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Synthesis and biological activity of novel cyanoacrylates containing ferrocenyl moiety

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Abstract

In a search for new herbicides with improved biological properties and different activity spectrum, we replaced phenyl moiety by ferrocenyl in cyanoacrylates, and synthesized a series of novel cyanoacrylates containing a ferrocene moiety by the reaction of aminomethylferrocene with ethoxyethyl 2-cyano-3-methylthioacrylate (or 2-cyano-3-alkoxyacrylates) in excellent yields. The title compounds were identified by IR, ^{1}H-NMR spectroscopy, EI MS and elemental analyses. The results of bioassay showed that some title compounds exhibit excellent herbicidal activities. In general, we found that the replacement of the phenyl with ferrocenyl in cyanoacrylates still retained excellent herbicidal activities. © 2002 Published by Elsevier Science B.V.

Keywords: Ferrocene; Aminomethylferrocene; Cyanoacrylates; Herbicidal activities

1. Introduction

Cyanoacrylates have been the subject of intense interest for the past decades as one kind of herbicides by disrupting photosynthetic electron transport [1]. Among these cyanoacrylates, (*Z*)-ethoxyethyl 2-cyano-3-(4-chloro-phenyl)methylamino-3-isopropyl-acrylate (**CPNPE**) has been a representative compound because of its excellent herbicidal activity. In our previous work, we modified its structure by replacement of phenyl-methylamino substituent with pyridinemethylamino and found that some of them still kept high herbicidal activities [2]. In addition, ferrocene is ideal for use in drug design because of the low toxicity of the molecule containing a ferrocenyl moiety and the ease of substitution of conventional phenyl or heteroaromatic group with ferrocene moiety. Moreover, ferrocene-containing compounds often possess unexpected biological activity [3]. Indeed, ferrocenyl groups have already been shown to advantageously replace phenyl moieties in biologically active compounds [4]. We thought that the substitution of a phenyl group or heterocycle with a ferrocenyl moiety in a bioactive compound would induce great changes in its molecular properties, such as the solubility and hydrophobicity. Therefore, in order to extend our research work of cyanoacrylates as herbicides, we designed and synthesized some novel cyanoacrylates by the replacement of the phenyl group with a ferrocenyl group.

2. Results and discussion

The reaction of ferrocenecarboxaldehyde with hydroxylamine hydrochloride in the presence of sodium acetate afforded ferrocenecarboxaldehyde oxime in 90.3% yield [5]. The reduction of ferrocenecarboxaldehyde oxime with lithium aluminum hydride or Raney Ni can give aminomethylferrocene, but the yield is very low because of the production of quantities of secondary amine, *N*-ferrocenyl-*N*-methylamine. Then we used sodium–1-butanol as reductive reagent to obtain aminomethylferrocene in 71.2% yield [6] as shown in Scheme 1, in order to avoid the formation of *N*-ferrocenyl-*N*-methylamine.

The aminomethylferrocene (**I**) was reacted with ethoxyethyl 2-cyano-3,3-dimethyl-thioacrylate (**II**) in

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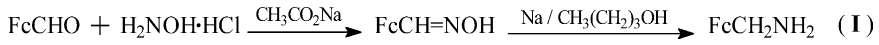
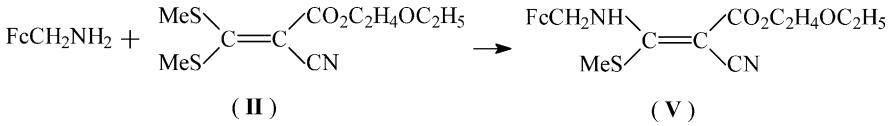


Scheme 1.

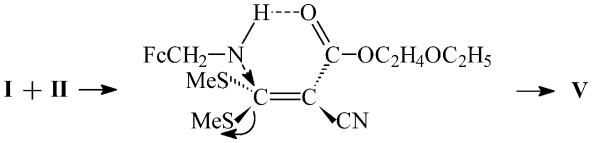


Scheme 2.

ethanol to give (*E*)-ethoxyethyl 2-cyano-3-ferrocene-methylamino-3-methylthioacrylate (**V**) in 93.8% yield as shown in Scheme 2. The compound **V** was obtained by means of addition and elimination procedure as shown in Scheme 3, which led to the product with single configuration (*E*) and was consistent with our previous research work [2b].

The compounds $\mathbf{VI_{1-3}}$ with single *Z* configuration were prepared by the reaction of aminomethylferrocene (**I**) with (*Z*+*E*)-2-cyano-3-alkoxyacrylates ($\mathbf{III_{1-3}}$) in excellent yields (> 90%) as shown in Scheme 4.

However, the reaction of aminomethylferrocene (**I**) with (*Z*+*E*)-ethoxyethyl 2-cyano-3-ethoxyacrylate (**IV**) gave a mixture of *Z* and *E* isomers (**VII** and **VIII**) as shown in Scheme 5. The formation of compound **VII** (*Z*) goes through a similar procedure as shown in Scheme 3, whereas the formation of compound **VIII** (*E*) is due to the predominance of steric hindrance of the ferrocenyl substituent. The two compounds (**VII** and **VIII**) can be discriminated by ^{1}H-NMR due to the existence of hydrogen bond between ester carbonyl and NH of ferrocenemethylamino group in the molecule structure of **VII** which leads to its chemical shift value of NH move to lower field. Indeed, the *Z* isomer (**VII**) shows the NH proton at 9.10 ppm as a broad singlet and the *E* isomer (**VIII**) at 6.35 ppm as a broad singlet.



Scheme 3.

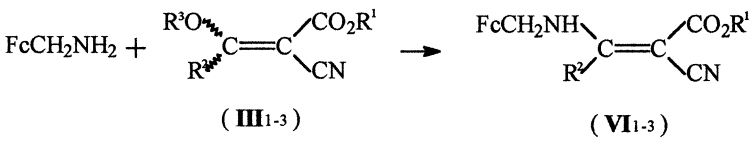
The title compounds **V**–**VIII** were characterized by IR and ^{1}H-NMR spectroscopy, EI MS and elemental analyses. The results are in accordance with the expected structures. Their ^{1}H-NMR spectra are characteristic: the ferrocenyl substituent gives rise to a five-proton singlet for the unsubstituted cyclopentadienyl ring and a multiplet for the monosubstituted ring. The characteristic bands of the ferrocenyl group in the IR spectra of the compound $\mathbf{VI_2}$ appear at 3083, 1431, 1272, 1116, 1079, 834, 809 and 778 cm^{-1}.

The results of bioassay given in Table 1 show that the title compounds **V** and $\mathbf{VI_1}$ exhibit excellent herbicidal activities for rape weeds. From the results, we found that the herbicidal activities increase with the order H < CH_3 < $(CH_3)_2CH$. At the same time, the results of compounds $\mathbf{VI_2}$ and $\mathbf{VI_3}$ prove that the existence of ethoxyethyl group is very important for remaining high herbicidal activities. In general, we found from the activities of compound $\mathbf{VI_1}$ and parent compound (**CPNPE**) that the replacement of the phenyl with ferrocenyl in cyanoacrylates still retained excellent herbicidal activities.

3. Experimental

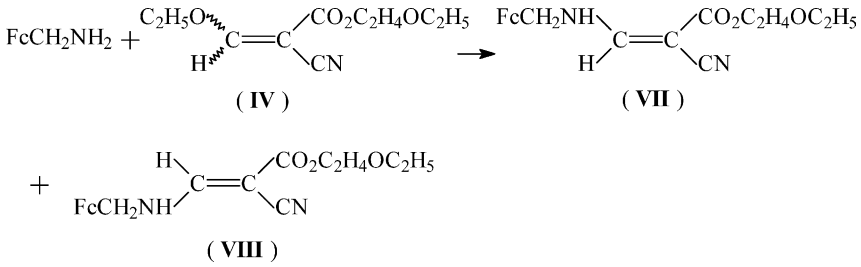
3.1. Instruments

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. IR spectra were recorded on a Shimadzu-435 spectrometer. Elemental analyses were determined



$\mathbf{III_1}$ and $\mathbf{VI_1}$:	$R^1 = C_2H_4OC_2H_5$,	$R^2 = CH(CH_3)_2$,	$R^3 = CH_3$
$\mathbf{III_2}$ and $\mathbf{VI_2}$:	$R^1 = C_2H_4OC_2H_5$,	$R^2 = CH_3$,	$R^3 = C_2H_5$
$\mathbf{III_3}$ and $\mathbf{VI_3}$:	$R^1 = C_2H_5$,	$R^2 = CH_3$,	$R^3 = C_2H_5$

Scheme 4.

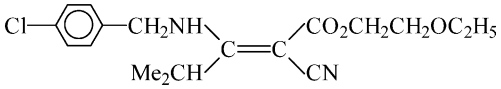


Scheme 5.

Table 1
Herbicidal activities of products **V**–**VIII** for rape (1.5 kg ha^{-1})

No.	Inhibition percent (%)
V	100
VI$_1$	100
VI$_2$	85.6
VI$_3$	15
VII	56.1
VIII	20.0
CPNPE	96.5

CPNPE:



on a MT-3 elemental analyzer. M.p.s were taken on a Thomas-Hoover melting-point apparatus and were uncorrected. MS were recorded with HP 5988A spectrometer using the EI method.

3.2. Synthesis

Ferrocencecarboxaldehyde was synthesized according to a reported procedure [7]. Ethoxyethyl 2-cyano-3,3-dimethylthioacrylate (**II**) and (*Z*+*E*)-2-cyano-3-alkoxyacrylates (**III**–**IV**) were prepared by previous methods [8].

3.2.1. General procedure for the preparation of products *V*–*VIII*

To a solution of ferrocenecarboxaldehyde (37.8 mmol) in EtOH (85 ml), the solution of hydroxylamine hydrochloride (75.6 mmol) in water (28 ml) was added under N_2, then followed by AcONa (113.4 mmol). The mixture was heated under reflux for 3 h, cooled and concentrated in vacuum. Then $CHCl_3$ (100 ml) was added dropwise and stirred for additional 0.5 h. The precipitated solid was filtered off and the filtrate was concentrated under vacuum to give brown–red solid (8.3 g) in 95.8% yield.

The solution of ferrocenecarboxaldehyde oxime (34.9 mmol) in 1-butanol (170 ml) was stirred under reflux, followed by the addition of Na (514 mmol) in small portions in 1 h. Then the refluxing was continued for an additional 1 h. The mixture was cooled to room temperature, acidified with 20% H_2SO_4 (150 ml) and extracted twice with ether. The water phase was alkalized with NaOH to pH 11–12 and then extracted with ether. The combined ether phase was dried with anhydrous K_2CO_3, filtered, concentrated under vacuum to give brown oil (5.35 g) in 71.2% yield. It was used for the following reactions directly without any further purification.

The mixture of the oil (0.5 g, 2 mmol) above and 2-cyanoacrylates (**II**–**IV**) (1.8 mmol) in EtOH (15 ml) was heated under reflux for 1 h. Then the mixture was cooled and concentrated under vacuum. The product was purified by vacuum column chromatography on a silica gel. Finally, products **V**–**VIII** were obtained in excellent yields.

3.2.1.1. (E)-Ethoxyethyl 2-cyano-3-ferrocenemethylamino-3-methylthioacrylate (V). Red–brown oil, yield 93.8%. ^{1}H-NMR ($CDCl_3$): δ 1.16 (t, 3H, CH_2CH_3), 2.65 (s, 3H, SCH_3), 3.55 (q, 2H, OCH_2CH_3), 3.65 (t, 2H, CH_2O), 4.14 (s, 4H, C_5H_4), 4.17 (s, 5H, C_5H_5), 4.27 (t, 2H, CO_2CH_2), 4.40 (d, 2H, CH_2N), 10.25 (br, 1H, NH). Anal. Found: C, 56.22; H, 5.66; N, 6.78. Calc. for $C_{20}H_{24}FeN_2O_3$: C, 56.07; H, 5.66; N, 6.54%.

3.2.1.2. Compound VI$_1$. Brown–red liquid, yield 94.3%. ^{1}H-NMR ($CDCl_3$): δ 1.19 (t, 3H, CH_2CH_3), 1.41 (d, 6H, $CH(CH_3)_2$), 3.20 (m, 1H, CH), 3.54 (q, 2H, OCH_2CH_3), 3.68 (t, 2H, CH_2O), 4.23–4.28 (m, 13H, C_5H_4, C_5H_5, CH_2N, CO_2CH_2), 10.35 (br, 1H, NH).

Anal. Found: C, 62.13; H, 6.71; N, 6.66. Calc. for $C_{22}H_{28}FeN_2O_3$: C, 62.26; H, 6.66; N, 6.60%.

3.2.1.3. Compound ***VI₂***. Yellow solid, m.p. 68–70 °C, yield 91.5%. ^{1}H-NMR ($CDCl_3$): δ 1.18 (t, 3H, CH_2CH_3), 2.31 (s, 3H, $=CCH_3$), 3.57 (q, 2H, OCH_2CH_3), 3.67 (t, 2H, CH_2O), 4.24–4.30 (m, 13H, C_5H_4, C_5H_5, CH_2N, CO_2CH_2), 10.05 (br, 1H, NH). Anal. Found: C, 60.59; H, 6.17; N, 7.20. Calc. for $C_{20}H_{24}FeN_2O_3$: C, 60.59; H, 6.12; N, 7.07%. IR (KBr): 3083, 1654, 1580, 1431, 1403, 1381, 1272, 1116, 1079, 834, 810, 778. EI MS (%): *m/z* 396.2 ([M^+], 87), 306.1 (63), 241.1 (9), 199.0 (100), 121.0 (47), 55.9 (13).

3.2.1.4. Compound ***VI₃***. Yellow crystalline, m.p. 130–132 °C, yield 92.5%. ^{1}H-NMR ($CDCl_3$): δ 1.31 (t, 3H, CH_2CH_3), 2.32 (s, 3H, $=CCH_3$), 4.19–4.35 (m, 13H, C_5H_4, C_5H_5, CH_2N, CO_2CH_2), 9.95 (br, 1H, NH). Anal. Found: C, 61.35; H, 5.59; N, 7.68. Calc. for $C_{18}H_{20}FeN_2O_2$: C, 61.37; H, 5.73; N, 7.95%.

*3.2.1.5. (Z)-Ethoxyethyl 2-cyano-3-ferrocenemethylaminoacrylate (**VII**)*. Yellow solid, m.p. 61–63 °C, yield 70.4%. ^{1}H-NMR ($CDCl_3$): δ 1.18 (t, 3H, CH_2CH_3), 3.52 (q, 2H, OCH_2CH_3), 3.66 (t, 2H, CH_2O), 4.12–4.29 (m, 13H, C_5H_4, C_5H_5, CH_2N, CO_2CH_2), 7.26 (d, 1H, =CH), 9.10 (br, 1H, NH). Anal. Found: C, 59.76; H, 5.78; N, 7.17. Calc. for $C_{19}H_{22}FeN_2O_3$: C, 59.69; H, 5.81; N, 7.33%.

*3.2.1.6. (E)-Ethoxyethyl 2-cyano-3-ferrocenemethylaminoacrylate (**VIII**)*. Yellow solid, m.p. 72–75 °C, yield 16.7%. ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, CH_2CH_3), 3.53 (q, 2H, OCH_2CH_3), 3.66 (t, 2H, CH_2O), 4.05–4.29 (m, 13H, C_5H_4, C_5H_5, CH_2N, CO_2CH_2), 7.95 (d, 1H, =CH), 6.35 (br, 1H, NH). Anal. Found: C, 59.68; H, 5.88; N, 7.03. Calc. for $C_{19}H_{22}FeN_2O_3$: C, 59.69; H, 5.81; N, 7.33%.

3.3. Herbicidal activity tests

3.3.1. Plant material

A broadleaf plant, rape (*Brassica napus*), was used to test the herbicidal activity of compounds. Seeds of rape were bought from the Institute of Crop, Tianjin Agroculture Science Academy, PR China.

3.3.2. Culture method

Seeds were planted in 6-cm-diameter plastic boxes containing artificial mixed soil. Before plant emergence, the boxes were covered with plastic film to keep moist. Plants were grown in the green house. The fresh weight of upground plants was measured 10 days after treatment. The inhibition percent of upground fresh weight is used to describe the control efficiency of compounds.

3.3.3. Pre-emergency treatment

The dosage (activity ingredient) for each compound is 1500 g per hectare. Purified compounds were dissolved in 100 ul DMF with the addition of a little Tween 20, and then were sprayed using a laboratory belt sprayer delivering at 750 l ha^{-1} spray volume. The same amount of water was sprayed as control. Compounds were sprayed immediately after seeds planting.

Acknowledgements

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