Heteroatom Chemistry
Volume 14, Number 6, 2003

Synthesis and Antivirus Activity of 1,3,5-Triazine Derivatives

Qingmin Wang, Gang Liu, Ruilian Shao, and Runqiu Huang

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

Received 27 March 2003; revised 4 April 2003

ABSTRACT: *Reaction of 6-phenyl-4-thioxo-1,3,5-triazine-2-one with alkyl halide in the presence of 1 equiv. of sodium hydroxide resulted in 4-alkylthio-6-phenyl-1,3,5-triazine-2-one in good yield, whereas the above reaction provided 2-alkoxyl-4-alkylthio-6-phenyl-1,3,5-triazine in the presence of 2 equiv. of sodium hydroxide. 6-Phenyl-4-thioxo-1,3,5-triazine-2-one was oxidized with hydrogen peroxide to give 6-phenyl-1,3,5-triazine-2,4-dione. Further treatment with ethyl bromoacetate or (substituted) benzyl bromides yielded 2,4-dialkoxy-6-phenyl-1,3,5-triazines. At the same time, a small amount of 2-dimethylamino-4-alkoxy-6-phenyl-1,3,5-triazines were isolated. Preliminary bioassays indicate that the title compounds possess good activities against tobacco mosaic virus.*
 Heteroatom Chem 14:542–545, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10189

INTRODUCTION

1,3,5-Triazines have attracted attention because of their marked antivirus activities [1–4]. 2,4-Dioxohexahydro-1,3,5-triazine (DHT) and 1,5-diacetyl-2,4-dioxohexahydro-1,3,5-triazine (DADHT) have been commercialized as plant virucides [5–8]. However, there is a major difficulty in using these plant virucides. They have very low solubility in water and limited solubility in common solvents, and so application of such triazines in water and as emulsible concentrates is not ordinarily feasible. Therefore, the discovery of new derivatives of 1,3,5-triazine, which might show similar or enhanced biological activity and possess favorable characteristics, could be significant. We designed and synthesized novel 1,3,5-triazine derivatives.

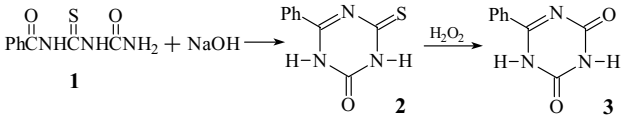
RESULTS AND DISCUSSION

1-Benzoyl-2-thiobiuret (**1**) was treated with sodium hydroxide to obtain 6-phenyl-4-thioxo-1,3,5-triazine-2-one (**2**) in 75.2% yield. Then **2** was oxidized with hydrogen peroxide to give 6-phenyl-1,3,5-triazine-2,4-dione (**3**) in 98.8% yield, as shown in Scheme 1.

Reaction of **2** with alkyl halides resulted in 4-alkylthio-6-phenyl-1,3,5-triazine-2-ones (**4**) in good yields as shown in Scheme 2 and Tables 1 and 2. Products **4a–i** were all white solids, and their structures were confirmed by ^{1}H NMR, IR spectroscopy, mass spectroscopy, and elemental analysis. The physical constants and ^{1}H NMR data of **4a–i** are listed in Tables 1 and 2. All absorption bands in IR of **4h** appear as expected. 1691.0, 1682.2, and 1663.9 cm^{-1} (s) correspond to C=O and C=N stretching absorption bands. The EI-MS of **4h** gives the molecular ion peak (353.20, M) and those of the main fragments.

However, in the presence of 2 equiv. of sodium hydroxide, the reaction with ethyl bromoacetate

Correspondence to: Runqiu Huang; e-mail: wang98h@263.net.
Contract grant sponsor: National Natural Science Foundation of China.
Contract grant number: 20002003.



SCHEME 1

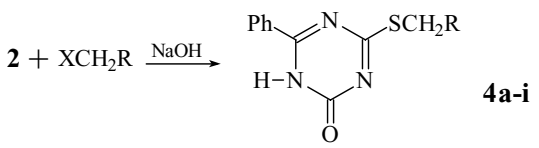
yielded the 2-alkoxyl-4-alkylthio-6-phenyl-1,3,5-triazine **5** as shown in Scheme 3.

Compound **3** underwent reaction with ethyl bromoacetate or (substituted) benzyl bromides to yield 2,4-dialkoxy-6-phenyl-1,3,5-triazines **6**. At the same time, a small amount of 2-dimethylamino-4-alkoxy-6-phenyl-1,3,5-triazines **7** were isolated as by-products (Scheme 4 and Tables 3 and 4). Compounds **6a–d** and **7a–c** were identified by IR and ^{1}H NMR spectroscopy and EI-MS and elemental analyses. All absorption bands in IR of **6d** and **7a** appear as expected. For **6d**, 1116.8 and 1064.9 cm^{-1} (s) correspond to C—O stretching. For **7a**, 1065.4 cm^{-1} (s) corresponds to C—O stretching. The EI-MS of **6d** gives the molecular ion peaks (459, M) and those of the main fragments; the EI-MS of the product **7a** gives the molecular ion peak (302.15, M) and those of the main fragments.

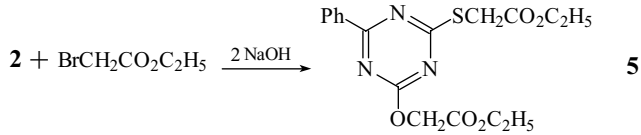
Molecular structure of compound **7a** was analyzed by X-ray diffraction (Fig. 1). Data were acquired with a Bruker SMART 1000 CCD diffractometer Mo Kα radiation ($\lambda = 0.71073$ Å), triclinic, $C_{15}H_{18}N_4O_3$ (MW 302.33), space group *P*-1, $a = 7.977(2)$ Å, $b = 10.394(3)$ Å, $c = 10.837(3)$ Å, $\alpha = 111.774(5)^\circ$, $\beta = 104.050(5)^\circ$, $\gamma = 99.446(5)^\circ$, $\mu = 0.093$ mm^{-1}, $V = 776.6(4)$ Å^3, $z = 2$, $Dx = 1.293$ Mg/m^3, F (000) = 320, $T = 293(2)$ K, $2.14^\circ \leq \theta \leq 25.03^\circ$, reflections collected 3225, observed 2718 ($I \geq 2\sigma(I)$), final R factor $R_1 = 0.0582$, $wR_2 = 0.1399$.

ANTIVIRUS ACTIVITY

Activity against tobacco mosaic virus (TMV) was tested by the conventional half-leaf method [9, 10]. Preliminary bioassays indicate that these title



SCHEME 2



SCHEME 3

compounds possess good antivirus activities. For example, at 500 ppm, inhibition rate of compounds **2, 4b**, and DHT to TMV is 40, 45, and 45%, respectively. Further studies are under way and will be reported in due course.

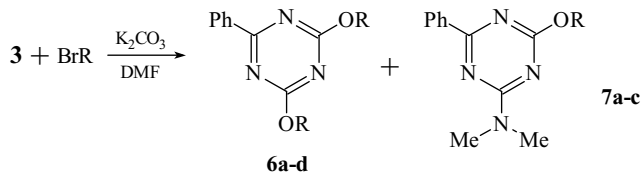
EXPERIMENTAL

All the melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu-435 spectrometer. ^{1}H NMR spectra were recorded with a Bruker AC-P200 instrument, tetramethylsilane being used as internal standards. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. Mass spectra were recorded with an HP5988A spectrometer using the EI method.

6-Phenyl-4-thioxo-1,3,5-triazine-2-one (**2**) was prepared according to the reported procedure [11].

*6-Phenyl-1,3,5-triazine-2,4-dione (**3**)*

To a stirred mixture of **2** (0.05 mol) and 1 mol/l aqueous sodium hydroxide (400 ml) was added dropwise a solution of 30% aqueous hydrogen peroxide (100 ml) at 0°C. Then the resulting mixture was stirred at 0°C for 15 min and then at room temperature for 15 min. After completion of the reaction, 1 mol/l aqueous sulfuric acid was added to adjust the pH to 7. Finally, a white solid (9.43 g) was obtained in 98.8% yield. mp 284–285°C. (Ref. [12], mp 286–288°C). Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.78; N, 22.22. Found: C, 57.32; H, 3.70; N, 22.19.



SCHEME 4

TABLE 1 Physical Constants of **4a–i**

					Found (Calcd)		
	X	*R*	*mp (°C)*	*Yield (%)*	*C*	*H*	*N*
4a	Cl	$-CH=CH_2$	157–158	74.2	58.75 (58.78)	4.30 (4.39)	17.20 (17.14)
4b	Br	C_6H_4-NO_2-p	200–201	72.7	56.40 (56.47)	3.39 (3.53)	16.20 (16.47)
4c	Br	C_6H_4-Cl-p	190–192	59.2	58.53 (58.27)	3.85 (3.64)	12.56 (12.75)
4d	Cl	2,4-Cl_2-C_6H_3-CO	200–202	83.2	52.21 (52.04)	3.00 (2.81)	10.78 (10.71)
4e	Cl	4-Cl-C_6H_4-CO	226–228	77.5	56.90 (57.06)	3.50 (3.36)	11.50 (11.75)
4f	Cl	4-F-C_6H_4-CO	228–230	76.8	59.84 (59.82)	3.09 (3.52)	11.97 (12.32)
4g	Cl	4-Br-C_6H_4-CO	223–224	74.7	50.75 (49.32)	3.24 (2.99)	10.25 (10.45)
4h	Cl	4-OCH_3-C_6H_4-CO	226–227	81.3	60.76 (61.19)	4.28 (4.25)	11.65 (11.84)
4i	Br	$-CO_2C_2H_5$	193–195	69.2	53.43 (53.61)	4.47 (4.47)	14.39 (14.43)

*4-Alkylthio-6-phenyl-1,3,5-triazine-2-ones (**4**): General Procedure*

To a stirred mixture of 0.5 mol/l aqueous sodium hydroxide (30 ml) and ethanol (70 ml) was added **2**. Then a solution of alkyl halide (12 mmol) in ethanol was added dropwise at 50°C. Following the addition, the reaction mixture was stirred for 1 h at 50°C, then cooled to room temperature, and filtered to obtain a white solid. The product **4** was purified by recrystallization or column chromatography on a silica gel.

*2-Ethoxycarbonylmethoxy-4-ethoxycarbonylmethylthio-6-phenyl-1,3,5-triazine (**5**)*

To a stirred mixture of 1 mol/l aqueous sodium hydroxide (30 ml) and ethanol (70 ml) was added **2**. Then a solution of ethyl bromoacetate (12 mmol) in ethanol was added dropwise at 50°C. Following the addition, the reaction mixture was stirred for 8 h at 50°C, then cooled to room temperature, and filtered to obtain a white solid. The product **5** was chromatographed on a silica gel column using a mixture of petroleum ether (60–90°C) and ethyl acetate as the eluent to give a while solid (0.86 g) in 45.6% yield. mp 147–149°C. Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.11; H, 5.04; N, 11.14. Found: C, 54.11; H, 5.00; N, 11.41. ^{1}H NMR (DMSO) δ 1.25 (t, 3H, CH_3, $^3J_{HH} = 4.1$ Hz), 1.31 (t, 3H, CH_3, $^3J_{HH} = 4.1$ Hz), 4.06 (s, 2H, SCH_2), 4.20–4.28 (m, 4H, CO_2CH_2), 4.83 (s, 2H, OCH_2), 7.45–8.45 (m, 5H, Ph).

*2,4-Dialkoxy-6-phenyl-1,3,5-triazines (**6**) and 2-Dimethylamino-4-alkoxy-6-phenyl-1,3,5-triazines (**7**): General Procedure*

Under a nitrogen atmosphere, to a stirred solution of **3** (5 mmol) and ethyl bromoacetate or

TABLE 2 ^{1}H NMR Data of **4a–i**

4a	2.90 (d, 2H, $-CH_2-$, $^3J_{HH} = 8.6$ Hz), 5.16–5.40 (m, 2H, $=CH_2$), 5.92–6.12 (m, 1H, CH), 7.56–8.36 (m, 5H, Ph)
4b	4.48 (s, 2H, $-CH_2-$), 7.44–8.36 (m, 9H, Ph)
4c	4.44 (s, 2H, $-CH_2-$), 7.34–8.33 (m, 9H, Ph)
4d	4.52 (s, 2H, $-CH_2-$), 7.48–8.24 (m, 8H, Ph)
4e	4.81 (s, 2H, $-CH_2-$), 7.48–8.28 (m, 9H, Ph)
4f	4.82 (s, 2H, $-CH_2-$), 7.36–8.20 (m, 9H, Ph), 12.97 (br, 1H, NH)
4g	4.88 (s, 2H, $-CH_2-$), 7.45–8.10 (m, 9H, Ph), 12.97 (br, 1H, NH)
4h	3.87 (s, 3H, OCH_3), 4.79 (s, 2H, CH_2), 7.08–8.08 (m, 9H, Ph), 13.05 (br, 1H, NH)
4i	1.16 (t, 3H, CH_3, $^3J_{HH} = 7.8$ Hz), 4.04 (s, 2H, SCH_2), 4.12 (q, 2H, OCH_2, $^3J_{HH} = 7.8$ Hz), 7.57–8.21 (m, 5H, Ph)

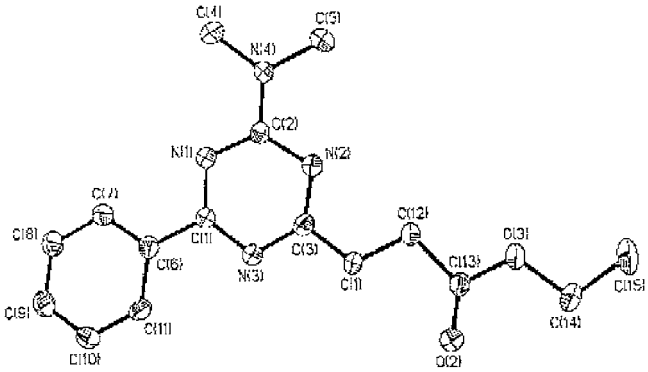


FIGURE 1 Molecular structure of compound **7a**.

TABLE 3 Physical Constants of **6a–d** and **7a–c**

				Found (Calcd)		
No	*R*	*mp (°C)*	*Yield (%)*	*C*	*H*	*N*
6a	$-CH_2CO_2C_2H_5$	73–74	61.5	56.66 (56.51)	5.11(5.26)	11.75 (11.63)
6b	$-CH_2C_6H_5$	144–146	56.2	74.62 (74.80)	5.40 (5.15)	11.36 (11.38)
6c	$-CH_2C_6H_4-Br$-p	110–111	53.7	52.20 (52.37)	3.41 (3.22)	7.68 (7.97)
6d	$-CH_2C_6H_4-NO_2$-p	136–138	65.3	60.08 (60.13)	4.01 (3.70)	15.31 (15.25)
7a	$-CH_2CO_2C_2H_5$	107–108	5.0	59.26 (59.60)	5.44 (5.96)	18.41 (18.54)
7b	$-CH_2C_6H_4-NO_2$-p	116–118	6.2	61.06 (61.54)	5.00 (4.84)	19.00 (19.94)
7c	$-CH_2CH=CH_2$	110–111	4.5	65.75 (65.62)	6.13 (6.25)	20.81 (21.87)

(substituted) benzyl bromide (12 mmol) in *N*,*N*-dimethylformamide (70 ml) was added potassium carbonate at 50°C. Then the resulting mixture was stirred at 50°C for 2 h and cooled to room temperature. Water and toluene were then added. The water phase was extracted three times with toluene. The organic phase was washed with water, and then dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated and chromatographed on a silica gel column using a mixture of petroleum ether (60–90°C) and ethyl acetate as the eluent. Finally, a white solid **6** and by-product **7** were obtained.

CCDC 208080 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).

TABLE 4 ^{1}H NMR Data of **6a–d** and **7a–c**

6a	1.26 (t, 3H, CH_3, $^3J_{HH} = 7.3$ Hz), 4.24 (q, 2H, $-COOCH_2-$, $^3J_{HH} = 7.3$ Hz), 4.99 (s, 2H, $-OCH_2COO-$), 7.28–8.44 (m, 5H, Ph)
6b	5.54 (s, 4H, CH_2), 7.34–8.49 (m, 15H, Ph)
6c	5.57 (s, 4H, CH_2), 7.32–8.62 (m, 13H, Ph)
6d	5.14 (s, 4H, CH_2), 7.10–8.19 (m, 13H, Ph)
7a	1.22 (t, 3H, CH_3, $^3J_{HH} = 7.3$ Hz), 3.15 (s, 3H, NCH_3), 3.29 (s, 3H, NCH_3), 4.21 (q, 2H, CO_2CH_2, $^3J_{HH} = 7.3$ Hz), 4.88 (s, 2H, OCH_2), 7.41–8.42 (m, 5H, Ph)
7b	3.19 (s, 3H, NCH_3), 3.33 (s, 3H, NCH_3), 5.38 (s, 2H, CH_2), 7.44–8.43 (m, 9H, Ph)
7c	3.20 (s, 3H, NCH_3), 3.32 (s, 3H, NCH_3), 5.23–5.46 (m, 2H, $=CH_2$), 5.90 (d, 2H, $=CH_2$, $^3J_{HH} = 5.3$ Hz), 6.02–6.24 (m, 1H, =CH), 7.43–8.45 (m, 5H, Ph)

REFERENCES

[1] Qu, F. Q.; Xiao, C. H.; Xu, X. J. J Wuhan Univ (Natur Sci Ed) 1999, 45(2), 143.
[2] Li, Z. G.; Huang, R. Q. Zhiwu Baohu 1999, 3, 37.
[3] Schuster, G.; Heinisch, L.; Schulze, W.; Ulbricht, H.; Willitzer, H. Phytopathol Z 1984, 111(2), 97.
[4] Esser, G.; Thust, U.; Winter, H.; Kiessling, W.; Kochmann, W.; Kramer, W.; Schmidt, H.; Steinke, U.; Steinke, W.; Voigt, D.; Schuster, G. Ger (East) DD 1986, 233, 482.
[5] Schuster, G.; Horingklee, W.; Winter, H.; Esser, G.; Steinke, U.; Kodimann, W.; Kramer, W. Acta Virol 1979, 23, 412.
[6] Schuster, G. J Phytopathol 1991, 132(2), 168.
[7] Kompiak, G. Acta Phytopathol Entomol Hung 1991, 26(1/2), 219.
[8] Schuster, G.; Huber, S. Biochem Physiol Pflanzen 1991, 187, 429.
[9] Chen, N. C. Pesticide's Bioassay Technique; Press of Beijing Agriculture University: Beijing, The People's Republic of China, 1990; p. 194.
[10] An, T. Y.; Huang, R. Q.; Yang, Z.; Zhang, D. K.; Li, G. R.; Yao, Y. C.; Gao, J. Phytochemistry 2001, 58, 1267.
[11] Basyoumi, M. N.; El-Khamry, A.-M. Bull Chem Soc Jpn 1979, 50(1/2), 3728.
[12] Joachim, G.; Jorg, N. Chem Ber 1971, 104, 1606.