction center. Among these cyanoacrylates, compound **B** (Figure 1) exhibits high inhibitory activity of the Hill reaction yet reported.[4-6] Bayer AG reported compound **C** (Figure 1), but little information was given on its herbicidal activity.[7] It has been reported that the

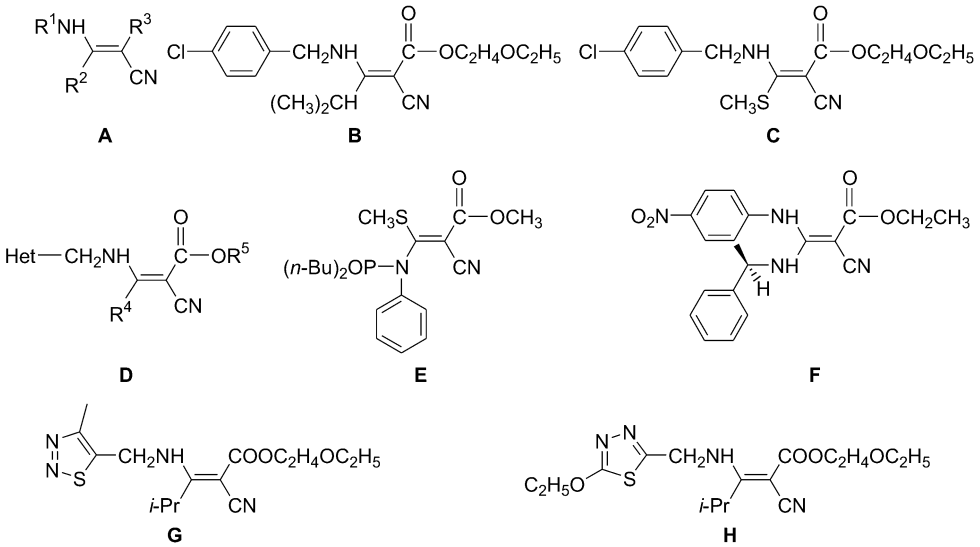

Figure 1 Chemical structures of compounds **A**—**H**.

* E-mail: fjx@nankai.edu.cn; Tel.: 0086-022-23505330; Fax: 0086-022-23503627
Received May 31, 2010; revised October 3, 2010; accepted January 26, 2011.
Project supported by the National Natural Science Foundation of China (NNSFC) (No. 20772068) and the National Key Project of Scientific and Technical Supporting Programs Funded by Ministry of Science & Technology of China (No. 2006BAE01A01-5).

D1 protein of PS II 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, Tyr 262) flanking this part of the binding domain.[4,8,9] However, the complete nature and topography of this hydrophobic domain of the D1 protein are unknown. Since cyanoacrylates have not commercialized as herbicides, so it has broad prospects for development.

Varous N- or S-containing heterocyclic derivatives always display broad-spectrum biological activities. In previous work on the synthesis of 2-cyanoacrylates, Wang *et al.*[10,11] reported that some compounds **D** (Figure 1) modified by replacing phenyl with heterocycles (pyridine or thiazole) showed higher herbicidal activity than parent compounds **B** and **C**. Recently, Song *et al.*[12,13] first reported that cyanoacrylates derivatives **E** and **F** (Figure 1) also exhibited moderate to excellent antiviral activity against tobacco mosaic virus (TMV) According to the bioisosterism principles, compounds **D**, **E** and **F** were all analogues of structures **A**, **B** and **C**.

In our previous work on the synthesis of cyanoacrylates we found that some compoumds with heterocycles showed good herbicidal activities.[14-17] For example, we have reported that compound **G** could control more than 90% of rape and amaranth pigweed at a dose of 1.5 kg/ha[17] and compound **H** could control 83.7% of amaranth pigweed even at a dose of 0.3 kg/ha.[16] At the same time we noticed that compounds **G** and **H** were also analogues of structures **A**, **B** and **C** which encouraged us to introduce thiadiazole rings with different polarity substitutents into 2-cyanoacrylates and further study the relationship of structure-herbicidal activity.

Experimental

General procedure

The melting points of the products were determined on an X-4 binocular microscope (Beijing Technology Instrument Co, Beijing, China) and were not corrected. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AC-P 300 spectrometer and 400 MHz using a Varian Mercury Plus 400 MHz spectrometer. Chemical shift values (δ) were downfield from internal tetramethylsilane. Elemental analyses were determined on a Yanaco CHN Corder MT-3 elemental analyzer, and HRMS data were obtained on an FTICR-MS spectrometer (Ionspec 7.0T). X-ray single-crystal diffraction was recorded using a Bruker SMART-1000 spectrometer. The reagents were all analytically or chemically pure. All solvents and liquid reagent were dried in advance and distilled before use. Compounds **6a**—**6f** were synthesized according to the reported methods.[10,11]

Synthesis of compound 1

To a solution of isopropanol (50 mL), water (60 mL) and postassium hydroxide (51.3 g, 0.75 mol), hydrazine hydrate (85%, 44.2 g, 0.75 mol) was added at the temperature of about 20 ℃, then carbon disulfide (57.5 g, 0.75 mol) was added dropwise at the temperature of about 9—10 ℃. After stirring at this temperature for 2 h, dimethyl sulfate (94.5 g, 0.75 mol) was added dropwise at the temperature of about 12—15 ℃, then keep stirring at the same temperature for 1 h. After filtration, the residue was washed with water then recrystallized with dichloromethane to obtain a white solid (71.5 g, 78.0%), m.p. 78—80 ℃ (Lit.[18] 80—82 ℃).

Synthesis of (5-methylthio-1,3,4-thiadiazol-2-yl)-methylchloride (3)

To a solution of **1** (61.1 g, 0.50 mol) in dioxane (100 mL) was added a solution of sodium acetate (53.0 g, 0.64 mol) in water (100 mL). The mixture was cooled to −15 ℃, and chloroacetylchloride (57.0 g, 0.50 mol) was then added dropwise. After stirring at 10 ℃ for 1 h, the mixture was extracted with ethyl ether, dried over $MgSO_4$, and evaporated *in vacuo* to yield a light yellow oil **2**. Then it was dumped in solution of 10% sodium bicarbonate to obtain a yellow solid. After filtration, the residue was washed with water and then recrystallized with methanol to obtain a light yellow solid (70.5 g, 78.0%), m.p. 71—73 ℃ (Lit.[19] 70—71 ℃).

Synthesis of (5-methylthio-1,3,4-thiadiazol-2-yl)-methylamine (5)

To a solution of **3** (9.0 g, 0.05 mol) in *N*,*N*-dimethylformamide was added potassium phthalimide (**4**) (9.3 g, 0.05 mol) in a small portion. After the mixture had been stirred at room temperature for 12 h, ice water (30 mL) was added, and lots of precipitate appeared. The precipitate was filtered with water to gave the desired *N*-substituted phthalimide intermediate (14.4 g, 99.9%).

To a suspension of *N*-substituted phthalimide intermediate (14.4 g, 0.05 mol) in ethanol (100 mL) was added hydrazinehydrate (80%, 10.7 g, 0.17 mol). The reaction mixture was refluxed for 3 h and then cooled. The precipitated phthalylhydrazide was filtered and washed with ethanol, and then the combined filtrate was evaporated under reduced pressure to give crude **5** (oil, 7.2 g, 90.0%), which underwent the next reaction without further purification.

General synthetic procedures for target compounds 7a—7f

A mixture of intermediates **6a**—**6f** (4.8 mmol) and **5** (5 mmol) in ethanol (30 mL) was refluxed for 3 h and then evaporated under reduced pressure to give crude products. The products were purified by column chromatography on a silica gel to give pure target compounds **7a**—**7f**.

(*Z*)-Ethoxyethyl 2-cyano-3-methylthio-3-(5-methylthio-1,3,4-thiadiazol-2-yl)methanaminoacrylate (7a) Yield 62.9%. m.p. 74—75 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.48 (br, 1H, CH_2NH), 5.15 (d, J = 6.2 Hz, 2H, CH_2NH), 4.31 (t, J=5.0 Hz, 2H, OCH_2), 3.70 (t, J=5.0

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Hz, 2H, CH_2O), 3.57 (q, J=7.6 Hz, 2H, OCH_2CH_3), 2.80 (s, 3H, CH_3S-thiadiazole), 2.73 (s, 3H, CH_3S), 1.21 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 172.43, 168.59, 167.68, 164.91, 117.35, 67.98, 66.84, 64.42, 44.01, 18.58, 16.48, 15.15. Anal. calcd for $C_{13}H_{18}N_4O_3S_3$: C 41.69, H 4.84, N 14.96; found C 41.64, H 4.80, N 14.90.

(*Z*)-Ethoxymethyl 2-cyano-3-methylthio-3-(5-methylthio-1,3,4-thiadiazol-2-yl)methanaminoacrylate (7b) Yield 59.1%. m.p. 89—90 ℃; ^1H NMR ($CDCl_3$) δ: 10.47 (br, 1H, CH_2NH), 5.15 (d, J=6.2 Hz, 2H, CH_2NH), 4.32 (t, J=4.8 Hz, 2H, OCH_2), 3.66 (t, J=4.8 Hz, 2H, CH_2O), 3.41 (s, 3H, CH_3O), 2.80 (s, 3H, CH_3S-thiadiazole), 2.73 (s, 3H, CH_3S); ^{13}C NMR ($CDCl_3$) δ: 172.48, 168.60, 167.64, 164.89, 117.40, 70.18, 64.16, 59.21, 44.03, 18.58, 16.49. Anal. calcd for $C_{12}H_{16}N_4O_3S_3$: C 39.98, H 4.47, N 15.54; found C 40.21, H 4.59, N 15.51.

(*E*)-Ethoxyethyl 2-cyano-3-ethyl-3-(5-methylthio-1,3,4-thiadiazol-2-yl)methanaminoacrylate (7c) Yield 64.6%. m.p. 57—58 ℃; ^1H NMR ($CDCl_3$) δ: 10.36 (br, 1H, CH_2NH), 4.90 (d, J=6.4 Hz, 2H, CH_2NH), 4.30 (q, J=5.0 Hz, 2H, OCH_2), 3.69 (t, J=4.9 Hz, 2H, CH_2O), 3.57 (q, J=7.0 Hz, 2H, OCH_2CH_3), 2.80 (s, 3H, CH_3S-thiadiazole), 2.70 (q, J=7.6 Hz, 2H, CH_3CH_2C=C), 1.28 (t, J=7.7 Hz, 3H, OCH_2CH_3), 1.21 (t, J=7.0 Hz, 3H, CH_3CH_2C=C); ^{13}C NMR ($CDCl_3$) δ: 174.94, 168.87, 168.52, 165.02, 117.76, 73.23, 68.05, 66.83, 63.99, 42.32, 24.51, 16.49, 15.15, 12.22. Anal. calcd for $C_{14}H_{20}N_4O_3S_2$: C 47.17, H 5.66, N 15.72; found C 47.01, H 5.52, N 15.58.

(*E*)-Ethoxymethyl 2-cyano-3-ethyl-3-(5-methylthio-1,3,4-thiadiazol-2-yl)methanaminoacrylate (7d) Yield 62.7%. m.p. 71—72 ℃; ^1H NMR ($CDCl_3$) δ: 10.38 (br, 1H, CH_2NH), 4.90 (d, J=6.4 Hz, 2H, CH_2NH), 4.31 (t, J=4.8 Hz, 2H, OCH_2), 3.65 (t, J=4.8 Hz, 2H, CH_2O), 3.41 (s, 3H, CH_3O), 2.81 (s, 3H, CH_3S-thiadiazole), 2.70 (q, J=7.7 Hz, 2H, CH_3CH_2C=C), 1.28 (t, J=7.6 Hz, 3H, CH_3CH_2C=C); ^{13}C NMR ($CDCl_3$) δ: 174.97, 168.86, 168.48, 164.97, 117.81, 72.94, 70.25, 63.74, 59.21, 42.32, 24.52, 16.50, 12.21. Anal. calcd for $C_{13}H_{18}N_4O_3S_2$: C 45.60, H 5.30, N 16.36; found C 45.34, H 5.18, N 16.14.

(*E*)-Ethoxyethyl 2-cyano-3-isopropyl-3-(5-methylthio-1,3,4-thiadiazol-2-yl)methanaminoacrylate (7e) Yield 62.6%. m.p. 70—71 ℃; ^1H NMR ($CDCl_3$) δ: 10.76 (br, 1H, CH_2NH), 4.95 (d, J=6.3 Hz, 2H, CH_2NH), 4.30 (t, J=5.1 Hz, 2H, OCH_2), 3.70 (t, J=5.1 Hz, 2H, CH_2O), 3.58 (q, J=7.0 Hz, 2H, OCH_2CH_3), 3.18—3.25 [m, 1H, CH $(CH_3)_2$], 2.80 (s, 3H, CH_3S-thiadiazole), 1.40 [d, J=7.1 Hz, 6H, CH $(CH_3)_2$], 1.21 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 178.93, 169.44, 168.73, 165.37, 118.11, 71.89, 68.05, 66.86, 64.11, 42.47, 30.25, 18.96, 16.48, 15.18. Anal. calcd for $C_{15}H_{22}N_4O_3S_2$: C 48.63, H 5.99, N 15.12; found C 48.70, H 5.72, N 14.98.

(*E*)-Ethoxymethyl 2-cyano-3-isopropyl-3-(5-methylthio-1,3,4-thiadiazol-2-yl)methanaminoacrylate (7f) Yield 59.6%. m.p. 88—89 ℃; ^1H NMR ($CDCl_3$) δ: 10.75 (br, 1H, CH_2NH), 4.97 (d, J=6.3 Hz, 2H, CH_2NH), 4.31 (t, J=4.8 Hz, 2H, OCH_2), 3.66 (t, J=4.8 Hz, 2H, CH_2O), 3.41 (s, 3H, CH_3O), 3.22 [m, 1H, $(CH_3)_2CHC$=C], 2.80 (s, 3H, CH_3S-thiadiazole), 1.40 [d, J=7.1 Hz, 6H, $(CH_3)_2CHC$=C]; ^{13}C NMR ($CDCl_3$) δ: 179.0, 169.4, 168.7, 165.3, 118.1, 71.7, 70.3, 63.9, 59.2, 42.5, 30.3, 18.9, 16.5; MS (ESI^+) m/z: 357.02 $[M+H]^+$. Anal. calcd for $C_{14}H_{20}N_4O_3S_2$: C 47.17, H 5.66, N 15.72; found C 46.96, H 5.48, N 15.84.

General synthetic procedures for target compounds 9a—9f

To a mixture of compounds **7a—7f** (3 mol) in 20 mL CH_2Cl_2 was added *m*-chloroperoxybenzoic acid (*m*-CPBA) (3.1 mol) in portions at 0 ℃. After the mixture was stirred at room temperature for 1 h, 6 mol/L NaOH (aq.) was added to pH≈8. The organic layer was separated and dried over $MgSO_4$. The filtrate was evaporated *in vacuo* and the products were purified by column chromatography on a silica gel to give the corresponding pure target compounds **9a—9f**.

(*Z*)-Ethoxyethyl 2-cyano-3-methylthio-3-(5-methylsulfinyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (9a) Yield 99.2%. oil. ^1H NMR ($CDCl_3$) δ: 10.57 (br, 1H, CH_2NH), 5.28 (d, J=6.3 Hz, 2H, CH_2NH), 4.32 (t, J=5.0 Hz, 2H, OCH_2), 3.71 (t, J=5.0 Hz, 2H, CH_2O), 3.58 (q, J=7.0 Hz, 2H, OCH_2CH_3), 3.15 (s, 3H, CH_3S=O), 2.75 (s, 3H, CH_3S), 1.21 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 180.24, 172.43, 170.31, 167.22, 117.37, 67.84, 66.57, 64.27, 44.25, 43.26, 18.55, 15.06; MS (ESI^-) m/z: 388.96 $[M-H]^-$. Anal. calcd for $C_{13}H_{18}N_4O_4S_3$: C 39.98, H 4.65, N 14.35; found C 39.80, H 4.40, N 14.23. HRMS (ESI) calcd for $C_{13}H_{18}N_4NaO_4S_3$ $(M+Na)^+$ 413.0382, found 413.0386.

(*Z*)-Ethoxymethyl 2-cyano-3-methylthio-3-(5-methylsulfinyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (9b) Yield 99.7%. oil. ^1H NMR ($CDCl_3$) δ: 10.56 (br, 1H, CH_2NH), 5.29 (d, J=6.3 Hz, 2H, CH_2NH), 4.33 (t, J=4.8 Hz, 2H, OCH_2), 3.67 (t, J=4.8 Hz, 2H, CH_2O), 3.41 (s, 3H, OCH_3), 3.15 (s, 3H, CH_3S=O), 2.75 (s, 3H, CH_3S); ^{13}C NMR ($CDCl_3$) δ: 180.75, 172.55, 170.08, 167.61, 117.11, 70.16, 64.27, 59.22, 44.13, 43.45, 18.64; HRMS (ESI) calcd for $C_{12}H_{16}N_4NaO_4S_3$ $(M+Na)^+$ 399.0226, found 399.0221.

(*E*)-Ethoxyethyl 2-cyano-3-ethyl-3-(5-methylsulfinyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (9c) Yield 95.7%. oil. ^1H NMR ($CDCl_3$) δ: 10.23 (br, 1H, CH_2NH), 4.95 (d, J=5.8 Hz, 2H, CH_2NH), 4.03 (t, J=4.4 Hz, 2H, OCH_2), 3.43 (t, J=4.4 Hz, 2H, CH_2O), 3.30 (q, J=6.9 Hz, 2H, OCH_2CH_3), 2.92 (s, 3H, CH_3S=O), 2.49 (q, J=7.4 Hz, 2H, CH_3CH_2C=C), 1.04 (t, J=7.4 Hz, 3H, CH_3CH_2C=C), 0.93 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 180.55, 174.90, 170.12, 168.02, 117.94, 72.62, 67.89, 66.43, 63.73, 43.26, 42.46, 24.52, 15.02, 12.08; HRMS (ESI) calcd for $C_{14}H_{20}N_4NaO_4S_2$ $(M+Na)^+$ 395.0818, found 395.0813.

(*E*)-Ethoxymethyl 2-cyano-3-ethyl-3-(5-methylsul-

finyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (9d) Yield 96.5%. oil. ^{1}H NMR ($CDCl_3$) δ: 10.46 (br, 1H, CH_2NH), 5.03 (d, J=6.5 Hz, 2H, CH_2NH), 4.32 (t, J=4.8 Hz, 2H, OCH_2), 3.66 (t, J=4.8 Hz, 2H, CH_2O), 3.41 (s, 3H, OCH_3), 3.15 (s, 3H, CH_3S=O), 2.72 (q, J=7.5 Hz, 2H, CH_3CH_2C=C), 1.30 (t, J=7.6 Hz, 3H, CH_3CH_2C=C); ^{13}C NMR ($CDCl_3$) δ: 180.52, 175.00, 170.09, 168.01, 118.04, 72.41, 70.12, 63.50, 58.83, 43.25, 42.47, 24.55, 12.07; HRMS (ESI) calcd for $C_{13}H_{18}N_4NaO_4S_2$ $(M+Na)^+$ 381.0664, found 381.0660.

(*E*)-Ethoxyethyl 2-cyano-3-isopropyl-3-(5-methylsulfinyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (9e) Yield 93.8%. oil. ^{1}H NMR ($CDCl_3$) δ: 10.86 (br, 1H, CH_2NH), 5.08 (d, J=6.4 Hz, 2H, CH_2NH), 4.31 (t, J=4.8 Hz, 2H, OCH_2), 3.71 (t, J=5.0 Hz, 2H, CH_2O), 3.58 (q, J=7.0 Hz, 2H, OCH_2CH_3), 3.15 (s, 3H, CH_3S=O), 3.19—3.24 [m, 1H, $CH(CH_3)_2$], 1.42 [d, J=7.0 Hz, $CH(CH_3)_2$], 1.21 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 180.96, 171.95, 170.50, 169.31, 117.97, 68.02, 66.87, 64.25, 64.20, 43.49, 19.01, 15.15; HRMS (ESI) calcd for $C_{15}H_{22}N_4NaO_4S_2$ $(M+Na)^+$ 409.0975, found 409.0976.

(*E*)-Ethoxymethyl 2-cyano-3-isopropyl-3-(5-methylsulfinyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (9f) Yield 97.7%. oil. ^{1}H NMR ($CDCl_3$) δ: 10.87 (br, 1H, CH_2NH), 5.09 (dd, J=6.5, 10.3 Hz, 2H, CH_2NH), 4.33 (t, J=4.8 Hz, 2H, OCH_2), 3.67 (t, J=4.8 Hz, 2H, CH_2O), 3.42 (s, 3H, OCH_3), 3.18—3.24 [m, 1H, $CH(CH_3)_2$], 3.14 (s, 3H, CH_3S=O), 1.42 [d, J=7.2 Hz, $CH(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ: 180.44, 171.96, 170.44, 169.06, 118.39, 70.18, 63.72, 59.00, 43.28, 38.78, 34.78, 19.24, 18.83; HRMS (ESI) calcd for $C_{14}H_{20}N_4NaO_4S_2$ $(M+Na)^+$ 395.0818, found 395.0814.

General synthetic procedures for target compounds 10a—10f

To a mixture of compounds **7a**—**7f** (3 mol) in 4 mL of AcOH and 2 mL of H_2O was added $KMnO_4$ (4.0 mol) in portions at 0 ℃. After the mixture was stirred at room temperature for 2 h, 3 mL of saturated $NaHSO_3$ (aq.) was added. The mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The products were purified by column chromatography on a silica gel to give the corresponding pure target compounds **10a**—**10f**.

(*Z*)-Ethoxyethyl 2-cyano-3-methylthio-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (10a) Yield 87.20%. m.p. 79—80 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.58 (br, 1H, CH_2NH), 5.29 (d, J=6.4 Hz, 2H, CH_2NH), 4.33 (t, J=5.0 Hz, 2H, OCH_2), 3.71 (t, J=5.0 Hz, 2H, CH_2O), 3.57 (q, J=7.0 Hz, 2H, OCH_2CH_3), 3.49 (s, 3H, CH_3SO_2), 2.76 (s, 3H, CH_3S), 1.22 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 172.52, 171.50, 169.97, 167.58, 117.00, 78.37, 67.91, 66.86, 64.59, 43.92, 43.03, 18.69, 15.15. Anal. calcd for $C_{13}H_{18}N_4O_5S_3$: C 38.41, H 4.46, N 13.78; found C 38.20, H 4.67, N 13.61.

(*Z*)-Ethoxymethyl 2-cyano-3-methylthio-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (10b) Yield 82.1%. m.p. 78—80 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.57 (br, 1H, CH_2NH), 5.29 (d, J=6.3 Hz, 2H, CH_2NH), 4.35 (t, J=4.8 Hz, 2H, OCH_2), 3.67 (t, J=4.8 Hz, 2H, CH_2O), 3.49 (s, 3H, CH_3SO_2), 3.41 (s, 3H, CH_3O), 2.76 (s, 3H, CH_3S); ^{13}C NMR ($CDCl_3$) δ: 172.49, 171.35, 170.11, 167.59, 116.89, 78.54, 70.15, 64.37, 59.21, 43.92, 43.02, 18.65. Anal. calcd for $C_{12}H_{16}N_4O_5S_3$: C 36.72, H 4.11, N 14.28; found C 36.71, H 3.98, N 14.42.

(*E*)-Ethoxyethyl 2-cyano-3-ethyl-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (10c) Yield 83.0%. m.p. 88—89 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.44 (br, 1H, CH_2NH), 5.16 (d, J=6.5 Hz, 2H, CH_2NH), 4.27 (t, J=4.8 Hz, 2H, OCH_2), 3.68 (t, J=4.8 Hz, 2H, CH_2O), 3.55 (q, J=7.0 Hz, 2H, OCH_2CH_3), 3.49 (s, 3H, CH_3SO_2), 2.71 (q, J=7.6 Hz, 2H, CH_3CH_2C=C), 1.29 (t, J=7.6 Hz, 3H, CH_3CH_2C=C), 1.18 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.96, 171.76, 170.04, 168.15, 117.82, 73.21, 67.94, 66.59, 63.92, 43.12, 42.38, 24.59, 15.06, 12.17. Anal. calcd for $C_{14}H_{20}N_4O_5S_2$: C 43.29, H 5.19, N 14.42; found C 43.16, H 5.36, N 14.63.

(*E*)-Ethoxymethyl 2-cyano-3-ethyl-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (10d) Yield 96.8%. m.p. 133—135 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.46 (br, 1H, CH_2NH), 5.08 (d, J=6.5 Hz, 2H, CH_2NH), 4.31 (t, J=4.8 Hz, 2H, OCH_2), 3.65 (t, J=4.8 Hz, 2H, CH_2O), 3.49 (s, 3H, CH_3SO_2), 3.40 (s, 3H, CH_3O), 2.71 (q, J=7.7 Hz, 2H, CH_3CH_2C=C), 1.30 (t, J=7.7 Hz, 3H, CH_3CH_2C=C); ^{13}C NMR ($CDCl_3$) δ: 174.78, 171.52, 170.25, 168.36, 117.42, 74.04, 70.22, 63.89, 59.17, 43.04, 42.35, 24.58, 12.27. Anal. calcd for $C_{13}H_{18}N_4O_5S_2$: C 41.70, H 4.85, N 14.96; found C 41.69, H 4.77, N 14.81.

(*E*)-Ethoxyethyl 2-cyano-3-isopropyl-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (10e) Yield 89.8%. m.p. 98—99 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.86 (br, 1H, CH_2NH), 5.12 (d, J=6.7 Hz, 2H, CH_2NH), 4.31 (t, J=5.1 Hz, 2H, OCH_2), 3.70 (t, J=5.1 Hz, 2H, CH_2O), 3.58 (q, J=7.0 Hz, 2H, OCH_2CH_3), 3.49 (s, 3H, CH_3SO_2), 3.18—3.21 [m, 1H, $CH(CH_3)_2$], 1.43 [d J=7.1 Hz, 6H, $CH(CH_3)_2$], 1.21 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 178.66, 171.84, 170.20, 169.28, 117.64, 72.95, 67.98, 66.84, 64.29, 43.02, 42.49, 30.50, 19.07, 15.13; HRMS (ESI) calcd for $C_{15}H_{22}N_4NaO_5S_2$ $(M+Na)^+$ 425.0924, found 425.0919.

(*E*)-Ethoxymethyl 2-cyano-3-isopropyl-3-(5-methylsulfonyl-1,3,4-thiadiazol-2-yl)methanaminoacrylate (10f) Yield 90.6%. m.p. 78—79 ℃; ^{1}H NMR ($CDCl_3$) δ: 10.85 (br, 1H, CH_2NH), 5.14 (d, J=6.4 Hz, 2H, CH_2NH), 4.31 (t, J=4.8 Hz, 2H, OCH_2), 3.66 (t, J=4.8 Hz, 2H, CH_2O), 3.49 (s, 3H, CH_3SO_2), 3.41 (s, 3H, CH_3O), 3.19—3.23 [m, 1H, $CH(CH_3)_2$], 1.42 [d, J=7.2 Hz, 6H, $CH(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ: 178.75, 171.80, 170.18, 169.22, 117.74, 72.69, 70.21, 63.99, 59.18, 43.02, 42.47, 30.46, 19.03; HRMS (ESI) calcd for $C_{14}H_{20}N_4NaO_5S_2$ $(M+Na)^+$ 411.0767, found 411.0769.

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X-ray diffraction

The crystal structure of compound **7b** was determined, and X-ray intensity data were record on a Bruker SMART 1000CCD diffraction meter using graphite monochromated Mo Kα radation (λ=0.71073 Å). In the range of 1.96°≤θ≤25.02°, 3055 independent reflections were obtained. All calculations were refined anistropically. All hydrogen atoms were located from a difference Fourier map and were placed at calculated positions and were included in the refinements in the riding mode with istropic thermal parameters (Figures 2, 3 and Table 1).

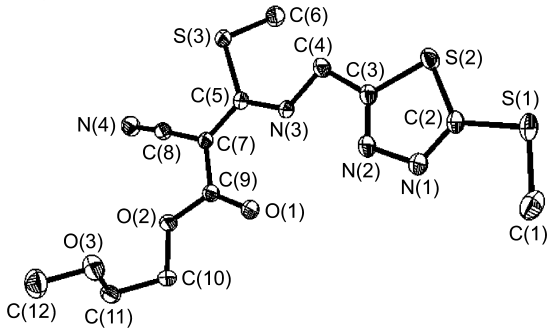


Figure 2 Molecular structure of **7b** in the crystal.

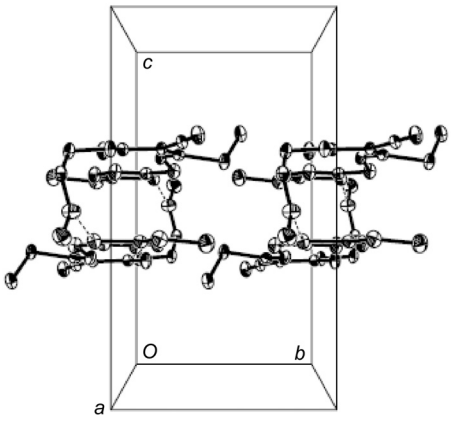


Figure 3 Packing diagram of crystal **7b**.

Herbicidal activity bioassay

The herbicidal activities of compounds **7a**—**7f**, **9a**—**9f** and **10a**—**10f** were evaluated using a previously reported procedure.[7,20]

Plant Material Two dicotyledonous weeds, amaranth pigweed (*Amaranthus retroflexus*) and rape (*Brassica napus* L.), and two monocotyledonous weeds, alfalfa (*Medicago sativa* L.) and hairy crabgrass [*Digitaria sanguinalis* (L.) Scop.] were used to test the herbicidal activities of the compounds. The seeds of amaranth pigweed 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 The seeds were planted in 6 cm diameter paper boxes containing artificial mixed soil. Before plant emerged, the boxes were covered with plastic film to retain moisture. Plants were grown in green house. Fresh weight of the above ground tissues was measured 10 d after treatment. Inhibition percentage was used to describe control efficiency of the compounds.

Treatment The dosage (activity ingredient) for each compound corresponded to 1.5 kg/ha. Purified compounds were dissoved in 100 μL of *N*,*N*-dimethylformamide with the addition of a little Tween 20 and then were sprayed using a laboratory belt sprayer delivering a 750 L/ha spray volume. Compounds were sprayed immediately after seed planting (preemergence treament) or after the expansion of the first true leaf (postemergence treatment). The mixture of same amount of water, *N*,*N*-dimethylformamide, and Tween 20 was sprayed as the control. Each treatment was tripilcated. The activity numbers represented the percent displaying herbicidal damage as compared to the control. The error of the experiments was 2%.

Results and discussion

Chemistry

The key intermediate [5-(methylthio)-1,3,4-thiadiazol-2-yl]methanamine (**5**) was synthesized starting from readily available dimethyl sulfate and carbon disulfide as shown in Scheme 1. Dimethyl sulfate was reacted with carbon disulfide and hydrazine hydrate in the presence of potassium hydroxide to give thiohydrazide **1**,[18] which was subsequently reacted with chloroacetylchloride at the temperature below −5 ℃ to obtain *N*-acylation intermediate **2**. Compound **2** was cyclized in 10% sodium bicarbonate to provide (5-methylthio-1,3,4-thiadiazol-2-

Table 1 Selected bond lengths (Å) and torsion angles (°) of crystal **7b**

S(1)—C(1)	1.831(5)	N(2)—C(3)	1.320(5)	N(3)-C(5)-C(7)-C(8)	−172.9(3)
S(2)—C(2)	1.770(4)	N(3)—C(4)	1.503(4)	N(3)-C(5)-C(7)-C(9)	8.9(5)
S(3)—C(5)	1.799(4)	N(4)—C(8)	1.150(4)	C(5)-C(7)-C(9)-O(1)	−9.8(5)
O(1)—C(9)	1.229(4)	C(3)—C(4)	1.514(5)	C(5)-C(7)-C(9)-O(2)	169.1(3)
O(2)—C(9)	1.376(4)	C(5)—C(7)	1.431(4)	C(8)-C(7)-C(9)-O(1)	171.9(3)
O(3)—C(11)	1.434(4)	C(7)—C(8)	1.446(5)	C(8)-C(7)-C(9)-O(2)	−9.2(4)
N(1)—N(2)	1.409(4)	C(7)—C(9)	1.490(5)	C(6)-S(3)-C(5)-C(7)	−131.3(3)
N(1)—C(2)	1.334(5)	C(10)—C(11)	1.523(5)	C(6)-S(3)-C(5)-N(3)	51.9(3)

yl)methylchloride **3** in a higher yield of 78.9% compared to the reported yield of 44.0%.[19] The reaction of **3** with potassium phthalimide **4** (prepared according to the published procedure[21]) gave intermediate *N*-substituted phthalimide which was subsequently refluxed with hydrazine in ethanol to afford the corresponding [5-(methylthio)-1,3,4-thiadiazol-2-yl]methanamine **5** in one pot.

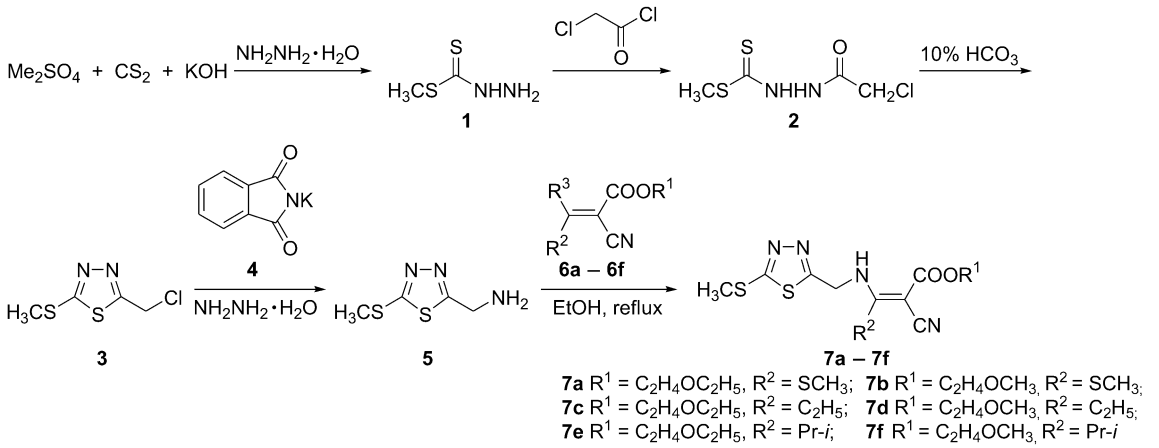
Intermediates 2-cyano-3,3-dimethylthioacrylates **6a**, **6b** were achieved by treating corresponding esters **8** with carbon disulfide and 2 mol of dimethyl sulfate in a one pot reaction using potassium hydroxide as alkali in good yield according to the reported methods (Scheme 2).[11]

Intermediate (*Z* + *E*)-2-cyano-3-methoxyacrylates **6c**—**6f** were synthesized by treating esters **8** with the corresponding acid chloride followed by methylation with diazomethane in good yield according to the reported methods (Scheme 3).[11]

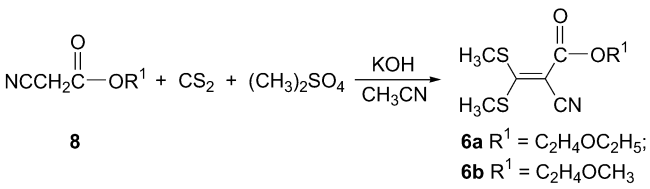
The target compounds (**7a**—**7f**) were synthesized by the reaction of methylamine **5** and 2-cyanoacrylates (**6a**—**6f**) with high yields. This reaction was assumed to go through a nucleophilic addition and elimination reaction (Scheme 4).[11] The methylamine attached the α, β-unsaturated double bond to form a transition state in which the orientation of thiadiazolemethylamino 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 **7b**, the X-ray data confirmed the *Z* sterochemistry of **7b** and demonstrated the presence of a planar core stablized by an intramolecular hydrogen bond between the ester carbonyl oxygen and the thiadiazolemethylamino hydrogen atom.

To further investigate the influence of polarity on herbicidal activity, two other series of 2-cyanoacrylates (**9a**—**9f** and **10a**—**10f**) with higher polarity such as sulfinyl or sulfonyl at the 5-position of 1,3,4-thiadiazole were synthesized by using different oxidation methods (*m*-CPBA, $KMnO_4$) as shown in Scheme 5 and Scheme 6, respectively. All these target compounds were confirmed by ^{1}H NMR and elemental analysis. The ^{1}H NMR ($CDCl_3$) spectra of these target compounds all have peaks between δ 10.30—10.80, which are the characteristic peaks of NH in these target compounds.

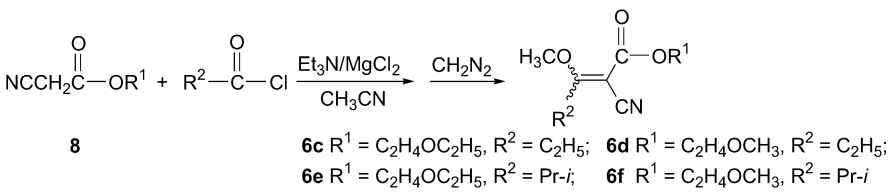
Scheme 1



Scheme 2



Scheme 3



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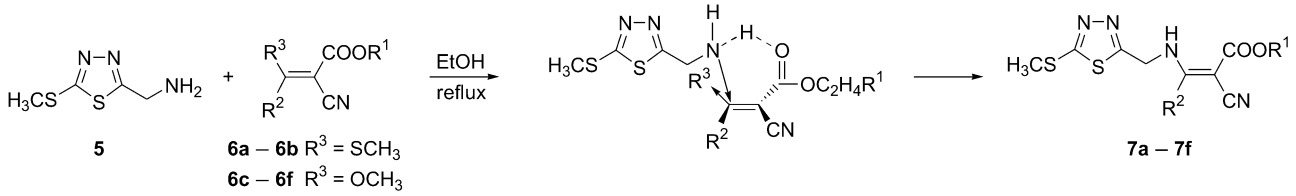
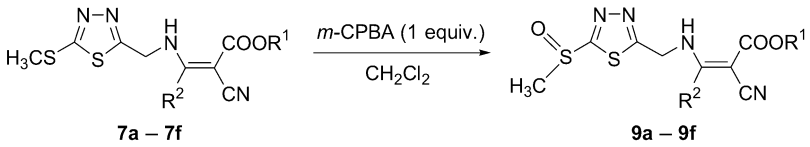
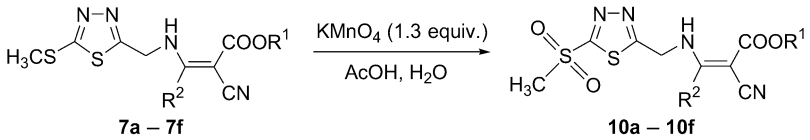
Scheme 4



Scheme 5



Scheme 6



Crystal structure analysis

Compound **7b** was recrystalized from ethyl acetate to give colorless crystals suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a=7.972(9) Å, b=14.171(16) Å, c=15.293(17) Å, α=90.00°, β=90.00°, γ=90.00°, μ=0.445 mm^{-1}, V=1728(3) Å^3. There are four molecules in the unit cell and the space group $P2_1/c$, z=4, D_x=1.386 mg/m^3, F(000)=752, T=294 (2) K, 1.96°$\leqslant\theta\leqslant$25.02°; and the final R factor, R_1=0.0485, wR_2=0.1211.

It could be seen from the X-ray single-crystal analysis that amino and carbonyl are of the same side of the vinyl, and there are intramolecular hydrogen bond between the nitrogen atom and oxygen of the carbonyl (Figures 2, 3). The bond length of C(5)—C(7) (1.431 Å) is longer than normal C=C (1.34 Å), the bond lengths of C(7)—C(8) (1.446 Å) and C(7)—C(9) (1.490 Å) are shorter than normal C—C (1.54 Å), the bond length of C(9)—O(1) (1.229 Å) is shorter than normal C=O (1.34 Å), the bond length of C(9)—O(2) (1.376 Å) is shorter than normal C—O (1.44 Å) , the bond length of C(5)—N(3) (1.349 Å) is shorter than normal C—N single bond (1.49 Å), which suggest that the electron density is localized among N(3)-C(5)-C(7)-C(9)-O(1) and O(2) (Table 1).

Herbicidal activities

Many papers have reported that cyanoacrylates containing heterocycles such as furan, tetrahydrofuran, thiazole, pyridine showed good herbicidal avtivities.[10,11,22,23] To further amplify the interaction of cyanoacrylates with the lipophilic binding domain, we introduced 1,3,4-thiadiazole to the cyanoacrylates, and their herbicidal activities have been evaluated (Tables 2 and 3). The result showed that most of the compounds (**7c**, **7d**—**7e**, **9a**—**9e**, **10a**, **10e**) showed higher herbicidal activities in postemergence treatment than in preemergence treatment. And in postemergence treatment, most of the compounds (**7c**, **7e**—**7f**, **9a**—**9f**, **10a**, **10d**—**10e**) showed greater herbicidal activities againat dicotyledonous weeds (rape and amaranth pigweed) than monocotyledon weeds (alfalfa and hairy crabgrass). The structure-activity relationship according to herbicidal activities of compounds **7a**—**7f** against rape and amaranth pigweed in postemergence treatment (Table 2) showed that a suitable isopropyl group (**7e**, **7f**) at the 3-position of acrylates was essential for high herbicidal activity. Compound **7e** which contains ethoxyethyl at the 3-position showed 100% herbicidal activities against dicotyledonous weeds (rape and amaranth pigweed) at 1.5 kg/ha. Compound **7f** which contains ethoxymethyl at the 3-position showed the same herbicidal activities (98.0%) against dicotyledonous weed (rape). At the rates of 0.6 and 0.3 kg/ha (Table 3), compound **7e** still exhibited excellent herbicidal activities, respectively.

Decreasing of herbicidal activities was observed when methylthio of 1,3,4-thiadizole was replaced by sulfinyl or sulfonyl (Table 2, compounds **9a**—**9f**, **10a**—**10f**), suggesting that introduction of substituent with higher polarity such as sulfinyl or sulfonyl to the 5-position of 1,3,4-thiadiazole decreased herbicidal activities.

Conclusions

In summary, three series of novel 2-cyanoacrylates containing 1,3,4-thiadiazole moieties which were substituted in 5-position by different polarity substituents

Table 2 Herbicidal activities of target compounds **7a**—**7f**, **9a**—**7f** and **10a**—**10f** (1.5 kg/ha, percent inhibition/%)

Compound	Postemergency treatment				Preemergency treatment			
	Rape	Amaranth pigweed	Alfalfa	Hairy crabgrass	Rape	Amaranth pigweed	Alfalfa	Hairy crabgrass
7a	0	0	0	0	0	0	0	0
7b	0	0	0	0	0	0	0	0
7c	66.2	0	15.0	0	49.1	0	0	0
7d	25.7	0	0.7	40.0	20.0	0	0	0
7e	100.0	100.0	0	5.0	86.6	0	0	5.0
7f	0	66.2	0.7	0	98.0	40.0	0	0
9a	12.1	26.7	5.8	5.0	0	0	10.0	0
9b	14.1	16.8	4.2	5.0	0	0	5.0	0
9c	23.7	8.9	8.9	10.0	0	0	5.0	10.0
9d	6.3	24.8	0	0	0	0	0	5.0
9e	15.2	18.8	9.7	5.0	2.7	0	5.0	10.0
9f	26.3	0	0	5.0	23.0	0	0	33.3
10a	20.0	10.0	5.0	0	0	0	0	0
10b	0	0	0	0	0	0	0	0
10c	0	0	20.0	15.0	30.1	0	0	0
10d	20.6	0	0	0	37.2	12.5	0	0
10e	32.5	0	5.0	0	0	5.0	0	16.1
10f	25.7	0	33.1	0	51.5	0	5.0	14.0

Table 3 High hebicidal activities of compounds **7e** and **7f** (percent inhibition/%)

Compound	Dose/(g•ha^{-1})	Postemergency treatment	
		Rape	Amaranth pigweed
7e	600	95	100
	300	74.2	73.1
7f	600	43.2	77.9
	300	20.1	0

were synthesized. Their herbicidal activities were evaluated. Their structure-activity relationships were also studied. Some compounds exhibited good herbicidal activities. It was found that a suitable group such as isopropyl at the 3-position of cyanoacrylates was essential for high herbicidal activities. Introduction of substituent with higher polarity such as sulfinyl or sulfonyl to the 5-position of 1,3,4-thiadiazole decreased herbicidal activities. It was found that the substitutents at the 5-position of thiadiazole ring were essential for herbicidal activities, compounds with lower polarity substitutents at 5-position of thiadiazole ring showed a higher level of herbicidal activities. Perhaps due to the higher polarity substitutents at 5-position of thiadiazole ring, the cyanoacrylates could not fits well into the hydrophobic domain of the site maximizing van der Waals ring-stacking interactions with D1 protein. We found that 2-cyanoacrylates containing 1,3,4-thiadiazole moieties are a noval class of herbicides which have the research potency, further study is underway.

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(E1005314 Li, L.; Zheng, G.)

