Chinese Journal of Chemistry, **2004**, *22*, 1308—1312 **Article**

Synthesis, Structure and Biological Activities of Novel Triazole Compounds Containing 4,6-Dimethyl-pyrimidin-2-ylthio Group

XU, Liang-Zhong(许良忠) JIAN, Fang-Fang*(建方方) SHI, Jian-Gang(时建刚)
LI, Lin(李琳)

New Materials & Functional Coordination Chemistry Laboratory, Qingdao University of Science and Technology, Qingdao, Shandong 266042, China

Four compounds were prepared by reacting 4,6-dimethyl-2-mercaptopyrimidine with α-bromo-α-(1,2,4-triazol-1-yl)-substituted acetylbenzene. Their structures were identified by means of elemental analysis, IR, and ^{1}H NMR spectra. The single crystal structure of 2-[1-(1,2,4-triazol-1-yl)-1-*p*-methoxyphenylcarbonylmethylthio]-4,6-dimethyl-pyrimidine was also determined. It crystallizes in monoclinic system, space group $P2_1/c$, a=0.8016(2) nm, b=1.2462(3) nm, c=1.7824(4) nm, β=99.89(3)°, Z=4, V=1.7540(7) nm^3, D_c=1.346 g/cm^3, μ=0.205 mm^{-1}, F(000)=744, final R_1=0.0452. There is obviously potentially weak C—H···N intermolecular interaction between the molecules in the crystal lattice, which stabilizes the crystal structure. The result of the biological test showed that the four compounds all have some fungicidal and plant growth regulating activities.

Keywords 4,6-dimethyl-2-mercaptopyrimidine, 1,2,4-triazole, substituted-acetylbenzene, crystal structure, biological activity

Introduction

As an important type of fungicides, triazole compounds are highly efficient, low poisonous and inward absorbent.[1-3] At present, the studies on triazole derivatives are mainly concentrated on compounds with triazole as the only active group. The report on triazole compounds that contain both triazole group and other active group in a single molecule has rarely been found. Some pyrimidines have been used as highly efficient and lowly poisonous fungicides[4] in controling powdery mildew. Taking advantage of the concept of bioisosterism, four novel compounds containing pyrimidine ring which have different fungicide mechanism from triazole compounds were designed and synthesized in order to search for the new triazole compounds with higher bioactivity. In this paper, we reported the synthesis, structure characterization and biological activities of four novel triazole compounds containing 4,6-dimethyl-pyrimidine-2-ylthio group. Also, the single crystal structure of the compound 2-[1-(1,2,4-triazol-1-yl)-1-*p*-methoxyphenylcarbonylmethylthio]-4,6-dimethyl-pyrimidine was determined by X-ray diffraction study. The synthetic route of these compounds is described as Scheme 1.

Experimental

Materials and general methods

All chemicals were obtained from commercial sources and used without further purification. Elemental analyses were measured with a Perkin-Elmer 1400C analyzer. IR spectra (4000—400 cm^{-1}), as KBr pellets, were recorded on a Nicolet FT-IR 170X spectrophotometer. ^{1}H NMR spectra were measured with a JEOL FX-90Q nuclear magnetic resonance spectrometer ($CDCl_3$ as solvent, TMS as internal standard). The melting points were determined on a Yanaco MP-500 melting point apparatus.

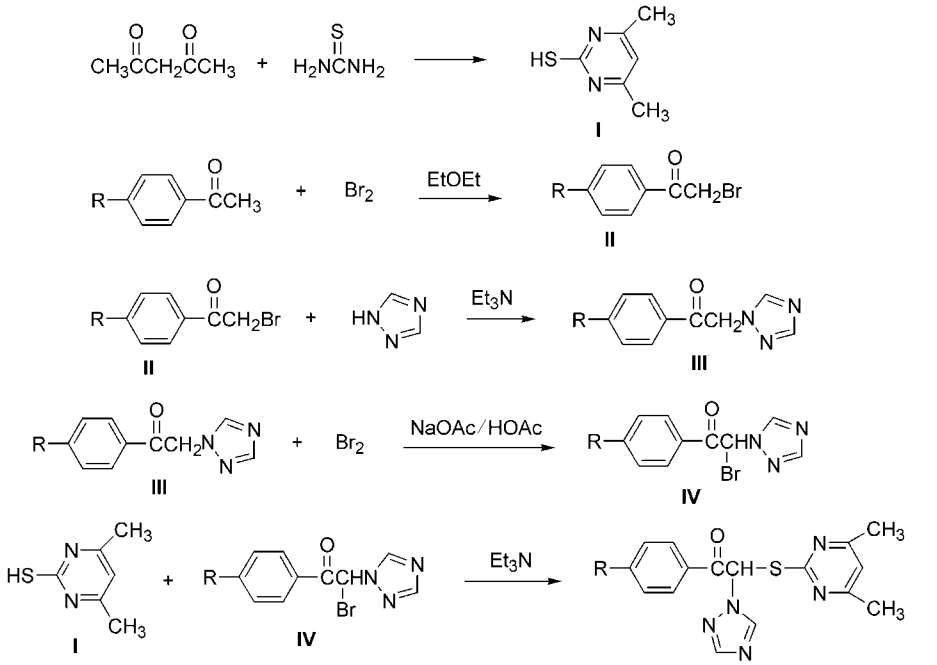
Synthesis of the target compounds

The intermediate **I** was prepared by reacting acetylacetone with thiourea according to the literature report.[5] Intermediate **II** was prepared by aryl methyl ketone reacting with bromine in anhydrous ether according to reference.[6] Intermediate **III** was prepared by the reactions of 1*H*-1,2,4-triazole with intermediate **II** in the presence of triethylamine in acetone according to literature.[7] The synthesis of the intermediate **IV** and the title four target compounds are described below.

To a 250 mL of flask were added 0.1 mol (18.7—22.1 g) of intermediate **III** in 20 mL of chloroform, 100 mL of acetic acid and 0.1 mol (8.2 g) of sodium acetate. Then 0.1 mol (8 g) of bromine was dropwise added with

* E-mail: ffj2003@163169.net
Received September 1, 2003; revised April 15, 2004; accepted July 6, 2004.
Project supported by the Educational Administration Key Project of Shandong Province (No. J01C05) and the Natural Science Foundation of Shandong Province (No. Y2002B06).

Scheme 1



stirring at room temperature. The reaction was maintained until the mixture was turned into colorless or light yellow for about 2—3 h. Then 50 mL of water and 50 mL of chloroform were added. Organic layer was successively washed with saturated sodium bicarbonate solution and brine, then dried over anhydrous magnesium sulfate and the chloroform solution containing intermediate **IV** was filtrated into a 100 mL flask. Cooled with ice-water, 30 mL of acetone solution of intermediate **I** (15 mmol) and 15 mmol of triethylamine which was used as the binding acid reagent were added under stirring, and the mixture was stirred at room temperature (about 18 ℃) for 1.5 h. The solution was filtered, concentrated and purified by flash column chromatography (silica gel, using $V_{\text{ethyl ethanoate}} : V_{\text{cyclohexane}} = 1 : 4$ as eluent) to afford the target four compounds: 2-[1-(1,2,4-triazol-1-yl)-1-phenylcarbonylmethylthio]-4,6-dimethyl-pyrimidine (**1**), 2-[1-(1,2,4-triazol-1-yl)-1-*p*-cholrophenylcarbonylmethylthio]-4,6-dimethylpyrimidine (**2**), 2-[1-(1,2,4-triazol-1-yl)-1-*p*-methylphenylmcarbonylmethylthio]-4,6-dimethylpyrimidine (**3**) and 2-[1-(1,2,4-triazol-1-yl)-1-*p*-methoxyphenylcarbonylmethylthio]-4,6-dimethylpyrimidine (**4**). Single crystals suitable for X-ray measurements of **4** were obtained by recrystallization from ethyl ethanoate/cyclohexane ($V : V = 1 : 3$) at room temperature. The physical and elemental analysis data are list in Table 1.

Determination of crystal structure of 4

In the determination of the structure of the single crystal, X-ray intensities were recorded by a Rigaku Raxis-IV diffractometer using Mo Kα radiation ($\lambda =$ 0.071073 nm) graphite monochromator. In the range of $2.00° < \theta < 27.53°$, 3257 independent reflections were obtained.

The summary of the key crystallographic information is given in Table 2. The structure was solved by direct methods using SHELXS-97 program.[8] All the non-hydrogen atoms were refined on F^2 anisotropically by full-matrix least squares method. Hydrogen atoms were located from the difference Fourier map and added to the structure calculations, but their positions were not refined. The contributions of these hydrogen atoms were included in structure-factor calculations. The final least-square cycle gave $R = 0.0452$, $R_w = 0.1152$ for 2189 reflections with $I > 2\sigma(I)$ and the weighting scheme, $w = 1/[\sigma^2(F_o^2) + (0.0696P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. The maximum and minimum difference

Table 1 The physical and elemental analysis data of compounds **1**—**4**

Compound	R	Yield/%	m.p./℃	Elemental analysis (Calcd./%)			Color
				C	H	N	
1	H	41 (13.3 g)	87—89	59.24 (59.06)	4.49 (4.56)	21.45 (21.52)	white
2	*p*-Cl	62.6 (22.5 g)	98—100	53.29 (53.41)	3.98 (3.92)	19.53 (19.46)	white
3	*p*-CH_3	53.9 (18.3 g)	120—122	60.27 (60.16)	5.02 (5.05)	50.5 4 (20.63)	white
4	*p*-CH_3O	67 (23.7 g)	147—148	57.39 (57.45)	4.87 (4.82)	19.77 (19.70)	white

Table 2 Crystal data and structure refinement for the compound **4**

Empirical formula	$C_{17}H_{17}N_5O_2S$
Formular weight	355.42
Temperature	293(2) K
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a=0.8016(2) nm
	b=1.2462(3) nm, β=99.89(3)°
	c=1.7824(4) nm
Volume	1.754(7) nm^3
Z, Calculated density	4, 1.346 Mg/m^3
Absorption coefficient	0.205 mm^{-1}
F(000)	744
Crystal size	0.22 mm×0.26 mm×0.34 mm
θ range for data collection	2.00° to 27.53°
Limiting indices	$-10\leqslant h\leqslant 10$
	$0\leqslant k\leqslant 16$
	$-23\leqslant l\leqslant 23$
Reflections collected/unique	5553/3257 [R_{int}=0.0310]
Completeness to θ=27.53°	80.5 %
Data/restraints/parameters	3257/0/227
Goodness-of-fit on F^2	1.036
Final R indices [$I>2\sigma(I)$]	R_1=0.0452, wR_2=0.1152
R indices (all data)	R_1=0.0827, wR_2=0.1251
Largest diff. peak and hole	245 and −242 e•nm^{-3}

peaks and holes are 245 and −242 e/nm^3, respectively. S = 1.036. The final position parameters of non-hydrogen atoms are given in Table 3.

Table 3 Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (nm^2×10) for the compound **4**

Atom	x	y	z	U_{eq}
S(1)	8080(1)	1914(1)	4334(1)	55(1)
O(1)	8926(1)	8329(1)	3380(1)	69(1)
O(2)	9401(2)	3265 (1)	3340(1)	61(1)
N(1)	5955(2)	3635(1)	4124(1)	41(1)
N(2)	5153(2)	3624(2)	3382(1)	52(1)
N(3)	3323(3)	4030(2)	4177(1)	59(1)
N(4)	7316(3)	513(2)	5295(1)	59(1)
N(5)	7046(2)	2347(2)	5662(1)	52(1)
C(1)	8356(4)	9060(2)	3900(2)	75(1)
C(2)	8865(3)	7257(2)	3525(1)	49(1)
C(3)	931632)	6590(2)	2963(1)	54(1)
C(4)	9286(3)	5500(2)	3050(1)	49(1)
C(5)	8792(2)	5034(2)	3691(1)	40(1)
C(6)	8388(3)	5711(2)	4251(1)	45(1)
C(7)	8430(3)	6813(2)	4176(1)	48(1)
C(8)	8733(3)	3854(2)	3744(1)	43(1)
C(9)	7741(3)	3355(2)	4320 (1)	41(1)
C(10)	4833(3)	3867(2)	4572(1)	48(1)
C(11)	3598(3)	3868(2)	3457(1)	57(1)
C(12)	7391(3)	1573(2)	5198(1)	50(1)
C(13)	6580(3)	2019(2)	6320(1)	55(1)
C(14)	6488(3)	938(2)	6481(2)	64(1)
C(15)	6863(3)	196(2)	5956(2)	63(1)
C(16)	6174(4)	2878(2)	6845(1)	71(1)
C(17)	6770(4)	−997(2)	6076(2)	90(1)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Results and discussion

Spectral characterization of target compounds

The experimental results with IR and ^{1}H NMR spectral data are shown in Table 4.

The IR spectra of compounds **1**—**4** show a little differences. The absorption peaks at about 3100 cm^{-1} are attributed to unsaturated =C—H bond stretching vibration, and the absorption peak at 900—650 cm^{-1} is assigned to the =C—H outside-plane bending vibration. The strong absorption in the range of 860 and 800 cm^{-1} is assigned to *p*-disubstituted phenyl. Corresponding absorption peak appears in this range in the compound, and the relation absorption peak frequency and *p*-disubstituted satisfy: $CH_3O>Cl>CH_3$. The strong absorption peaks at 1650—1720 cm^{-1} are assigned to carbonyl. The *p*-disubstituted phenyl effects the absorption of carbonyl, and the absorption peak frequency satisfy: $H>Cl>CH_3>CH_3O$. The conjugation with *p*-disubstituted phenyl ring can make carbonyl stretching vibration absorption change. The medium absorption band at around 1500 cm^{-1} can be attributed to C=N stretching vibration absorption of trizole ring. The weak absorption at around 705—570 cm^{-1} can be attributed to the C—S absorption band.

The ^{1}H NMR data for compounds **1**—**4** are the same as predicted. Pyrimidine ring is an isolated coupling system, and environment has no big effect on it. The chemical shift of hydrogen of pyrimidine ring is about δ 6.8. The chemical shifts of hydrogen of two methyl groups appear at around δ 2.45. The chemical shift of R group changes along with substituent variety. If R is phenyl, there are five obvious peaks at δ 7—8 and if R is *p*-substituted phenyl, it shows two peaks: one doublet at around δ 8.0 and the other doublet at 7.25. The ^{1}H NMR data are in good agreement with the crystal structures described below.

Description of the crystal structure of 4

Figure 1 shows a perspective view of compound **4** with atomic numbering scheme, and Figure 2 shows a perspective view of the crystal packing. Selected bond lengths and angles are presented in Table 5.

In compound **4**, the bond lengths and angles are generally normal in phenyl ring and triazole ring.[9,10] The bond lengths and angles in 4,6-dimethyl-pyrimidin-2-ylthio group are in good agreement with those in the earlier report.[11] The triazole ring [N(1), N(2), N(3), C(11) and C(12)] and the conjunction carbon atom C(9)

Table 4 IR and ^{1}H NMR spectral data of compounds **1**—**4**

Compound	IR/cm^{-1}						
	C—H	=C—H	C=O	C=C	C=N	=C—H	outside C—S
1	1376		1716		1499		583
2	1370	3102	1702	1589	1502	811	677
3	1370	3146, 3039	1697	1604 1578	1503	810	677
4	1422	3121, 3010	1689	1574	1504	817	677

Compound	^{1}H NMR δ
1	8.65 (s, 1H, TrH), 8.27 (s, 1H, TrH), 7.94 (s, 1H, CH), 7.26—8.27 (m, J=7.4 Hz, 5H, PhH), 6.84 (s, 1H, PyH), 2.46 (s, 6H, $PyCH_3$)
2	8.64 (s, 1H, TrH), 8.22 (s, 1H, TrH), 7.98 (s, 1H, CH), 7.26 (d, J=8.5 Hz, 2H, PhH), 8.09 (d, J=8.5 Hz, 2H, PhH), 6.85 (s, 1H, PyH), 2.46 (s, 6H, $PyCH_3$)
3	8.66 (s, 1H, TrH), 8.25 (s, 1H, TrH), 7.94 (s, 1H, CH), 7.21 (d, J=8.1 Hz, 2H, PhH), 8.04 (d, J=8.1 Hz, 2H, PhH), 6.83 (s, 1H, PyH), 2.45 (s, 6H, $PyCH_3$), 2.41 (s, 3H, $PhCH_3$)
4	8.67 (s, 1H, TrH), 8.23 (s, 1H, TrH), 7.93 (s, 1H, CH), 6.87 (d, J=8.9 Hz, 2H, PhH), 8.14 (d, J=8.9 Hz, 2H, PhH), 6.83 (s, 1H, PyH), 3.87 (s, 3H, CH_3O), 2.45 (s, 6H, $PyCH_3$)

Table 5 Selected bond lengths (nm) and angles (°) for compound **4**

S(1)—C(12)	0.1775(3)	S(1)—C(9)	0.1816(2)
O(1)—C(2)	0.1364(3)	O(1)—C(1)	0.1429(3)
O(2)—C(8)	0.1215(3)	N(1)—C(10)	0.1332
N(1)—N(2)	0.1368(2)		
C(12)-S(1)-C(9)	100.40(11)	C(2)-O(1)-C(1)	118.3(2)
O(2)-C(8)-C(9)	118.9	O(2)-C(8)-C(5)	122.9
C(5)-C(8)-C(9)	118.2	N(1)-C(9)-C(8)	110.07
N(1)-C(9)-S(1)	112.26		

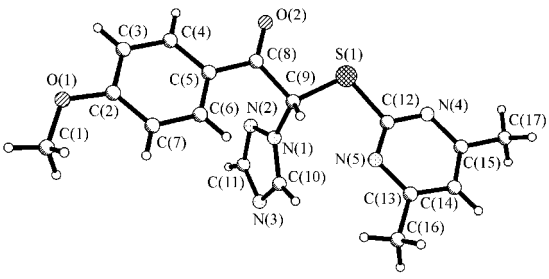


Figure 1 Molecular structure for compound **4** with the atomic numbering scheme.

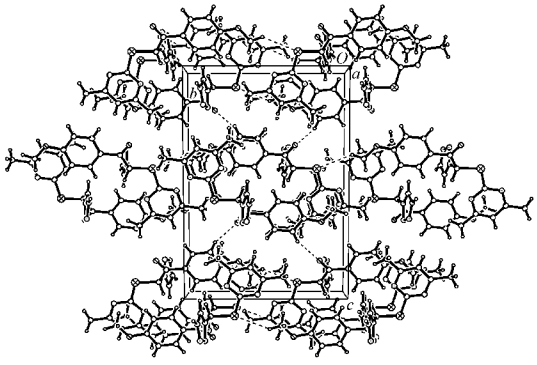


Figure 2 A view of the crystal packing down the *a*-axis for compound **4**.

are fairly coplanar, and the deviation from the least squares plane through the ring atoms is smaller than 0.0023(3) nm. Plane equation: $1.8850x+12.0802y-1.9669z=4.6792$. The phenyl ring [C(2), C(3), C(4), C(5), C(6) and C(7)], carbon atom C(8) and oxygen O(1) atom in methoxy group are also quite coplanar with plane equation: $7.1445x+0.1236y+5.2308z=8.2745$, and the largest deviation from the least squares plane through the ring atoms is 0.0026(3) nm. The dihedral angle between the triazole ring moiety and the phenyl ring is 79.22(2)°. Nine non-H atoms in 4,6-dimethyl-pyrimidin-2-ylthio group are also quite coplanar, and the largest deviation from the least squares plane is 0.0021(3) nm. Plane equation: $7.1310x+0.0394y+5.2958z=8.0433$. This plane is nearly parallel to the plane of *p*-methoxyphenyl ketone, with the dihedral angle of 0.44(2)°. The dihedral angle between the plane of 4,6-dimethyl-pyrimidin-2-ylthio group with the plane of triazole moiety is 79.64(2)°.

In the crystal lattice, there are two kinds of potentially weak C—H···N hydrogen bond intermolecular interactions.[12,13] The donor and acceptor distanc of C(3)···O(2) is 0.34092 (1) nm [symmetry code: $2-x$, $1/2+y$, $1/2-z$] with bond angle 159.42(2)° and C(6)···N(3) 0.33399(1) nm [symmetry code: $1-x$, $1-y$, $1-z$] with bond angle 139.86(2)°. The crystal packing is stabilized by these extensive hydrogen bonds.

Biological activity

The experimental results with fungicidal and plant growth regulating activities of these compounds are shown in Table 6. All of the four title compounds except compound **1** have some fungus-inhibiting activity but not significantly at 50 mg/mL. On the whole, they exhibit better efficiency on P. piricola. As far as R is concerned, compound **2** has the best comprehensive fungus-inhibiting activities with R=Cl, and the activity order for R is: Cl>CH_3>CH_3O>H. This result for the active order is possibly related with atom-fit and field-fit of action site.[14] In the same condition, triazole and pyrimidine (intermediate **I**) have no activities towards tested fungus. All of them have plant growth regulating activities. Some of them have strong regulative promoting activities. The promoting rate of compound **4** towards Rooting cucumber cotyladon reached 47.5% at 10 mg/mL. They possess lower inhibiting activity towards Wheat coleoptile elongation. The highest inhibiting rate is 6.2%.

Table 6 The fungicidal and plant grown regulating activities of compounds **1**—**4**

Compound	Fungicidal activities (c=0.005%, inhibition)					Plant growth regulating activities (c=0.005%)		
	P. zeae	A. solani	P. asparagi	P. piricola	C. arachidicala	Wheat coleoptile elougation	Rooting of cum-cumber cotyledon	Rape hypocotyl inhibition
1	0	0	0	0	0	−0.8	3.8	−1.3
2	11.5	0	0	12.3	0	−3.1	20.2	−5.9
3	7.7	0	0	9.2	0	−6.2	−12.5	1.3
4	0	0	11.1	7.7	0	−2.3	47.5	−3.6
Triazole	0	0	0	0	0	0.7	1.1	0.4
Pyrimidine	0	0	0	0	0	0.9	1.7	0.6

References

1 Anderson, N. H. *Proceeding of 5th International Congress of Pesticide Chemistry* (*IUPAC*), Kyoto, Japan, **1982**, 345.

2 Shi, Y. N.; Lu, Y. C.; Fang, J. X. *Chem. J. Chin. Univ*. **1995**, *16*, 1710.

3 Xu, L. Z.; Zhang, S. S.; Li, H. J.; Jiao, K. *Chem. Res. Chin. Univ*. **2002**, *18*, 284.

4 Tang, C. C.; Li, Y. C., *Pesticide Chemistry*, Nankai University, Press, Tianjin, **1998**, 345.

5 Lewina, J. E.; Ma, Y. Y. *J. Chem. Soc., Perkin Trans. 2* **1990**, *7*, 1077.

6 Xu, L. Z.; Jiao, K.; Zhang, S. S. *Bull Korean Chem. Soc.* **2002**, *23*, 1699

7 Shi, Y. N.; Fang, J. X.; Lu, Y. C. *Chin. J. Synth. Chem.* **1995**, *3*, 360 (in Chinese).

8 Sheldrick, G. M. *SHELXTL V5.1*, Software Reference Manual, Bruker AXS, Inc., Madison, Wisconsin, U. S. A., **1997**.

9 Ji, B. M.; Du, C. X.; Zhu, Y.; Wang, Y. *Chin. J. Struct. Chem.* **2002,** *21*, 252.

10 Liu, J. C.; Guo, G. C.; Ma, H. W.; Yang, C.; Zhou, G. W.; Zheng, F. K.; Lin, S. H.; Wang, M. S.; Huang, J. S. *Chin. J. Struct. Chem.* **2002**, *21*, 371.

11 Low, J. N.; Quesada, A.; Marchal, A.; Melguizo, M.; Nogueras, M.; Glidewell, C. *Acta Crystal.* **2002**, *C58*, o289.

12 Steiner, T. *Cryst. Rev*. **1996**, *6*, 1.

13 Jeffrey, G. A.; Maluszynska, H.; Mitra, J. *Int. J. Biol. Macromol*, **1985**, *7*, 336.

14 Liu, X. L.; Zhang, W. N.; Zhou, Y. J.; Zhu, J.; Li, K.; Lu, J. G.; Liu, N. *Chin. J. Med. Chem.* **1997**, *7*, 264 (in Chinese).

(E0309015 LU, Y. J.)