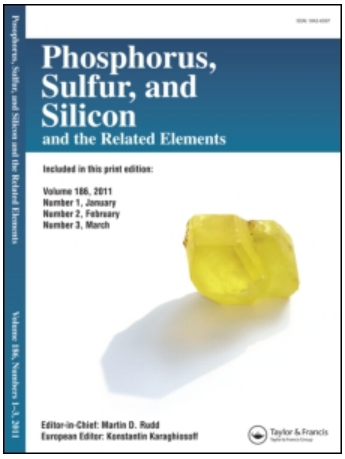


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# Synthesis and Fungicidal Activity of *O,O'*-Dimethyl α-[(5-Ethoxycarbonyl-4- Methyl-1,3-Thiazol-2-YL-Amino)Arylmethane] Phosphonates

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# SYNTHESIS AND FUNGICIDAL ACTIVITY OF *O,O′*-DIMETHYL α-[(5-ETHOXYCARBONYL-4-METHYL-1,3-THIAZOL-2-YL-AMINO)ARYLMETHANE] PHOSPHONATES

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***A series of dialkyl [(5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)arylmethane] phosphonates was synthesized by the reaction of ethyl 2-amino-4-methylthiazole-5-carboxylate, with dialkyl phosphite and aromatic aldehydes using $Mg(ClO_4)_2$ as the catalyst. All new compounds were identified by elemental analysis, IR, $^1H$ NMR, and $^{13}C$ NMR spectra. O,O'-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)arylmethane] phosphonate was further analyzed by a single-crystal X-ray diffraction analysis. The result of a preliminary bioassay indicated that some compounds exhibit inhibition activities against*** **Rhizoctonia solani** ***and*** **Botrytis cinereapers** ***at a dosage of 100 mg/L.***

***Supplemental materials are available for this article. Go to the publisher's online edition of*** **Phosphorus, Sulfur, and Silicon and the Related Elements** ***to view the free supplemental file.***

**Keywords** Amino phosphonate; fungicidal activity; synthesis; thiazole



## INTRODUCTION

α-Aminophosphate derivatives as bioisostersamino acids are known to display diverse and useful biological properties such as pharmaceutical or pesticide activities.[1] In addition, the useful biological properties of compounds containing a thiazole structural unit have received special attention due to the broad spectrum of biological and pharmaceutical activities. Some of them have been reported as pharmaceutical lead compounds, possessing anti-inflammatory,[2] antitumor,[3] or antihyperlipidemic[4] activities.

In order to examine the effect of the introduction of a thiazole ring on the biological properties of aminophosphonates, we have designed and synthesized a series of *O,O'*-dialkyl α-[(5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)arylmethane] phosphonates **8a–r**. In this article, we report on the synthesis of the title compounds and their fungicidal activity against *Rhizoctonia solani* and *Botrytis cinereapers*.

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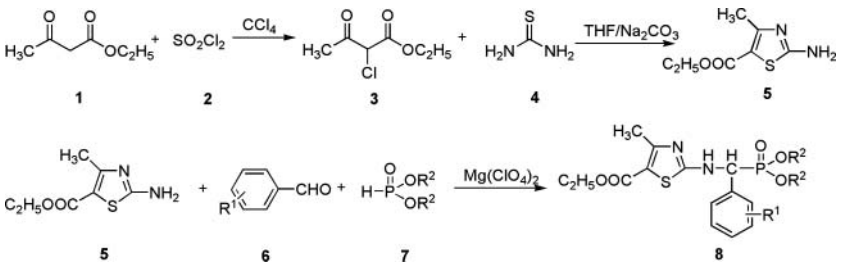
## RESULTS AND DISCUSSION

### Syntheses

A typical method for the synthesis of substituted $\alpha$-aminophosphonates is the one-pot reaction of aldehydes, amine, and dialkyl phosphite by Mannich-type addition reaction. Since the synthesis of the title compounds has not been described in the literature, we were interested in finding a mild and efficient method for their preparation. We noticed that a few $\alpha$-aminophosphonates containing a heterocycle such as a benzothiazole moiety have been reported,[5,6] which could be synthesized by a three-component condensation of aldehydes, aminobenzothiazole, and dialkyl phosphite at 100–102°C in ionic liquids.[6] Therefore, a one-pot, three-component reaction of ethyl 2-amino-4-methylthiazole-5-carboxylate, an aromatic aldehyde, and dialkyl phosphite was chosen to prepare the title compounds.



**Scheme 1** Synthesis of the title compounds **8**.

The multistep procedure for the synthesis of the title compounds is outlined in Scheme 1. We chose a convenient route to obtain the title compounds **8a–t** starting from ethyl acetoacetate **1**. Compound **1** was chlorinated with sulfuryl chloride **2** in tetrachloromethane to provide ethyl 2-chloroacetoacetate **3**, which was further transferred to ethyl 2-amino-5-carbethoxy-4-methylthiazole-5-carboxylate **5**[12] by reaction with thiourea **4**. The title compounds **8a–r** were then obtained by the three-component condensation reactions of **5**, an aromatic aldehyde **6**, and dialkyl phosphite **7**.

In order to optimize the reaction conditions for the synthesis of **8** (Table I), the condensation reaction of **5**, the aromatic aldehyde **6**, and dialkyl phosphite **7** was carried out under various conditions. The experiment showed that the reactions were affected by the catalyst, the reaction temperature, and the solvent. The condensation reaction of aldehydes, amine, and dialkyl phosphite were usually catalyzed by magnesium perchlorate,[7] acetic acid,[5] or acetyl chloride.[8] However, the latter catalysts had no effect for the synthesis of the title compounds. The reactions resulted in low conversion rates and low yields, and required complex workup procedures. It was found that the condensation could be effectively catalyzed by magnesium perchlorate. The results showed that the best reaction temperature was 80–85°C. At lower or higher temperatures, the reactions gave very poor yields. The effect of the solvent used for these condensation reactions was also examined. The results are summarized in Table II. The experiments showed that the title compounds could be obtained in much higher yield by stirring **5**, **6**, and **7** for only 1–3 h under solvent-free conditions. Compared with the effect of the solvent on the synthesis of **8**, the solvent-free condition appears to be the best choice for the preparation of the title compounds.

**Table I** Preparation of **8a–r** by use of $Mg(ClO_4)_2$ as catalyst under solvent-free conditions

| Compounds | $R^1$ | $R^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| **8a** | H | $CH_3$ | 1 | 90.2 |
| **8b** | 3-$CH_3$ | $CH_3$ | 1.5 | 83.5 |
| **8c** | 4-$OCH_3$ | $CH_3$ | 1.5 | 78.9 |
| **8d** | 4-Cl | $CH_3$ | 1.5 | 70.3 |
| **8e** | 2,4-$Cl_2$ | $CH_3$ | 1 | 82.1 |
| **8f** | 4-F | $CH_3$ | 0.8 | 83.1 |
| **8g** | 3,4-$Cl_2$ | $CH_3$ | 2 | 84.6 |
| **8h** | 4-$NO_2$ | $CH_3$ | 2 | 87.0 |
| **8i** | 4-$CH_3$ | $CH_3$ | 2 | 87 |
| **8j** | H | $C_2H_5$ | 1 | 90.2 |
| **8k** | 3-$CH_3$ | $C_2H_5$ | 2 | 87.5 |
| **8l** | 4-$OCH_3$ | $C_2H_5$ | 2 | 89.0 |
| **8m** | 4-Cl | $C_2H_5$ | 2.5 | 93.2 |
| **8n** | 2,4-$Cl_2$ | $C_2H_5$ | 2 | 93.1 |
| **8o** | 4-F | $C_2H_5$ | 2.5 | 96.1 |
| **8p** | 3,4-$Cl_2$ | $C_2H_5$ | 2 | 96.3 |
| **8q** | 4-$NO_2$ | $C_2H_5$ | 3 | 94.0 |
| **8r** | 4-$CH_3$ | $C_2H_5$ | 2 | 91.2 |



The structures of **8a–r** were established by comprehensive IR, $^1H$ NMR, and $^{13}C$ NMR spectroscopic studies, and by elemental analyses. The structure of **8a** was further corroborated by an X-ray crystal[9] diffraction analysis (Figure 1). The bond lengths N2—C10 and C10—S1 are longer than those observed in free thiazole [1.286 and 1.728 Å][10]. The N1—C9 bond is a little longer than the neighboring N1—C10 bond. The bond angles O1—P1—O3, O1—P1—O2, and O1—P1—C9 are larger than those of O3—P1—O2, O2—P1—C9, and O3—P1—C9 (Table III), respectively, indicating that the phosphorus atom adopts a slightly distorted tetrahedral configuration. Some weak intramolecular C—H—N and C—H—O hydrogen-bonding interactions exist in the crystal (Table S1, available online in the Supplemental Materials). In addition, the crystal is also stabilized by intermolecular N—H—O hydrogen-bonding interactions that form dimers.

**Table II** Effect of the solvent on the synthesis of **8**

| Compounds | | | Condition 1[a] | | Condition 2[b] | |
|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | | Time (h) | Yield (%) | Time (h) | Yield (%) |
| **8e** | 2,4-$Cl_2$ | $CH_3$ | 5 | 54.1 | 1 | 82.1 |
| **8g** | 3,4-$Cl_2$ | $CH_3$ | 9 | 48.6 | 2 | 84.6 |
| **8h** | 4-$NO_2$ | $CH_3$ | 11 | 45.0 | 2 | 87.0 |
| **8n** | 2,4-$Cl_2$ | $C_2H_5$ | 12 | 51.1 | 2 | 93.1 |
| **8p** | 3,4-$Cl_2$ | $C_2H_5$ | 12 | 63.3 | 2 | 96.3 |
| **8q** | 4-$NO_2$ | $C_2H_5$ | 22 | 73.2 | 3 | 94.0 |

[a]Condition 1: catalyzed by $Mg(ClO_4)_2$ in THF.
[b]Condition 2: catalyzed by $Mg(ClO_4)_2$ under solvent-free condition.

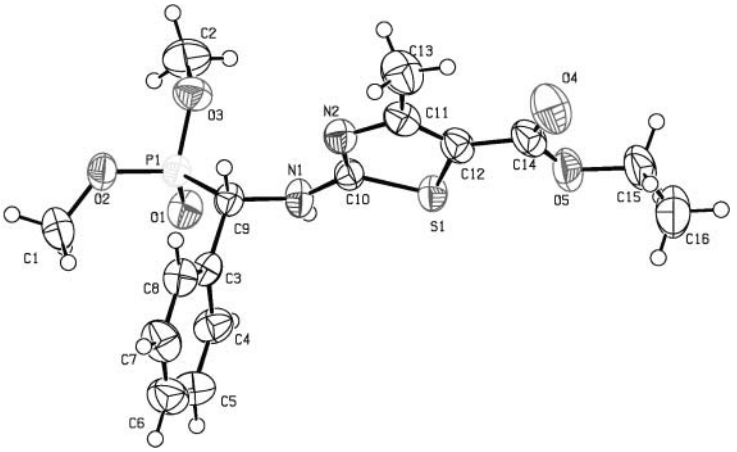



**Figure 1** View and atom labeling of **8a**.

### Fungicidal Activity

The fungicidal activity[11] of compounds **8** was screened against six fungus species, namely *Fusarium oxysporium*, *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Dothiorella gregaria*, and *Colletotrichum gossypii* according to the reported method at a dosage of 100 mg/L. (See the Supplemental Materials.)



## CONCLUSIONS

In summary, *O*,*O*'-dialkyl[(5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-yl-amino)aryl-methane]phosphonates can be prepared with good yields by a one pot reaction of ethyl 2-amino-4-methylthiazole-5-carboxylate, an aromatic aldehyde, and dialkyl phosphite by use of magnesium perchlorate as a catalyst under solvent-free conditions. This provides a simple and efficient procedure for the synthesis of $\alpha$-aminophosphonates containing a thiazole group.

## EXPERIMENTAL

Melting points were determined using a X-4 model apparatus (Beijing Taike Company, Beijing, People's Republic of China) and were uncorrected. IR spectra were recorded on a Nicolet 7500 NXR infrared spectrometer (Thermonicolet Company, Waltham, Massachusetts) as KBr pellets with absorption given in $cm^{-1}$. MS were measured on a HP5988A spectrometer (Hewlett-Packard, Palo Alto, California). $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 400 (400 MHz) spectrometer (Varian, Palo

**Table III** Selected bond angles [°]

| | | | |
|---|---|---|---|
| O1-P1-O3 | 115.59 (10) | O1-P1-C9 | 113.98 (9) |
| O1-P1-O2 | 114.25 (9) | O3-P1-C9 | 103.11 (10) |
| O3-P1-O2 | 102.76 (9) | O2-P1-C9 | 105.80 (10) |

Alto, California). Chemical shifts ($\delta$) are given in ppm using $(CH_3)_4Si$ as an internal reference ($\delta = 0$). Elementary analyses were taken on a Perkin-Elmer CHN2400 elemental analysis instrument (Perkin-Elmer, Waltham, Massachusetts).

## X-Ray Diffraction

Colorless blocks of compound **8a** (0.20 mm × 0.20 mm × 0.10 mm) were mounted on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 291 K on a Bruker SMART CCD area detector diffractometer with graphite-monochromated Mo K$\alpha$ radiation ($\lambda = 0.71073$ Å); $\theta_{max} = 25.03$; 7622 independent reflections ($R_{int} = 0.0282$) of which 3294 contributing reflections had $I > 2\sigma(I)$. The structure was solved by direct methods using SHELXS-97; all other calculations were performed with the Bruker SAINT system and Bruker SMART programs. Full-matrix least-squares refinement gave final values of $R = 0.0646$, $\omega R = 0.1954$. Max/min residual electron density = 1.281/-0.851 e Å$^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter. The molecular structure of compound **8a** is shown in Figure 1**,** and a summary of data collection statistics is given in Table IV. CCDC 667412 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, B2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).



**Table IV** Crystal structure and data refinement parameters

| Compound | **8a** |
|---|---|
| Empirical Formula | C16 H21 N2 O5 P S |
| Formula Weight | 384.38 |
| Crystal System / Space Group | Triclinic |
| a/Å | 8.1821(4) |
| b/Å | 9.9884(5) |
| c/Å | 11.9142(6) |
| $\alpha$/° | 98.2490(10) |
| $\beta$/° | 103.2990(10) |
| $\gamma$/° | 95.6180(10) |
| V/Å$^3$ | 929.08(8) |
| Z | 2 |
| $D_{calc}$ (g/cm$^3$) | $1.374 \times 10^{-3}$ |
| $\mu$ (mm$^{-1}$) | 0.289 |
| Crystal size (mm$^3$) | 0.20 × 0.20 × 0.10 |
| Color/Shape | colorless |
| Temp (K) | 291(2) |
| Theta range for collection | 1.78 to 25.99° |
| Reflections collected | 8937 |
| Independent reflections | 3610 [R(int) = 0.0321] |
| Data/restraints/parameters | 3610/0/230 |
| Goodness of fit on F$^2$ | 1.073 |
| Final R indices [$I > 2\sigma(I)$] | R1 = 0.0449, wR2 = 0.1251 |
| R indices (all data) | R1 = 0.0532, wR2 = 0.1358 |
| Largest difference peak/hole | 0.406 and -0.213 e.Å−3 |

### *O,O′*-Dialkyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino) arylmethane]-phosphonates (8a–8r): General Procedure

The mixture of arylaldehyde (5 mmol) and $Mg(ClO_4)_2$ (5 mol%) was stirred for 11–15 min. Then **5** (5 mmol) and dialkyl phosphite (5 mmol) were added, and the reaction mixture was stirred at 80°C for 6 h. The mixture was extracted with EtOH (3 × 10 mL), then the combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the crude products, which, on passing through a column of silica gel by elution with acetone-petroleum ether(v/v, 1/4), gave pure **8a–8r**.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino) phenyl methane]phosphonate (8a).** White solid, yield 90.2%, mp 145.2–146.4°C. IR: ν:3230, 3041, 2956, 2853, 1705, 1494, 1371, 1267, 1099, 755, 704. $^1$H NMR: δ 1.29 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 2.51 (s, 3H, $CH_3$), 3.50–3.79 (dd, 6H, $J$ = 10.8 Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}CH_3$), 5.14 (d, 1H, $J$ = 22.8 Hz, CH), 7.32–7.51 (m, 5H, ArH). $^{13}$C NMR: δ 14.3, 17.5, 53.7, 53.8, 54.7, 55.7, 60.2, 110.2, 126.2, 128.2, 128.7, 136.2, 159.2, 162.6, 168.7, 169.3. Anal. Calcd. for $C_{16}H_{21}N_2O_5PS$: C, 49.99; H, 5.51; N, 7.29. Found: C, 49.69; H, 5.49; N, 7.01.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-3-methyl-phenylmethane]phosphonate (8b).** White solid, yield 83.5%, mp 141.3–143.2°C. IR: ν 3226, 2979, 2426, 1708, 1499, 1373, 1275, 1090, 757, 703. $^1$H NMR: δ 1.29 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 2.35 (s, 3H, $ArCH_3$), 2.51 (s, 3H, $CH_3$), 3.50–3.78 (dd, 6H, $J$ = 10.8 Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}$ $CH_3$), 5.08 (d, 1H, $J$ = 22.0 Hz, CH), 7.13–7.29 (m, 4H, ArH). $^{13}$C NMR: δ 14.3, 17.4, 21.3, 53.7, 53.8, 54.1, 56.2, 60.2, 110.2, 125.2, 128.4, 128.6, 128.7, 134.1, 138.3, 158.9, 162.6, 169.0. Anal. Calcd. for $C_{17}H_{23}N_2O_5PS$: C, 51.25; H, 5.82; N, 7.03. Found: C, 50.98; H, 5.53; N, 7.08.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-methoxyphenylmethane]phosphonate (8c).** White solid, yield 78.9%, mp 133.1–134.2°C. IR: ν 3240, 2958, 2854, 1693, 1494, 1374, 1276, 1106, 838. $^1$H NMR: δ 1.29 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.51–3.79 (dd, 6H, $J$ = 10.4 Hz, $OCH_3$), 4.21 (q, 2H, $J$ = 7.0 Hz, $\underline{CH_2}CH_3$), 5.16 (d, 1H, $J$ = 22.0 Hz, CH), 6.89 (d, 2H, $J$ = 8.8 Hz, $H^{2,3}$-Ph), 7.45 (d, 2H, $H^{5,6}$-Ph). $^{13}$C NMR: δ 14.3, 16.2, 17.4, 52.2, 53.7, 53.8, 54.1, 56.2, 60.2, 112.9, 126.4, 129.3, 129.4, 158.2, 162.7, 169.0. Anal. Calcd. for $C_{17}H_{23}N_2O_6PS$: C, 49.27; H, 5.59; N, 6.76. Found: C, 49.17; H, 5.31; N, 6.69.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-chlorophenylmethane]phosphonate (8d).** White solid, yield 70.3%, mp 126.4–127.3°C. IR: ν 3236, 3029, 2957, 2852, 1691, 1494, 1372, 1274, 1090, 839. $^1$H NMR: δ 1.29 (t, 3H, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.56–3.81 (dd, 6H, $J$ = 10.6 Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.0 Hz, $\underline{CH_2}CH_3$), 5.25 (d, 1H, $J$ = 22.4 Hz, CH), 7.34 (d, 2H, $J$ = 8.0 Hz, $H^{2,3}$-Ph), 7.45 (d, 2H, $H^{5,6}$-Ph). $^{13}$C NMR: δ 14.3, 16.1, 17.1, 52.2, 53.1, 53.4, 55.0, 56.1, 63.7, 112.3, 128.6, 129.5, 129.6, 133.1, 134.1, 158.1, 162.4, 168.9. Anal. Calcd. for $C_{16}H_{20}ClN_2O_5PS$: C, 45.88; H, 4.81; N, 6.69. Found: C, 45.63; H, 4.58; N, 6.53.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-2,4-dichlorophenylmethane]phosphonate (8e).** Light yellow solid, yield 82.1%, mp 146.7–147.9°C. IR: ν 2935, 2425, 1723, 1276, 1089, 725, 617. $^1$H NMR: δ 1.30 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.55–3.84 (dd, 6H, $J$ = 10.8 Hz, $OCH_3$), 4.24 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}CH_3$), 5.62 (d, 1H, $J$ = 22.8 Hz, CH), 7.27 (d, 1H, $J$ = 8.4 Hz, $H^5$-Ph), 7.45 (s, 1H, $H^3$-Ph), 7.54 (d, 1H, $J$ = 10.4 Hz, $H^6$-Ph). $^{13}$C NMR: δ 14.3, 17.5,

51.4, 53.3, 53.8, 60.3, 63.9, 110.9, 127.5, 129.2, 130.1, 132.0, 134.5, 134.9, 159.2, 162.6, 168.6, 168.8. Anal. Calcd. for $C_{16}H_{19}Cl_2N_2O_5PS$: C, 42.40; H, 4.22; N, 6.18. Found: C, 42.68; H, 4.02; N, 6.13.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-fluorophenylmethane]phosphonate (8f).** White solid, yield 83.1%, mp 189.6–190.2°C. IR: ν 3235, 3039, 2956, 1703, 1494, 1374, 1268, 1101, 841. $^1$H NMR: δ 1.28 (t, 3H, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.54–3.81 (dd, 6H, $J$ = 10.6 Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.4 Hz, $\underline{CH_2}CH_3$), 5.26 (d, 1H, $J$ = 22.8 Hz, CH), 7.04–7.08 (m, 2H, $H^{2,3}$-Ph), 7.48–7.52 (m, 2H, $H^{5,6}$-Ph). $^{13}$C NMR: δ 14.3, 17.4, 53.7, 53.8, 53.9, 60.3, 110.7, 115.5, 115.7, 129.8, 130.0, 159.0, 162.6, 168.7, 168.8. Anal. Calcd. for $C_{16}H_{20}FN_2O_5PS$: C, 47.76; H, 5.01; N, 6.96. Found: C, 47.62; H, 5.01; N, 7.01.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-3,4-dichlorophenylmethane]phosphonate (8g).** Light yellow solid, yield 84.6%, mp 127.8–128.9°C. IR: ν 3221, 3033, 2958, 2854, 1691, 1495, 1372, 1270, 1098, 845, 761. $^1$H NMR: δ 1.30 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.55–3.84 (dd, 6H, $J$ = 10.8 Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}CH_3$), 5.42 (d, 1H, $J$ = 22.8 Hz, CH), 7.36–7.65 (m, 2H, $H^{5,6}$-Ph), 7.46 (s, 1H, $H^2$-Ph). $^{13}$C NMR: δ 14.3, 17.5, 54.2, 54.3, 60.4, 110.5, 127.5, 129.9, 130.5, 132.5, 132.8, 135.1, 158.8, 162.6, 168.6, 168.7. Anal. Calcd. for $C_{16}H_{19}Cl_2N_2O_5PS$: C, 42.40; H, 4.22; N, 6.18. Found: C, 42.54; H, 3.99; N, 6.13.



**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-nitrophenylmethane]phosphonate (8h).** Light yellow solid, yield 87.0%, mp 152.7–153.4°C. IR: ν 3233, 3032, 2854, 1688, 1495, 1370, 1348, 1276, 1098, 864. $^1$H NMR: δ 1.28 (t, 3H, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.63–3.86 (dd, 6H, $J$ = 10.6 Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}CH_3$), 5.48 (d, 1H, $J$ = 23.2 Hz, CH), 7.69 (d, 2H, $J$ = 10.8 Hz, $H^{2,3}$-Ph), 8.22 (d, 2H, $J$ = 8.8 Hz, $H^{5,6}$-Ph). $^{13}$C NMR: δ 14.3, 17.4, 54.1, 54.1, 54.4, 54.5, 60.4, 111.2, 123.7, 128.9, 129.0, 142.2, 147.6, 158.6, 162.4, 168.1, 168.3. Anal. Calcd. for $C_{16}H_{20}N_3O_7PS$: C, 44.76; H, 4.69; N, 9.79. Found: C, 44.96; H, 4.52; N, 9.76.

**O,O′-Dimethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-methylphenylmethane]phosphonate (8i).** White solid, yield 87%, mp 137.5–138.2°C. IR: ν 3238, 3030, 2953, 2855, 1693, 1498, 1373, 1277, 1106, 838. $^1$H NMR: δ 1.29 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 2.34 (s, 3H, $ArCH_3$), 2.52 (s, 3H, $CH_3$), 3.50–3.78 (dd, 6H, $J$ = 10.6Hz, $OCH_3$), 4.22 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}CH_3$), 5.08 (d, 1H, $J$ = 22.0 Hz, CH), 6.58 (s, 1H, NH), 7.17–7.37 (m, 4H, ArH). $^{13}$C NMR: δ 14.3, 16.1, 17.4, 54.2, 56.7, 60.2, 63.4, 63.7, 110.7, 128.1, 128.20, 128.5, 134.5, 159.2, 162.7, 169.1, 169.3. Anal. Calcd. for $C_{17}H_{23}N_2O_5PS$: C, 51.25; H, 5.82; N, 7.03. Found: C, 51.45; H, 5.54; N, 6.92.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)phenylmethane]phosphonate (8j).** White solid, yield 90.2%, mp 206.1–207.3°C. IR: ν 3229, 3035, 2981, 2930, 1700, 1494, 1371, 1273, 1100, 759, 703. $^1$H NMR: δ 1.09 (t, 3H, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 1.26–1.3 (m, 6H, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.69–3.99 (m, 4H, $\underline{CH_2}CH_3$), 4.10–4.23 (m, 2H, $\underline{CH_2}CH_3$), 5.15 (d, 1H, $J$ = 22.4 Hz, CH), 7.29–7.51 (m, 5H, ArH). $^{13}$C NMR: δ 14.3, 16.1, 16.2, 17.5, 21.1, 54.6, 56.4, 60.2, 63.4, 63.4, 110.2, 126.2, 128.2, 128.7, 136.2, 159.2, 162.7, 169.3. Anal. Calcd. for $C_{18}H_{25}N_2O_5PS$: C, 52.42; H, 6.11; N, 6.79. Found: C, 52.29; H, 6.11; N, 6.87.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-3-methylphenylmethane]phosphonate (8k).** White solid, yield 87.5%, mp 168.4–170.2°C. IR: ν 3232, 3033, 2980, 2934, 1694, 1493, 1372, 1275, 1099, 759, 704. $^1$H NMR:

$\delta$ 1.13 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 1.26–1.34 (m, 6H, $CH_2\underline{CH_3}$), 2.35 (s, 3H, $ArCH_3$), 2.54 (s, 3H, $CH_3$), 3.73–4.12 (m, 4H, $\underline{CH_2}CH_3$), 4.14–4.25 (m, 2H, $\underline{CH_2}CH_3$), 4.90 (d, 1H, $J = 22.4$ Hz, CH), 7.13(d, 1H, $J = 6.4$ Hz, NH), 7.22–7.27 (m, 4H, ArH). $^{13}$C NMR: $\delta$ 14.3, 16.2, 16.3, 17.4, 24.3, 50.1, 51.1, 60.3, 63.6, 63.7, 110.2, 125.2, 128.4, 128.6, 128.7, 134.1, 138.3, 158.7, 162.5, 168.3, 168.4. Anal. Calcd. for $C_{19}H_{27}N_2O_5PS$: C, 53.51; H, 6.38; N, 6.57. Found: C, 53.25; H, 6.10; N, 6.32.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-methoxyphenylmethane]phosphonate (8l).** White solid, yield 89%, mp 110.8–111.7°C. IR: $\nu$ 3238, 2988, 2930, 2836, 1690, 1492, 1369, 1278, 1100, 829. $^1$H NMR: $\delta$ 1.14 (t, 3H, $J = 7.0$ Hz, $CH_2\underline{CH_3}$), 1.26–1.30 (m, 6H, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 2.96 (s, 3H, $OCH_3$), 3.76–4.13 (m, 4H, $\underline{CH_2}CH_3$), 4.13–4.23 (m, 2H, $\underline{CH_2}CH_3$), 4.90 (d, 1H, $J = 22.4$ Hz, CH), 6.89 (d, 2H, $J = 8.8$ Hz, $H^{2,3}$-Ph), 7.45 (d, 2H, $H^{5,6}$-Ph). $^{13}$C NMR: $\delta$ 14.3, 16.2, 17.4, 52.2, 54.1, 55.2, 60.2, 63.3, 63.6, 113.9, 126.4, 129.4, 129.4, 159.2, 159.5, 162.7, 169.2. Anal. Calcd. for $C_{19}H_{27}N_2O_6PS$: C, 51.58; H, 6.15; N, 6.33. Found: C, 51.87; H, 5.91; N, 6.39.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-chlorophenylmethane]phosphonate (8m).** White solid, yield 93.2%, mp 120.8–122.6°C. IR: 3223, 2983, 2903, 1705, 1493, 1372, 1275, 1100, 838. $^1$H NMR: $\delta$ 1.16 (t, 3H, $J = 7.0$ Hz, $CH_2\underline{CH_3}$), 1.27–1.31 (m, 6H, $CH_2\underline{CH_3}$), 2.52 (s, 3H, $CH_3$), 3.77–4.24 (m, 6H, $\underline{CH_2}CH_3$), 5.09 (d, 1H, $J = 22.4$ Hz, CH), 7.34 (d, 2H, $J = 8.0$ Hz, $H^{2,3}$-Ph), 7.45 (d, 2H, $H^{5,6}$-Ph). $^{13}$C NMR: $\delta$ 14.3, 16.1, 17.1, 52.2, 54.1, 60.4, 63.6, 63.7, 110.3, 128.6, 129.5, 129.6, 133.1, 134.1, 158.1, 162.4, 168.9. Anal. Calcd. for $C_{18}H_{24}ClN_2O_5PS$: C, 48.38; H, 5.41; N, 6.27. Found: C, 48.56; H, 5.31; N, 6.16.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-2,4-dichlorophenylmethane]phosphonate (8n).** White solid, yield 93.1%, mp 164.6–170.9°C. IR: $\nu$ 3238, 2984, 2931, 1703, 1370, 1271, 1098, 787, 634. $^1$H NMR: $\delta$ 1.14 (t, 3H, $J = 7.0$ Hz, $CH_2\underline{CH_3}$), 1.27–1.35 (m, 6H, $CH_2\underline{CH_3}$), 2.49 (s, 3H, $CH_3$), 3.76–4.01 (m, 4H, $\underline{CH_2}CH_3$), 4.16–4.26 (m, 2H, $\underline{CH_2}CH_3$), 5.60 (d, 1H, $J = 22.8$ Hz, CH), 7.25 (d, 1H, $J = 8.4$ Hz, $H^5$-Ph), 7.44 (s, 1H, $H^3$-Ph), 7.54 (d,1H, $J = 10.4$ Hz, $H^6$-Ph). $^{13}$C NMR: $\delta$ 14.3, 16.1, 16.4, 17.5, 51.4, 52.6, 60.3, 63.8, 63.9, 110.8, 127.5, 129.2, 130.1, 132.0, 134.5, 134.9, 159.2, 162.6, 168.6, 168.8. Anal. Calcd. for $C_{18}H_{23}Cl_2N_2O_5PS$: C, 44.92; H, 4.82; N, 5.82. Found: C, 45.00; H, 4.86; N, 5.86.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-fluorophenylmethane]phosphonate (8o).** White solid, yield 96.1%, mp 147.2–149.2°C. IR: $\nu$ 3225, 2982, 2904, 1702, 1494, 1373, 1280, 1103, 850. $^1$H NMR: $\delta$ 1.15 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 1.27–1.31 (m, 6H, $CH_2\underline{CH_3}$), 2.53 (s, 3H, $CH_3$), 3.79–4.25 (m, 6H, $\underline{CH_2}CH_3$), 5.03 (d, 1H, $J = 22.4$ Hz, CH), 7.03–7.08 (m, 2H, $H^{2,3}$-Ph), 7.45–7.48 (m, 2H, $H^{5,6}$-Ph). $^{13}$C NMR: $\delta$ 14.3, 16.1, 17.3, 54.1, 54.9, 60.3, 63.5, 63.8, 110.3, 115.3, 115.5, 129.9, 130.4, 158.7, 162.6, 169.1. Anal. Calcd. for $C_{18}H_{24}FN_2O_5PS$: C, 50.23; H, 5.62; N, 6.51. Found: C, 49.96; H, 5.37; N, 6.39.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-3,4-dichlorophenylmethane]phosphonate (8p).** Light yellow solid, yield 96.3%, mp 143–143.2°C. IR: $\nu$ 3219, 2985, 2915, 1705, 1495, 1372, 1276, 1100, 856, 758. $^1$H NMR: $\delta$ 1.19 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 1.20–1.34 (m, 6H, $CH_2\underline{CH_3}$), 2.50 (s, 3H, $CH_3$), 3.88–4.25 (m, 6H, $\underline{CH_2}CH_3$), 5.01 (d, 1H, $J = 22.4$ Hz, CH), 7.25–7.60 (m, 3H, ArH). $^{13}$C NMR: $\delta$ 14.3, 16.2, 16.3, 17.4, 53.4, 54.9, 60.3, 63.8, 63.9, 110.6, 127.5, 130.0, 130.2, 132.6, 135.4, 158.8, 162.6, 168.6, 168.7. Anal. Calcd. for $C_{18}H_{23}C_{12}N_2O_5PS$: C, 44.92; H, 4.82; N, 5.82. Found: C, 45.15; H, 5.11; N, 5.82.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-nitrophenylmethane]phosphonate (8q).** Light yellow solid, yield 94.0%, mp 128.8–130.3°C. IR: ν 3235, 3039, 2980, 1704, 1495, 1372, 1348, 1266, 1093, 864. $^1$H NMR: δ 1.20 (t, 3H, $J$ = 7.0 Hz, $CH_2\underline{CH_3}$), 1.27–1.35 (m, 6H, $CH_2\underline{CH_3}$), 2.55 (s, 3H, $CH_3$), 3.89–4.06 (m, 4H, $\underline{CH_2}CH_3$), 4.14–4.25 (m, 2H, $\underline{CH_2}CH_3$), 5.30 (d, 1H, $J$ = 22.8 Hz, CH), 7.69 (d, 2H, $J$ = 10.8 Hz, $H^{2,3}$-Ph), 8.22 (d, 2H, $J$ = 8.8 Hz, $H^{5,6}$-Ph). $^{13}$C NMR: δ 14.3, 16.1, 16.3, 17.4, 54.2, 54.9, 60.4, 63.8, 64.0, 110.9, 123.5, 129.0, 142.6, 147.5, 158.7, 162.5, 168.3, 168.4. Anal. Calcd. for $C_{18}H_{24}N_3O_7PS$: C, 47.26; H, 5.29; N, 9.19. Found: C, 47.08; H, 5.27; N, 9.26.

**O,O′-Diethyl α-[(5-Ethoxycarbonyl-4-methyl-1,3-thiazol-2-ylamino)-4-methylphenylmethane]phosphonate (8r).** White solid, yield 91.2%, mp 146.2–147.7°C. IR: ν 3227, 3028, 2982, 2928, 1704, 1494, 1371, 1278, 1105, 758. $^1$H NMR: δ 1.13 (t, 3H, $J$ = 7.2 Hz, $CH_2\underline{CH_3}$), 1.24–1.32 (m, 6H, $CH_2\underline{CH_3}$), 2.33 (s, 3H, $ArCH_3$), 2.52 (s, 3H, $CH_3$), 3.74–4.24 (m, 6H, $\underline{CH_2}CH_3$), 4.94 (d, 1H, $J$ = 22.4 Hz, CH), 7.15–7.36 (m, 4H, ArH). $^{13}$C NMR: δ 14.3, 16.1, 16.3, 17.4, 21.1, 49.0, 50.4, 60.2, 63.3, 63.4, 110.2, 128.1, 129.2, 131.3, 138.0, 159.0, 162.6, 169.2. Anal. Calcd. for $C_{19}H_{27}N_2O_5PS$: C, 53.51; H, 6.38; N, 6.57. Found: C, 53.59; H, 6.64; N, 6.51.



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