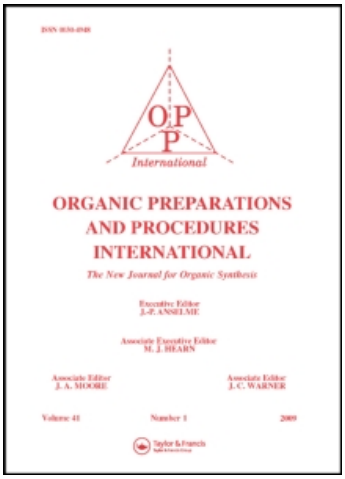

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FACILE AND EFFICIENT SYNTHESIS OF α-AMINOPHOSPHONATE DERIVATIVES OF 1,3,4-OXADIAZOLE AND 1,3,4-THIADIAZOLE

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FACILE AND EFFICIENT SYNTHESIS OF α-AMINOPHOSPHONATE DERIVATIVES OF 1, 3, 4-OXADIAZOLE AND 1, 3, 4-THIADIAZOLE

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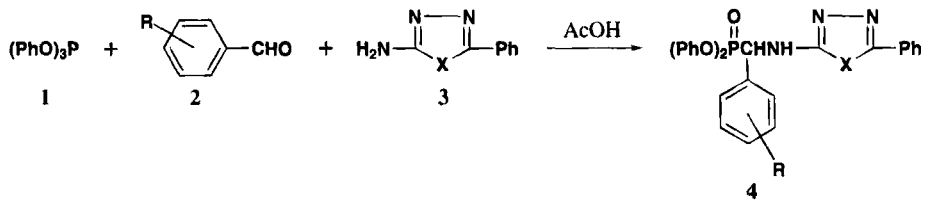
α-Aminophosphonic acid derivatives which are phosphonic analogs of naturally occurring α-amino acids, have attracted much attention due to their biological activities[1] and extensive application in organic chemistry.[2] Over the past three decades, many studies on the synthesis of these compounds have been carried out.[3] On the other hand, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives have received increasing interest in the agrochemical and pharmaceutical fields because of their unique and diverse potential biological properties such as antitumor,[4] bactericidal,[5] insecticidal,[6] herbicidal[7] and fungicidal[8] activities. However, little attention has been paid to the synthesis of α-aminophosphonates bearing these heterocycles. To the best of our knowledge, only one example of the preparation of such compounds has appeared in the literature. Hafez described the synthesis of 1,3,4-oxadiazolyl containing a-aminophosphonates by condensation of 2-amino-5-substituted-1,3,4-oxadiazoles with aromatic aldehydes and subsequent addition of a dialkyl phosphite to the resulting Schiff bases.[9]

As part of our ongoing program and interest in the development of new biologically active organophosphorus compounds,[10] we now report a facile and efficient one-step synthesis of α-aminophosphonate derivatives of 1,3,4-oxadiazole and 1,3,4-thiadiazole by a three-component condensation reaction. As shown in *Scheme 1*, 2-amino-5-phenyl-1,3,4-oxadiazole and 1,3,4-thiadiazole were allowed to react with triphenyl phosphite and an aromatic aldehyde in the presence of acetic acid to give the desired diphenyl 1- (5-phenyl-1,3,4-oxadiazol-2-yl and 1,3,4-thiadiazol-2-yl)amino arylmethylphosphonates (**4**) in good yields.[11]



Scheme 1

We investigated the three-component condensation of 2-amino-5-phenyl-1,3,4-oxadiazole and 1,3,4-thiadiazole with triphenyl phosphite and aromatic aldehydes under different reaction conditions. It was found that the reaction temperature was a key factor. Below 75°, the reaction was very slow and almost no product **4** could be obtained. Conversely, over 85°, side-reactions occurred and the yield of **4** was reduced significantly. In addition, the effect of solvent was studied. With the use of acetic anhydride instead of acetic acid as the solvent, no remarkable improvement of the yield of product was observed. Furthermore, we also examined the effects of time and molar ratio of the substrates on the condensation reaction. The best result was obtained with a ratio of **1**(0.95):**2**(1.05):**3**(1) for 3-5 h. The results are summarized in Tables 1 and 2.

Table 1. Yields, mps and Elemental Analyses of Compounds **4**

No.	X	R	Time (h)	Yield (%)	mp (°C)	Elemental Analysis (Found) C	H	N
4a	O	H	5	80.5	232-233	67.08(66.95)	4.55(4.58)	8.70(8.78)
4b	O	4-Cl	5	81.2	188-189	62.67(62.49)	4.06(4.01)	8.12(8.04)
4c	O	4-NO_2	5	80.8	205-206	61.36(61.25)	3.98(3.94)	10.61(10.63)
4d	O	3-NO_2	5	74.7	227-228	61.36(61.42)	3.98(3.92)	10.61(10.53)
4e	O	4-CH_3	5	78.6	193-194	67.61(67.72)	4.83(4.79)	8.45(8.38)
4f	O	4-CH_3O	5	77.5	241-242	65.50(65.60)	4.68(4.67)	8.19(8.11)
4g	S	H	4	85.2	214-215	64.93(64.88)	4.41(4.37)	8.42(8.37)
4h	S	4-F	3	85.6	227-228	62.67(62.49)	4.06(4.00)	8.12(8.05)
4i	S	4-Cl	4	84.7	210-211	60.79(60.65)	3.94(3.91)	7.88(7.89)
4j	S	4-Br	5	83.5	201-202	56.06(55.91)	3.63(3.60)	7.27(7.21)
4k	S	4-NO_2	3	85.4	195-196	59.56(59.43)	3.86(3.81)	10.29(10.23)
4l	S	3-NO_2	4	77.2	230-231	59.56(59.49)	3.86(3.82)	10.29(10.22)
4m	S	4-CH_3	5	81.6	181-182	65.50(65.41)	4.68(4.63)	8.19(8.12)
4n	S	4-CH_3O	5	80.8	243-244	63.52(63.40)	4.54(4.51)	7.94(7.89)

In conclusion, a facile and efficient one-step procedure has been developed for the synthesis of α-aminophosphonate derivatives of 1,3,4-oxadiazole and 1,3,4-thiadiazole by the three-component condensation reaction, with the advantages of mild conditions, simple operation and good yields.

Table 2. IR, ^{1}H NMR and MS Spectra of Compounds **4**

No.	IR (cm^{-1})	^{1}H NMR (δ, ppm, J, Hz)	MS (m/z)
4a	3340,1610,1560, 1255,1070,925	6.12 (d, 1H, CH, $^2J_{P-H}$ = 21.85), 6.95-7.50 (m, 21H, ArH, NH)	483(M^+, 5), 248(100), 233(50), 140(38), 104(33), 94(94)
4b	3380,1600,1570, 1240,1070,945	6.15 (d, 1H, CH, $^2J_{P-H}$ = 22.05), 6.90-7.58 (m, 20H, ArH, NH)	517(M^+, 6), 282(100), 233(48), 140(35),138(25),94(91)
4c	3400,1605,1560, 1250,1050,930	6.18 (d, 1H, CH, $^2J_{P-H}$ = 21.58), 6.92-8.05 (m, 20H, ArH, NH)	528(M^+, 7), 293(100), 233(38), 149(31), 140(26), 94(88)
4d	3375,1610,1565, 1250,1075,940	6.16 (d, 1H, CH, $^2J_{P-H}$ = 21.57), 6.90-7.88 (m, 20H, ArH, NH)	528(M^+, 5), 293(100), 233(40), 149(32), 140(21), 94(96)
4e	3375,1610,1570, 1260,1085,935	2.27 (s, 3H, CH_3), 6.12 (d, 1H, CH, $^2J_{P-H}$ =22.01, 6.95-7.67 (m, 20H, ArH, NH)	497(M^+, 10), 262(100), 233(50), 140(31), 118(27), 94(95)
4f	3365,1605,1565, 1245,1080,945	3.75 (s, 3H, OCH_3), 6.15(d, 1H, CH, $^2J_{P-H}$ =21.55), 6.90-7.56 (m, 20H, ArH, NH)	513(M^+,6), 278(100), 233(56), 140(31), 134(27), 94(89)
4g	3340,1600,1564, 1260,1065,940	6.11 (d, 1H, CH, $^2J_{P-H}$ = 22.15), 6.98-7.55 (m, 21H, ArH, NH)	499(M^+, 7), 264(100), 233(45), 140(35), 104(27), 94(92)
4h	3375,1605,1565, 1255,1078,935	6.15 (d, 1H, CH, $^2J_{P-H}$ = 21.95), 6.95-7.88 (m, 20H, ArH, NH)	517(M^+, 11), 282(100), 233(48), 140(37), 132(29), 94(95)
4i	3400,1598,1573, 1250,1075,925	6.15 (d, 1H, CH, $^2J_{P-H}$ = 22.05), 6.91-7.42 (m, 20H, ArH, NH)	533(M^+, 9), 298(100), 233(40), 140(35), 138(27), 94(95)
4j	3360,1600,1570, 1250,1050,940	6.15 (d, 1H, CH, $^2J_{P-H}$ = 22.10), 6.90-7.53 (m, 20H, ArH, NH)	577(M^+, 6), 342(100), 233(49), 182(35), 140(29), 94(90)
4k	3350,1610,1570, 1250,1070,930	6.17 (d, 1H, CH, $^2J_{P-H}$ = 22.11), 6.88-8.05 (m, 20H, ArH, NH)	544(M^+, 11), 309(100), 233(46), 149(37), 140(29), 94(87)
4l	3380,1605,1572, 1240,1055,925	6.16 (d, 1H, CH, $^2J_{P-H}$ = 22.06), 6.95-7.89 (m, 20H, ArH, NH)	544(M^+, 10), 309(100), 233(50), 149(38), 140(32), 94(90)
4m	3375,1605,1565, 1260,1085,925	2.25 (s, 3H, CH_3), 6.13 (d, 1H, CH, $^2J_{P-H}$ = 21.58), 6.89-7.54 (m, 20H, ArH, NH)	513(M^+, 8), 278(100), 233(50), 140(38), 118(31), 94(95)
4n	3350,1600,1565, 1250,1080,940	3.76 (s, 3H, OCH_3), 6.15 (d, 1H, CH, $^2J_{P-H}$ = 21.91), 6.88-7.43 (m, 20H, ArH, NH)	529(M^+, 6), 294(100), 233(46), 140(35), 134(28), 94(90)

EXPERIMENTAL SECTION

The melting points are uncorrected. Elemental analyses were determined on a PE 2400 instrument. IR spectra were recorded on a Shimadzu 440 spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ on a Varian XL 200 spectrometer using TMS as an internal standard (δ values are reported in ppm and J values are given in Hz). Mass spectra were measured on a HP 5988 spectrometer. 2-Amino-5-phenyl-1,3,4-oxadizole and 1,3,4-thiadiazole (**3**) were prepared by literature methods.[12]

General Procedure for Preparation of Compounds 4. -To a stirred solution of 2-amino-5-phenyl-1,3,4-oxadiazole or 1,3,4-thiadiazole (10 mmol) and an aromatic aldehyde (10.5 mmol) in glacial acetic acid (10 mL), was added triphenyl phosphite (2.95 g, 9.5 mmol) at room temperature. The

mixture was then heated at 80° for 3-5 h and the solvent was removed under reduced pressure. The oily residue was dissolved in methanol (15 mL) and left for crystallization at -15°. After 3 h the crystalline solid was collected by filtration and recrystallized from ethanol, a white crystal being obtained as product **4**.

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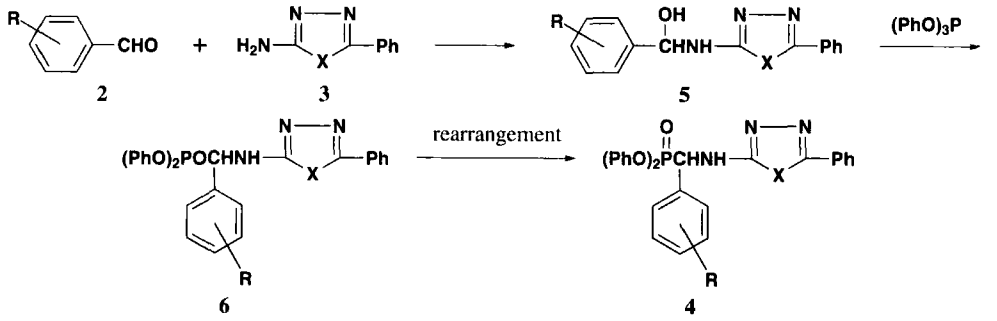
11. Although the mechanism of this type of reaction has not been established, it is suggested to be as follows based on the literature[13] and our results.



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