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# Synthesis and Properties of Novel α-(1,2,4-Triazolo[1,5-a]Pyrimidine-2-Oxyl)Phosphonate Derivatives

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ABSTRACT: *In an attempt to discover novel compounds with high activity and low toxicity, a series of new phosphonate derivatives containing triazolo[1,5-a]pyrimidine moieties have been designed and synthesized by a nucleophilic substitution between α-hydroxyphosphonates and 2-methanesulfonyl-1,2,4-triazolo[1,5-a]pyrimidines. The structures of all compounds prepared were confirmed by elemental analyses and by NMR and MS spectroscopy. The results of preliminary bioassay indicate that the title compounds possess certain selective herbicidal activity against rape and also, to some extent, inhibit of acetolactase synthase activity.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:313–316, 2000

## *INTRODUCTION*

The derivatives of triazolo[1,5-*a*]pyrimidine moieties possess many kinds of biological activities [1]. Some of them such as Metosulam and Flumetsulam, have shown extremely high herbicidal activities. They are also involved in drugs [2–5]. Therefore, various triazolo[1,5-*a*]pyrimidines and their derivatives are now in great demand. In our work searching for herbicidal heterocycles [6–7], we designed and synthesized novel kinds of triazolo[1,5-*a*]pyrimidine (thio)ether derivatives in view of the isosterism of the 4,6-dimethoxylpyrimidin-2-yl group and the 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidin-2-yl group and reported for the first time their significant herbicidal activities and their ability to inhibit acetolactate synthase (ALS), which has been identified as a very fruitful target for herbicides over the last four decades [8].

As a continuation of our research work, we decided to introduce a phosphoryl group, which may overcome the shortcoming of a long residual time in the soil of many ALS inhibitors, into the structure of a triazolo[1,5-*a*]pyrimidine ether, and therefore we designed and synthesized a series of new phosphonate derivatives containing triazolo[1,5-*a*]pyrimidine moieties. The results of bioassay showed that some of them possess potential herbicidal activity and inhibition of acetolactate synthase to some extent.

## *RESULTS AND DISCUSSION*

### *Synthesis and Structure Characterization of the Title Compounds*

The title compounds **5** were synthesized by the multistep route outlined in Scheme **1**.

Cyclization of 5-amino-3-methylthio-1,2-4-triazole **1** with 1,3-diones afforded the corresponding 2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidines **2**, which, when followed by oxidation with the $H_2O_2$/HOAc system, gave the key intermediates 2-metha-

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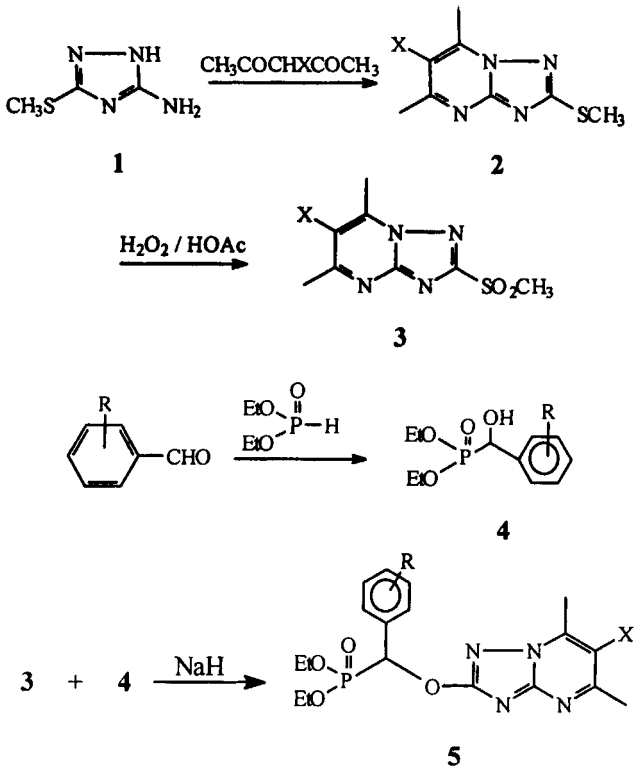

**SCHEME 1**

nesulfonyl-1,2,4-triazolo[1,5-*a*]pyrimidines **3** in good yields. Treatment of **3**, in the presence of sodium hydride, with the α-hydroxyphosphonates **4** afforded the target α-(1,2,4-triazolo[1,5-*a*]pyrimidine-2-oxyl)phosphonates **5**.

The reaction between **3** and **4** is a typical nucleophilic substitution process. It was found that two main factors affected the conversion of **3** to **5**. One is the apparent steric hindrance of the system, especially the bulky groups of the α-hydroxyphosphonates. The other one, which is predominent, is the electronic effect of the substituents R of the α-hydroxyphosphonates. Thus, the yields of products were satisfactory with most of the α-hydroxyphosphonates bearing an electron-donating group; however, when R is an electron-withdrawing or more sterically hindered group, no or only a trace of product was obtained (Table 1). To our knowledge, this is the first reported example of the synthesis of phosphonates containing the triazolo[1,5-*a*]pyrimidine heterocycle.

All the products **5** were purified by flash column chromatography on silica gel. The structures of compounds **5** were confirmed by $^1$H NMR and $^{31}$P NMR, spectroscopy, MS, and elemental analyses.

In the $^1$H NMR spectra of **5**, the corresponding methyl and methylene protons of the two ethoxy groups are magnetically nonequivalent and therefore display two sets of signals. The proton in the P–C–O moiety exhibits a double peak due to the coupling effects of the phosphorus atom. The $^1$H NMR resonance of the protons in the heterocycle moiety have a similar regularity to other triazolo[1,5-*a*]pyrimidine derivatives and can be clearly assigned. In addition, the EI-MS spectra of **5** demonstrate the existence of the molecular ion peaks ($M^+$, ~20%). All the fragmentation ions were consistent with their structures and can be clearly assigned. For example, compound **5b**, under electron impact, gave the molecular ion peak *m/z* (%): 404 (25.50), and the other conspicuous peaks: 367 (100.00), 213 (15.55), 105 (70.06), 65 (12.64).

**TABLE 1** Physical Constants for α-(1,2,4-triazolo[1,5-a]pyrimidine-2-oxyl)phosphonates **5**

| *No.* | *R* | *X* | *Formula* | *m.p.* (°C) | *Reaction Solvent** | *Reaction Time* (*hr*) | Yields (%)** |
|---|---|---|---|---|---|---|---|
| 5a | H | H | $C_{18}H_{23}N_4P$ | 84 ~ 86 | A | 14 | 70.1 |
| 5b | 4-$CH_3$ | H | $C_{19}H_{25}N_4O_4P$ | 113 ~ 114 | A | 16 | 72.3 |
| 5c | 4-$CH_3O$ | H | $C_{19}H_{25}N_4O_5P$ | 86 ~ 89 | A | 19.5 | 78.6 |
| 5d | 4-$CH_3$ | $CH_3$ | $C_{20}H_{27}N_4O_4P$ | 108 ~ 109 | B | 17 | 67.2 |
| 5e | 2-$NO_2$ | H | $C_{18}H_{22}N_5O_6P$ | – | B | 20 | 0 |
| 5f | 2,4-$Cl_2$ | H | $C_{18}H_{21}N_4O_4Cl_2P$ | – | B | 18 | trace |
| 5g | 4-Cl | H | $C_{18}H_{22}N_4O_4ClP$ | 129 ~ 122 | A | 15 | 58.7 |
| 5h | 2-Cl | $CH_3$ | $C_{19}H_{24}N_4O_4ClP$ | – | A | 16 | trace |
| 5i | 3-Br | $CH_3$ | $C_{19}H_{24}N_4O_4BrP$ | 102 ~ 103.5 | A | 16 | 56.5 |
| 5j | 3-Br | H | $C_{18}H_{22}N_4O_4BrP$ | 117 ~ 119 | A | 15.5 | 63.8 |
| 5k | 2-Cl | H | $C_{18}H_{22}N_4O_4ClP$ | 115 ~ 117 | B | 16 | 35.6 |
| 5l | H | $CH_3$ | $C_{19}H_{25}N_4O_4P$ | 78 ~ 80 | A | 18 | 68.7 |
| 5m | 4-$CH_3O$ | $CH_3$ | $C_{20}H_{27}N_4O_5P$ | 82 ~ 83 | A | 15 | 70.3 |
| 5n | 2-F | H | $C_{18}H_{22}N_4O_4FP$ | 101 ~ 103 | B | 17 | 47.8 |
| 5o | 2-F | $CH_3$ | $C_{19}H_{24}N_4O_4FP$ | 96–97 | 13 | 18 | 39.5 |

*A; benzene; B; 1,4-dioxane; **isolated yield based on α-hydroxyphosphonates **4**

**TABLE 2** Spectral and Analytical Data of Compounds 5

| No. | $^{31}$PNMR ($\delta$, ppm) | $^{1}$HNMR (TMS, $CDCl_3$, $\delta$, ppm) | Analysis (%) Calcd/Found | | |
|---|---|---|---|---|---|
| | | | C | H | N |
| 5a | 16.504 | 1.13 ~ 1.22 (m, 6H, $2CH_3$), 2.49 (s, 3H, $CH_3$), 2.58 (s, 3H, $CH_3$), 4.04 ~ 4.08 (m, 4H, $2CH_2$), 6.33 (d, 1H, CH, J = 13.3 Hz), 6.62 (s, 1H, CH), 7.24 ~ 7.56 (m, 5H, $C_6H_5$). | 55.38 (55.96) | 5.90 (5.85) | 14.36 (14.65) |
| 5b | 16.798 | 1.14 ~ 1.25 (m, 6H, $2CH_3$), 2.26 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 2.52 (s, 3H, $CH_3$), 4.08 ~ 4.12 (m, 4H, $2CH_2$), 6.40 (d, 1H, CH, J = 13.4Hz), 6.66 (s, 1H, CH), 7.06 ~ 7.60 (m, 4H, $C_6H_4$). | 56.43 (56.58) | 6.19 (6.31) | 13.86 (14.21) |
| 5c | 16.345 | 1.17 ~ 1.26 (m, 6H, $2CH_3$), 2.58 (s, 3H, $CH_3$), 2.63 (s, 3H, $CH_3$), 3.78 (s, 3H, $CH_3$), 4.11 ~ 4.14 (m, 4H, $2CH_2$), 6.36 (d, 1H, CH, J = 13.3Hz), 6.70 (s, 1H, CH), 6.88 ~ 7.60 (m, 4H, $C_6H_4$). | 54.29 (53.82) | 5.95 (5.65) | 13.33 (13.30) |
| 5d | 16.683 | 1.12 ~ 1.23 (m, 6H, $2CH_3$), 2.25 (s, 3H, $CH_3$), 2.47 (s, 3H, $CH_3$), 2.51 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 4.07 ~ 4.11 (m, 4H, $2CH_2$), 6.42 (d, 1H, CH, J = 13.3Hz), 7.04 ~ 7.59 (m, 4H, $C_6H_4$). | 57.42 (57.38) | 6.46 (6.31) | 13.39 (13.21) |
| 5g | 15.745 | 1.16 ~ 1.27 (m, 6H, $2CH_3$), 2.48 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 4.09 ~ 4.13 (m, 4H, $2CH_2$), 6.40 (d, 1H, CH, J = 13.3Hz), 6.66 (s, 1H, CH), 7.08 ~ 7.60 (m, 4H, $C_6H_4$ | 50.88 (50.67) | 5.18 (5.42) | 13.19 (13.31) |
| 5i | 16.579 | 1.14 ~ 1.25 (m, 6H, $2CH_3$), 2.44 (s, 3H, $CH_3$), 2.51 (s, 3H, $CH_3$), 2.57 (s, 3H, $CH_3$), 4.06 ~ 4.11 (m, 4H, $2CH_2$), 6.43 (d, 1H, CH, J = 13.1Hz), 7.10 ~ 7.64 (m, 4H, $C_6H_4$). | 47.20 (47.46) | 4.96 (5.12) | 11.59 (11.73) |
| 5j | 16.284 | 1.16 ~ 1.28 (m, 6H, $2CH_3$), 2.47 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 4.07 ~ 4.11 (m, 4H, $2CH_2$), 6.40 (d, 1H, CH, J = 13.1Hz), 6.64 (s, 1H, CH), 7.09 ~ 7.62 (m, 4H, $C_6H_4$). | 46.05 (46.32) | 4.69 (4.81) | 11.94 (11.67) |
| 5k | 16.931 | 1.15 ~ 1.29 (m, 6H, $2CH_3$), 2.43 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 4.09 ~ 4.15 (m, 4H, $2CH_2$), 6.41 (d, 1H, CH, J = 13.2Hz), 6.63 (s, 1H, CH), 7.11 ~ 7.64 (m, 4H, $C_6H_4$). | 50.88 (50.59) | 5.18 (5.46) | 13.19 (13.54) |
| 5l | 15.872 | 1.11 ~ 1.23 (m, 6H, $2CH_3$), 2.48 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 2.59 (s, 3H, $CH_3$), 4.08 ~ 4.11 (m, 4H, $2CH_2$), 6.39 (d, 1H, CH, J = 13.3Hz), 7.02 ~ 7.59 (m, 5H, $C_6H_5$). | 56.43 (56.74) | 6.18 (6.52) | 13.86 (14.02) |
| 5m | 16.864 | 1.20 ~ 1.28 (m, 6H, $2CH_3$), 2.50 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 2.62 (s, 3H, $CH_3$), 3.82 (s, 3H, $CH_3$), 4.09 ~ 4.12 (m, 4H, $2CH_2$), 6.38 (d, 1H, CH, J = 13.3Hz), 6.90 ~ 7.66 (m, 4H, $C_6H_4$). | 55.29 (54.97) | 6.22 (6.49) | 12.90 (12.68) |
| 5n | 16.473 | 1.19 ~ 1.30 (m, 6H, $2CH_3$), 2.45 (s, 3H, $CH_3$), 2.57 (s, 3H, $CH_3$), 4.12 ~ 4.16 (m, 4H, $2CH_2$), 6.43 (d, 1H, CH, J = 13.1Hz), 6.69 (s, 1H, CH), 7.18 ~ 7.72 (m, 4H, $C_6H_4$). | 52.94 (53.18) | 5.39 (5.74) | 13.72 (13.49) |
| 5o | 16.289 | 1.17 ~ 1.29 (m, 6H, $2CH_3$), 2.47 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 2.59 (s, 3H, $CH_3$), 4.10 ~ 4.15 (m, 4H, $2CH_2$), 6.42 (d, 1H, CH, J = 13.1Hz), 7.15 ~ 7.64 (m, 4H, $C_6H_4$). | 54.02 (54.35) | 5.68 (5.41) | 13.27 (13.68) |

## *Biological Activities*

The preliminary screening tests were carried out by spraying the seedling of rape with the solutions of compounds **5**, respectively, in acetone at the dosage of 1500g/ha. It was found that most of the products showed an inhibition effect (> 50%) against rape rather than barnard grass. For example, the inhibitory rate of compound **5a** and **5n** to rape was 84.2% and 98.7%, respectively. Further assay of enzyme activity according to a previous method [11] showed that **5** also displayed ALS inhibition activities at the concentration of 100 ppm. For example, the inhibiting effects of compounds **5a**, **5b**, and **5g** were, respectively, 0.7006, 0.5472, and 0.8103 times at 100 ppm as great as that of the contrast compound DPX-4189, which is a commercial herbicide and has high potent ALS-inhibiting activity. Although $\alpha$-heterocycleoxylphosphonate derivatives have been reported to possess various biological activities, as far as we know there is no report on their ALS-inhibition activity. Further study on the ALS-inhibition activity of the products is underway.

## *EXPERIMENTAL*

### *Instruments*

NMR spectra were taken on a BRUKER AC-P200 spectrometer. Tetramethylsilane (TMS) was used as an internal standard for $^1$H NMR, and 85% $H_3PO_4$ was used as an external standard for $^{31}$P NMR. The nuclei that are deshielded relative to their respective standards are assigned a positive chemical shift. Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Elemental analyses were carried out on a Yana MT-3 instrument.

$\alpha$-Hydroxyphosphonates **4** [9] and 5-amino-3-methylthio-1,2,4-triazoles **1** [10] were prepared according to the conventional methods.

*General Procedure for the Syntheses of 2-Methylthio-1,2,4-triazolo[1,5-***a***]pyrimidines* **2.** A solution of 0.5 mol of 5-amino-3-methylthio-1,2,4-triazoles **1** and 0.5 mol of 1,3-diketone in 150 mL of glacial AcOH was heated at reflux for 18 hours. The reaction mixture was cooled to room temperature and evaporated at reduced pressure. The residual solid was recrystallized from ethanol to afford the pure products as white crystals. **2a**: X = H, yield 90%, m.p. 154–156°C. $^1$H NMR $\delta$ ($CDCl_3$) 2.52(s,3H,$CH_3$), 2.64(s,3H,$CH_3$), 2.68(s, 3H,$CH_3$), 6.72(s, 1H,CH). **2b:** X = $CH_3$, yield 87%, m.p. 148–149°C. $^1$HNMR $\delta$($CDCl_3$) 2.26 (s,3H, $CH_3$), 2.50 (s,3H,$CH_3$), 2.64 (s,3H,$CH_3$), 2.69 (s, 3H, $CH_3$).

*General Procedure for the Syntheses of 2-Methylsulfonyl-1,2,4-Triazolo[1,5-a*]pyrimidines **3.** To a stirred mixture of 27 mmol of 2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidines **2** and 20 mL of acetic acid, 0.08 mmol of sodium tungstate dihydrate was added at room temperature. To the vigorously stirred solution, 6.12 g (54mmol) of hydrogen peroxide as a 30% aqueous solution was added slowly at 40°C. Stirring was continued at 50°C for an additional 3 hours. The excess hydrogen peroxide was destroyed by the addition of an aqueous solution of sodium sulfite, and the solid was filtered off and recrystallized from ethanol to give the pure products as colorless crystals. **3a:** X = H, yield 85%, m.p. 186–188°C. $^1$H NMR $\delta$ ($CDCl_3$) 2.53(s,3H,$CH_3$), 2.64(s,3H, $CH_3$), 3.36(s,3H, $CH_3$), 6.71(s,1H,CH). 3b: X = $CH_3$, yield 83%, m.p. 179–180°C. $^1$H NMR $\delta$ ($CDCl_3$) 2.26(s, 3H, $CH_3$), 2.52(s,3H,$CH_3$), 2.65(s, 3H, $CH_3$), 3.37(s,3H,$CH_3$).

*General Procedure for the Synthesis of* $\alpha$*-(1,2,4-triazolo[1,5-***a***]pyrimidine-2-oxyl)phosphonate Derivatives* **5.** A mixture of 2 mmol of each $\alpha$-hydroxyphosphonate **4** and 2 mmol of sodium hydride in 20 mL of anhydrous 1,4-dioxane or benzene was stirred at room temperature in a stream of nitrogen for approximately 20 minutes. Then, 2 mmol of each 2-methanesulfonyl-1,2,4-triazolo[1,5-*a*]pyrimidine **3** was added, and the resulting reaction mixture was refluxed for about 10–20 hours. After filtration, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/acetone, v/v 8:5, as the eluent).

The physical constants and $^1$H NMR, $^{31}$P NMR, and elemental analyses results for compounds **5** are listed in Tables **1** and **2**, respectively.

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