SYNTHESIS AND HERBICIDAL ACTIVITY OF NOVEL α-(1,2,4-TRIAZOLO[1,5-a]PYRIMIDINE-2-OXYL)PHOSPHONATES

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Abstract: Some novel phosphonate derivatives containing triazolo[1,5-a]pyrimidine moieties have been synthesized in good yields by the nucleophilic substitution between α-hydroxyphosphonates and 2-methanesulfonyl-1,2,4-triazolo[1,5-a]pyrimidines. The structure has been comfirmed by elementary analyses , NMR and MS. The results of preliminary bioassay indicates that the title compounds possess selective herbicidal activity.

Introduction

Triazolo[1,5-a]pyrimidines are important heterocycles bearing good biological activities (1). Some of them have shown superhigh herbicidal activities, such as metosulam and flumetsulam. They are also involved in drugs (2-5). Therefore, various triazolo[1,5-a]pyrimidines and their derivatives are in great demand now. In our work searching for herbicidal heterocycles (6-7), we designed and synthesized a novel kinds of triazolo[1,5-a]pyrimidine (thio)ether derivatives 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 decades (8).

This communication deals with the design and synthesis of another kinds of novel phosphonate derivatives containing triazolo[1,5-a]pyrimidine moieties.

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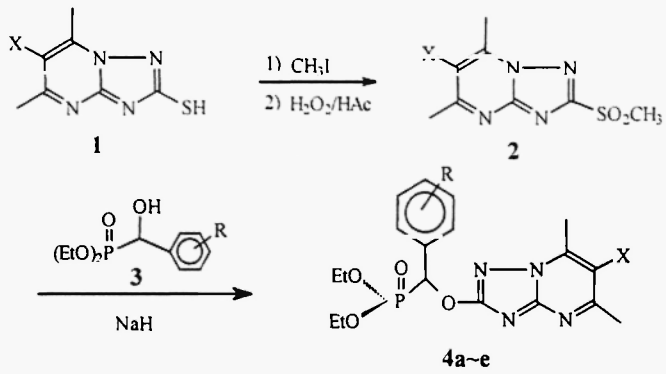
Results and Discussion

The synthetic route are outlined in Scheme **1**. Treatment of the easily accessible 2-mercapto-1,2,4-triazolo[1,5-a]pyrimidines **1** with iodomethane in the presence of sodium hydroxide followed by oxidation with H_2O_2/HAc system afforded the key intermediates. 2-methanesulfonyl-1,2,4-triazolo[1,5-a]pyrimidines **2**. which were allowed to react with α-hydroxyphosphonates **3** in the presence of sodium hydride to give the target α-(1,2,4-triazolo[1,5-a]pyrimidine-2-oxyl)phosphonates **4a~h** in good yields.



SCHEME 1

The reaction between **2** and **3** is a typical nucleophilic substitution process. The yields of products were satisfactory with most of the α-hydroxyphosphonates used, however when R are electron-withdrawing or more steric groups, no or trace product was obtained determined by GC-MS due to their weak nucleaphilicity and steric hindrance (See Table).

Table Preparation of α-(1,2,4-triazolo[1,5-a]pyrimidine-2-oxyl)phosphonates 4

Compounds	R	X	Reaction Solvent	Reaction Time	Yields(%)**
4a	H	H	A*	14hr	70.1
4b	4-CH_3	H	A	16hr	72.3
4c	4-CH_3O	H	A	19.5hr	78.6
4d	4-CH_3	CH_3	B	17hr	67.2
4e	2-NO_2	H	B	20hr	0
4f	2,4-Cl_2	H	B	18hr	trace
4g	4-Cl	H	A	15hr	48.7
4h	2-Cl	CH_3	A	16hr	trace

* A: benzene; B: 1,4-dioxane; ** isolated yield based on α-hydroxyphosphonates 3

The structures of compounds **4a~e** were confirmed by ^{1}HNMR, ^{31}PNMR, MS spectroscopy and elemental analyses. In the ^{1}HNMR spectra of **4**, the corresponding methyl and methylene protons of the two ethoxy groups are magnetically nonequivalent and therefore display two sets of signals. The α-methylidyne proton in the P-C-O moiety exhibits a double peak due to the coupling effects of the phosphorus atom. The ^{1}HNMR of the protons in the heterocycle moiety have the similar regularity to the other triazolo[1,5-a]pyrimidine derivatives and can be cleary assigned. In addition, the EI-MS spectra of **4** displayed the molecular ion peaks and all the fragmentation products were consistent with their structures.

Preliminary bioassays indicated that the phosphonates derivatives **4** gave 82~100% control of rape at a rate of 1500g/ha. Further assay of enzyme activity showed that **4** also displayed ALS inhibition activities to some extent. To our knowledge, this is the first reported example of the synthesis of phosphonates containing triazolo[1,5-a]pyrimidine heterocycles exhibiting ALS inhibition activities.

Experimental

NMR spectra were taken on a BRUKER AC-P200 spectrometer. Tetramethylsilane (TMS) was used as an internal standard for ^{1}HNMR, and 85% H_3PO_4 was used as an external standard for ^{31}PNMR. 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.

α-Hydroxy phosphonates **3** (9)and 2-methanesulfonyl-1,2,4-triazolo[1,5-a]pyrimidines **2** (10) were prepared according to the conventional methods.

General Procedure for the Synthesis of α-(1,2,4-triazolo[1,5-a]pyrimidine-2-oxyl)phos-phonate derivatives **4a~e**:

A mixture of 2 mmol of α-Hydroxy phosphonates **3** and 2mmol of sodium hydride in 20mL of anhydrous 1,4-dioxane or benzene was stirred at room temperature in a stream of nitrogen for approximately 20 min. Then, 2mmol of 2-methanesulfonyl-1,2,4-triazolo[1,5-a]pyrimidines **2** was added, the resulted reaction mixture was refluxed for about 10~20h. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silical gel (petroleum ether/acetone, v/v 8:5, as the eluent).

^{1}HNMR, ^{31}PNMR, MS and elemental analyses for some compounds **4**:

4a: ^{1}HNMR($CDCl_3$,ppm): δ 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=13.3Hz), 6.62(s,1H,CH), 7.24~7.56(m,5H, C_6H_5). ^{31}PNMR($CDCl_3$,ppm): δ 16.504. Anal. cacld. for $C_{18}H_{23}N_4O_4P$: C, 55.38; H, 5.90; N, 14.36. Found: C, 55.96, H: 5.85; N,14.65. EI-MS(m/z, %): 390(M^+, 20.0), 253(100), 210(9.2), 165(8.0), 91(27.2), 65(9.4).

4b: ^{1}HNMR($CDCl_3$,ppm): δ 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). ^{31}PNMR($CDCl_3$,ppm): δ

16.798. Anal. cacld. for $C_{19}H_{25}N_4O_4P$: C, 56.43; H, 6.19; N, 13.86. Found: C, 56.58, H; 6.31; N,14.21. EI-MS(m/z, %): 404(M^+, 21.2), 267(100), 213(16.1), 105(70.0), 65(13.2).

4c : ^{1}HNMR($CDCl_3$,ppm) : δ 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). ^{31}PNMR($CDCl_3$,ppm): δ 16.345. Anal. cacld. for $C_{19}H_{25}N_4O_5P$: C, 54.29; H, 5.95; N, 13.33. Found: C, 53.82, H; 5.65; N,13.30.

4d : ^{1}HNMR($CDCl_3$,ppm) : δ 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). ^{31}PNMR($CDCl_3$,ppm): δ 16.683. Anal. cacld. for $C_{20}H_{27}N_4O_4P$: C, 57.42; H, 6.46; N, 13.39. Found: C, 57.38, H; 6.31; N,13.21.

4g : ^{1}HNMR($CDCl_3$,ppm) : δ 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). ^{31}PNMR($CDCl_3$,ppm): δ 15.745. Anal. cacld. for $C_{18}H_{22}N_4O_4ClP$: C, 50.88; H, 5.18; N, 13.99. Found: C, 50.67, H; 5.42; N,13.31.

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