DOI:10.1021/jf902861m

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

Synthesis and Antiviral Bioactivities of 2-Cyano-3-substituted-amino(phenyl) Methylphosphonylacrylates (Acrylamides) Containing Alkoxyethyl Moieties†

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An efficient reaction under microwave irradiation has been developed for the synthesis of a series of novel 2-cyano-3-substituted-amino(phenyl) methylphosphonylacrylates (acrylamides) **II**. The products obtained in shorter reaction time with moderate yields are fully characterized by elemental analysis, IR, ^{1}H, ^{13}C, and ^{31}P NMR spectral data. The role of introducing various substituents and the effect of incorporating α-aminophosphonates with an alkoxyethyl moiety into the parent cyanoacrylate (acrylamide) structure are investigated. Among the studied compounds, both **II-17** and **II-24** displayed good in vivo curative, protection, and inactivation effects, which were comparable to those of the commercial reference ningnanmycin (inhibitory rates of 58.8, 60.2, 78.9% and 60.0, 58.9, 85.5%, respectively, at 500 mg/L against TMV). To the best of the authors' knowledge, this is the first report on the synthesis and antiviral activity of the title compounds **II**.

KEYWORDS: 2-Cyanoacrylate; alkoxyethyl; α-aminophosphonate; microwave irradiation; anti-TMV activity

INTRODUCTION

2-Cyanoacrylates and their derivatives act as potent growth inhibitors of weeds due to their ability to disrupt photosystem II (PSII) electron transport at a common binding domain on the 32 kDa polypeptide at the PSII reaction center (*1*−*4*). These compounds exhibit a wide range of bioactivities with immense potential to be employed as herbicides, fungicides, plant virucides, and antitumor agents (*5*−*13*). Some of these cyanoacrylate derivatives obtained by conventional nucleophilic displacement of methylthio moieties of 2-cyano-3-(methylthio) acrylates by (*R*)- or (*S*)-1-phenylethanamine, phenylamino group, and aryl (heterocyclic) amine displayed moderate to good effect against tobacco mosaic virus (TMV) in vivo (*14*, *15*). Unfortunately, the reactions leading to these acrylates are generally sluggish but could be accelerated by the application of microwave irradiation (*14*). Encouraged by our earlier result that cyanoacrylates bearing phosphonyl moieties possessed high in vivo curative, protection, and inactivation effects against TMV (*16*), we recently prepared similar cyanoacrylate derivatives bearing an α-aminophosphonate unit to obtain novel structure **A** (**Figure 1**) having good effect against TMV with inhibitory rate at 500 mg/L (*17*). However, these compounds **A** derived from simple dialkyl phosphites did not have the desired anti-TMV activity to combat the severity of the plant disease caused by the virus. Fortunately, certain suitably derivatized phosphonates (*18*−*20*), particularly those bearing two alkoxyethyl moieties instead of simple dialkyl ones (*21*), are associated with high antiviral activities. To meet the ever-increasing demand for the development of effective environmentally benign antiviral agents for protecting crops from the deadly TMV, we envisioned that the introduction of phosphonates bearing alkoxyethyl moiety into the parent cyanoacrylate (acrylamide) scaffold might lead to the generation of new potent agents with desired activity. The rationale behind the synthetic design of novel structure **II** containing an alkoxyethyl moiety tunable by variation of substituents R_1, R_2, and R_3 is shown in **Figure 1**. Although cyonoacrylate derivatives containing an α-aminophosphonate moiety derived from dialkyl phosphites have previously been prepared (*17*) (structure **A**, **Figure 1**), to the best of our knowledge to date no attempt has been made to prepare similar compounds bearing an alkoxyethyl moiety. As the introduction of fluorine may lead to a marked change in the bioactivity of phosphonates (*22*−*26*), we also studied the role of fluorine atom (R_1) in some of our title compounds and explored the potential of cyanoacrylate (cyanoacrylamide) derivatives of α-aminophosphonates **II** (**Figure 1**) in protecting crops against viral attack. The various methods reported for the preparation of cyanoacrylate derivatives suffer from serious drawbacks such as long reaction times accompanied by the formation of side reaction products (*5*−*9*, *17*). The poor nucleophilicity of α-aminophosphonates containing alkoxyethyl and fluorinated groups can further retard the rate of the reaction, making the design of the synthetic route to the title compounds more difficult.

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 Published on Web 12/10/2009

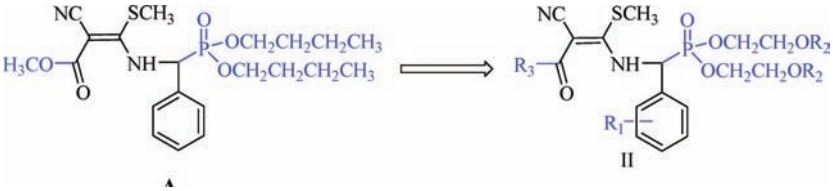
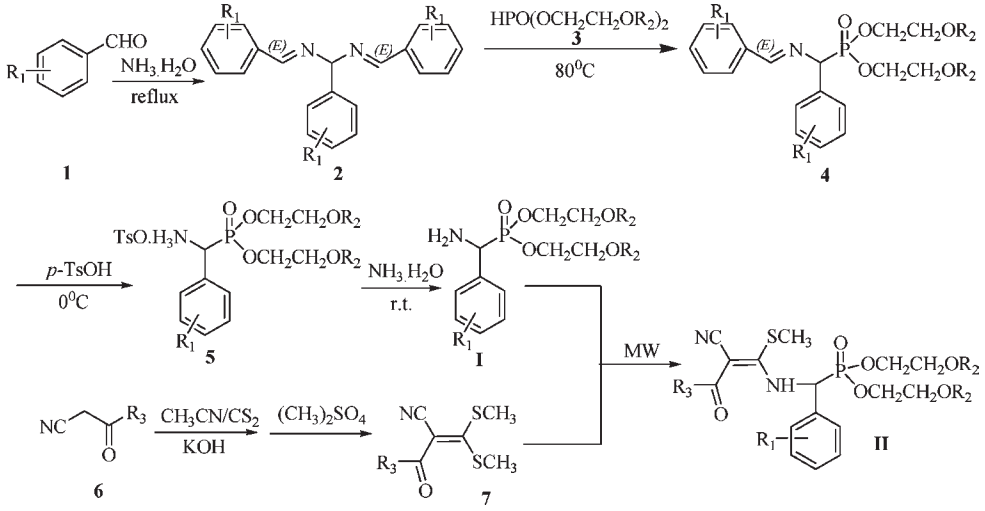


Figure 1. Strategic design of the target cyanoacrylates (acrylamides **II**) bearing alkoxyethyl moieties.

Scheme 1. Synthetic Route to 2-Cyano-3-substituted-amino(phenyl) Methylphosphonylacrylate (Acrylamide) Analogues **II** Containing Alkoxyethyl Moieties



Because the reaction rates for the synthesis of cyanoacrylates and α-aminophosphonates are found to be markedly accelerated under microwave irradiation (*14*, *21*), we undertook the synthesis of the title compounds under similar conditions for improving reaction yields and shortening reaction times (**Scheme 1**). Compounds **II** were completely characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR, and elemental analysis data. Some of the synthesized compounds showed excellent anti-TMV activities. To the best of our knowledge, this is the first report on the synthesis and the anti-TMV bioactivity of the title compounds.

MATERIALS AND METHODS

Instruments. The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in a KBr disk. ^{1}H, ^{13}C, and ^{31}P NMR (solvent $CDCl_3$) spectra were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using tetramethylsilane as an internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Microwave irradiations were carried out in a CEM-Auto Focused Coupling. Analytical thin-layer chromatography was performed on silica gel GF_{254}. Column chromatographic purification was carried out using silica gel. All reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated, and redistilled before use.

Synthetic Procedures. Compounds **3**, intermediates **4**, and intermediates **5** were synthesized according to the literature methods (*4*, *27*, *28*), as described, with minor modifications of reaction temperature and reaction time.

General Procedure for the Preparation of *O*,*O*′-Bis(2-alkoxyethyl)-1-amino(phenyl) Methylphosphonate Intermediates I. The aldehyde (15 mmol) was added to ammonium hydroxide (30%, 15 mL), and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed, which was removed by filtration and then dried. Dialkoxyethyl phosphite (6 mmol) was added to this solid, and the resulting solution was stirred for 12 h at 80 °C. *p*-Toluenesulfonic acid (6 mmol) in 50 mL of THF was added to the reaction mixture, which was stirred for 4 h at 0 °C. The precipitate was removed by filtration, washed with THF (20 mL), and then added to 15 mL of aqueous ammonium hydroxide (10%). The mixture was stirred for 2 h at room temperature, extracted with ethyl acetate (3 × 20 mL), and the solvent was removed under reduced pressure. Pure products were obtained as oils by silica gel column chromatography using ethyl acetate/petroleum ether (2:1). The data for **Ia**−**Id** can be found in the Supporting Information.

General Procedure for the Preparation of 2-Cyano-3,3-dimethylthioacrylate (Acrylamide) Intermediates 7. Esters **6a**−**6e** were prepared conveniently from cyanoacetic acid and primary alcohols in the presence of a catalytic amount of anhydrous H_2SO_4 under reflux condition. Amides **6f** and **6g** were synthesized from ethyl cyanoacetate and the corresponding amine in excellent yields by carrying out the reaction at room temperature for 1 h. Compound **6** (20 mmol) was added dropwise to a mixture of potassium hydroxide powder (40 mmol) and anhydrous acetonitrile (30 mL) at 5 °C. The mixture was stirred for 1.5 h, and then a solution of carbon disulfide (20 mmol) in anhydrous acetonitrile (5 mL) was added over a period of 15 min. The reaction mixture was stirred for 4 h at room temperature. After the solution had been cooled to 0 °C, dimethyl sulfate (40 mmol) was added, and the resulting mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and then water (30 mL) and ethyl acetate (50 mL) were added to the residue. The organic layer was separated and dried with anhydrous magnesium sulfate. Ethyl acetate was evaporated to afford the corresponding **7**. The data for **7a**−**7g** can be found in the Supporting Information.

General Procedure for Conventional Preparation of 2-Cyano-3-substituted-amino(phenyl) Methylphosphonylacrylates (Acrylamides) II. A mixture of 2-cyano-3,3-dimethylthioacrylate (acrylamide) (**7a**−**7g**) (0.15 mmol) and α-aminophosphonate containing an alkoxyethyl moiety (**Ia**−**Id**) (0.15 mmol) in ethanol (10 mL) was refuxed and stirred for 12 h. The progress of the reaction was monitored by TLC; the solvent was evaporated under reduced pressure, and the residue was washed with water, filtered off, and purified by silica gel column chromatography (petroleum ether/ethyl acetate, 1:2, v/v) to give the title compounds.

General Procedure for Microwave Preparation of 2-Cyano-3-substituted-amino(phenyl) Methylphosphonylacrylates (Acrylamides) II. A mixture of 2-cyano-3,3-dimethylthioacrylate (acrylamide) (**7a**−**7g**) (0.15 mmol) and α-aminophosphonate containing an alkoxyethyl moiety (**Ia**−**Id**) (0.15 mmol) in ethanol (10 mL) was placed in a microwave tube, which was then sealed and placed in the Discovery synthesizer and irradiated at 100 °C and 140 W and 100 psi for 30 min. Upon completion

of the reaction, the solvent was removed under reduced pressure, and the residue was washed with water, filtered off, and purified by silica gel column chromatography (petroleum ether/ethyl acetate, 1:2, v/v) to give the title compounds. The data for **II-1** are shown below, whereas data for **II-2**−**II-28** can be found in the Supporting Information.

Data for **II-1**: colorless oil; IR (KBr, cm^{-1}) ν 3127.1, 3096.0, 2857.2, 2834.3, 2206.9, 1670.3, 1593.2, 1554.6, 1516.0, 1492.9, 1396.4, 1348.2, 1284.5, 1207.3, 1055.6, 781.3, 742.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53 (s, 3H, SCH_3), 3.32 (s, 6H, $2OCH_3$), 3.43−3.54 (m, 4H, $2OCH_2$), 3.82 (s, 3H, OCH_3), 4.00−4.18 (m, 4H, $2OCH_2$), 5.73 (q, J = 5.74 Hz, 1H, CH), 7.39−7.42 (m, 5H, ArH), 10.95 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 172.2, 168.3, 129.0, 128.7, 128.6, 128.0, 127.8, 127.7, 117.9, 71.4, 71.3, 66.3, 66.2, 58.9, 58.8, 52.1, 51.9, 18.4; ^{31}P NMR (200 MHz, $CDCl_3$) δ 20.08. Anal. Calcd for $C_{19}H_{27}N_2O_7PS$: C, 49.78; H, 5.94; N, 6.11. Found: C, 49.92; H, 5.82; N, 6.28.

Antiviral Biological Assay. Purification of Tobacco Mosaic Virus. Using Gooding's method (*29*), the upper leaves of *Nicotiana tabacum* L. inoculated with TMV were selected, ground in phosphate buffer, and then filtered through a double-layer pledget. The filtrate was centrifuged at 10000*g*, treated twice with poly(ethylene glycol), and centrifuged again. The whole experiment was carried out at 4 °C. Absorbance values were estimated at 260 nm using an ultraviolet spectrophotometer.

$$\text{virus concn} = (A_{260} \times \text{dilution ratio})/E_{1\text{cm}}^{0.1\%,\,260\text{nm}}$$

Protective Effect of Compounds against TMV in Vivo. The compound solution was smeared on the left side, whereas the solvent served as the control on the right side of growing *N. tabacum* L. leaves of the same ages. The leaves were then inoculated with the virus after 12 h. A brush was dipped in TMV of 6×10^{-3} mg/mL to inoculate the leaves, which were previously scattered with silicon carbide. The leaves were then washed with water and rubbed softly along the nervature once or twice. The local lesion numbers appearing 3−4 days after inoculation were counted. The experiment was repeated three times with each compound.

Inactivation Effect of Compounds against TMV in Vivo. The virus was inhibited by mixing with the compound solution at the same volume for 30 min. The mixture was then inoculated on the left side of the leaves of *N. tabacum* L., whereas the right side of the leaves was inoculated with the mixture of solvent and the virus for control. The local lesion numbers were recorded 3−4 days after inoculation. The experiment was repeated three times with each compound.

Curative Effect of Compounds against TMV in Vivo. Growing leaves of *N. tabacum* L. of the same ages were selected. The TMV (concentration of 6×10^{-3} mg/mL) was dipped and inoculated on the whole leaves. Then the leaves were washed with water and dried. The compound solution was smeared on the left side, and the solvent was smeared on the right side for control. The local lesion numbers were then counted and recorded 3−4 days after inoculation. The experiment was repeated three times with each compound. The inhibition rate of the compound was then calculated according to the following formula (av denotes average, and controls were not treated with compound).

$$\text{inhibition rate (\%)} = \{[\text{av local lesion no. of control (not treated with compd)} - \text{av local lesion no. smeared with drugs}]/\text{av local lesion no. of control}\} \times 100\%$$

RESULTS AND DISCUSSION

Synthesis. As can be observed from **Scheme 1**, the preparation of title compound **II** involves a multistep synthesis, and the overall yield is therefore affected by complexity of individual steps. The microwave reaction conditions for the final step leading to the synthesis of title compounds were optimized for various reaction parameters, for example, reaction time, temperature, and power input, by taking **II-1** as the model. Unlike conventional synthesis where the temperature could not be raised beyond the boiling point of ethanol (75−80 °C), the microwave-assisted syntheses could be successfully executed at higher temperature as the reactions were carried out in a sealed tube under a pressurized atmosphere. To study the effect of reaction time on the synthesis of the model compound, at first all of the reactions were carried at a fixed power of 100 W and temperature of 100 °C. The isolated yields of compound **II-1** varied from 10.3 to 43.4% when the reaction time was between 5 and 40 min (**Table 1**). The optimum reaction time corresponding to maximum yield was found to be 30 min (entry 6 in **Table 1**), beyond which a slight reduction in the yield occurred. The synthesis of the model compound was further studied at various temperatures, keeping the power constant at 100 W (**Table 2**). The highest yield in this case was recorded at 100 °C, and above this temperature the yield was lowered (entries 5 and 6 in **Table 2**), presumably due to the thermal decomposition of the intermediate α-aminophosphonate at high temperature. For power optimization, the reaction was executed under the same set of conditions (**Table 3**) at different microwave powers. In the beginning, the yield of compound **II-1** increased appreciably from 26.4 to 46.6% with increasing power input from 60 to 140 W (entries 1−5 in **Table 3**). However, this upward trend in the yield was less noticeable at higher powers (entries 6−7 in **Table 3**). Thus, under the optimized conditions, the best result can be achieved when 1 equiv of the nucleophilic component *O*,*O*′-bis(2-alkoxyethyl)-1-amino-(phenyl) methylphosphonate reacts with 2-cyano-3,3-dimethylthioacrylate (acrylamide) under microwave conditions in ethanol at 100 °C and 140 W microwave power for 30 min. A comparison of the yields from the conventional and microwave-assisted

Table 1. Time Optimization of Microwave-Assisted Synthesis of **II-1**

entry	time (min)	yield[a] (%)
1	5	10.3
2	10	16.8
3	15	27.6
4	20	42.8
5	25	43.1
6	30	43.4
7	35	42.9
8	40	41.6

[a] Yields of isolated products.

Table 2. Temperature Optimization of Microwave-Assisted Synthesis of **II-1**

entry	temp (°C)	yield[a] (%)
1	40	10.3
2	60	16.8
3	80	27.6
4	100	43.4
5	120	40.5
6	140	36.5

[a] Yields of isolated products.

Table 3. Power Optimization of Microwave-Assisted Synthesis of **II-1**

entry	power (W)	yield[a] (%)
1	60	26.4
2	80	33.7
3	100	43.4
4	120	45.8
5	140	46.6
6	160	47.0
7	200	47.0

[a] Yields of isolated products.

Table 4. Comparison of Conventional and Microwave-Assisted Procedures for the Synthesis of Compounds **II**

				traditional heating		microwave irradiation	
compd	R_1	R_2	R_3	time (h)	yield[a] (%)	time (min)	yield[a] (%)
II-1	H	CH_3	OCH_3	12	19.6	30	46.6
II-2	H	CH_3	OC_2H_5	12	20.3	30	43.2
II-3	H	CH_3	$OC_2H_4OCH_3$	12	21.2	30	44.1
II-4	H	CH_3	$OC_2H_4OC_2H_5$	12	18.8	30	44.3
II-5	H	CH_3	OC_2H_4OPh	12	18.0	30	49.4
II-6	H	CH_3	NH_2	12	22.9	30	50.1
II-7	H	CH_3	$NHCH_2Ph$	12	21.7	30	41.8
II-8	2-F	CH_3	OCH_3	12	20.1	30	41.2
II-9	2-F	CH_3	OC_2H_5	12	21.2	30	49.3
II-10	2-F	CH_3	$OC_2H_4OCH_3$	12	19.7	30	47.1
II-11	2-F	CH_3	$OC_2H_4OC_2H_5$	12	19.9	30	45.5
II-12	2-F	CH_3	OC_2H_4OPh	12	18.5	30	42.1
II-13	2-F	CH_3	NH_2	12	24.6	30	53.3
II-14	2-F	CH_3	$NHCH_2Ph$	12	23.3	30	50.0
II-15	H	C_2H_5	OCH_3	12	20.0	30	49.1
II-16	H	C_2H_5	OC_2H_5	12	18.9	30	45.3
II-17	H	C_2H_5	$OC_2H_4OCH_3$	12	19.1	30	42.5
II-18	H	C_2H_5	$OC_2H_4OC_2H_5$	12	19.5	30	44.6
II-19	H	C_2H_5	OC_2H_4OPh	12	17.2	30	44.0
II-20	H	C_2H_5	NH_2	12	22.6	30	42.7
II-21	H	C_2H_5	$NHCH_2Ph$	12	22.8	30	49.6
II-22	2-F	C_2H_5	OCH_3	12	20.7	30	48.0
II-23	2-F	C_2H_5	OC_2H_5	12	21.0	30	45.3
II-24	2-F	C_2H_5	$OC_2H_4OCH_3$	12	19.2	30	41.8
II-25	2-F	C_2H_5	$OC_2H_4OC_2H_5$	12	19.0	30	44.3
II-26	2-F	C_2H_5	OC_2H_4OPh	12	17.2	30	40.9
II-27	2-F	C_2H_5	NH_2	12	22.9	30	52.2
II-28	2-F	C_2H_5	$NHCH_2Ph$	12	23.1	30	42.5

[a] Yields of isolated products.

syntheses was performed, and the results are shown in **Table 4**. We can conclude from **Table 4** that although the improvement in the yield was marginal (e.g., for compound **II-5** an overall improvement of 31.4% from conventional to MV mode), the microwave-assisted synthesis brought about a significant reduction of reaction time from 12 h to 30 min.

All of the products were unequivocally characterized by IR and NMR spectral data and elemental analyses. The characteristic IR absorption bands for NH (3100−3430 s cm^{-1}), C═N (2200−2210 s cm^{-1}), C═O (1640−1720 s cm^{-1}), C═C (1520−1590 s cm^{-1}), P═O (1240−1280 cm^{-1}), C—OC (1200−1230 cm^{-1}), and PO—C (1001−1040 cm^{-1}) confirmed the presence of the functional groups. In ^{1}H NMR spectra, all aromatic protons revealed the expected multiplet near 6.91−7.50 ppm. The NH protons of compounds **II** appeared considerably downfield in the region of 10.75−12.05 ppm due to the existence of hydrogen bonding with the acrylate (acrylamide). The chemical shift of SCH_3 appeared near 2.25−2.57 ppm and PCH of ester showed up at 5.52−6.10 ppm. The H atom at the α-C exhibited a quartet due to the coupling with the adjacent phosphorus. The chemical shifts of OCH_2 generally appeared in the region of 3.17−4.55 ppm. The typical phosphorus resonance at 18.78−20.80 ppm in the ^{31}P NMR spectra of all target compounds confirmed the presence of a phosphorus center coupled to adjacent CH. All of the nonequivalent carbon atoms were identified in ^{13}C NMR and the total number of protons calculated from the integration curve accorded (in ^{1}H NMR) with the assigned structures.

Antiviral Activity and Structure−Activity Relationship. To study the role of different substituents (R_1, R_2, and R_3) in imparting antiviral activity and to establish a structure−activity relationship based on the experimental data, the antiviral potencies of the title cyanoacylates (acrylamides) **II** were compared against that of Ningnanmycin, a commercially available nitrogenous virucide usually produced by *Strepcomces noursei* var. *xichangensisn* var. TMV was assayed by the earlier methods reported in the literature (*14*, *30*). The compounds were evaluated for their suitability as antiviral agents against TMV. The antiviral activities were measured at 500 mg/L in vivo, and the data are presented in **Table 5**. Among the studied compounds, cyanoacrylate derivatives **II-17** (R_1 = H, R_2 = Et, R_3 = $OC_2H_4OCH_3$) and **II-24** (R_1 = 2-F, R_2 = Et, R_3 = $OC_2H_4OCH_3$) displayed remarkable protection activities (60.2 and 58.9%, respectively) and curative rates (58.8 and 60.0%, respectively) against TMV, which were comparable to the protection activity (57.7%) and curative rate (58.9%) shown by the commercial reference Ningnanmycin. It can also be noted from the data presented in **Table 5** that cyanoacrylamide derivatives such as **II-6**, **II-7**, **II-14**, **II-20**, **II-21**, and **II-28**, contrary to **II-17** and **II-24**, showed only moderate to good protection activities of 50.0, 39.7, 39.9, 54.4, 34.5, and 55.4%, respectively, at 500 mg/L, and nonfluorinated cyanoacrylates **II-1**, **II-4**, and **II-15** and fluorinated cyanoacrylates **II-9**, **II-10**, and **II-22** were found to be completely ineffective against TMV. The curative activities of the title compounds depend to a certain extent on the nature of the substituents; compounds **II-3**, **II-6**, **II-12**, **II-16**, **II-18**, **II-19**, **II-20**, **II-21**, **II-23**, **II-25**, and **II-28** showed curative activities of up to 43.1, 43.2, 41.8, 51.1, 46.4, 44.1, 56.7, 47.3, 45.6, 41.9, and 54.3%, respectively, at 500 mg/L against TMV. As for inactivation bioactivities, except for cyanoacrylates **II-17** and **II-24** and cyanoacrylamides **II-6**, **II-20**, and **II-28**, which showed moderate to good inactivation bioactivities (78.9, 85.5, 66.7, 80.0, and 79.9%, respectively), all other compounds exhibited lower inactivation bioactivities against TMV at the concentration of 500 mg/L. Comparison of biological activities among all target compounds leads us to conclude that the

Table 5. Protection Effect, Inactivation Effect, and Curative Effect of the New Compounds against TMV in Vivo

agent	concn (mg/L)	protection effect (%)	inactivation effect (%)	curative effect (%)
II-1	500	0	0	28.8
II-2	500	21.0	28.3	32.1
II-3	500	40.0	41.9	43.1
II-4	500	0	12.2	23.7
II-5	500	14.4	21.0	31.0
II-6	500	50.0	66.7	43.2
II-7	500	39.7	32.1	29.6
II-8	500	22.0	41.0	34.5
II-9	500	0	0	21.7
II-10	500	0	0	9.9
II-11	500	21.9	33.3	31.4
II-12	500	29.0	44.0	41.8
II-13	500	30.0	44.8	22.0
II-14	500	39.9	40.8	28.6
II-15	500	0	0	4.3
II-16	500	45.9	35.4	51.1
II-17	500	60.2	78.9	58.8
II-18	500	40.7	29.5	46.4
II-19	500	3.8	31.9	44.1
II-20	500	54.4	80.0	56.7
II-21	500	34.5	40.1	47.3
II-22	500	0	12.0	33.0
II-23	500	12.9	33.4	45.6
II-24	500	58.9	85.5	60.0
II-25	500	31.0	40.2	41.9
II-26	500	30.7	23.7	27.7
II-27	500	30.0	33.9	30.6
II-28	500	55.4	79.9	54.3
Ningnanmycin	500	57.7	96.0	58.9

anti-TMV activities of the products are higher if the cyanoacrylate ester is derived from $R_3 = OC_2H_4OCH_3$ instead of OCH_3 or OC_2H_4OPh, and the aminophosphonate component is derived from R_2 = Et instead of Me. The cyanoacrylamide derivatives, in general, displayed greater anti-TMV activities compared to their cyanoacrylate analogues. The screening of our experimental data (**Table 5**) clearly showed that **II-17** and **II-24** had excellent protection effects, appreciable curative activity, and moderate inactivation activity against TMV, which are different from most of the 2-cyanoacrylate derivatives reported in our previous work (*14*−*17*). As the two most effective compounds **II-17** and II-24 are structurally similar except for the fluorine substitution at the ortho position in the aromatic ring, the role of fluorine incorporation for changing activity of the studied compounds appears to be insignificant.

In conclusion, a series of novel cyanoacrylate (cyanoacrylamide) derivatives incorporating α-aminophosphonate moieties derived from dialkoxyethyl phosphites were synthesized via microwave-assisted procedure. The method offers several advantages such as fast reaction rate, moderate yields, and environmental friendliness. Fortunately, some of the synthesized compounds possessing excellent anti-TMV activities have potential to reduce the economic loss caused by TMV. The preliminary structure−activity relationships have established the importance of the presence of an ethoxyethyl moiety in the phosphonate component to obtain title compounds with desired antiviral activity. Normally, cyanoacrylamide derivatives showed higher anti-TMV activities than their corresponding cyanoacrylate ester analogues. The cyanoacrylates **II-17** and **II-24** showed excellent protection effects and appreciable curative activities comparable to those of the standard Ningnanmycin against TMV. The changes in hydrophobic and electrostatic interactions obtained by structural variation with different substituents might be responsible for the observed enhancement in anti-TMV activities of these compounds. Although the idea behind this study was to obtain a potent antiviral agent by preparing different title compounds containing alkoxyethyl and fluorinated moieties, the role of the latter was found to be relatively less pronounced compared to the former. The present work successfully demonstrated that the antiviral activity of the parent cyanoacrylate derivatives could be significantly improved by the incorporation of an α-aminophosphonate scaffold bearing alkoxyethyl moieties. Further studies on structural optimization and mode of action are currently underway in our laboratories.

Supporting Information Available: Analytical data for **Ia**−**Id**, **7a**−**7g**, and **II-2**−**II-28**. This information is available free of charge via the Internet at http://pubs.acs.org.

LITERATURE CITED

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Received for review June 2, 2009. Revised manuscript received October 22, 2009. Accepted November 19, 2009. We thank the National Key Program for Basic Research (No. 2003CB114404) and the National Natural Science Foundation of China (No. 20672024) for financial support.