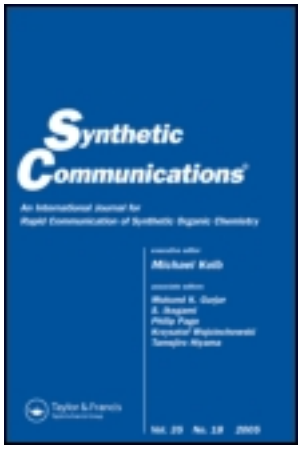

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Microwave-Assisted Synthesis of Propesticides 1,3,4-Thiadiazole Aminophosphonates

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MICROWAVE-ASSISTED SYNTHESIS OF PROPESTICIDES 1,3,4-THIADIAZOLE AMINOPHOSPHONATES

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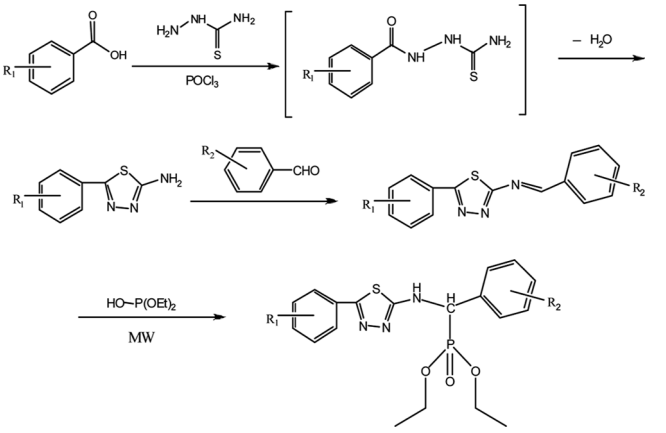
GRAPHICAL ABSTRACT



Abstract *A novel and easy synthetic route to diethyl (5-substituted phenyl-1,3,4-thiadiazol-2-ylamino) (substituted phenyl) methylphosphonates has been achieved by the reaction of substituted benzylidene-5-(substituted phenyl)-1,3,4-thiadiazol-2-amines and diethyl phosphite under microwave irradiation. These 1,3,4-thiadiazole aminophosphonates were identified by infrared, ^{1}H NMR, and elemental analyses. The target compounds were obtained in better yields (71–89%) and shorter time (10 min) than with conventional heating.*

Keywords Microwave irradiation; synthesis; 1,3,4-thiadiazole aminophosphonates

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INTRODUCTION

The discovery of new structures is one of the most important topics of research in medicinal and pesticide chemistry. Among various biological heterocyclic compounds, 1,3,4-thiadiazole derivatives have attracted specific interest because of their promising biological activity. For example, some 1,3,4-thiadiazole derivatives have been reported to possess anti-inflammatory, antiproliferative, antibacterial, and fungicidal activities.[1–5]

α-Aminophosphonate derivatives have received wide attention in medicinal, bioorganic, and organic chemistry. The applications of α-amino phosphonates have ranged from agriculture to medical uses such as anticancer agents,[6] enzyme inhibitors,[7] peptide mimetics,[8] antibiotics, and herbicides.[9]

In view of this research and our desire to develop new insecticidal agents of high potency, we fused biological 1,3,4-thiadiazole and aminophosphonate structures to obtain compounds possessing better biological activity.

Conventional organic synthesis reactions suffered from drawbacks such as the use of high-boiling solvents, long reaction times, and poor yields. Microwave (MW) irradiation is currently used to carry out a wide range of reactions.[10,11] Compared with traditional reactions under refluxing, the MW reaction technique is often rapid and more convenient and has environmental and economic advantages.

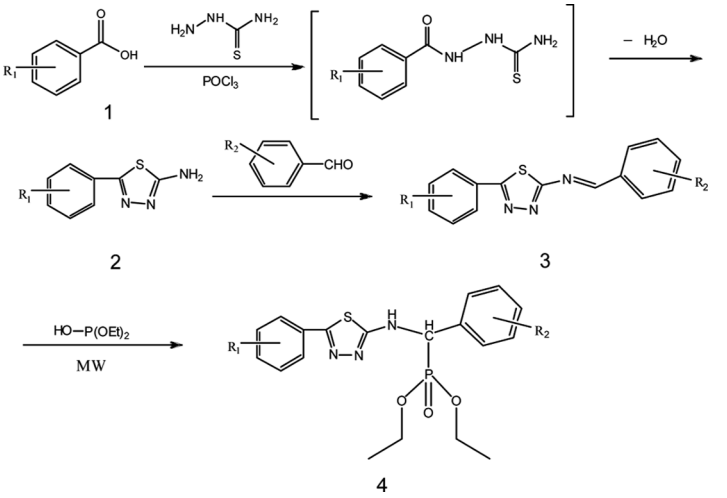
In this study, we have designed and synthesized a series of new compounds containing 1,3,4-thiadiazole and aminophosphonate under MW irradiation.

RESULTS AND DISCUSSION

The diethyl (5-substituted phenyl-1,3,4-thiadiazol-2-ylamino) (substituted phenyl) methylphosphonates (**4a–k**) were designed and prepared by the reaction of N-(substituted benzylidene)-5-(substituted phenyl)-1,3,4-thiadiazol-2-amines (**3a–k**) and diethyl phosphite under MW irradiation as shown in Scheme 1. The compounds **3a–k** were prepared by the reaction of 5-(substituted phenyl)-1,3,4-thiadiazol-2-amines (**2a–k**) with substituted benzaldehydes in toluene under a Dean–Stark trap. Compounds **2a–k** were synthesized by substituted benzoic acids with thiosemicarbazide in the presence of phosphorus oxychloride.

Preliminary experiments to examine the reaction time and irradiation power were performed using **3a** (10 mmol) and diethyl phosphite (50 mmol) as a model system to synthesize the compound **4a** (Table 1). Various reaction times and irradiation power were tested (Table 1, entries 1–5). All comparative reactions were conducted under optimized conditions, and compound **4a** was obtained under MW irradiation. The best yield of **4a** (85%) was obtained by carrying out the reaction under MW irradiation (300 W) for 10 min. The reaction was also carried out with conventional heating (Table 1, entry 7), which required more heating time (8 h) but gave a lesser yield (60%).

The formation of diethyl aryl (5-aryl-1,3,4-thiadiazol-2-ylamino) methylphosphonates (**4a–k**) was confirmed by recording elemented analyses (EA), infrared (IR), and ^{1}H NMR. The IR spectrums of **4a–k** displayed bands at 3188–3274 cm^{-1}, 1652 cm^{-1}, 1220–1278 cm^{-1}, and 1020–1058 cm^{-1} due to N-H, C=N, P=O, and P-O stretching frequencies, respectively. The ^{1}H NMR spectrum of **4a** exhibited a



Scheme 1. Synthesis route of compounds **4a–k**. $R_1 = 2,4$-dichloro (a), 3-methyl (b), 3,5-dimethyl (c), 4-methoxy (d), 2,4-dichloro (e), 4-nitro (f), 4-fluoro (g), 3,5-dimethyl (h), 3,5-dimethyl (i), 3-methyl-4-nitro (j), and 3-fluoro (k). $R_2 = 4$-methoxy (a), 4-chloro (b), 4-chloro (c), 4-fluoro (d), H (e), 4-methoxy (f), H (g), 4-methoxy (h), 2,4-dichloro (i), 4-chloro (j), and 4-chloro (k).

singlet at δ8.28, which accounts for the NH proton; a multiplet appeared at δ6.85–8.13, which accounts for the aromatic protons of the phenyl ring; a doublet appeared at δ5.50, which accounts for CH proton; a multiplet appeared at δ3.86–4.24, which accounts for the CH_2 proton; and a triplet appeared at δ1.14–1.32, which accounts for CH_3 proton.

In conclusion, we have developed a fast, convenient, and efficient method for the preparation of diethyl (5-substituted phenyl-1,3,4-thiadiazol-2-ylamino) (substituted phenyl) methylphosphonates under MW irradiation. The simplification of the reaction procedure together with very short reaction time and a greater yield made this procedure more useful and attractive than the currently available methods.

Table 1. Synthesis of **4a**

Entry	Mode of activation	Time	Power/temp.	Yield (%)[b]
1	MW	3 min	300 W	40
2	MW	7 min	300 W	55
3	MW	10 min	300 W	85
4	MW	15 min	300 W	85
5	MW	10 min	200 W	60
6	MW	10 min	400 W	77
7	Δ[a]	8 h	80 °C	60

MW, microwave irradiation; Δ, conventional heating.
[a]The reaction was conducted with **3a** (10 mmol) and diethyl phosphite (50 mmol) at 80 °C.
All the products were investigated thoroughly by ^{1}H NMR, IR, and elemental analysis.
[b]Isolated yields.

EXPERIMENTAL

Instrumentation and Chemicals

All nonaqueous reactions were carried out under a nitrogen atmosphere. Unless otherwise noted, all reagents and solvents were used as received. Reactions were monitored by thin-layer chromatography (TLC) with visualization by ultraviolet light.

Melting points were recorded on an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and were corrected in advance. Elemental analyses were performed on an Elementer Vario EL III elementary analysis instrument. ^{1}H NMR spectra were obtained in $CDCl_3$ and dimethylsulfoxide (DMSO-d_6), and they were recorded on a Bruker DRX500 spectrometer. Resonances were given in parts per million (ppm, δ) relative to tetramethylsilane (TMS), and peak multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or b (broad). IR spectra in KBr were recorded by a Perkin-Elmer PE-683 infrared spectrometer. MW experiments were carried out on a WF-4000M microwave fast reaction system (Shanghai Qiyao Analysis Instrument Co., Shanghai, China).

General Synthetic Procedure for the Preparation of 5-(Substituted phenyl)-1,3,4-thiadiazol-2-amines (2a–k)

To a mixture of substituted benzoic acid **1** (0.1 mol) and thiosemicarbazide (0.1 mol), $POCl_3$ (0.3 mol) was added dropwise at 0–5 °C and maintained for 30 min. The temperature reaction mixture was allowed to rise until reflux, and the mixture was stirred for 4 h. After cooling, 50 mL water were added into the reaction mixture. The pH of the reaction solution was adjusted to the range of 8–9 with a solution of 50% NaOH. The crude product was precipitated, filtered, washed with water, dried, and recrystallized from ethanol to afford compounds **2a–k**.

General Synthetic Procedure for the Preparation of N-(Substituted benzylidene)-5-(substituted phenyl)-1,3,4-thiadiazol-2-amines (3a–k)

A mixture of **2** (5 mmol) and substituted benzaldehyde was stirred and allowed to rise in temperature until reflux in toluene under a Dean–Stark trap. The reaction was monitored by TLC until the reaction ended. After the reaction, the toluene was evaporated under reduced pressure. The crude product was precipitated, filtered, washed with ethanol, dried, and recrystallized from acetone to afford compounds **3a–k**.

General Synthetic Procedure for the Preparation of Diethyl (5-substituted phenyl-1,3,4-thiadiazol-2-ylamino)(substituted phenyl) Methylphosphonates (4a–k)

A mixture of **3** (10 mmol) and diethyl phosphite (50 mmol) was stirred in an open vessel and irradiated in an experimental MW instrument at 300 W for 10 min

(max. temp. 120 °C). After completion of the reaction, the remaining diethyl phosphite was evaporated under reduced pressure. The resulting viscous liquid was recrystallized form EtOH to obtain **4a–k**. The physical constants and spectral analyses are listed.

Data

Compound 4a. Yield: 85%. Yellow crystals. Mp 150–152 °C (153 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.14–1.32 (t, 6H, CH_3), 3.76 (s, 3H, CH_3), 3.86–4.24 (m, 4H, CH_2), 5.50 (d, 1H, CH), 6.85–8.13 (m, 7H, Ph), 8.28 (s, 1H, NH). IR (KBr) ν: 3226, 3012, 2935, 1652, 1506, 1456, 1301, 1261, 1222, 1186, 1091, 1054 cm^{-1}. Anal. calcd. for $C_{20}H_{22}Cl_2N_3O_4PS$: C, 47.82; H, 4.41; N, 8.36; S, 6.38. Found: C, 47.61; H, 4.32; N, 8.18; S, 6.19.

Compound 4b. Yield: 87%. White crystals. Mp 184–185 °C (187 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.18–1.32 (t, 6H, CH_3), 2.36 (s, 3H, CH_3), 3.94–4.22 (m, 4H, CH_2), 5.47 (d, 1H, CH), 7.17–7.57 (m, 7H, Ph), 7.86 (s, 1H, NH). IR (KBr) ν: 3242, 3016, 2929, 2906, 1652, 1506, 1456, 1269, 1234, 1180, 1089, 1045 cm^{-1}. Anal. calcd. for $C_{20}H_{23}ClN_3O_3PS$: C, 53.16; H, 5.13; N, 9.30; S, 7.10. Found: C, 53.01; H, 4.98; N, 9.22; S, 6.89.

Compound 4c. Yield: 80%. White crystals. Mp 173–176 °C (179 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.18–1.32 (t, 6H, CH_3), 2.32 (s, 6H, CH_3), 3.93–4.19 (m, 4H, CH_2), 5.39 (d, 1H, CH), 7.01–7.54 (m, 7H, Ph). IR (KBr) ν: 3274, 3031, 2985, 2910, 1652, 1506, 1456, 1271, 1244, 1195, 1091, 1049 cm^{-1}. Anal. calcd. for $C_{21}H_{25}ClN_3O_3PS$: C, 54.13; H, 5.41; N, 9.02; S, 6.88. Found: C, 53.89; H, 5.32; N, 8.89; S, 6.76.

Compound 4d. Yield: 89%. White crystals. Mp 160–164 °C (160 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.16–1.32 (t, 6H, CH_3), 3.83 (s, 3H, CH_3), 3.90–4.22 (m, 4H, CH_2), 5.52 (d, 1H, CH), 6.87–7.98 (m, 7H, Ph), 8.08 (s, 1H, NH). IR (KBr) ν: 3215, 3026, 2987, 2935, 1652, 1506, 1456, 1299, 1255, 1218, 1081, 1031 cm^{-1}. Anal. calcd. for $C_{20}H_{23}FN_3O_4PS$: C, 53.21; H, 5.14; N, 9.31; S, 7.10. Found: C, 53.01; H, 5.02; N, 9.11; S, 6.95.

Compound 4e. Yield: 79%. White crystals. Mp 168–170 °C (170 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.11–1.33 (t, 6H, CH_3), 3.83–4.24 (m, 4H, CH_2), 5.59 (d, 1H, CH), 7.25–8.50 (m, 8H, Ph), 8.66 (s, 1H, NH). IR (KBr) ν: 3215, 3012, 2937, 2904, 1652, 1506, 1456, 1232, 1220, 1105, 1047, 1020 cm^{-1}. Anal. calcd. for $C_{19}H_{20}Cl_2N_3O_3PS$: C, 48.32; H, 4.27; N, 8.90; S, 6.79. Found: C, 48.18; H, 4.06; N, 8.76; S, 6.62.

Compound 4f. Yield: 82%. White crystals. Mp 175–178 °C (176 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.17–1.34 (t, 6H, CH_3), 3.76 (s, 3H, CH_3), 3.89–4.24 (m, 4H, CH_2), 5.53 (d, 1H, CH), 6.84–8.21 (m, 8H, Ph), 8.24 (s, 1H, NH). IR (KBr) ν: 3218, 3026, 2979, 2904, 1652, 1515, 1506, 1456, 1251, 1230, 1182, 1049, 1024 cm^{-1}. Anal. calcd. for $C_{20}H_{23}N_4O_6PS$: C, 50.21; H, 4.85; N, 11.71; S, 6.70. Found: C, 50.15; H, 4.68; N, 11.62; S, 6.56.

Compound 4g. Yield: 75%. Yellow crystals. Mp 180–183 °C (185 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.13–1.32 (t, 6H, CH_3), 3.84–4.21 (m, 4H, CH_2), 5.51 (d, 1H, CH), 7.03–7.72 (m, 9H, Ph). IR (KBr) ν: 3230, 3028, 2908, 2866, 1652, 1506, 1456, 1292, 1278, 1228, 1060, 1020 cm^{-1}. Anal. calcd. for $C_{19}H_{21}FN_3O_3PS$: C, 54.15; H, 5.02; N, 9.97; S, 7.61. Found: C, 53.89; H, 4.89; N, 9.63; S, 7.48.

Compound 4h. Yield: 83%. White crystals. Mp 154–158 °C (160 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.15–1.30 (t, 6H, CH_3), 2.31 (s, 6H, CH_3), 3.76 (s, 3H, CH_3), 3.88–4.18 (m, 4H, CH_2), 5.32 (d, 1H, CH), 6.85–7.52 (m, 7H, Ph). IR (KBr) ν: 3190, 3031, 2933, 2912, 1652, 1506, 1456, 1284, 1249, 1191, 1041, 1020 cm^{-1}. Anal. calcd. for $C_{22}H_{28}N_3O_4PS$: C, 57.25; H, 6.12; N, 9.10; S, 6.95. Found: C, 57.16; H, 5.96; N, 8.91; S, 6.63.

Compound 4i. Yield: 82%. Grey crystals. Mp 181–183 °C (185 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.17–1.35 (t, 6H, CH_3), 2.31 (s, 6H, CH_3), 3.94–4.26 (m, 4H, CH_2), 5.87 (d, 1H, CH), 7.01–7.68 (m, 6H, Ph). IR (KBr) ν: 3265, 3016, 2975, 2916, 1652, 1506, 1475, 1268, 1255, 1186, 1049, 1037 cm^{-1}. Anal. calcd. for $C_{21}H_{24}Cl_2N_3O_3PS$: C, 50.41; H, 4.83; N, 8.40; S, 6.41. Found: C, 50.22; H, 4.62; N, 8.16; S, 6.14.

Compound 4j. Yield: 71%. White crystals. Mp 176–179 °C (175 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.19–1.34 (t, 6H, CH_3), 2.62 (s, 3H, CH_3), 3.94–4.24 (m, 4H, CH_2), 5.53 (d, 1H, CH), 7.25–8.01 (m, 7H, Ph). IR (KBr) ν: 3218, 3029, 2987, 2906, 1652, 1521, 1506, 1456, 1224, 1178, 1054, 1029 cm^{-1}. Anal. calcd. for $C_{20}H_{22}ClN_4O_5PS$: C, 48.34; H, 4.46; N, 11.27; S, 6.45. Found: C, 48.19; H, 4.29; N, 11.03; S, 6.28.

Compound 4k. Yield: 76%. White crystals. Mp 196–199 °C (200 °C[12]). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.18–1.34 (t, 6H, CH_3), 3.80–4.25 (m, 4H, CH_2), 5.45 (d, 1H, CH), 7.06–7.53 (m, 8H, Ph). IR (KBr) ν: 3188, 3066, 2989, 2850, 1652, 1506, 1280, 1257, 1188, 1091,1049, 1014 cm^{-1}. Anal. calcd. for $C_{19}H_{20}ClFN_3O_3PS$: C, 50.06; H, 4.42; N, 9.22; S, 7.03. Found: C, 49.90; H, 4.43; N, 9.15; S, 7.00.

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