Synthesis, crystal structure and herbicidal activity of novel 1,2,3-thiadiazole substituted 2-cyanoacrylates

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Abstract

A series of novel 2-cyanoacrylates containing the 1,2,3-thiadiazole ring moiety were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis and, in one case, by X-ray crystallography. Most of these cyanoacrylates exhibited good herbicidal activities. In particular, (*Z*)-methoxyethyl- and (*Z*)-ethoxyethyl-2-cyano-3-isopropyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate **9h** and **9g** showed 100% herbicidal activities against rape and amaranth pigweed at a dose of 1.5 kg/ha. 2-Cyanoacrylates containing the thiadiazole ring are a new variation of this class of compound which still retain herbicidal activities.

Keywords: 2-Cyanoacrylates, 1,2,3-thiadiazole, photosystem II electron transportation, herbicidal activity, synthesis

Introduction

Herbicidal activity of cyanoacrylates has been the subject of intense interest for the past decades. A detailed study of compounds with general structure **A** (Figure 1) revealed that cyanoacrylates are inhibitors of photosystem II (PS II) electron transportation, which inhibit the weed growth by disrupting photosynthetic electron transportation at a common binding domain on the 32kDa polypeptide (D1 protein) of the PS II reaction center.[1-3] Among these cyanoacrylates, compound **B** (Figure 1) exhibits high herbicidal activity 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 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, and cyanoacrylates have not been commercialized as herbicides because of their high dose rates.

In previous work on synthesis of 2-cyanoacrylates, Wang et al. reported that some compounds **D** (Figure 1) whose phenyl were replaced by heterocycles (pyridine or thiazole) showed higher herbicidal activity than parent compounds **B** and **C**.[10,11,12] Recently, Song et al. first reported that cyanoacrylates derivatives **E** and **F** (Figure 1) also exhibited moderate to excellent antiviral activity against tobacco mosaic virus (TMV).[13,14] According to the bioisosterism principles, compounds **D**, **E**, and **F** are all analogues of structures **A**, **B** and **C**, which encouraged us to introduce novel 1,2,3-thiadiazole ring into 2-cyanoacrylates and further study the relationship of structure-herbicidal activity. Herein, we are reporting the synthesis of novel 2-cyanoacrylates containing the 1,2,3-thiadiazole moiety and the evaluation of their herbicidal activities.

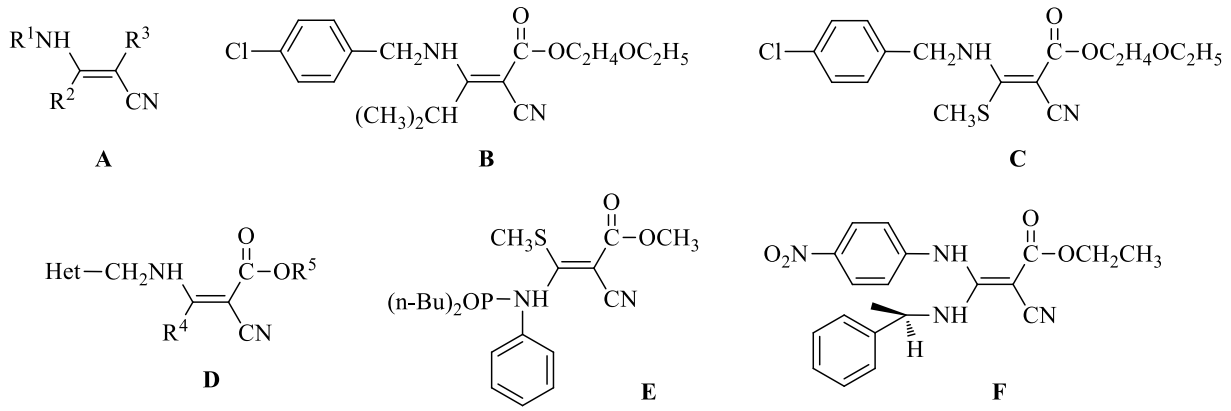


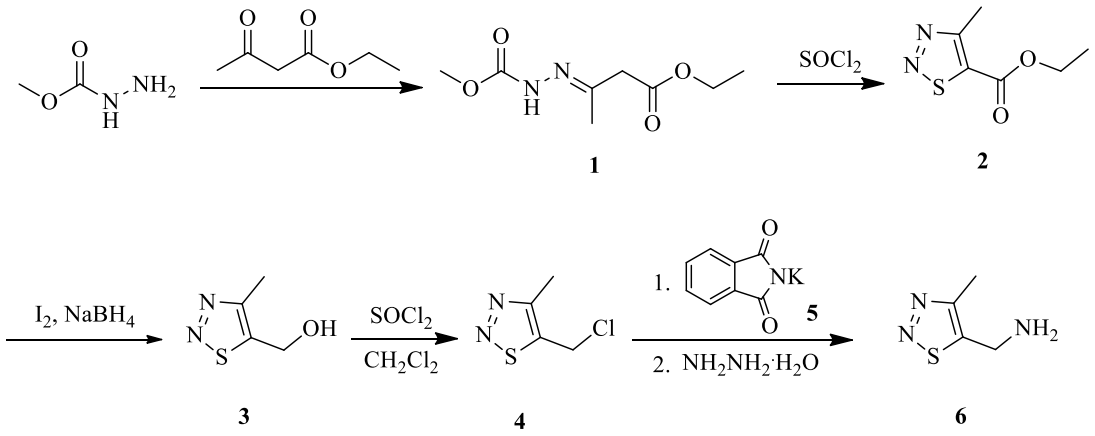
Figure 1. Chemical structures of cyanoacrylates A-F.

Results and Discussion

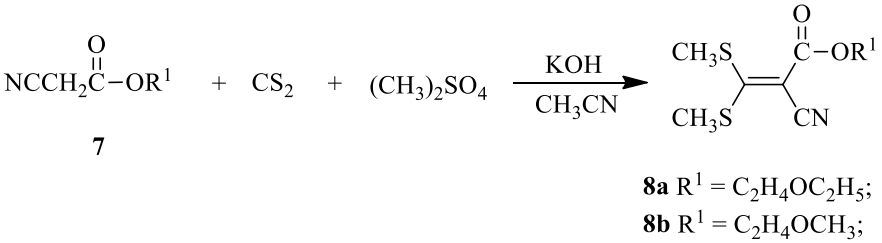
Synthesis

The key intermediate, [(4-methyl-1,2,3-thiadiazol-5-yl)methyl]amine **6**, was synthesized from readily available methyl hydrazinecarboxylate and ethyl acetoacetate as shown in **Scheme 1**. Methyl hydrazinecarboxylate and ethyl acetoacetate reacted at room temperature to obtain intermediate **1**. Then **1** was cyclized with thionyl chloride to obtain 4-methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester **2**.[15] Ester **2** was reduced by sodium borohydride in the presence of iodine to give 4-methyl-1,2,3-thiadiazole-5-methanol **3**,[16] which was chlorinated by using thionyl chloride to obtain 5-chloromethyl-4-methyl-1,2,3-thiadiazole **4**. The reaction of **4** with potassium phthalimide **5** gave intermediate N-substituted phthalimide which was subsequently treated with hydrazine to afford the corresponding aminomethyl compound **6** in one step.

Intermediates 2-cyano-3,3-dimethylthioacrylates **8a**, **8b** were achieved by treating corresponding esters **7** with carbon disulfide and 2 mole 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 **8c**-**h** were synthesized by treating esters **7** with the corresponding acid chloride followed by methylation with diazomethane in good yield according to the reported methods (Scheme 3).[11]

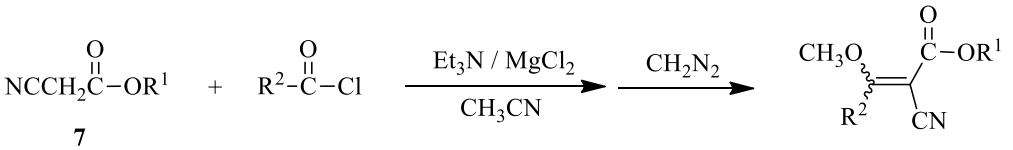


Scheme 1. Synthetic route to intermediate compound **6.**



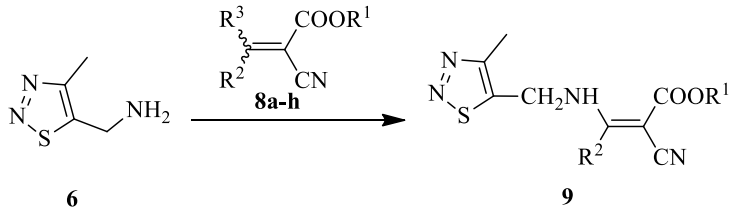
8a $R^1 = C_2H_4OC_2H_5$;
8b $R^1 = C_2H_4OCH_3$;

Scheme 2. Synthetic route to intermediates **8a** and **8b.**



8c $R^1 = C_2H_4OC_2H_5$, $R^2 = CH_3$; **8d** $R^1 = C_2H_4OCH_3$, $R^2 = CH_3$;
8e $R^1 = C_2H_4OC_2H_5$, R^2 = Et; **8f** $R^1 = C_2H_4OCH_3$, R^2 = Et;
8g $R^1 = C_2H_4OC_2H_5$, R^2 = Pr-*i*; **8h** $R^1 = C_2H_4OCH_3$, R^2 = Pr-*i*;

Scheme 3. Synthetic route to intermediates **8c-8h.**



6 **9**

9a $R^1 = C_2H_4OC_2H_5$, R^2 = MeS, R^3 = MeS; **9b** $R^1 = C_2H_4OCH_3$, R^2 = MeS, R^3 = MeS;
9c $R^1 = C_2H_4OC_2H_5$, R^2 = Me, R^3 = MeO; **9d** $R^1 = C_2H_4OCH_3$, R^2 = Me, R^3 = MeO;
9e $R^1 = C_2H_4OC_2H_5$, R^2 = Et, R^3 = MeO; **9f** $R^1 = C_2H_4OCH_3$, R^2 = Et, R^3 = MeO;
9g $R^1 = C_2H_4OC_2H_5$, R^2 = Pr-*i*, R^3 = MeO; **9h** $R^1 = C_2H_4OCH_3$, R^2 = Pr-*i*, R^3 = MeO;

Scheme 4. Synthesis of the title compounds **9a-h.**

The target compounds **9a-h** were synthesized by the nucleophilic addition and elimination reaction of aminomethyl compound **6** and **8a-h** (Scheme 4).

Crystal Structure Analysis

Compound **9c** was recrystallized from ethyl acetate to give colorless crystals suitable for X-ray single-crystal diffraction (Figure 2) with the following crystallographic parameters (Table 1): a = 5.9030(12)Å, b = 7.3409(15)Å, c = 19.045(4)Å, α = 80.15(3)°, ß = 85.61(3)°, γ = 67.30(3)°, μ = 0.232mm-1, ν = 750.1(3)Å3, the fact that there are four molecules in the unit cell and the space group P-1/c, z = 2, Dx = 1.374 mg/m^3, F(000) = 328, T = 113 (2) K, 2.17° ≤ θ ≤ 25.02°; and the final R factor, R_1 = 0.0345, wR_2 = 0.0949. CCDC 764261 contains the supplementary crystallographic data for this paper.

Table 1. Selected bond lengths (Å) and torsion angles (°) of crystal **9c**

Selected bond	Lengths (Å)	Selected angles	Angles (°)	Selected torsion angles (°)	Torsion angles (°)
S1-N2	1.6866(15)	N1-C2-C1	119.79(14)	N1-N2-S1-C3	-0.5(13)
S1-C3	1.6907(17)	N1-N2-S1	111.25(11)	N2-N1-C2-C1	-179.46(15)
O1-C9	1.2185(18)	N2-N1-C2	114.10(14)	N2-N1-C2-C3	0.7(2)
O2-C10	1.4520(18)	O2-C9-C7	111.38(12)	N3-C4-C3-C2	-173.60(14)
O3-C12	1.426(2)	C1-C2-C3	126.77(15)	N4-C8-C7-C5	-141(11)
N1-N2	1.296(2)	C2-C3-C4	126.79(15)	C1-C2-C3-C4	-0.5(3)
N1-C2	1.372(2)	C4 -N3 -C5	125.12(13)	C3-C4-N3-C5	92.64(17)
N3-C4	1.4578(19)	C5-C7-C8	119.43(13)	C4-N3-C5-C7	177.91(13)
N3-C5	1.3276(19)	C5-C7-C9	123.10(13)	C6-C5-C7-C9	-179.98(13)
N4-C8	1.1501(19)	C7-C5-C6	120.85(13)	C5-C7-C9-O1	-0.4(2)
C5-C7	1.399(2)	C9-O2-C10	117.48(11)	C9-O2-C10-C11	177.77(12)
C3-C4	1.503(2)	C11-O3-C12	114.81(12)	C10-C11-O3-C12	-92.96(16)

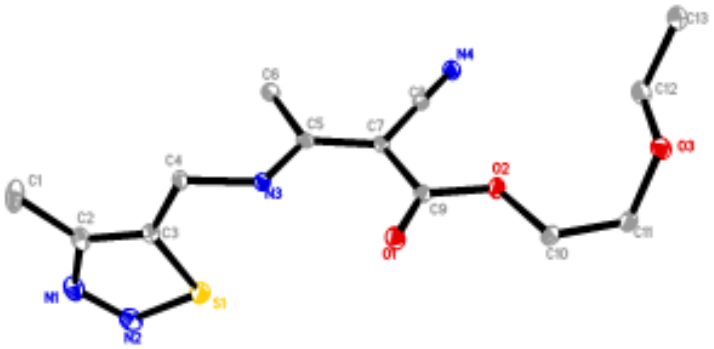


Figure 2. Molecular structure of **9c** in the crystal.

Structure-Activity Relationships. In our previous work, the cyanoacrylate structure modified by replacing phenyl with 4,5-dihydro-1,3,4-thiadiazol-5-one showed relatively lower herbicidal activities than the parental compound.[17] This is possibly due to the relatively high polarity and the decrease in the overall molecular lipophilicity.

Table 2. Herbicidal activities of products **9a-h** and contrast compound **10** (1.5 kg/ha)[a]

	R^1	R^2	Postemergence treatment				Preemergence treatment			
			rape	amaranth pigweed	alfalfa	hairy crabgrass	rape	amaranth pigweed	alfalfa	hairy crabgrass
9a	C_2H_4OEt	MeS	59	66	43	59	0	11	11	14
9b	C_2H_4OMe	MeS	45	10	10	0	10	19	19	34
9c	C_2H_4OEt	Me	74	92	5	40	5	19	27	0
9d	C_2H_4OMe	Me	70	83	0	35	10	3	0	19
9e	C_2H_4OEt	Et	95	84	0	90	10	0	44	27
9f	C_2H_4OMe	Et	73	100	23	64	5	3	0	10
9g	C_2H_4OEt	Pr-*i*	100	100	63	100	91	5	60	88
9h	C_2H_4OMe	Pr-*i*	100	100	59	93	72	10	47	75
10[b]			99	100	100	100	100	80	56	31

[a] Triplicate each treatment. Activity numbers represent percent diplaying herbicidal damage as compared to control. 0 mean no activity. Error of these numbers is 2%.

[b] Compound (Z)-ethoxyethyl 2-cyano-3-methylthio-3-(2-chloro-5-pyridyl)methaneaminoacrylate **10** and its activity were reported in Ref.12, while all of the data here of it came from our own work.

To further strengthen interaction of these cyanoacrylates with the lipophilic binding domain of the PS Ⅱ reaction center and explore influence of aromatic ring and their substitutions on the activity, we introduced a low polarity 1,2,3-thiadiazole group to the cyanoacrylates. Their herbicidal activities were evaluated as shown in Table 2. From biological assay results in Table

2, most of the compounds synthesized showed good herbicidal activities. They showed greater herbicidal activities in postemergence treatment than in preemergence treatment. So, we herein analyzed the structure-activity relationship mainly according to the data of biological assay in the postemergence treatment.

In postemergence treatment, most of the compounds showed greater herbicidal activities against dicotyledonous weeds (amaranth pigweed and rape) than monocotyledon weeds (alfalfa and hairy crabgrass). Compounds **9g** and **9h**, which each bear an isopropyl group at 3-position (the largest group tested), showed the highest activities. In particular, compound **9g** showed excellent herbicidal activities against dicotyledonous weeds (amaranth pigweed and rape) and monocotyledonous weeds (alfalfa and hairy crabgrass) both in postemergence treatment and in preemergence treatment as compared with other compounds.

Conclusions

We have demonstrated that 2-cyanoacrylates containing a 1,2,3-thiadiazole moiety displayed herbicidal activity. Some structure-activity relationships were studied and in particular, it was found that an isopropyl at the 3-position of the cyanoacrylates afforded highest herbicidal activities. (*Z*)-methoxyethyl- and (*Z*)-ethoxyethyl 2-cyano-3-isopropyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate **9h** and **9g** showed 100% herbicidal activities against rape and amaranth pigweed at a dose of 1.5 kg/ha. Further study of structure-activity relationships with 2-cyanoacrylates containing a 1,2,3-thiadiazole moiety are underway.

Experimental Section

Synthetic Procedures. Melting points of the products were determined on an X-4 binocular microscope (Beijing Tech. Instrument Co., Beijing, China) and were not corrected. Proton 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) are given in ppm and were downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded using a Bruker AC-P 400 spectrometer (100 MHz) using $CDCl_3$ or DMSO as a solvent. Chemical shift values (δ) are reported in parts per million from the solvent peak (77.0 ppm). X-ray single-crystal diffraction was recorded using Bruker SMART-1000 spectrometer. Elemental analyses were performed on a Yanaco CHN Corder MT-3 elemental analyzer in the State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, People's Republic of China. The products were purified by column chromatography over silica gel of 100-200 mesh. All solvents and liquid reagents were dried in advance and distilled before use. Potassium phthalimide (**5**) was prepared according to the published procedure.[18]

Ethyl 3-(methoxycarboxyhydrazone)-butyrate (1). Methyl hydrazinecarboxylate (18.0 g, 0.20 mol) dissolved in pure ethanol was added dropwise to a solution of ethyl acetoacetate (26.0 g, 0.20 mol) in absolute alcohol at the temperature of 0 °C. After stirring at room temperature for about 12 h, the solvent was removed in vacuo, then imine **1** was collected as a light yellow solid (40.5 g, 93% yield, mp, 49-52 °C.) which was used without further purification.[15]

4-Methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester (2). To thionyl chloride (39.3 g, 0.33 mol) was added a solution of **1** (21.8 g, 0.1 mol) in dichloromethane (50 mL) dropwise at the temperature of 0 °C. The mixture was stirred for 10 h at room temperature and concentrated, the residue was dissolved in dichloromethane. The dichloromethane solution was washed with water and saturated brine, dried with sodium sulfate and evaporated in vacuo. After vacuum distillation (78-80 °C / 400 Pa) a colorless oil was obtained (28.0 g, 81% yield).[15]

4-Methyl-1,2,3-thiadiazole-5-methanol (3). Sodium borohydride (1.52 g, 0.04 mol) was added to a stirring solution of **2** (3.5 g, 0.02 mol) in tetrahydrofuran (30 mL). Iodine (5.1 g, 0.02 mol) in tetrahydrofuran (30 mL) was added dropwise at 0 °C. The reaction mixture was heated at reflux for 8 h, cooled to room temperature and then quenched with methanol. Solvent was removed under reduced pressure. The residue was dissolved in dichloromethane. The dichloromethane solution was washed with water and saturated brine, dried with sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography over silica gel, elution with the co-solvents ethyl acetate-petroleum ether to obtain a colorless oil (1.20 g, 46% yield).[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.61 (s, 3H, CH_3), 5.00 (s, 2H, CH_2OH), 5.00 (br, 1H, CH_2OH).

5-Chloromethyl-4-methyl-1,2,3-thiadiazole (4). Thionyl chloride (23.8 g, 0.20 mol) was added to the solution of **3** (13.0 g, 0.10 mol) in dichloromethane (100 mL) at 0°C. The mixture was stirred for 10 h at room temperature and then quenched with ice water. The aqueous layer was extracted with dichloromethane, and the combined organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired product **4** as a light yellow oil (13.8 g) in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.67 (s, 3H, CH_3), 4.81 (s, 2H, CH_2Cl).

[(4-Methyl-1,2,3-thiadiazol-5-yl)methyl]amine (6). To a mixture of **4** (14.9 g, 0.10 mol) in *N*, *N*-dimethylformamide (100 mL) was added potassium phthalimide **5** (18.5 g, 0.10 mol) in portions. The mixture was stirred for 10 h at room temperature and then quenched with ice water (100 mL), filtered to obtain a light yellow solid. The solid was dissolved in anhydrous ethanol (200 mL) and 85% hydrazine hydrate (20.0 g, 0.34 mol) was added. Then, the mixture was heated to reflux for 4 h. After the mixture was cooled, filtered and concentrated, aminomethyl compound **6** was collected as a light yellow oil (12.3 g, 95% yield). ^{1}H NMR (400 MHz, DMSO) δ: 2.54 (s, 3H, CH_3), 4.00 (s, 2H, CH_2NH_2), 2.61-2.94 (br, 2H, CH_2NH_2). ^{13}C NMR (400 MHz, DMSO) δ: 158.0, 153.3, 37.4, 12.0. m/z (ESI$^+$) 130.17 $[M+H]^+$.

General synthetic procedure for target compounds 9a-h

The mixture of **8a-h** (5 mmol), (4-methyl-1,2,3-thiadiazol-5-yl)methylamine **6** (6 mmol) and anhydrous ethanol (30 mL) was heated at reflux for 3 h and then evaporated in vacuo to give crude products **9a-h**. The products were purified by column chromatography over silica gel, elution with the different concentrations of co-solvents ethyl acetate-petroleum ether.

(*Z*)-Ethoxyethyl-2-cyano-3-methylthio-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9a). Yellow oil, yield, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.70 (s, 3H, CH_3-thiadiazole), 2.72 (s, 3H, CH_3S), 3.56 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.68 (t, *J* = 5.0 Hz, 2H, CH_2O), 4.30 (t, *J* = 5.0 Hz, 2H, OCH_2), 5.02 (d, *J* = 6.1 Hz, 2H, CH_2NH), 10.41 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 172.3, 167.8, 156.5, 146.6, 117.3, 68.0, 66.8, 64.4, 39.8, 18.5, 15.2, 12.6; Elemental Anal. Calcd. for $C_{13}H_{18}N_4O_3S_2$: C, 45.60; H, 5.30; N, 16.36; Found: C, 45.36; H, 5.53; N, 16.20.

(*Z*)-Methoxyethyl-2-cyano-3-methylthio-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9b). Yield, 78%, mp, 57-58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.68 (s, 3H, CH_3-thiadiazole), 2.70 (s, 3H, CH_3S), 3.41 (s, 3H, OCH_3), 3.66 (t, *J* = 4.8 Hz, 2H, CH_2O), 4.32 (t, *J* = 4.7Hz, 2H, OCH_2), 5.02 (d, *J* = 6.1Hz, 2H, CH_2NH), 10.42 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 172.3, 167.9, 159.5, 146.4, 117.2, 70.2, 64.2, 59.2, 39.3, 18.5, 12.6; Elemental Anal. Calcd. for $C_{12}H_{16}N_4O_3S_2$: C, 43.89; H, 4.91; N, 17.06; Found: C, 44.01; H, 5.16; N, 16.81.

(*Z*)-Ethoxyethyl-2-cyano-3-methyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9c). Yield, 76%, mp, 60-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.34 (s, 3H, CH_3C=C), 2.73 (s, 3H, CH_3-thiadiazole), 3.57 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.69 (t, *J* = 4.9 Hz, 2H, CH_2O), 4.30 (t, *J* = 4.9 Hz, 2H, OCH_2), 4.81 (d, *J* = 6.0 Hz, 2H, CH_2NH),10.33 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 169.3, 168.2, 156.4, 146.5, 118.1, 74.0, 68.0, 66.7, 63.9, 38.7, 17.8, 15.1, 12.5; Elemental Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.31; H, 5.85; N, 18.05. Found: C, 50.39; H, 5.62; N, 18.14.

(*Z*)-Methoxyethyl-2-cyano-3-methyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9d). Yield, 81%, mp, 69-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H, CH_3C=C), 2.73 (s, 3 H, CH_3-thiadiazole), 3.40 (s, 3H, OCH_3), 3.65 (t, *J* = 4.7 Hz, 2H, CH_2O), 4.31 (t, *J* = 4.7 Hz, 2H, OCH_2), 4.80 (d, *J* = 6.1 Hz, 2H, CH_2NH), 10.31 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 169.1, 168.3, 156.4, 146.2, 117.9, 70.3, 63.8, 59.3, 38.7, 17.8, 12.6; Elemental Anal. Calcd. for $C_{12}H_{16}N_4O_3S$: C, 48.64; H, 5.44; N, 18.91; Found: C, 48.84; H, 5.28; N, 19.01.

(*Z*)-Ethoxyethyl-2-cyano-3-ethyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9e). Yield, 79%, mp, 48-50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.29 (t, *J* = 7.7 Hz, 3H, CH_3CH_2C=C), 2.65 (q, 2H, *J* = 7.7 Hz, CH_3CH_2C=C), 2.72 (s, 3H, CH_3-thiadiazole), 3.56 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.69 (t, *J* = 5.0 Hz, 2H, CH_2O), 4.29 (t, *J* = 5.0 Hz, 2H, OCH_2), 4.81 (d, *J* = 6.1 Hz, 2 H, CH_2NH),10.26 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 174.2, 168.6, 156.3, 146.4, 117.6, 68.0, 66.9, 64.1, 38.4, 24.5, 15.2, 12.6, 12.3; Elemental Anal. Calcd. for $C_{14}H_{20}N_4O_3S$: C, 51.83; H, 6.21; N, 17.27; Found: C, 51.91; H, 6.28; N, 17.22.

(*Z*)-Methoxyethyl-2-cyano-3-ethyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9f). Yield, 75%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, *J* = 7.6 Hz, 3H,

CH_3CH_2C=C), 2.65 (q, 2H, *J* = 7.7 Hz, CH_3CH_2C=C), 2.71 (s, 3H, CH_3-thiadiazole), 3.39 (s, 3H, OCH_3), 3.64 (t, *J* = 4.8 Hz, 2H, CH_2O), 4.29 (t, *J* = 4.8 Hz, 2H, OCH_2), 4.81 (d, *J* = 6.1 Hz, 2H, CH_2NH), 10.23 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 174.2, 168.6, 156.4, 146.3, 117.6, 70.3, 63.9, 59.3, 38.4, 24.6, 12.6, 12.3; Elemental Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.31; H, 5.85; N, 18.05; Found: C, 50.24; H, 5.92; N, 18.09.

(*Z*)-Ethoxyethyl-2-cyano-3-isopropyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9g). Yield, 74%, yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.41 (d, *J* = 7.2 Hz, 6H, $CH(CH_3)_2$), 2.72 (s, 3H, CH_3-thiadiazole), 3.10-3.15 (m, 1 H, $CH(CH_3)_2$), 3.57 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 3.69 (t, *J* = 5.0 Hz, 2H, CH_2O), 4.29 (t, *J* = 5.0 Hz, 2H, OCH_2), 4.85 (d, *J* = 6.0 Hz, 2H, CH_2NH),10.66 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 178.2, 169.4, 156.2, 146.9, 118.0, 71.7, 68.0, 66.8, 64.1, 38.6, 34.0, 19.0, 15.2, 12.6; Elemental Anal. Calcd. for $C_{15}H_{22}N_4O_3S$: C, 53.23; H, 6.55; N, 16.56; Found: C, 53.04; H, 6.82; N, 16.39. m/z (ESI$^-$) 337.11 $[M-H]^-$.

(*Z*)-Methoxyethyl-2-cyano-3-isopropyl-3-(4-methyl-1,2,3-thiadiazol-5-yl)methylaminoacrylate (9h). Yield, 72%, mp, 58-60 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.38 (d, *J* = 7.2 Hz, 6H, $CH(CH_3)_2$), 2.69 (s, 3H, CH_3-thiadiazole), 3.08-3.11 (m, 1H, $CH(CH_3)_2$), 3.37 (s, 3H, OCH_3), 3.62 (t, *J* = 4.8 Hz, 2H, CH_2O), 4.27 (t, *J* = 4.8 Hz, 2H, OCH_2), 4.85 (d, *J* = 6.0Hz, 2H, CH_2NH),10.63 (br, 1H, CH_2NH); ^{13}C NMR ($CDCl_3$) δ: 178.2, 169.5, 156.2, 146.8, 118.0, 70.2, 63.9, 59.3, 38.6, 30.5, 19.0, 12.6; Elemental Anal. Calcd. for $C_{14}H_{20}N_4O_3S$: C, 51.83; H, 6.21; N, 17.27; Found: C,51.62; H, 6.34; N, 17.40.

Herbicidal activity bioassay

The herbicidal activities of compounds **9a-h** were evaluated using a previously reported procedure.[7,19]

Plant material. Two dicotyledonous weeds, amaranth pigweed (*Amaranthus retroflexus*) and rape (*Brassica napus L.*), and two monocotyledonous weed, alfalfa (*Medicago sativa L.*) and hairy crabgrass (Digitaria sanguinalis(L.) scop.), were used to test herbicidal activities of the compounds. The seeds of amaranth pigweed were produced out doors and storded at room temperature. Seeds of alfalfa and rape and hairy crabgrass 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 days after treatment. Inhibition percentage was used to describe control efficiency of the compounds.

Treatment. Dosage (activity ingredient) for each compound corresponded to 1.5 kg/ha. Purified compounds were dissoved in 100 μL of *N*, *N*-dimethylformamide with 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 triplicated. The activity numbers represented the percent displaying herbicidal damage as compared to the control. The error of the experiments was 2%.

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