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A Convenient and Facile Synthesis of O,O-Diphenyl 1-(5-Alkyl-1,3,4-thiadiazol-2-yl) Amino-1-arylmethylphosphonates

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A CONVENIENT AND FACILE SYNTHESIS OF O,O-DIPHENYL 1-(5-ALKYL-1,3,4-THIADIAZOL -2-YL)AMINO-1-ARYLMETHYLPHOSPHONATES

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Abstract : Nineteen novel O,O-diphenyl 1-(5-alkyl-1,3,4-thiadiazol-2-yl) amino-1-arylmethylphosphonates were synthesized by the three-component condensation reactions of 2-amino-5-alkyl-1,3,4-thiadiazoles with triphenyl phosphite and aromatic aldehydes in the presence of acetic acid.

The chemistry of α-aminophosphonates and their derivatives is one of the most active research fields in organic phosphorus chemistry, These phosphorus compounds have attracted much attention since they have found widespread application in organic synthesis and also due to their various biologically activities[1-4]. On the other hand , 1 , 3 , 4 - thiazole and - oxadiazole derivatives are great practical significance as raw material for medicine and agricultural chemicals. They are found in a variety of

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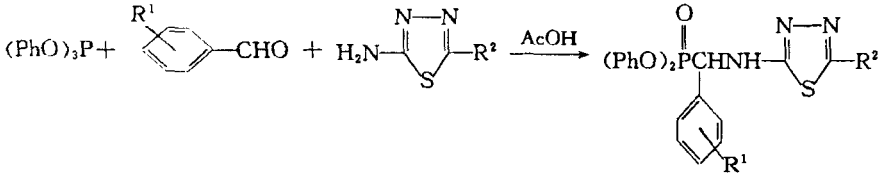
biologically active molecules, which have been shown to exhibit bacteriostatic[5], hypoglycemic[6], insecticidal[7], herbicidal[8] and fungicidal[9] properties. However, little attention has been paid to the synthesis of α-aminophosphonates bearing these N-heterocycles. To the best of our knowledge, only one example of the preparation of such compounds has appeared in the literature. Hafez et al have described that 1, 3, 4-oxadiazolyl-containing α-aminophosphonates were synthesized by condensation of 2-amino-5-aryl-1, 3, 4-oxadiazoles with aromatic aldehydes and subsequent addition of dialkylphosphite to the resulting Schiff bases[14].

In view of the above observations and our interest in the organic phosphorus chemistry and biologically active compounds[11-14]. Herein we wish to report a convenient and facile one-pot synthesis of O, O-diphenyl-1-(5-alkyl-1, 3, 4-thiadiazol-2-yl) amino-1-arylmethylphosphonates based on the three-component condensation reactions of 2-amino-5-alkyl-1, 3, 4-thiadiazoles with triphenyl phosphite and aromatic aldehydes in the presence of acetic acid.



1 2

In order to optimize the reaction conditions, the condensation reaction was carried out under several conditions. As a result, it was found the reaction temperature should be kept below 85℃, otherwise side reactions occur and the yield of product **2** was significantly reduced. An 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. Futher, we also examined the effects of reaction time and the molar ratio of the substrates on the Mannich-type reaction. The best result was obtained when 2-amino-5-alkyl-thiadiazole **1** reacted with 1.05 equiv of aromatic aldehyde and 0.95 equiv of triphenyl phosphite in acetic acid (10mL) at 85℃ for 3-5h. Under the reaction conditions described above, the condensation reaction proceeded smoothly and the results are summaried in the Table.

Table. Compounds Prepared

Product	R^1	R^2	Time(h)	Yield(%)[a]
2a	H	H	3	80.4
2b	4-Cl	H	3	81.1
2c	3-Cl	H	5	64.3
2d	2-Cl	H	5	24.2
2e	4-NO_2	H	3	80.9
2f	3-NO_2	H	5	64.2
2g	2-NO_2	H	5	25.6
2h	H	CH_3	4	78.8
2i	4-Cl	CH_3	4	79.2
2j	4-NO_2	CH_3	4	80.5
2k	3-NO_2	CH_3	5	62.3
2l	H	C_2H_5	4	76.6
2m	4-Cl	C_2H_5	4	77.2
2n	4-NO_2	C_2H_5	4	75.4
2o	3-NO_2	C_2H_5	5	60.8
2p	H	CF_3	3	87.1
2q	4-Cl	CF_3	3	88.4
2r	4-NO_2	CF_3	3	85.2
2s	3-NO_2	CF_3	3	70.2

[a]Isolated yield based on triphenyl phosphite

The yield of product **2** is obviously dependent on the position of substituent of benzene ring, for the same substituent, the yield decreases in the order of *para*, *meta*, and *orth*. On the other hand, this reaction was also affected by electronic effect of substituent of heterocycle, an electron-withdrawing substitution results in a better yield.

In conclusion, we provides a convenient and facile one-pot synthesis of O, O-diphenyl 1-(5-alkyl-1, 3, 4-thiadiazol-2-yl) amino-1-arylmethylphosphonates via the three-component condensation reaction, with the advantages of mild conditions, simple operation and satisfactory yields.

Experimental

Melting points were uncorrected. Elemental analyses were carried on a Yanaco CHN Corder MT-3 apparatus. IR spectra were recorded on a Shimadu-435 instrument. ^1H NMR spectra were measured by using a Bruker AC-200 spectrometer with $CDCl_3$ as solvent and TMS as internal standard. **1a**[15], **1b**[15], **1c**[15] and **1d**[16] were prepared by literature methods.

General procedure for the synthesis of O, O-diphenyl 1-(5-alkyl-1, 3, 4-thiadiazol-2-yl)amino-1-arylmethylphosphonates 2a-s.

The mixture of 2-amino-5-alkyl-1, 3, 4-thiadiazole (10mmol), aromatic aldehyde (10. 5mmol) and triphenyl phosphite (2. 95g, 9. 5mmol) in glacial acetic acid (10mL) was heated at 85℃ for 3-5h. The solvent was removed under reduced pressure, the oily residue was dissolved in method (15mL) and left for crystallization at -15℃, After 1-3h the crystalline solid was collected by filtration and recrystallized from ethanol, a white crystal was obtained as product **2**.

2a : m. p. 170-171℃. IR(KBr), ν : 3344, 1600, 1532, 1480, 1266, 1175, 1050, 930cm^{-1}. ^1H NMR, δ : 6. 02 (d, P(O)CH, $^2J_{P-H}$=21. 19Hz), 6. 70-7. 57 (m, 16H, 3×C_6H_5, NH), 8. 30(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{18}N_3O_3PS$: C, 59. 57; H, 4. 26; N, 9. 93. Found : C, 59. 42; H, 4. 19; N, 9. 79.

2b : m. p. 201-202℃. IR(KBr), ν : 3304, 1610, 1563, 1480, 1250, 1165, 1110, 950cm^{-1}. ^{1}H NMR, δ : 5.98(d, P(O)CH, $^2J_{P-H}$=21.10Hz), 6.81-7.54(m, 15H, 2×C_6H_5, C_6H_4, NH), 8.31(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{17}ClN_3O_3PS$: C, 54.14; H, 3.72; N, 9.19. Found : C, 54.20; H, 3.64; N, 9.06.

2c : m. p. 149-150℃. IR(KBr), ν : 3350, 1615, 1532, 1475, 1220, 1150, 1080, 945cm^{-1}. ^{1}H NMR, δ : 5.88(d, 1H, P(O)CH, $^2J_{P-H}$=22.08Hz), 6.75-7.53(m, 15H, 2×C_6H_5, C_6H_4, NH), 8.31(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{17}ClN_3O_3PS$: C, 54.14; H, 3.72; N, 9.19. Found : C, 54.22; H, 3.61; N, 9.11.

2d : m. p. 221-222℃. IR(KBr), ν : 3325, 1620, 1575, 1485, 1225, 1150, 1050, 940cm^{-1}. ^{1}H NMR, δ : 5.74(d, 1H, P(O)CH, $^2J_{P-H}$=22.13Hz), 6.78-7.54(m, 15H, 2×C_6H_5, C_6H_4, NH), 8.32(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{17}ClN_3O_3PS$: C, 54.14; H, 3.72; N, 9.19. Found : C, 54.01; H, 3.68; N, 9.14.

2e : m. p. 177-178℃. IR(KBr), ν : 3380, 1625, 1550, 1470, 1240, 1180, 1090, 935cm^{-1}. ^{1}H NMR, δ : 6.12(d, 1H, P(O)CH, $^2J_{P-H}$=21.98Hz), 6.82-8.05(m, 15H, 2×C_6H_5, C_6H_4, NH), 8.36(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{17}N_4O_5PS$: C, 53.85; H, 3.63; N, 11.96. Found : C, 53.65; H, 3.58; N, 11.79.

2f : m. p. 225-226℃. IR(KBr), ν : 3350, 1620, 1563, 1475, 1240, 1190, 1075, 940cm^{-1}. ^{1}H NMR, δ : 6.04(d, 1H, P(O)CH, $^2J_{P-H}$=22.15Hz), 6.89-8.01(m, 15H, 2×C_6H_5, C_6H_4, NH), 8.35(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{17}N_4O_5PS$: C, 53.85; H, 3.63; N, 11.96. Found : C, 53.75; H, 3.59; N, 11.78.

2g : m. p. 238-239℃. IR(KBr), ν : 3380, 1610, 1565, 1480, 1240, 1185, 1060, 925cm^{-1}. ^{1}H NMR, δ : 5.98(d, 1H, P(O)CH, $^2J_{P-H}$=21.88Hz), 6.91-7.98(m, 15H, 2×C_6H_5, C_6H_4, NH), 8.34(s, 1H, CH=N). Anal. Calcd for $C_{21}H_{17}N_4O_5PS$: C, 53.85; H, 3.63; N, 11.96. Found : C, 53.67; H, 3.52; N, 11.85.

2h : m. p. 194-195℃. IR(KBr), ν : 3350, 1620, 1580, 1450, 1240, 1190, 1075, 930cm^{-1}. ^{1}H NMR, δ : 2.48(s, 3H, CH_3), 6.23(d, 1H, P(O)CH,

$^2J_{P-H}$ = 22. 15Hz), 6. 84-7. 63(m, 16H, 3×C_6H_5, NH). Anal. Calcd for $C_{22}H_{20}N_3O_3PS$: C, 60. 41; H, 4. 58; N, 9. 61. Found : C, 60. 22; H, 4. 59; N, 9. 47.

2i : m. p. 152-153℃. IR (KBr), ν : 3405, 1610, 1575, 1475, 1250, 1180, 1060, 945cm^{-1}. ^{1}H NMR, δ : 2. 45(s, 3H, CH_3), 6. 04(d, 1H, P(O)CH, $^2J_{P-H}$ = 21. 98Hz), 6. 87-7. 42(m, 15H, 2×C_6H_5, C_6H_4, NH). Anal. Calcd for $C_{22}H_{19}ClN_3O_3PS$: C, 56. 05; H, 4. 03; N, 8. 92. Found : C, 55. 97; H, 3. 98; N, 8. 77.

2j : m. p. 201-202℃. IR (KBr), ν : 3380, 1600, 1575, 1450, 1240, 1185, 1075, 930cm^{-1}. ^{1}H NMR, δ : 2. 46(s, 3H, CH_3), 6. 12(d, 1H, P(O)CH, $^2J_{P-H}$ = 22. 05Hz), 6. 92-8. 01(m, 15H, 2×C_6H_5, C_6H_4, NH). Anal. Calcd for $C_{22}H_{19}N_4O_5PS$: C, 54. 77; H, 3. 94; N, 11. 62. Found : C, 54. 56; H, 3. 87; N, 11. 42.

2k : m. p. 245-246℃. IR (KBr), ν : 3410, 1610, 1580, 1475, 1250, 1125, 1045, 935cm^{-1}. ^{1}H NMR, δ : 2. 44(s, 3H, CH_3), 6. 22(d, 1H, P(O)CH, $^2J_{P-H}$ = 21. 85Hz), 6. 88-8. 01(m, 15H, 2×C_6H_5, C_6H_4, NH), Anal. Calcd for $C_{22}H_{19}N_4O_5PS$: C, 54. 77; H, 3. 94; N, 11. 62. Found : C, 54. 52; H, 3. 89; N, 11. 55.

2l : m. p. 182-183℃. IR (KBr), ν : 3390, 1610, 1580, 1475, 1250, 1190, 1050, 940cm^{-1}. ^{1}H NMR, δ : 1. 22(t, 3H, CH_3), 2. 79(q, 2H, CH_2), 5. 70 (d, 1H, P(O)CH, $^2J_{P-H}$ = 22. 05Hz), 6. 79-7. 50(m, 16H, 3×C_6H_5, NH). Anal. Calcd for $C_{23}H_{22}N_3O_3PS$: C, 61. 20; H, 4. 88; N, 9. 31. Found : C, 61. 02; H, 4. 82; N, 9. 25.

2m : m. p. 227-228℃. IR (KBr), ν : 3405, 1600, 1560, 1465, 1240, 1160, 1075, 945cm^{-1}. ^{1}H NMR, δ : 1. 24(t, 3H, CH_3), 2. 78(q, 2H, CH_2), 5. 72 (d, 1H, P(O)CH, $^2J_{P-H}$ = 22. 13Hz), 6. 98-7. 52(m, 15H, 2×C_6H_5, C_6H_4, NH). Anal. Calcd for $C_{23}H_{21}ClN_3O_3PS$: C, 56. 91; H, 4. 33; N, 8. 66. Found : C, 56. 72; H, 4. 22; N, 8. 58.

2n : m. p. 195-196℃. IR (KBr), ν : 3405, 1610, 1575, 1450, 1240, 1165, 1060, 945cm^{-1}. ^{1}H NMR, δ : 1. 25(t, 3H, CH_3), 2. 81(q, 2H, CH_2), 5. 75 (d, 1H, P(O)CH, $^2J_{P-H}$ = 22. 21Hz), 6. 84-8. 03(m, 15H, 2×C_6H_5, C_6H_4, NH). Anal. Calcd for $C_{23}H_{21}N_4O_5PS$: C, 55. 64; H, 4. 23; N, 11. 29.

Found : C,55.47;H,4.18;N,11.19.

2o : m. p. 235-236℃. IR(KBr),ν : 3365,1600,1565,1485,1250,1180, 1075,945cm^{-1}. ^{1}H NMR,δ : 1.23(t,3H,CH_3),2.77(q,2H,CH_2),5.69 (d,1H,P(O)CH,$^2J_{P\text{-}H}$=22.16Hz),6.91-7.54(m,15H,2×C_6H_5,C_6H_4, NH). Anal. Calcd for $C_{23}H_{21}N_4O_5PS$: C,55.64;H,4.23;N,11.29. Found : 54.45;H,4.17;N,11.15.

2p : m. p. 188-189℃. IR(KBr),ν : 3400,1610,1570,1490,1250,1155, 1060,940cm^{-1}. ^{1}H NMR,δ : 5.60(d,1H,P(O)CH,$^2J_{P\text{-}H}$=22.18Hz),6. 94-7.42(m,16H,3×C_6H_5,NH). Anal. Calcd for $C_{22}H_{17}F_3N_3O_3PS$: C, 53.77;H,3.46;N,8.55. Found : C,53.65;H,3.40;N,8.42.

2q : m. p. 159-160℃. IR(KBr),ν : 3350,1600,1570,1485,1240,1150, 1050,945cm^{-1}. ^{1}H NMR,δ : 5.71(d,1H,P(O)CH,$^2J_{P\text{-}H}$=21.85Hz),6. 91-7.53 (m, 15H, 2 × C_6H_5, C_6H_4, NH). Anal. Calcd for $C_{22}H_{16}ClF_3N_3O_3PS$: C,50.28;H,3.05;N,8.00. Found : C,50.17;H,3.11;N, 7.89.

2r : m. p. 179-180℃. IR(KBr),ν : 3405,1600,1563,1488,1230,1160, 1075,925cm^{-1}. ^{1}H NMR,δ : 5.74(d,1H,P(O)CH,$^2J_{P\text{-}H}$=21.58Hz),6. 94-8.05(m,15H,2×C_6H_5,C_6H_4,NH). Anal. Calcd for $C_{22}H_{16}F_3N_4O_5PS$: C,49.25;H,2.98;N,10.45. Found : C,49.11;H,2.92;N,10.33.

2s : m. p. 158-159℃. IR(KBr),ν : 3360,1605,1570,1490,1250,1168, 1075,945cm^{-1}. ^{1}H NMR,δ : 5.66(d,1H,P(O)CH,$^2J_{P\text{-}H}$=21.77Hz),6. 92-7.89(m,15H,2×C_6H_5,C_6H_4,NH). Anal. Calcd for $C_{22}H_{16}F_3N_4O_5PS$: C,49.25;H,2.98;N,10.45. Found : C,49.14;H,2.95;N,10.35.

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