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Synthesis and herbicidal activity of 2-cyano-3-(2-fluoro-5-pyridyl)methylaminoacrylates

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Abstract

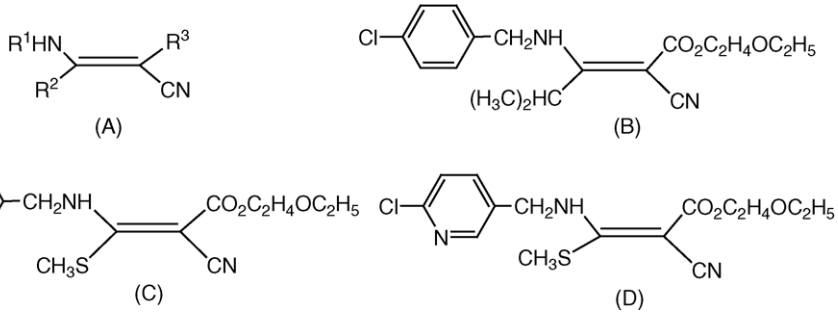
A series of 2-cyano-3-(2-fluoro-5-pyridyl)methylaminoacrylates were synthesized as herbicidal inhibitors of photosystem II (PSII) electron transport. 2-Fluoro-5-pyridinemethylamine was prepared from 2-amino-5-methylpyridine, subsequent reaction with 2-cyano-3,3-dimethylthioacrylates or 2-cyano-3-methoxyacrylates to yield these title compounds. All of these compounds were confirmed by ^{1}H NMR, IR, mass spectrum and elemental analyses. Their herbicidal activities were evaluated. All of the title compounds showed excellent herbicidal activities to amaranth pigweed and rape in post-emergence treatment. At the rate of 150 g/ha, one compound exhibited similar activity to Cl-analogue. The replacement of chlorine by fluorine group showed the same herbicidal activity.

Keywords: 2-Cyanoacrylates; 2-Fluoro-5-pyridylmethylamine; Herbicidal activity

1. Introduction

The herbicidal activity of cyanoacrylates has been the subject of intense interest for past decades [1–3]. A detailed study of compounds with general structure **A** revealed that cyanoacrylates are inhibitors of photosystem II (PSII) electron transport, which inhibits the growth of weeds by disrupting photosynthetic electron transport at a common binding domain on the 32 kDa polypeptide of the PSII reaction center. Among these cyanoacrylates, the compound **B** exhibits the highest inhibitory activity of the Hill reaction yet reported [4–6]. Bayer AG reported compound **C**, but little information was given on herbicidal activity [7]. In previous work [8,9] we reported that **D** showed excellent herbicidal activity, controlling more than 95% of rape (*Brassicanapus*) at 1.5 kg/ha.

Many examples demonstrated that the introduction of fluorine into certain pesticide molecular could improve its bioactivity [10–14]. In this paper, structure **D** is modified by replace of chlorine with fluorine atom, with the intention of getting higher herbicidal activity. Here the synthesis and herbicidal activities of these 2-cyano-3-(2-fluoro-5-pyridyl)methylaminoacrylates are reported.



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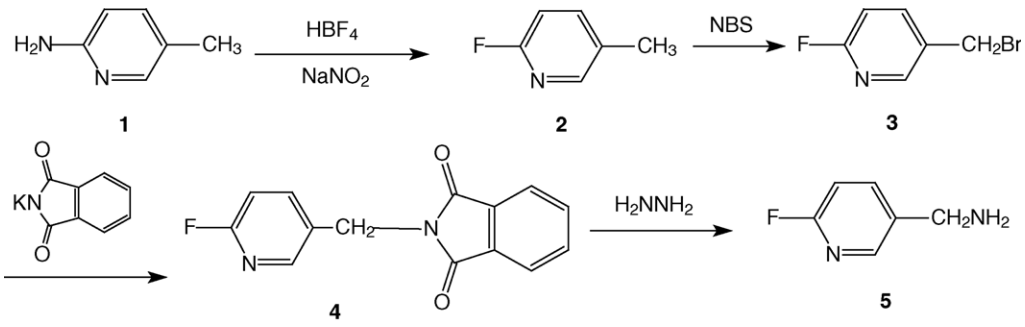
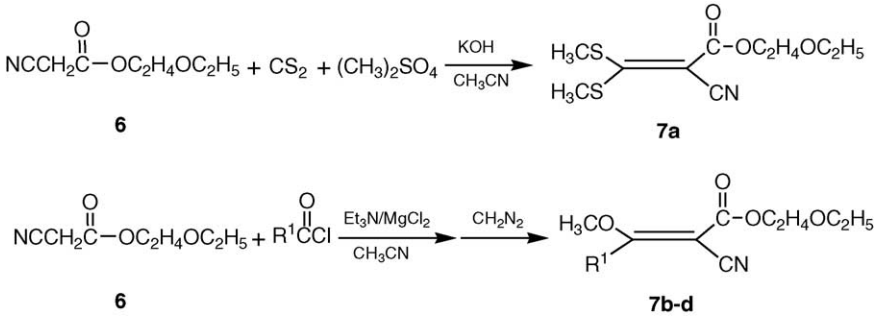


Scheme 1.



Scheme 2.

2. Results and discussion

2.1. Synthesis

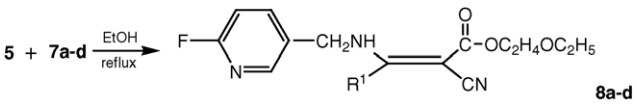
2-Fluoro-5-pyridylmethylamine (**5**) was prepared from 2-amino-5-methylpyridine (**1**) (Scheme 1) [15]. Aminopyridine **1** was treated with fluoroboric acid and sodium nitrite to give 2-fluoro-5-methylpyridine (**2**) with respect to Schiemann reaction [16]. Bromination of **2** with *N*-bromosuccinimide in refluxing carbon tetrachloride afforded 2-fluoro-5-bromomethylpyridine (**3**) by using benzoyl peroxide or azodiisobutyronitrile as irrigator [17,18]. After workup the reaction solution as described in the literature, yellow oil was obtained. GC-detection and ^{1}H NMR showed this oil contained 2-fluoro-5-bromomethylpyridine (67%), unreacted 2-fluoro-5-methylpyridine (15%) and dibromide of 2-fluoro-5-methylpyridine (18%). Since 2-fluoro-5-bromomethylpyridine (**3**) is irritant to eyes and skin, **3** was not purified. Crude **3** was treated with potassium phthalimide to afford *N*-(2-fluoro-5-pyridylmethyl)phthalimide (**4**), which was then converted to 2-fluoro-5-pyridylmethylamine (**5**) by hydrazine cleavage [19–21].

Cyanoacrylates **7** were synthesized from ethoxyethyl 2-cyanoacetate **6** according to the reporting method (Scheme 2) [9,22].

Intermediates **7** were reacted with 2-fluoro-5-pyridylmethylamine (**5**) in refluxing ethanol to give the target compounds **8** (Scheme 3).

2.2. Biological activities

The herbicidal activities of the compounds **8a–d** were evaluated using the previously reported procedure [9,22]. Their herbicidal activities are summarized in Tables 1 and 2. All of the compounds **8a–d** showed excellent herbicidal activities to amaranth pigweed and rape in post-emergence treatment. The compounds **8a–d** had higher herbicidal activity to alfalfa than Cl-analogue **D** in pre-emergence treatment. At the rate of 150 g/ha, the compounds **8a–d** still



Scheme 3.

Table 1
Herbicidal activities of products **8a–d** (1.5 kg/ha)

	Post-emergence treatment			Pre-emergence treatment		
	Alfalfa	Amaranth pigweed	Rape	Alfalfa	Amaranth pigweed	Rape
8a	98.7	100	100	52.8	75.0	73.8
8b	73.6	100	100	61.8	92.8	63.1
8c	78.7	100	100	70.7	92.8	73.2
8d	100	100	100	72.0	94.6	97.0
D	89.1	100	100	19.1	12.5	35.7

Table 2
Herbicidal activities of products **8** against rape (post-emergence treatment) (150 g/ha)

8a	61.5
8b	61.9
8c	63.9
8d	88.1
D	90.9

gave a good herbicidal activity, especially **8d** exhibited similar activity to **D**. The replacement of chlorine by fluorine group showed the same herbicidal activity. When R^1 = *i*-Pr, the compounds **8d** exhibited better activities than other compounds **8a–c** to rape, which indicated a suitable group at the 3-position of acrylate was essential for high herbicidal activity.

3. Experimental

All of the reactions were carried out under a nitrogen atmosphere with the exclusion of moisture. Proton NMR spectra were obtained using a Bruker AC-P 300 spectrometer. Chemical shift values are given in ppm and downfield from internal tetramethylsilane. Infrared spectra were recorded on a Shimadzu-435 spectrometer. Elemental analyses were determined on an MT-3 elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and were uncorrected. Mass spectra were recorded with HP 5988A spectrometer using the EI method.

3.1. Synthesis of 2-fluoro-5-methylpyridine (*2*)

2-Amino-5-methylpyridine (70 g, 0.48 mol) was dissolved in 40% fluoroboric acid (290 mL) at −10 °C. Sodium nitrite (46 g, 0.66 mol) was added slowly, in a small portion, so as not to allow the temperature to rise above 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then warmed to 50 °C for 30 min. Sodium carbonate was added to make the solution alkaline. The mixture was steam distilled until the distillate was no longer cloudy. The yellowish oil that separated from the water layer was separated and the water layer was extracted with ethyl ether (3 mL × 50 mL). The ether extracts and oil layer were combined, dried with sodium sulfate and the solvent was removed in vacuo. The remaining residue was distilled to give 2-fluoro-5-methylpyridine as a colorless oil in 45% yield (32.4 g) having a boiling point of 52–557 °C/2 mmHg. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 6.80 (dd, J_{HH} = 8.3 Hz, $^3J_{HF}$ = 3.0 Hz, 1H, pyridine), 7.56–7.54 (m, 1H, pyridine), 7.99 (s, 1H, pyridine).

3.2. Synthesis of 2-fluoro-5-bromomethylpyridine (*3*)

A mixture of 2-fluoro-5-methylpyridine (16.65 g, 0.15 mol), *N*-bromosuccinimide (26.7 g, 0.15 mol), benzoyl peroxide (0.7 g) and carbon tetrachloride (200 mL) was refluxed for 2 h. After cooling, the precipitate was filtered and the filtrate was washed with water and dried. Finally, the solvent was distilled off to give crude 2-fluoro-5-bromomethylpyridine (30.1 g, purity 67% analysis from GC. ^{1}H NMR ($CDCl_3$) δ 4.40 (s, 2H, CH_2), 6.87 (dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HF}$ = 3.1 Hz, 1H, pyridine), 7.80–7.76 (m, 1H, pyridine), 8.16 (s, 1H, pyridine).

3.3. Synthesis of N-(2-fluoro-5-pyridylmethyl)phthalimide (*4*)

To a solution of crude 2-fluoro-5-bromomethylpyridine (10.4 g, purity 67%, 0.037 mol) in *N*,*N*-dimethylformamide (25 mL) was added potassium phthalimide (9.25 g, 0.05 mol) in a small portion. The mixture was stirred at room temperature for 5 h, and then water (50 mL) was added. The precipitate was collected by filtration and washed with water. Recrystallization of the crude product from ethanol gave white crystal in 59% yield (calculated on 2-fluoro-5-methylpyridine, 7.53 g) mp 157–159 °C. ^{1}H NMR ($CDCl_3$) δ 4.85 (s, 2H, CH_2), 6.89 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 2.9 Hz, 1H, pyridine), 7.94–7.90 (m, 1H, pyridine), 8.34 (s, 1H, pyridine), 7.73–7.88 (m, 4H, benzene); Anal. Calcd. for $C_{14}H_9FN_2O_2$: C, 65.62; H, 3.54; N, 10.93. Found: C, 65.50; H, 3.46; N, 10.78.

3.4. Synthesis of 2-fluoro-5-pyridylmethylamine (*5*)

To a suspension of *N*-(2-fluoro-5-pyridylmethyl)phthalimide (10.2 g, 0.04 mol) in 95% ethanol (40 mL) was added hydrazine hydrate (2.25 g, 0.04 mol). The reaction mixture was refluxed for 5 h, and then cooled to 0 °C, acidified to pH = 2–3 with 36% aqueous hydrochloric acid, and refluxed again for 30 min. The precipitated *N*,*N*-phthaloylhydrazine was filtered and washed with water, and then the combined solution was alkalized to pH 12–13 with 25% sodium hydroxide and extracted with chloroform (3 mL × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and distilled under reduced pressure to give a colorless liquid in 44% yield (2.21 g) bp 63–65 °C/75 Pa. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 2H, NH_2), 3.83 (s, 2H, CH_2N), 6.84 (dd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HF}$ = 3.0 Hz, 1H, pyridine), 7.75–7.71 (m, 1H, pyridine), 8.08 (s, 1H, pyridine). n_D^{27} = 1.5131. IR (oil, cm^{-1}) 3371, 3299, 1597, 1484, 1399, 1245, 826. EI-MS m/e (100%): 126.1 (M^+, 100).

3.5. Ethoxyethyl 2-cyanoacetate (*6*), 2-cyano-3,3-dimethylthioacrylates (*7a*) and (Z + E)-2-cyano-3-methoxyacrylates (*7b–d*)

Ethoxyethyl 2-cyanoacetate (**6**), 2-cyano-3,3-dimethylthioacrylates (**7a**) and (Z + E)-2-cyano-3-methoxyacrylates (**7b–d**) were synthesized according to the reporting method [9,15].

3.6. General synthetic procedures for target compounds **8a–d**

The mixture of intermediates **7** (5 mmol), 2-fluoro-5-pyridylmethylamine (**5**) (6 mmol), and ethanol (12 mL) was refluxed for 3 h, and then evaporated under reduced pressure to give crude products **8**. The product was purified by vacuum column chromatography on silica gel using ethyl acetate and petroleum ether as the eluent.

3.6.1. Ethoxyethyl 2-cyano-3-methylthio-3-(2-fluoro-5-pyridyl)methylaminoacrylate (**8a**)

Ethoxyethyl 2-cyano-3-methylthio-3-(2-fluoro-5-pyridyl)methylaminoacrylate (**8a**). Yield, 81%; mp, 54–55 °C. ^{1}H NMR ($CDCl_3$) δ 1.13 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 2.62 (s, 3H, SCH_3), 3.49 (q, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2), 3.62 (t, $^3J_{HH}$ = 5.2 Hz, 2H, CH_2O), 4.22 (t, $^3J_{HH}$ = 5.2 Hz, 2H, CO_2CH_2), 4.73 (d, $^3J_{HH}$ = 5.2 Hz, 2H, CH_2N), 6.91 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 3.0 Hz, 1H, pyridine), 7.67–7.62 (m, 1H, pyridine), 8.09 (s, 1H, pyridine), 10.27 (s, 1H, NH); Anal. Calcd. for $C_{15}H_{18}FN_3O_3S$: C, 53.08; H, 5.35; N, 12.38. Found: C, 53.11; H, 5.22; N, 12.20.

3.6.2. Ethoxyethyl 2-cyano-3-methyl-3-(2-fluoro-5-pyridyl)methylaminoacrylate (**8b**)

Ethoxyethyl 2-cyano-3-methyl-3-(2-fluoro-5-pyridyl)-methylaminoacrylate (**8b**). Yield, 70%; mp, 63–64 °C. ^{1}H NMR ($CDCl_3$) δ 1.13 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.49 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2), 3.61 (t, $^3J_{HH}$ = 4.8 Hz, 2H, CH_2O), 4.21 (t, $^3J_{HH}$ = 4.8 Hz, 2H, CO_2CH_2), 4.50(d, $^3J_{HH}$ = 5.2 Hz, 2H, CH_2N), 6.94 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 3.0 Hz, 1H, pyridine), 7.62–7.67 (m, 1H, pyridine), 8.10 (s, 1H, pyridine), 10.16 (s, 1H, NH); Anal. Calcd. for $C_{15}H_{18}FN_3O_3$: C, 58.62; H, 5.90; N, 13.67. Found: C, 58.48; H, 6.00; N, 13.52.

3.6.3. Ethoxyethyl 2-cyano-3-ethyl-3-(2-fluoro-5-pyridyl)methylaminoacrylate (**8c**)

Ethoxyethyl 2-cyano-3-ethyl-3-(2-fluoro-5-pyridyl)-methylaminoacrylate (**8c**). Yield, 49%; mp, 64–65 °C. ^{1}H NMR ($CDCl_3$) δ 1.22 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.30 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3), 2.68 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2), 3.58 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2), 3.71(t, $^3J_{HH}$ = 4.9 Hz, 2H, CH_2O), 4.30 (t, $^3J_{HH}$ = 4.9 Hz, 2H, CO_2CH_2), 4.59 (d, $^3J_{HH}$ = 5.2 Hz, 2H, CH_2N), 7.02 (dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HF}$ = 2.9 Hz, 1H, pyridine), 7.76–7.71 (m, 1H, pyridine), 8.18 (s, 1H, pyridine), 10.18 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{20}FN_3O_3$: C, 59.80; H, 6.27; N, 13.08. Found: C, 59.66; H, 6.38; N, 13.08.

3.6.4. Ethoxyethyl 2-cyano-3-isopropyl-3-(2-fluoro-5-pyridyl)methylaminoacrylate (**8d**)

Ethoxyethyl 2-cyano-3-isopropyl-3-(2-fluoro-5-pyridyl)-methylaminoacrylate (**8d**). Yield, 35%; mp, 95–97 °C. ^{1}H NMR ($CDCl_3$) δ 1.13 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3), 1.33 (d, $^3J_{HH}$ = 7.5 Hz, 6H, $C(CH_3)_2$), 3.18–3.05 (m, 1H, CH), 3.50 (q, $^3J_{HH}$ = 6.9 Hz, 2H, OCH_2), 3.62(t, $^3J_{HH}$ = 4.9 Hz, 2H, CH_2O), 4.21(t, $^3J_{HH}$ = 4.9 Hz, 2H, CO_2CH_2), 4.56(d, $^3J_{HH}$ = 6.1 Hz, 2H, CH_2N), 6.93 (dd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HF}$ = 3.2 Hz, 1H, pyridine), 7.62–7.67 (m, 1H, pyridine), 8.09 (s, 1H, pyridine), 10.49 (s, 1H, NH); Anal. Calcd. for $C_{17}H_{22}FN_3O_3$: C, 60.88; H, 6.61; N, 12.53. Found: C, 60.69; H, 6.57; N, 12.48. IR (KBr, cm^{-1}) 3414, 3237, 2201,1671, 1589, 1485, 1357, 1285, 1084. EI-MS m/e (%): 307 (M^+, 32), 235 (30), 218 (42), 191 (34), 190 (23), 110 (100).

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