JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Synthesis and Antiviral Activities of Amide Derivatives Containing the α-Aminophosphonate Moiety

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Starting from (substituted-)benzaldehydes, the title compounds **6** were synthesized through five step reactions. Benzaldehydes were treated with ammonium hydroxide, followed by dialkyl phosphite, to give dialkyl *N*-(arylmethylene)-1-amino-1-aryl methylphosphonates (**3**). Phosphonates **3** were then easily hydrolyzed to give dialkyl 1-amino-1-aryl-methylphosphonates **5**. Target compounds **6** were then obtained by the reaction of **5** and substituted benzoic or cinnamic acid. Their structures were clearly verified by spectroscopic data (IR, ^{1}H, ^{13}C, and ^{31}P NMR, and elemental analysis). These compounds were shown to be antivirally active in the bioassay. It was found that title compounds **6g**, **6l**, and **6n** had the same inactivation effect of TMV (EC_{50} = 54.8, 60.0, and 65.2 μg/mL, respectively) as commercial product Ningnanmycin (EC_{50} = 55.6 μg/mL). To the best of our knowledge, this is the first report on the synthesis and antiviral activity of amide derivatives containing an α-aminophosphonate moiety.

KEYWORDS: Amide; α-aminophosphonate moiety; antiviral activity; synthesis

INTRODUCTION

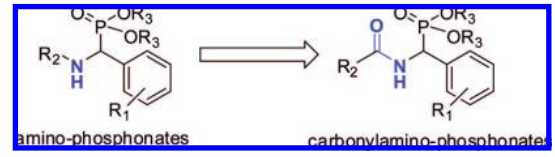
Recently, a variety of the reports regarding synthetic studies of the amide derivatives have been presented because they were documented to exhibit a wide range of biological activities. Some derivatives of amide can serve not only as agrochemicals such as fungicide, insecticide, and plant virucide, but also as medicines such as antitumor agents (*1–6*). A large volume of research on their synthesis and biological activities has been reported during the last ten years (*7, 8*). On the other hand, α-aminophosphonates have broad bioactivities and are widely used as fungicide, plant virucide, and herbicide. Among these compounds, studies are mainly concentrated on those containing heterocycle moieties such as thiophene, furan, pyrole, 1,3,4-thiadiazole, and benzothiazole moieties, and many compounds were reported with excellent bioactivities (*9–15*).

In our previous work, many substituted aryl aminophosphonate derivatives were synthesized and wer found to have good antiviral activities (*16–20*). Hence, it is naturally interesting whether or not the amide derivatives of α-aminophosphonates will improve their antiviral activies. Also, few literatures have yet reported this kind of amidylphosphonate compounds (*21–23*). To extend our research work of developing α-aminophosphonates as antiviral agent, we designed and synthesized some novel amidyl phosphonate derivatives, (**Scheme 1**). The synthetic route is shown in **Scheme 2**. The bioassay test showed that the new compounds **6** possessed weak-to-good antiviral activities. To the best of our knowledge, this is the first report on the synthesis and antifungal and antiviral activity of amide derivatives containing an α-aminophosphonate moiety.

MATERIAL AND METHODS

The melting points of the products were determined on a 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 KBr disks. ^{1}H, ^{13}C, and ^{31}P NMR (solvent dimethyl sulfoxide (DMSO)) spectra were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. All reagents were analytical reagent grade or were chemically pure. All solvents were dried, deoxygenated, and redistilled before use. Diethyl

Scheme 1. Structure comparison of amino-phosphonates and carbonylamino-phosphonates



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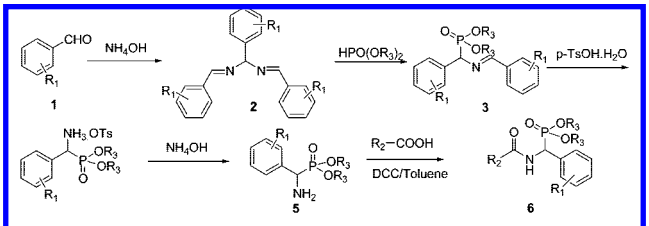
10.1021/jf072394k CCC: $40.75
Published on Web 01/10/2008

Scheme 2. Synthetic route of amide analogues containing α-aminophosphonate **6**



Compd.	R_1	R_2	R_3	Compd.	R_1	R_2	R_3
6a	H	3,4,5-trimethoxyphenyl	Et	**6b**	2-F	3,4,5-trimethoxyphenyl	Et
6c	H	Phenyl	Et	**6d**	2-F	Phenyl	Et
6e	2-F	2-fluorophenyl	Et	**6f**	H	2-fluorophenyl	Et
6g	H	4-fluorophenyl	Et	**6h**	H	3-fluorophenyl	Et
6i	H	2-trifluoromethylphenyl	Et	**6j**	2-F	3-fluorophenyl	Et
6k	2-F	2-trifluoromethylphenyl	Et	**6l**	H	2-chlorophenyl	Et
6m	2-F	2-chlorophenyl	Et	**6n**	H	cinnamido	Et
6o	2-F	cinnamido	Et	**6p**	H	2-trifluoromethylphenyl	n-Pr
6q	H	3-fluorophenyl	n-Pr	**6r**	H	3,4,5-trimethoxyphenyl	n-Pr
6s	H	phenyl	n-Pr				

phosphite and di-*n*-propyl phosphite were prepared according to literature methods as described (*24*). Intermediates **5a**−**c** were prepared according to the reported methods (*25*), and the detailed procedure can be found in the Supporting Information.

General Procedure for the Preparation of Compounds 6a−**s.** A solution of aromatic acid (1 mmol) in toluene (10 mL) was stirred, followed by the addition of intermediate **5** (1 mmol), and then the reaction system was cooled down to 0 °C. Then, 1,3-dicyclohexylcarbodiimide (DCC) (1 mmol) in toluene (10 mL) was added. The mixture was reacted for 10∼24 h at 25 °C, and then the 1,3-dicyclohexylurea (DCU) was filtered off. The toluene solvent was evaporated to the crude product, which was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (4:1) as an eluant to give the target compounds in yields of 40.5−90.6%. The example data of **6a** was shown as follows, and data for **6b**−**s** can be found in the Supporting Information.

*Data for Diethylphenyl(3,4,5-trimethoxybenzamido)methylphosphonate (***6a***).* White crystal; mp, 149∼151 °C; yield, 40.5%; IR (KBr): ν_{max} 3246.2, 2995.5, 1649.1, 1246.0, 1031.9; ^{1}H NMR (500 MHz, DMSO) δ: 1.10 (t, J = 7.45 Hz, 3H, CH_3), 1.32 (t, J = 7.15 Hz, 3H, CH_3), 3.72∼4.19 (m, 13H, $3OCH_3 + 2OCH_2$), 5.69∼5.73 (m, 1H, CH), 7.04∼7.53 (m, 7H, Ar-H + NH); ^{13}C NMR (125 MHz, DMSO) δ: 166.53, 153.19, 141.30, 135.17, 129.13, 128.24, 28.19, 104.74, 63.57, 63.51, 60.90, 56.36, 51.33, 50.12, 16.45, 16.15; ^{31}P NMR (200 MHz, DMSO) δ: 22.18; Anal. Calcd for $C_{21}H_{28}NO_7P$: C, 57.66; H, 6.45; N, 3.20. Found: C, 57.84; H, 6.62; N, 3.17.

Antiviral Biological Assay. *Purification of Tobacco Mosaic Virus.* Using Gooding's method (*26*), the upper leaves of *Nicotiana tabacum L* inoculated with TMV were selected and were ground in phosphate buffer and then filtered through double layer pledget. The filtrate was centrifuged at 10 000*g*, treated twice with PEG, and then centrifuged again. The whole experiment was carried out at 4 °C. Absorbance values were estimated to be at 260 nm using an ultraviolet spectrophotometer. Virus concentration = $(A_{260} \times \text{dilution ratio})/E_{1cm}^{0.1\%,260nm}$.

Protective Effects of Compounds on TMV In Vivo. The compound solution was smeared on the left side while solvent was served as control on the right side of growing *Nicotiana tabacum. L*leaves of the same ages. The leaves were then inoculated with the virus after 12 h. A brush was dipped in tobacco mosaic virus 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 d after inoculation were counted (*27*). Three repetitions were conducted for each compound.

Inactivation Effect of Compounds on 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 *Nicotiana tabacum. L.*, while 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 d after inoculation (*27*). Three repetitions were conducted for each compound.

Curative Effect of Compounds on TMV In Vivo. Growing leaves of *Nicotiana tabacum. L* of the same ages were selected. The tobacco mosaic virus (with a 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 d after inoculation (*27*). For each compound, three repetitions were measured. The inhibition rate of the compound was then calculated according to the following formula ("av", average).

$$\text{Inhibition rate (\%)} = \left(\frac{\begin{array}{c}\text{av local lesion numbers of control}\\ \text{(not treated with compound)} -\\ \text{av local lesion numbers smeared with drugs}\end{array}}{\begin{array}{c}\text{av local lesion numbers of control}\\ \text{(not treated with compound)}\end{array}}\right) \times 100\%$$

RESULTS AND DISCUSSION

Synthesis. Amide compounds can be synthesized by treating amine with acyl chloride. However, the side products HCl generated in this method are harmful to the current reaction because the ester group of the phosphonate is easily removed by acidolysis. Thus, amide compounds containing phosphonate were synthesized by the coupling reaction of dialkyl amino-(substituted)phenyl-methylphosphonate and substituted benzoic of cinnamic acid in the presence of DCC. The reaction temperature during drop addition of DCC is crucial in this exthothermal reaction. When DCC was dropped into the reactants, the reaction temperature rises quickly and side reactions become significant. Thus, the reaction temperature during drop addition of DCC was controlled at 0 °C. This method is easy, rapid, and moderate-yielding for the synthesis of title compounds **6**. Under this condition, target compounds **6** were synthesized in the yields from 40.5 to 90.6%, and their structures were established by well defined IR, NMR, and elemental analysis (see Supporting Information).

Antiviral Activity. The antiviral activity of compounds **6a**−**s** against TMV is assayed by the reported method (*26, 27*). The results of in vivo bioassay against TMV are given in **Table 1**. Commercially available plant virucide Ningnanmycin (*28*), also probably the most successful registered plant antiviral agent by now in China, was used as a reference antiviral agent. The data provided in **Table 1** indicate that the introduction of dialkylphosphonyl in amide might improve their protective activities. The title compounds **6a**−**s** showed protection activity of 39.1–58.8%. Compound **6h** (R_1 is H, R_2 is 3-FC_6H_4, and R_3 is Et), **6l** (R_1 is H, R_2 is 2-ClC_6H_4, and R_3 is Et), **6n** (R_1 is H, R_2 is C_6H_5CH=CH, and R_3 is Et), and **6r** (R_1 is H, R_2 is 3,4,5-tri-$MeOC_6H_2$, and R_3 is *n*-Pr) have the same protection activity (56.0, 58.0, 58.7, and 58.8%, respectively) as that of the standard reference (60.2%). The highest protective activity was achieved when R_1 is H, R_2 is 4-FC_6H_4, and R_3 is Et (**6g**), with a protection activity of 65.7% against TMV at 500 μg/mL recorded in this case, which is equivalent to that of Ningnanmycin. From the data presented in **Table 1**, it can be observed that the title compounds **6a**−**s** possess potential inactivation bioactivities, with values of 45.6, 33.7, 42.4, 70.0, 80.0, 78.0, 99.1, 82.1, 45.3, 70.7, 62.2, 90.6, 39.0, 88.2, 51.5, 80.0, 86.6, 83.4, and 78.9% at 500 μg/mL, respectively. Among these compounds, **6g** is much more active against TMV than the other ones, with the inactivation rate of 99.1%, which is equivalent to Ningnanmycin (100%) against TMV at 500 μg/mL. The data also

Table 1. The Protection Effect, Inactivation Effect, and Curative Effect of the New Compounds against TMV In Vivo[a]

agents	concentration (μg/mL)	protection effect (%)	inactivation effect (%)	curative effect(%)
6a	500	42.0* ± 1.9	45.6** ± 1.1	35.6* ± 0.6
6b	500	41.2* ± 4.4	33.7* ± 0.8	17.1* ± 1.2
6c	500	39.1* ± 1.2	42.4* ± 2.0	8.7 ± 0.6
6d	500	43.1* ± 0.9	70.0** ± 3.1	32.2* ± 2.0
6e	500	50.0* ± 1.4	80.0* ± 2.9	20.8* ± 1.2
6f	500	42.0* ± 2.1	78.0** ± 1.1	53.6* ± 0.4
6g	500	65.7* ± 4.9	99.1** ± 2.0	19.2* ± 0.5
6h	500	56.0* ± 2.9	82.1* ± 1.7	24.6* ± 1.0
6i	500	41.1 ± 3.9	45.3* ± 1.6	2.4 ± 0.9
6j	500	41.0* ± 5.9	70.7* ± 0.8	6.2 ± 0.8
6k	500	39.2* ± 1.0	62.2* ± 0.6	2.1 ± 0.2
6l	500	58.0* ± 3.3	90.6* ± 1.3	20.0* ± 1.9
6m	500	40.9* ± 0.5	39.0* ± 1.8	19.7* ± 15
6n	500	58.7 ± 6.6	88.2** ± 2.2	50.0* ± 0.5
6o	500	39.0* ± 2.2	51.5* ± 0.6	22.4* ± 1.2
6p	500	44.0* ± 1.9	80.0* ± 2.0	53.7 ± 0.9
6q	500	50.9* ± 1.9	86.6* ± 2.9	44.1 ± 2.0
6r	500	58.8* ± 4.5	83.4* ± 1.6	55.0* ± 0.7
6s	500	49.9* ± 2.2	78.9** ± 2.2	45.3* ± 2.6
ningnamycin	500	60.2* ± 1.6	100** ± 1.2	55.4* ± 1.9

[a] All results are expressed as mean ± SD; $n = 3$ for all groups; * $P < 0.05$, ** $P < 0.01$.

Table 2. Antiviral Activities In vivo (%) of Compounds **6a**−**6s**

TMV	curative effect				inactivation effect			
concentration (μg mL^{-1})	500	250	125	EC_{50} (μg mL^{-1})	250	125	62.5	EC_{50} (μg mL^{-1})
6f	56.0	49.0	34.0	255.6	70.9	47.2	36.7	119.1
6g	22.0				100.0	76.1	70.0	54.8
6l	19.0				82.2	60.9	59.0	60.0
6n	51.0	39.9	32.3	438.8	79.9	61.2	49.1	65.2
6p	54.0	38.0	31.6	421.9	60.0	39.2	31.2	198.9
6q	43.0	21.0	12.9	545.5	65.0	46.0	40.1	149.9
6r	56.7	50.6	40.9	250.1	61.0	30.3	28.8	210.0
6s	42.0	23.9	14.0	559.8	51.0	23.0	10.0	278.9
ningnamycin	60.0	51.0	40.9	245.9	100.0	78.4	69.0	55.6

indicate that a change in the substituent might also affect the curative activity of title compounds **6a**−**s**. Compound **6f** (R_1 is H, R_2 is 2-FC_6H_4, and R_3 is Et), **6p** (R_1 is H, R_2 is 2-$CF_3C_6H_4$, and R_3 is *n*-Pr), and **6r** (R_1 is H, R_2 is 3,4,5-tri-$MeOC_6H_2$, and R_3 is *n*-Pr) have curative activities against TMV of up to 53.6, 53.7, and 55.0% at 500 μg/mL. The other compounds have a relatively lower curative activity than those of **6f, 6p**, and **6r.**

In addition, as shown in **Table 1**, compounds **6f**, **6g**, **6l**, **6n**, **6p**, **6q**, **6r**, and **6s** were found to display good antiviral activities. Thus, these eight compounds were further bioassayed to investigate their activities at different concentrations, with Ningnanmycin also used as the control. As shown in **Table 2**, the curative effect against TMV of compounds **6f** and **6r** are significant. Their EC_{50} values on TMV were 255.6 and 250.1 μg/mL, respectively, which are similar to that of Ningnanmycin (245.9 μg/mL). Compounds **6g, 6l**, and **6n** were highly effective at inactivating TMV, and the EC_{50} values were 54.8, 60.0, and 65.2 μg/mL, respectively. Among these compounds, **6g** had more potent antiviral activities against TMV than the other ones, with the same antiviral activity against TMV as Ningnanmycin. To the best of our knowledge, this is the first report about the syntheses and antiviral activity of amide-based α-aminophosphonate derivatives. Further structural optimization and mode of action (MOA) investigation are well under way.

Besides antiviral assay, we also tested the antifungal bioactivity of the title compounds. However, their fungicidal activities were all found to be very weak.

Supporting Information Available: Preparation of intermediates **5a**−**c** and compounds **6a**−**s** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

The authors wish to thank the National Key Program for Basic Research (No. 2003CB114404), the Cultivation Fund of the Key Scientific and Technical Innovation Project, Ministry of Education of China (Nos. 705039 and 706051), and the National Basic Research Priorities Program (No. 2005CCA01500) for the financial support.

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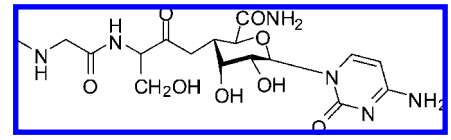
(28) Ningnanmycin is produced by *Strepcomces noursei* var. xichangensisn. var. Ningnanmycin is now commercially available in China as a registered plant virucide. However, it's action mechanism is not yet clear. Its structure is as follows:



Received for review August 9, 2007. Revised manuscript received November 28, 2007. Accepted November 30, 2007.

JF072394K