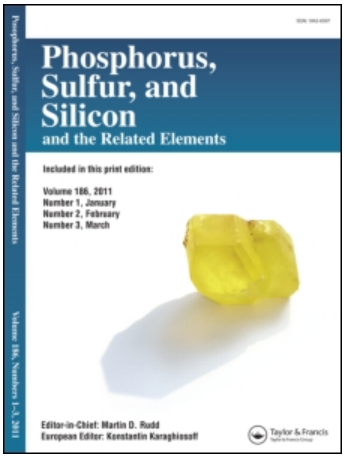

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THE SYNTHESIS OF α-(4-ANTIPYRYL)AMINO-(SUBSTITUTED) PHENYL-METHYLPHOSPHONIC ACID DERIVATIVES

Zai-Guo Li[a]; Run-Qiu Huang[a]; Rui-Lian Shao[a]; Yang Zhao[a]; Yun-Xian Long[a]
[a] Institute and State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, P. R. China

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THE SYNTHESIS OF α-(4-ANTIPYRYL)AMINO-(SUBSTITUTED) PHENYL-METHYLPHOSPHONIC ACID DERIVATIVES

ZAI-GUO LI*, RUN-QIU HUANG, RUI-LIAN SHAO, YANG ZHAO and YUN-XIAN LONG

Institute and State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China

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α-(4-antipyryl)amino-(substituted)phenylmethylphosphonic acid diesters (**2**) were synthesized by the addition of phosphite diesters to corresponding imine (**1**). A five-member cyclic transition state was proposed, and the influence of substituents on the reactivity of substrate was discussed. The net atomic charges of some imine **1** was calculated to support the mechanism. In the presence of NaI or KI, the cleavage of methyl esters of **2a** and **2c** vere realized by trimethyl silylition of **2** with trimethylchlorosilane. The structures of the compounds were confirmed by ^{1}H NMR spectroscopy.

Keywords: 4-aminoantipyrine; imine; α-aminophosphonic acid; trimethyl silylition; net atomic charge; phosphite diester

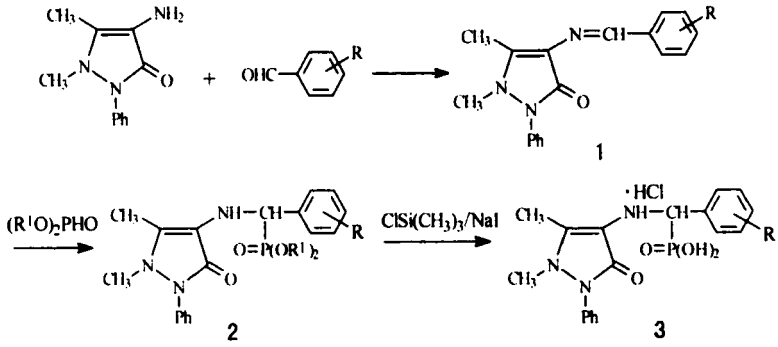
INTRODUCTION

α-Aminophosphonic acid derivatives are of considerable chemical and pharmacological importance as isosteres of aminocarboxylic acids[1]. Various related compounds of these also can serve in agrochemistry as antifungal agents[2], herbicides[3], plant regulators[4] and plant virucides[5]. In addition, pyrazole derivatives showed wide biological activities[6–9]. Considering the wide application of these compounds, we have prepared a series of new α-aminophosphonic acid diethyl esters with pyrazole moiety[10]. They

* Correspondence Author.

exhibited good anti-TMV(tobacco mosaic virus) activity. In this article, some new α-(4-antipyryl)amino-(substituted)phenyl-methylphosphonic acids and their esters were synthesized as potential plant virucides.

The approach to the title compounds is summarized in scheme 1.



SCHEME 1

RESULTS AND DISCUSSION

Synthesis of Compounds

The physical data and elementary analyses of compounds **2** and **3** are list in table I, and the ^{1}H NMR data are list in table II.

In the addition of phosphite diesters to imine **1**, the reactivities of phosphite diesters are different. The reaction of dimethyl phosphite with imine completed in 8 hours at 80~90°C, while the temperatures for diphenyl phosphite, diethyl phosphite and diisopropyl phosphite are 90°C, 100~110°C and 110~130°C, respectively. Therefore, the order of reactivities of phosphite diesters should be as follows:

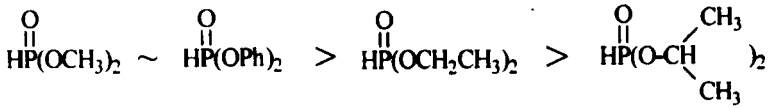


TABLE I Physical data and elementary analyses of **2** and **3**

No.	*R'*	*R*	*Yield (%)*	*m.p. (°C)*	*elementary analyses (calcd.)*		
					C%	*H%*	*N%*
2a	Me	H	65.5	105–107	59.81(59.85)	5.97(6.03)	10.54(10.47)
2b	Me	2-Cl	84.1	140–141	55.16(55.12)	5.47(5.32)	9.58(9.64)
2c	Me	4-OCH_3	87.9	96–97	58.49(58.46)	6.03(6.07)	9.54(9.74)
2d	Me	2,4-$(OCH_3)_2$	78.4	113–115	56.72(57.21)	6.00(6.11)	8.83(9.10)
2e	Et	2,4-$(OCH_3)_2$	97.8	129–130	58.60(58.89)	6.72(6.59)	8.88(8.58)
2f	Et	2-NO_2	89.7	114–117	55.46(55.69)	5.81(5.74)	1.69(11.81)
2g	Et	3-Br	82.5	80–81	51.94(51.98)	5.36(5.35)	8.16(8.27)
2h	Et	3,4-OCH_2O-	79.4	67–69	58.13(58.35)	5.96(6.15)	8.68(8.88)
2i	i-Pr	2,4-$(OCH_3)_2$	84.8	103–105	60.25(60.33)	6.92(7.01)	8.25(8.12)
2j	i-Pr	4-OCH_3	72.9	76–78	61.28(61.59)	7.14(7.03)	8.71(8.62)
2k	i-Pr	2,4-Cl_2	63.0	121–123.5	54.81(54.76)	5.73(5.74)	7.66(7.98)
2m	i-Pr	2-NO_2	76.9	107–109	57.00(57.37)	6.17(6.22)	1.30(11.15)
2n	Ph	3-Br	81.0	95–97	59.82(59.61)	4.42(4.50)	6.77(6.95)
2o	Ph	2,4-Cl_2	75.3	viscous liquid	60.61(60.62)	4.70(4.41)	7.05(7.07)
2p	Ph	2-Cl	83.1	119–121	64.34(64.35)	5.08(4.86)	7.45(7.50)
3a	H	H	48.3	180–182	53.07(52.76)	5.24(5.17)	10.30(10.25)
3b	H	4-OCH_3	52.0	155–157	51.64(51.89)	5.15(5.27)	9.77(9.55)

TABLE II ^{1}H NMR data of compounds **2** and **3**

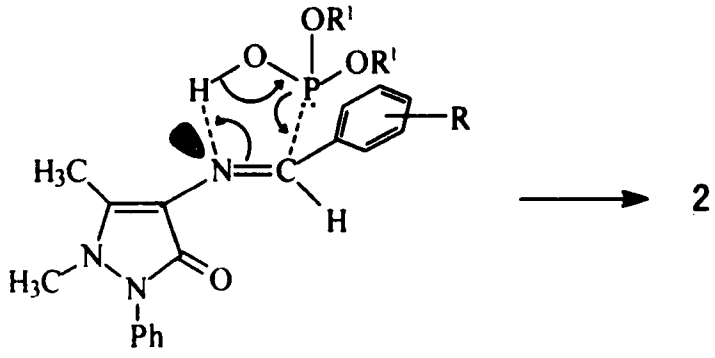
No.	*δ(CDCl$_3$, ppm)*
2a	1.99(s, 3H, C$\underline{H}_3$C=); 2.76(s, 3H, N-C$\underline{H}_3$); 3.04(br, 1H, N-$\underline{H}$); 3.52(d, J^3_{PH}=10.5Hz, 3H, POC$\underline{H}_3$); 3.81(d, $J_{PH}{}^3$=10.6Hz, 3H, POC$\underline{H}_3$); 5.06(d, J^2_{PH}=22.5Hz, 1H, C$\underline{H}$); 7.17–7.50(m, 9H, H_{arom})
2b	2.06(s, 3H, C$\underline{H}_3$C=); 2.79(s, 3H, N-C$\underline{H}_3$); 3.33(br, 1H, N-$\underline{H}$); 3.55(d, J^3_{PH}=10.5Hz, 3H, POC$\underline{H}_3$); 3.92(d, $J_{PH}{}^3$=10.8Hz, 3H, POC$\underline{H}_3$); 5.44(d, J^2_{PH}=23.3Hz, 1H, C$\underline{H}$); 7.13–7.79(m, 9H, H_{arom})
2c	1.99(s, 3H, C$\underline{H}_3$C=); 2.77(s, 3H, N-C$\underline{H}_3$); 3.46(br, 1H, N-$\underline{H}$); 3.53(d, J^3_{PH}=10.4Hz, 3H, POC$\underline{H}_3$); 3.75(s, 3H, OC$\underline{H}_3$); 3.81(d, J^3_{PH}=10.5Hz, 3H, POC$\underline{H}_3$); 4.99(d, J^2_{PH}=20.6Hz, 1H, C$\underline{H}$); 6.80–7.38(m, 9H, H_{arom})
2d	2.03(s, 3H, C$\underline{H}_3$C=); 2.76(s, 3H, N-C$\underline{H}_3$); 3.60(d, J^3_{PH}=10.4Hz, 3H, POC$\underline{H}_3$); 3.76(s, 6H, 2×OC$\underline{H}_3$); 3.82(d, J^3_{PH}=10.8Hz, 3H, POC$\underline{H}$3); 3.93(br, 1H, N-$\underline{H}$); 5.31(d, J^2_{PH}=22.9Hz, 1H, C$\underline{H}$); 6.38–7.50(m, 8H, H_{arom})
2e	1.11(t, J^3_{HH}=7.1Hz, 3H, OCH$_2$C$\underline{H}_3$); 1.29(t, J^3_{HH}=7.1Hz, 3H, OCH$_2$C$\underline{H}_3$); 2.03(s, 3H, C$\underline{H}_3$C=); 2.73(s, 3H, NC$\underline{H}_3$); 3.75(s, 6H, 2×OC$\underline{H}_3$); 3.81(br, 1H, N-$\underline{H}$); 3.83(m, 2H, OC$\underline{H}_2$CH$_3$); 4.17(m, 2H, OC$\underline{H}_2$CH$_3$); 5.23(d, J^2_{PH}=22.6Hz, 1H, C$\underline{H}$); 6.35–7.42(m, 8H, H_{arom})
2f	1.13(t, J^3_{HH}=7.1Hz, 3H, OCH$_2$C$\underline{H}_3$); 1.29(t, J^3_{HH}=6.9Hz, 3H, OCH$_2$C$\underline{H}_3$); 2.14(s, 3H, C$\underline{H}_3$C=); 2.79(s, 3H, NC$\underline{H}_3$); 3.75(m, 2H, OC$\underline{H}_2$CH$_3$); 4.18(m, 2H, OC$\underline{H}_2$CH$_3$); 4.85(br, 1H, N-$\underline{H}$); 5.91(d, J^2_{PH}=24.7Hz, 1H, C$\underline{H}$); 7.15–7.96(m, 9H, H_{arom})
2g	**2g** 1.14(t, J^3_{HH}=7.0Hz, 3H, OCH$_2$C$\underline{H}_3$); 1.30(t, J^3_{HH}=7.0Hz, 3H, OCH$_2$C$\underline{H}_3$); 2.03(s, 3H, C$\underline{H}_3$C=); 2.79(s, 3H, N-C$\underline{H}_3$); 3.65(br, 1H, N-$\underline{H}$); 3.92(m, 2H, OC$\underline{H}_2$CH$_3$); 4.16(m, 2H, OC$\underline{H}_2$CH$_3$); 5.04(d, J^2_{PH}=20.8Hz, 1H, C$\underline{H}$); 7.16–7.59(m, 9H, H_{arom})
2h	1.14(t, J^3_{HH}=6.9Hz, 3H, OCH$_2$C$\underline{H}_3$); 1.29(t, J^3_{HH}=7.0Hz, 3H, OCH$_2$C$\underline{H}_3$); 2.04(s, 3H, C$\underline{H}_3$C=); 2.80(s, 3H, N-C$\underline{H}_3$); 3.96(m, 2H, OC$\underline{H}_2$CH$_3$); 4.16(m, 2H, OC$\underline{H}_2$CH$_3$); 4.94(d, J^2_{PH}=20.1Hz, 1H, C$\underline{H}$); 5.35(br, 1H, N-$\underline{H}$); 5.90(s, OC$\underline{H}_2$O); 6.67–7.39(m, 8H, H_{arom})
2i	1.01(d, J^3_{HH}=6.2Hz, 3H, C$\underline{H}_3$CHCH$_3$); 1.21(d, J^3_{HH}=6.2Hz, 3H, CH$_3$CHC$\underline{H}_3$); 1.30(d, J^3_{HH}=6.2Hz, 6 H, C$\underline{H}_3$CHC$\underline{H}_3$); 2.06(s, 3H, C$\underline{H}_3$C=); 2.76(s, 3H, N-C$\underline{H}_3$); 3.75(s, 6H, 2×OC$\underline{H}_3$); 4.33(br, 1H, N-$\underline{H}$); 4.51(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 4.77(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 5.18(d, J^2_{PH}=22.0Hz, 1H, C$\underline{H}$); 6.37–7.50(m, 8H, H_{arom})

No.	*δ(CDCl$_3$, ppm)*
2j	1.00(d, J^3_{HH}=6.1Hz, 3H, C$\underline{H}_3$CHCH3); 1.23(d, J^3_{HH}=6.2Hz, 3H, CH$_3$CHC$\underline{H}_3$); 1.30(d, J^3_{HH}=5.2Hz, 6H, C$\underline{H}_3$CHC$\underline{H}_3$); 2.01(s, 3H, C$\underline{H}_3$C=); 2.76(s, 3H, N-C$\underline{H}_3$); 3.75(s, 3H, OC$\underline{H}_3$); 3.96(br, 1H, N-$\underline{H}$); 4.50(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 4.75(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 4.85(d, J^2_{PH}=20.5Hz, 1H, C$\underline{H}$); 6.78–7.39(m, 9H H$_{arom}$)
2k	1.03(d, J^3_{HH}=6.1Hz, 3H, C$\underline{H}_3$CHCH$_3$); 1.24(d, J^3_{HH}=6.1Hz, 3H, CH$_3$CHC$\underline{H}_3$); 1.33(d, J^3_{HH}=6.0Hz, 6H, C$\underline{H}_3$CHC$\underline{H}_3$); 2.09(s, 3H, C$\underline{H}_3$C=); 2.77(s, 3H, N-C$\underline{H}_3$); 3.81(br, 1H, N-$\underline{H}$); 4.52(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 4.79(m, 1H, CH(CH$_3$)$_2$); 5.23(d, J^2_{PH}=24.2Hz, 1H, C$\underline{H}$); 7.17–7.71(m, 8H, H$_{arom}$)
2m	1.03(s,J^3_{HH}=6.1Hz,3H,C$\underline{H}_3$CHCH$_3$); 1.23(d,J^3_{HH}=6.1Hz,3H,CH$_3$CHC$\underline{H}_3$); 1.28(s,J^3_{HH}=6.2Hz, 6H,C$\underline{H}_3$CHC$\underline{H}_3$); 2.17(s,3H,C$\underline{H}_3$C=); 2.80(s,3H,N-C$\underline{H}_3$); 3.94(br,1H,N-$\underline{H}$); 4.58(m, H, C$\underline{H}$(CH$_3$)$_2$); 4.73(m,1H,C$\underline{H}$(CH$_3$)$_2$); 5.90(d,J^2_{PH}=25.0Hz,1H,C$\underline{H}$); 7.12–7.96(m,9H,H$_{arom}$)
2n	2.04(s, 3H, C$\underline{H}_3$C=); 2.80(s, 3H, NC$\underline{H}_3$); 3.33(br, 1H, N-$\underline{H}$); 5.44(d, J^2_{PH}=18.4Hz, 1H, C$\underline{H}$); 6.88–7.67(m, 19H, H$_{arom}$)
2o	2.06(s, 3H, C$\underline{H}_3$C=); 2.79(s, 3H, NC$\underline{H}_3$); 3.54(br, 1H, N-$\underline{H}$); 5.69(d, J^2_{PH}=21.7Hz, 1H, C$\underline{H}$); 6.96–7.75(m, 18H, H$_{arom}$)
2p	2.07(s, 3H, C$\underline{H}_3$C=); 2.78(s, 3H, NC$\underline{H}_3$); 3.42(br, 1H, N-$\underline{H}$); 5.76(d, J^2_{PH}=22.5Hz, 1H, C$\underline{H}$); 6.92–7.94(m, 19H, H$_{arom}$)
3a[a]	1.99(s, 3H, CH$_3$C); 3.09(s, 3H, CH$_3$N); 4.63(d, J^2_{PH}=17.2Hz, 1H, PCH); 7.23–7.55(m, 10H, H$_{arom}$)
3b[a]	1.86(s, 3H, CH$_3$C); 3.02(s, 3H, CH$_3$N); 3.71(s, 3H, OCH$_3$); 4.46(d, $J_{P\text{-}C\text{-}H}$=15.1Hz, 1H, PCH); 6.87- 7.48(m, 9H, H$_{arom}$)

a. solvent: D_2O

The influence of the imine substituent R on the reactivity of imine proved to be interesting than expected. When imine was treated with phosphite diesters, electron-withdrawing substituents caused the reaction to be slower and the reaction temperature should be higher if the reaction needed to finish in certain time. On the contrary, electron-donating substituents accelerated the reaction. For example, the addition of diisopropyl phosphite and the imine can finished in 8 hours at 110°C when R=2,4-$(OCH_3)_2$, but the reaction temperature must be maintained at 130°C when R=2-NO_2.

A five-member cyclic transition state may be exist in the reaction of phosphite diesters and imine (Scheme 2). The phosphorus atom coordinated with the positive carbon with its lone electron pair, while a hydrogen bond formed between the hydrogen of the phosphite diesters and the negative nitrogen atom of C=N bond. The formation of phosphorus-carbon bond and hydrogen-nitrogen bond may be insymmetry. When R was an electron-withdrawing substituent, the positive charge of carbon and negative charge of nitrogen were reduced. Therefore, the difference between the atomic charges of carbon and nitrogen became smaller, which retarded the formation of the transition state. To support this statement, the net atomic charges of carbon and nitrogen atom on some imines were calculated by quantum chemistry method (see table III). The results indicated that when there were electron-donating substituents on the benzene ring, the difference between the charges of carbon and nitrogen became larger. Therefore the formation of transition state was promoted and the reaction was accelerated.



SCHEME 2

TABLE III The net atomic charges of the carbon and nitrogen atom on some imines **1** (method: MINDO/3)

R	*H*		*4-NO_2*		*2,4-$(OCH_3)_2$*	
atom	N	C	N	C	N	C
net atomic charge	–0.134	0.157	–0.111	0.128	–0.155	0.189
difference of atomic charges[a]	0.291		0.239		0.344	

a. difference of atomic charges = net atomic charge of carbon – net atomic charge of nitrogen

Characteristics of ^{1}H NMR Spectra of Compounds 2

The two ester groups in compounds **2** are magnetically nonequivalent because they are affected differently by the groups attached to the chiral α-carbon in optimum conformation. The chemical shift of one ester group moves toward higher field because it locates in the shielding area of α-benzene ring, while the other ester group is not affected by the benzene ring.

The chemical shifts of the two methoxy groups in dimethyl esters **2a-2d** are about 3.55ppm and 3.85ppm respectively. Each of them exhibits a doublet due to the coupling of P atom, J^3_{PH}=10.5Hz.

The two methyl groups in the two ethoxys of compounds **2e-2h** exhibit triplets at 1.13ppm and 1.30ppm respectively. One methylene group exhibits a multiplet at 4.17ppm due to the coupling of phosphorus atom and methyl group. The two hydrogens on the other methylene that locates in the shield area of α-benzene ring are magnetically nonequivalent due to the different shielding levels.

In compounds **2i-2m**, the two methyl groups on the isopropoxy that was not affected by the α-benzene ring are magnetically equivalent, while two methyl groups on the isopropoxy that locats in the shielding area of benzene ring are magnetically nonequivalent due to different shielding level.

Under the coupling of phosphorus atom, the hydrogen on α-methenyl exhibited a doublet, J^2_{PH}=18.4~25.0Hz.

Bioactivity

The preliminary bioassay showed that some compounds exhibited anti-TMV activity.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-500 apparatus and are uncorrected. ^{1}H NMR spectra were taken on a Bruker AC-P200 spectrometer operating at 200 MHz with TMS as internal standard (solvent was $CDCl_3$ if not specifically mentioned). The elemental analyses were measured by a Yanaco CHN Cored MT-3 apparatus.

The reagents and solvents were of analytical purity and were purified where necessary. Ethanol was treated with sodium and distilled free from moisture prior to use. Acetonitrile was distilled from P_2O_5 and trimethylchlorosilane was distilled and stored in a dry vessel.

The imine **1** are prepared by standard procedures[10].

α-(4-Antipyryl)amino(substituted)phenylmethylphosphonic Acids Diesters (2); General Procedure

A mixture of imine **1** (2.85mmol) and phosphite diesters (5.7mmol) was heated at 90~130°C. After the reaction finished (controlled by TLC), the mixture was cooled to room temperature.

In the case of dialkyl esters, the reaction mixture was dissolved in 20ml ethyl acetate, and washed with 2×20ml 5% Na_2CO_3 aq. and 3×20ml water in turn. The ethyl acetate was removed under reduced pressure, and the residue was treated with ethyl ether. The solid obtained was recrystallized from carbon tetrachloride to give **2** as a pale yellow crystal.

In the case of diphenyl esters, the reaction mixture was purified directly by column on silica gel. Evaporation of the solvent gave diphenyl esters **2**.

α-(4-Antipyryl)amino(substituted)phenylmethylphosphonic Acids (3); General Procedure

To a mixture of **2** (3mmol) and Nal or KI (6.6mmol) in 10ml anhydrous acetonitrile, trimethylchlorosilane (13.2mmol) was added dropwise with stirring. After stirred at room temperature over night, the mixture was filtered, and the filtration was evaporated to dryness under reduced pressure. The residue was treated with water and recrystallized from methanol to give **3** as a yellow solid.

Acknowledgements

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