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Synthesis and Herbicidal Activity of (*Z*)-Ethoxyethyl 2-Cyano-3-(2-methylthio-5-pyridylmethylamino)acrylates

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ABSTRACT: *2-Methylthio-5-pyridinemethylene amine was prepared from 2-chloro-5-methylpyridine. Ethoxyethyl 2-cyano-3,3-dimethylthioacrylate was prepared from ethoxyethyl cyanoacetate, carbon disulfide, and dimethyl sulfate in 86.2% yield. Its reaction with 2-methylthio-5-pyridinemethylene amine yielded (Z)-ethoxyethyl 2-cyano-3-methylthio-3-(2-methylthio-5-pyridylmethylamino)acrylate. Ethoxyethyl (Z+E)-2-cyano-3-ethoxyacrylate was synthesized from ethoxyethyl 2-cyanoacetate and triethyl orthoacetate in 90.7% yield, and its reaction with 2-methylthio-5-pyridinemethylene amine yielded (Z)-ethoxyethyl 2-cyano-3-methyl-3-(2-methylthio-5-pyridylmethylamino)acrylate. The structures of all of the products were confirmed by* ^{1}*H NMR, elemental analysis, IR, and mass spectroscopy. The herbicidal activities of the products were evaluated, and the results of bioassay showed that (Z)-ethoxyethyl 2-cyano-3-methyl-3-(2-methylthio-5-pyridylmethylamino)acrylate exhibits good herbicidal activity on rape (*Brassica napus*) at a dose of 1.5 kg/ha.*
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INTRODUCTION

Cyanoacrylates have been the subject of intense interest for past decades as one kind of herbicides that disrupt photosynthetic electron transportation at a common binding domain on the 32 kD polypeptide of the photosystem II (PSII) reaction center [1–3] Among these cyanoacrylates, (*Z*)-ethoxyethyl 2-cyano-3-(4-chloro-phenyl)methylamino-3-isopropylacrylate (CPNPE) exhibits the highest Hill inhibitory activity yet reported [4–6].

In our previous work about synthesis of (*Z*)-ethyl 2-cyano-3-methylthio-3-(2-chloro-5-pyridylmethylamino)acrylate as one kind of pesticides, we found that this compound showed some insecticidal activity and excellent herbicidal activity [7–8], which could kill more than 90% of rape (*Brassica napus*) even at 150 g/ha and had a promising future to be developed. At the same time, we noticed that this compound was one analogue of cyanoacrylate that encouraged us to introduce 2-methylthio-5-pyridine heterocycle into 2-cyanoacrylate. So we synthesized a series of new (*Z*)-ethoxyethyl 2-cyano-3-(2-methylthio-5-pyridylmethylamino)acrylates and hoped to screen compounds with higher herbicidal activity.

RESULTS AND DISCUSSION

2-Methylthio-5-pyridinemethylene amine (**6**) was prepared from 2-chloro-5-methylpyridine as shown in Scheme 1. 2-Chloro-5-methylpyridine was treated with potassium permanganate to give 2-chloro-5-

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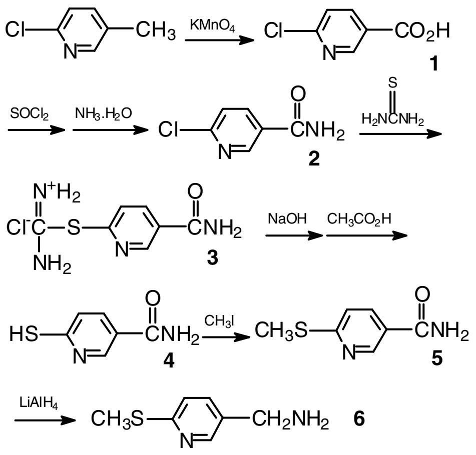
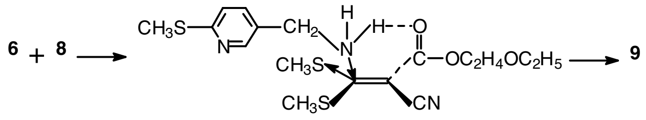


SCHEME 1



SCHEME 3

pyridinecarboxylic acid (**1**), and subsequent reaction with thionyl chloride and aqueous ammonia yielded 2-chloro-5-pyridinecarboxamide (**2**) in overall 86.2% yield. Compound **2** was reacted with thiourea to obtain *S*-(5-carbamyl-2-pyridyl)thiouronium chloride (**3**), and further hydrolysis provided 2-mercapto-5-pyridinecarboxamide (**4**). Compound **4** was reacted with iodomethane to give 2-methylthio-5-pyridinecarboxamide (**5**), and its reduction with lithium aluminum hydride yielded 2-methylthio-5-pyridinemethanamine (**6**).

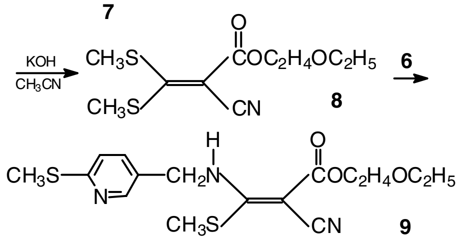
Ethoxyethyl 2-cyano-3,3-dimethylthioacrylate (**8**) was prepared from ethoxyethyl cyanoacetate, carbon disulfide, and dimethyl sulfate in 86.2% yield. Its reaction with **6** yielded (*Z*)-ethoxyethyl 2-cyano-3-methylthio-3-(2-methylthio-5-pyridylmethylamino)acrylate (**9**) as shown in Scheme 2. This reaction was assumed to go through a nucleophilic addition and elimination reaction as shown in Scheme 3. The amine attached to the α,β-unsaturated double bond to form a transition state in which the orientation of pyridinemethylamino and ester carbonyl is the cis because of the presence of an intramolecular hydrogen bonding. The configuration of target compounds was kept with loss of a mole of methylthio group (or ethoxy as shown in Scheme 4) and was confirmed by the X-ray single crystal structure of a similar compound synthesized by our research group [9].

Ethoxyethyl (*Z* + *E*)-2-cyano-3-ethoxyacrylate (**11**) was synthesized from ethoxyethyl 2-cyanoacetate (**10**) and triethyl orthoacetate in 90.7% yield. Its reaction with **6** yielded (*Z*)-ethoxyethyl 2-cyano-3-methyl-3-(2-methylthio-5-pyridylmethylamino)-acrylate (**12**) as shown in Scheme 4. The structures of all of the products were confirmed by ^{1}H NMR, elemental analysis, IR, and mass spectroscopy.

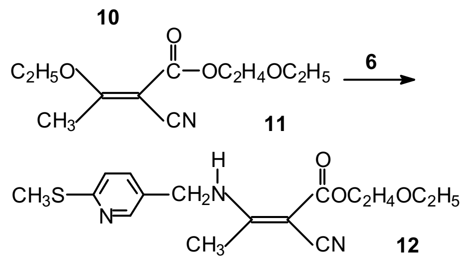
BIOLOGICAL ACTIVITY

The herbicidal activities of the title compounds **9** and **12** and the reported compound CPNPE were evaluated using a previously reported procedure [10, 11]. Dosage for each compound is 1.5 kg/ha. Purified compounds were dissolved in 100 μl *N*,*N*-dimethylformamide with the addition of a little Tween 20, and then were sprayed using a laboratory belt sprayer delivering at 750 l/ha spray-volume. Compounds were sprayed when the first leave was expanding. The results of biological assay are given in Table 1.

The results of biological assay given in Table 1 show that the title compound **12** exhibited good herbicidal activity on rape (*Brassica napus*) at a dose of 1.5 kg/ha.



SCHEME 2



SCHEME 4

TABLE 1 Herbicidal Activities of the Title Compounds **9** and **12**, and the Reported Compound CPNPE (1.5 kg/ha)

	Postemergency Treatment		
	Alfalfa	*Amaranth Pigweed*	*Rape*
9	56.5	14.3	29
12	0	39.6	98.4
CPNPE	28.1	93.9	96.5

EXPERIMENTAL

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. 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 are uncorrected. Mass spectra were recorded with HP 5988A spectrometer using the EI method. Column chromatographic purification was carried out by using silica gel.

*2-Chloro-5-pyridinecarboxylic Acid (**1**)*

A mixture of potassium permanganate (36.42 g, 230.5 mmol), distilled water (350 ml), and 2-chloro-5-methylpyridine (12.0 g, 94.1 mmol) was stirred and refluxed for 5 h. Then the solid was filtered off and the filtrate was concentrated under vaccum to 50 ml. Aqueous hydrochloric acid (15 ml) was added to give a white solid (9.04 g). The solid was then recrystallized to obtain a colorless crystalline solid **1**. Yield: 60.1%, m.p. 188–190°C.

*2-Chloro-5-pyridinecarboxamide (**2**)*

A mixture of **1** (8.31 g, 52.8 mmol) and distilled thionyl chloride (9.42 g) was refluxed for 15 h, and evaporated in vacuo to dryness. The residue was dissolved in toluene (30 ml) and added to aqueous ammonia (50 ml). Then the reaction mixture was stirred at room temperature for 8 h and filtered to give a white solid. The solid was then recrystallized from distilled water to obtain a colourless crystalline solid **2** (7.15 g). Yield: 86.2%, m.p. 211–213°C (lit. ref. [12], m.p. = 211°C).

Intermediates **3–5** were synthesized according to the reported procedure [12].

*2-Methylthio-5-pyridinemethanamine (**6**)*

To a suspension of 2-methylthio-5-pyridinecarboxamide (**5**) (0.4 g, 2.4 mmol) and anhydrous tetrahydrofuran (30 ml) was added lithium aluminum hydride (0.24 g, 7.3 mmol). Then the mixture was heated under reflux for 12 h and cooled. Cool water (1.0 g) was added to the solution carefully. The mixture was stirred for another 30 min and solvent was evaporated under reduced pressured. The residue was used for further operations without purification.

*2-Cyano-3,3-dimethylthioacrylate (**8**)*

To a mixture of potassium hydroxide powder (2.24 g, 40 mmol) and anhydrous acetonitrile (30 ml) under 5°C was added dropwise compound **7** (20 mmol). 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 and the reaction was over in 4 h. The solvent was removed off 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 by anhydrous magnesium sulfate. Ethyl acetate was evaporated to afford corresponding **8**. Yield: 86.2%, m.p. 32–34°C.

*(Z)-Ethoxyethyl 2-Cyano-3-methylthio-3-(2-methylthio-5-pyridylmethylamino)acrylate (**9**)*

A mixture of intermediates **8** (5 mmol), **6** (6 mmol), and ethanol (12 ml) was refluxed for 3 h and concentrated under reduced pressure to give a crude product. The product was purified by vacuum column chromatography on a silica gel to obtain yellow liquid. Yield: 18.2% (yield from **5**). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, C—CH_3), 2.50 (s, 3H, Py—SCH_3), 2.60 (s, 3H, =$CSCH_3$), 3.49 (q, 2H, OCH_2), 3.61 (t, 2H, CH_2O), 4.21 (t, 2H, CO_2CH_2), 4.65 (d, 2H, CH_2N), 7.14–8.30 (m, 3H, C_5H_3N), 10.2 (s, 1H, NH). Anal. Found: C, 52.29; H, 5.71; N, 11.46. Calcd for $C_{16}H_{21}N_3O_3S_2$: C, 52.34; H, 5.77; N, 11.44. IR (KBr, cm^{-1}): 3446, 2200, 1653, 1593, 1566, 1468, 1275, 1251, 1118, 1052. EI MS: *m/z* (%) 295 (M^+, 3.7), 138 (100).

(Z + E)-2-Cyano-3-ethoxyacrylate **11**

A mixture of ethoxyethyl 2-cyanoacetate (**10**) (8.0 g, 48.4 mmol), triethyl orthoacetate (61.6 mmol), and acetic acid (0.15 g, 2.5 mmol) was heated under reflux for 2.5 h and the solvent was then removed off under reduced pressure to afford a yellow oil, which was purified by column chromatography using a silica gel. Colorless liquid was obtained. Yield: 90.7%.

*(Z)-Ethoxyethyl 2-Cyano-3-methyl-3-(2-methylthio-5-pyridylmethylamino)-acrylate (**12**)*

A mixture of intermediates **11** (6 mmol), **6** (6 mmol), and ethanol (15 ml) was heated under reflux for 2 h. The solvent was removed under reduced pressure to afford a crude product. The product was purified by vacuum column chromatography on a silica gel to give a yellow liquid. Yield: 20.6% (yield from **5**). ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, C—CH_3), 2.27 (s, 3H, =CCH_3), 2.52 (s, 3H, Py—SCH_3), 3.51 (q, 2H, OCH_2), 3.63 (t, 2H, CH_2O), 4.22 (t, 2H, CO_2CH_2), 4.45 (d, 2H, CH_2N), 7.18–8.31 (m, 3H, C_5H_3N), 10.1 (s, 1H, NH). Anal. Found: C, 57.30; H, 6.14; N, 12.47. Calcd for $C_{16}H_{21}N_3O_3S$: C, 57.28; H, 6.32; N, 12.53.

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