Heteroatom Chemistry
Volume 14, Number 7, 2003

Syntheses and Biological Activities of *S*-1,2,4-Triazolo[1,5-*a*]pyrimidinylalkyl Dithiophosphates

Wen-Bin Chen and Gui-Yu Jin

The State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

Received 30 April 2003; revised 19 May 2003

ABSTRACT: *We introduced dithiophosphate moieties into the fused heterocyclic compound to prepare the title derivatives and characterized their structures by elemental analysis, ^1H NMR, and IR spectral data. We found that these compounds show good fungicidal and herbicidal activities and good plant growth regulation activity.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:607–611, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10198

INTRODUCTION

The substituted 1,2,4-triazolo[1,5-*a*]pyrimidines are a class of highly active herbicides [1]. Some products such as DE-498, DE-511, and TP have been commercialized. The herbicide activity is believed to be due to the inhibition of acetolacetate synthase (ALS), which participates in the synthesis of branched-chain amino acids in the plant body [2,3]. As we all know, organophosphorus compounds possess activities such as herbicides, fungicides, and insecticides, but fused heterocyclic compounds containing phosphorus are seldom reported. To find novel active compounds, we designed and synthesized the title compounds **3** (Scheme 1). The starting compounds **1** [4] and **2** [5–8] were prepared as described. Their reaction in aqueous sodium hydroxide at room temperature gave **3** (Table 2).

Correspondence to: Gui-Yu Jin; e-mail: wbchen@nankai.edu.cn.
Contract grant sponsor: National Natural Science Foundation of China.
Contract grant number: 29832050.

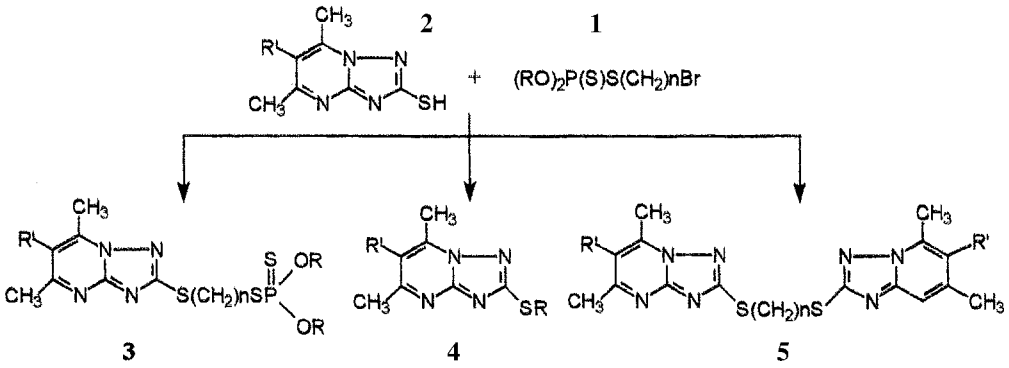
EXPERIMENTAL

^1H NMR spectra were recorded in $CDCl_3$ as solvent on an AC-P200 instrument using TMS as an internal standard. IR spectra were measured on a Nicolet 5DX IR spectrometer. Elemental analyses were conducted on an MF-3 automatic analyzer. Melting points were determined on an MP-500 melting point apparatus. All temperatures and pressures are uncorrected.

The phosphorodithioates **1** were prepared as described in literature [4] and their structures were determined by ^1H NMR spectral data (Table 1) and the triazolopyrimidines **2** were synthesized according to the known procedure [5,6].

Preparation of **3a**

To the solution of sodium hydroxide (0.09 g, 2.2 mmol) in 10 ml of water, were added 0.36 g (2.0 mmol) of **2a** and a catalytic amount of tetrabutyl ammonium bromide (TBAB) and stirred to give a clear solution. To the mixture was added **1a** in 10 ml of methanol. After being stirred overnight, the mixture was diluted with 20 ml of chloroform, the organic phase was separated, and the aqueous layer was extracted with chloroform (10 ml × 3). The combined organic phase was washed with water



SCHEME 1

(20 ml × 3) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by silicon gel chromatography with petroleum ether and ethyl acetate as elution to give the title compound **3a**.

The other compounds **3** were prepared according to the same procedure, and their structures were determined by elementary analysis, ^{1}H NMR, and IR spectral data and the compound **3f** was also characterized by X-ray diffraction. Their data are outlined in Tables 2–4.

RESULTS AND DISCUSSION

Preparation of **3**

In this reaction, we found that *n* and R have much effect on the products. When R was CH_3 and *n* was 2, the title compound **3** could not be obtained, only the by-product **4** (R = CH_3, R′ = H) was obtained. ^{1}H NMR δ (ppm, $CDCl_3$/TMS) 2.59 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 6.73 (s, 1H, CH), m.p. 155–157°C (lit. [9] 154–155°C). When R was C_2H_5 and *n* was 2, compound **3** was obtained in good yield and the by-product **4** was also obtained. When R was C_3H_7, or *i*-C_3H_7, the compounds **3** were obtained, but no by-product **4** was observed, and the other by-product **5** was separated. ^{1}H NMR δ (ppm, $CDCl_3$/TMS) 2.34 (m, 2H, $SCH_2\underline{CH_2}CH_2S$), 2.62 (s, 6H, 2 × CH_3), 2.74 (s, 6H, 2 × $\overline{CH_3}$), 3.45 (t, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 6.78 (s, 2H, 2 × CH), *m/e* = 400. When *n* was 2, the yields were higher than those when *n* was 3.

To explain these results, an ionic isomer of **1** may be anticipated, the cyclic cation of which will easily be attacked by the nucleophilic anion of **2**. The

TABLE 1 Physical Data of Phosphorodithionate **1**

	R	*n*	$n^{25}{}_D$	*Yield (%)*	*^{1}H NMR δ (ppm, $CDCL_3$/TMS)*
1a	Et	2	1.5341	46.2	1.35 (t, 6H, 2 × $\underline{CH_3}CH_2O$), 3.25 (dt, 2H, CH_2S), 3.55 (t, 2H, CH_2Br), 4.17 (dq, 4H, 2 × $CH_3\underline{CH_2}O$)
1b	Et	3	1.5262	42.3	1.35 (t, 6H, 2 × $\underline{CH_3}CH_2O$), 2.19 (m, 2H, $SCH_2\underline{CH_2}CH_2Br$), 2.98 (m, 2H, $S\underline{CH_2}CH_2CH_2Br$), 3.51 (t, 2H, $SCH_2CH_2\underline{CH_2}Br$), 4.13 (m, 4H, 2 × $CH_3\underline{CH_2}O$)
1c	*n*-Pr	2	1.5228	65.6	0.93 (t, 6H, 2 × $\underline{CH_3}CH_2CH_2O$), 1.67 (t, 4H, 2 × $CH_3\underline{CH_2}CH_2O$), 3.18 (dt, 2H, $S\underline{CH_2}CH_2Br$), 3.52 (t, 2H, $\underline{CH_2}Br$), 4.04 (m, 4H, 2 × $\underline{CH_3}CH_2\underline{CH_2}O$)
1d	*n*-Pr	3	1.5192	67.4	0.96 (t, 6H, 2 × $\underline{CH_3}CH_2CH_2O$), 1.71 (t, 4H, 2 × $CH_3\underline{CH_2}CH_2O$), 2.21 (m, 2H, $SCH_2\underline{CH_2}CH_2Br$), 3.01 (m, 2H, $S\underline{CH_2}CH_2CH_2Br$), 3.48 (t, 2H, $\underline{CH_2}Br$), 4.04 (m, 4H, 2 × $\underline{CH_3}CH_2\underline{CH_2}O$)
1e	*i*-Pr	2	1.5149	67.2	1.31 (d, 12H, 2 × $(\underline{CH_3})_2CHO$), 3.24 (m, 2H, $S\underline{CH_2}CH_2Br$), 3.49 (t, 2H, $SCH_2\underline{CH_2}Br$), 4.78 (m, 2H, 2 × $(CH_3)_2\underline{CH}O$)
1f	*i*-Pr	3	1.5122	59.8	1.33 (d, 12H, 2 × $(\underline{CH_3})_2CHO$), 2.19 (m, 2H, $SCH_2\underline{CH_2}CH_2Br$), 3.00 (dt, 2H, $S\underline{CH_2}CH_2CH_2Br$), 3.46 (t, 2H, $\underline{CH_2}Br$), 4.82 (m, 2H, 2 × $(CH_3)_2\underline{CH}O$)

TABLE 2 Physical Data of **3a–3k**

	n	*R*	*R′*	*m.p. (°C)*	*Yield (%)*	*Analysis (%, Calcd)*		
						C	*H*	*N*
3a	2	Et	H	68–70	80.4	39.74 (39.79)	5.24 (5.36)	14.03 (14.29)
3b	3	Et	H	25–27	61.6	41.49 (41.38)	5.54 (5.67)	13.75 (13.79)
3c	2	*n*-Pr	H	49–50	72.6	42.74 (42.86)	5.65 (5.95)	13.23 (13.33)
3d	3	*n*-Pr	H	36–38	56.5	44.13 (44.24)	6.38 (6.22)	12.73 (12.91)
3e	2	*i*-Pr	H	64–65	74.8	42.85 (42.86)	5.84 (5.95)	13.27 (13.33)
3f	3	*i*-Pr	H	61–63	44.9	44.43 (44.24)	6.16 (6.22)	12.66 (12.91)
3g	2	Et	Me	Thick liquid	57.9	41.30 (41.38)	5.42 (5.67)	13.78 (13.79)
3h	2	*n*-Pr	Me	Thick liquid	53.2	44.21 (44.24)	6.01 (6.22)	13.05 (12.91)
3i	3	*n*-Pr	Me	Thick liquid	48.4	45.27 (45.54)	6.34 (6.47)	12.35 (12.50)
3j	2	*i*-Pr	Me	Thick liquid	49.7	44.18 (44.24)	5.99 (6.22)	13.12 (12.91)
3k	3	*i*-Pr	Me	68–69	41.9	45.38 (45.54)	6.47 (6.47)	12.63 (12.50)

TABLE 3 IR Data of **3**

	IR (KBr or film, cm^{-1})				
	P=S	*P–S*	*P–O–C*	*C–H*	*C=C, C=N*
3a	650.9	530.8	1013.0, 1152.0, 786.3	3046.5	1628.0, 1549.9, 1442.0
3b	653.9	538.4	1006.4, 1154.6, 783.7	3037.4	1618.7, 1544.8, 1439.4
3c	657.9	542.3	973.7, 1150.0, 772.4	3039.5	1628.6, 1548.8, 1448.6
3d	657.8	540.9	978.7, 1146.2, 772.3	3047.0	1640.9, 1549.2, 1445.8
3e	648.5	553.3	985.1, 1173.9, 771.8	3036.2	1625.1, 1549.4, 1448.2
3f	651.3	542.3	984.4, 1172.6, 772.2	3067.5	1621.9, 1548.4, 1437.5
3g	654.8	537.5	1006.8, 1154.0, 764.7	–	1614.0, 1526.7, 1438.5
3h	656.3	534.6	974.5, 1158.5, 770.7	–	1612.5, 1525.5, 1460.0
3i	657.7	530.1	974.8, 1156.9, 771.2	–	1618.2, 1543.8, 1433.8
3j	649.2	538.3	985.3, 1171.7, 770.9	–	1612.7, 1525.9, 1461.2
3k	648.2	532.7	983.8, 1172.6, 770.3	–	1636.6, 1540.7, 1448.8

TABLE 4 ^{1}H NMR Spectral Data of **3**

	^{1}H NMR δ (ppm, $CDCl_3$/TMS)
3a	1.34 (t, 6H, 2 × CH_3CH_2O), 2.66, 2.77 (ds, 6H, 2 × CH_3), 3.36 (m, 2H, SCH_2CH_2SP), 3.57 (t, 2H, SCH_2CH_2SP), 4.17 (m, 4H, 2 × CH_3CH_2O), 6.87 (s, 1H, CH)
3b	1.23 (t, 6H, 2 × CH_3CH_2O), 2.09 (m, 2H, $SCH_2CH_2CH_2SP$), 2.49, 2.61 (ds, 6H, 2 × CH_3), 2.89 (dt, 2H, $SCH_2CH_2CH_2SP$), 3.24 (t, 2H, $SCH_2CH_2CH_2SP$), 4.06 (dq, 4H, 2 × CH_3CH_2O), 6.65 (s, 1H, CH)
3c	0.94 (t, 6H, 2 × $CH_3CH_2CH_2O$), 1.71 (m, 4H, 2 × $CH_3CH_2CH_2O$), 2.61, 2.72 (ds, 6H, 2 × CH_3), 3.31 (dt, 2H, SCH_2CH_2SP), 3.31 (t, 2H, SCH_2CH_2SP), 4.04 (m, 4H, 2 × $CH_3CH_2CH_2O$), 6.73 (s, 1H, CH)
3d	0.93 (t, 6H, 2 × $CH_3CH_2CH_2O$), 1.69 (m, 4H, 2 × $CH_3CH_2CH_2O$), 2.19 (m, 2H, $SCH_2CH_2CH_2SP$), 2.61, 2.71 (ds, 6H, 2 × CH_3), 3.01 (dt, 2H, $SCH_2CH_2CH_2SP$), 3.35 (t, 2H, $SCH_2CH_2CH_2SP$), 4.02 (m, 4H, 2 × $CH_3CH_2CH_2O$), 6.71 (s, 1H, CH)
3e	1.32 (d, 12H, 2 × $(CH_3)_2CHO$), 2.62, 2.72 (ds, 6H, 2 × CH_3), 3.32 (m, 2H, SCH_2CH_2SP), 3.55 (t, 2H, SCH_2CH_2SP), 4.81 (m, 2H, 2 × $(CH_3)_2CHO$), 6.75 (s, 1H, CH)
3f	1.32 (d, 12H, 2 × $(CH_3)_2CHO$), 2.19 (m, 2H, $SCH_2CH_2CH_2SP$), 2.60, 2.71 (ds, 6H, 2 × CH_3), 3.06 (m, 2H, $SCH_2CH_2CH_2SP$), 3.35 (t, 2H, $SCH_2CH_2CH_2SP$), 4.79 (m, 2H, 2 × $(CH_3)_2CHO$), 6.71 (s, 1H, CH)
3g	1.34 (t, 6H, 2 × CH_3CH_2O), 2.31, 2.62, 2.75 (ts, 9H, 3 × CH_3), 3.33 (m, 2H, SCH_2CH_2SP), 3.53 (t, 2H, SCH_2CH_2SP), 4.19 (m, 4H, 2 × CH_3CH_2O)
3h	0.94 (t, 6H, 2 × $CH_3CH_2CH_2O$), 1.73 (m, 4H, 2 × $CH_3CH_2CH_2O$), 2.29, 2.59, 2.73 (ts, 9H, 3 × CH_3), 3.28 (dt, 2H, SCH_2CH_2SP), 3.51 (t, 2H, SCH_2CH_2SP), 4.04 (m, 4H, 2 × $CH_3CH_2CH_2O$)
3i	0.93 (t, 6H, 2 × $CH_3CH_2CH_2O$), 1.72 (m, 4H, 2 × $CH_3CH_2CH_2O$), 2.18 (m, 2H, $SCH_2CH_2CH_2SP$), 2.29, 2.59, 2.73 (ts, 9H, 3 × CH_3), 2.99 (m, 2H, $SCH_2CH_2CH_2SP$), 3.34 (t, 2H, $SCH_2CH_2CH_2SP$), 4.06 (m, 4H, 2 × $CH_3CH_2CH_2O$)
3j	1.32 (d, 12H, 2 × $(CH_3)_2CHO$), 2.28, 2.59, 2.73 (ts, 9H, 3 × CH_3), 3.36 (m, 2H, SCH_2CH_2SP), 3.53 (t, 2H, SCH_2CH_2SP), 4.83 (m, 2H, 2 × $(CH_3)_2CHO$)
3k	1.32 (d, 12H, 2 × $(CH_3)_2CHO$), 2.23 (m, 2H, $SCH_2CH_2CH_2SP$), 2.29, 2.60, 2.74 (ts, 9H, 3 × CH_3), 3.07 (m, 2H, $SCH_2CH_2CH_2SP$), 3.35 (t, 2H, $SCH_2CH_2CH_2SP$), 4.79 (m, 2H, 2 × $(CH_3)_2CHO$)

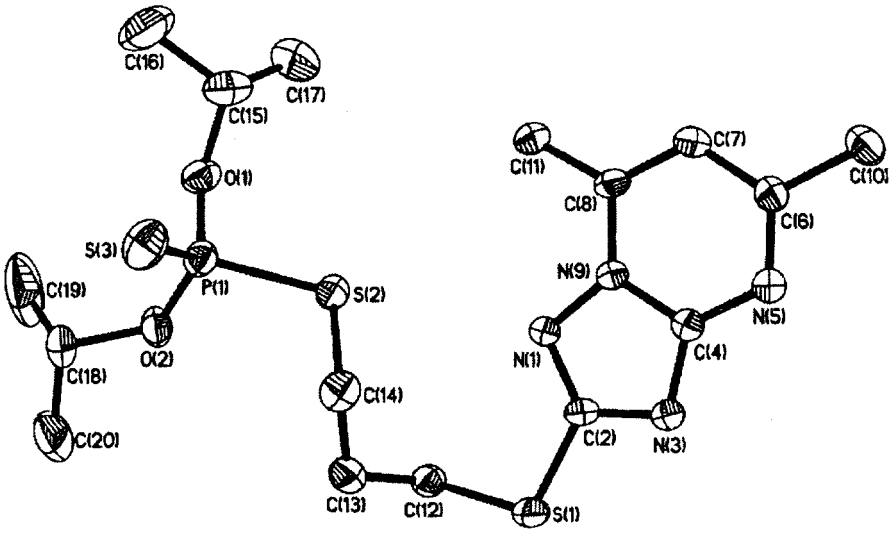


FIGURE 1 Molecular structure of **3f**.

attack of different carbon atoms of the cation will result in the products **3, 4**, and **5**. Because of different steric hindrance, the different starting materials reacted with nucleophile **2** to obtain particular products.

Structure of **3f**

Okabe et al. [10] once reported that 3-amino-5-mercapto-1,2,4-triazole reacted with acetylacetone in acetic acid on refluxing to give 1,2,4-triazolo[4,3-*a*]pyrimidine. But Novinson et al. [11] described that in this reaction, the final product should be 1,2,4-triazolo[1,5-*a*]pyrimidine **2** via ^{13}C NMR spectroscopy. Even though there was 1,2,4-triazolo[4,3-*a*]pyrimidine in the reaction, it can rearrange to **2** on mild conditions. To determine the structure, we selected compound **3f** to make a single crystal X-ray diffraction analysis (Fig. 1) [12]. We find that the fused heterocyclic structure is triazolo[1,5-*a*]pyrimidine and not triazolo[4,3-*a*]pyrimidine. The triazolopyrimidine rings are almost coplanar, and the bond lengths of N—C are shorter than that of the normal C—N bond (1.47 Å), but very close to that of the C=N bond (1.33 Å), indicating that all C and N atoms are sp^2-hybridized.

Biological Activity of **3**

From the screening results of biological activities, we found that most compounds show good fungicidal activities against *Phoma asparagi*, highly active herbicide on rape at postemergence, and good plant growth regulation to rooting of cucumber cotyledon. These data are outlined in Table 5.

TABLE 5 Biological Activities of Some Compounds **3**

	Fungicidal (50 ppm) (%)	*Herbicidal (1.5 kg/ha) (%)*		*PGR[a] (10 ppm) (%)*
	Phoma asparagi	*Rape*	*Medicago sativa Lam*	*Rooting of Cucumber Cotyledon*
3a	75.0	54.8	49.3	130.8
3b	75.0	85.4	47.8	107.7
3c	81.2	97.6	35.8	53.8
3e	75.0	63.4	19.4	100
3g	81.2	100	92.5	92.3
3k	75.0	100	86.6	84.6

[a]PGR: Plant growth regulation.

REFERENCES

[1] Kleschick, W. A.; Costales, M. J.; Dunbar, J. E.; Meikle, R. W.; Monte, W. T.; Pearson, N. R.; Snider, S. W.; Vinogradoff, A. P. Pestic Sci 1990, 29, 341–355.

[2] Nezu, Y.; Wada, N.; Saitoh, Y.; Takahashi, S.; Miyazawa, T. J. Pestic Sci 1996, 21, 293–303.

[3] Yukio, N.; Nobuhide, W.; Fumitaka, Y.; Takeshige, M.; Tsutomu, S.; Toshio, F. Pestic Sci 1998, 52, 343–353.

[4] Schrader, G. German Patent 1005058.

[5] Kozlowski, K.; Kucybala, Z.; Gaca, J.; Jurkowski, R.; Gogolin, R.; Paczkowska, B.; Hyzewicz, K. Polish Patent 126718, 1984.

[6] Leonard, E. A. G.; Frederick, K. J Chem Soc 1960, 3437–3444.

[7] Johnson, A. W.; Markham, E.; Price, P. Org Syn Coll Vol 5, 785–786.

[8] Kleschick, W. A.; Ehr, R. J.; Gerwick, B. C.; Moute, W. T.; Pearson, N. R.; Costales, M. J.; Meikle, R. W. Eur Patent EP 0142152, 1984.

[9] Thomas, N.; Robert, S.; O'Brien, D. E.; Scholten, M. B.; Miller, J. P.; Robins, R. K. J Med Chem 1982, 25(4), 420–426.

[10] Okabe, T.; Taniguchi, E.; Maekawa, K. Agric Biol Chem 1973, 37(2), 441–443.

[11] Novinson, T.; Okabe, T.; Robins, R. K.; Dea, P. J Heterocycl Chem 1975, 12, 1187–1190.

[12] CCDC 210681 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).