Chinese Journal of Chemistry, **2004**, *22*, 698—701 **Article**

Synthesis, Structure and Biological Activities of Novel Triazole Compounds Containing *N,N*-Dialkyldithiocarbamate Moiety

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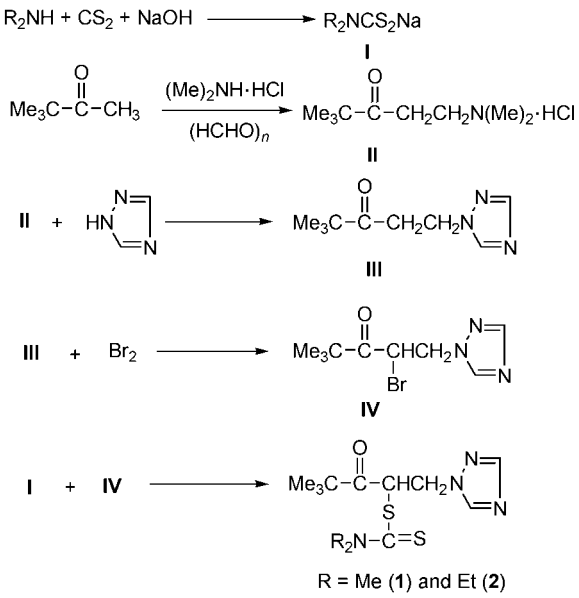
The two compounds, 2,2-dimethyl-4-*S*-(*N*,*N*-dimethyldithiocarbamato)-5-(1,2,4-triazol-1-yl)-propione (**1**) and 2,2-dimethyl-4-*S*-(*N*,*N*-diethyldithiocarbamato)-5-(1,2,4-triazol-1-yl)-3-propione (**2**), were prepared by reacting *N*,*N*-dialkyldithiocarbamate sodium with 2,2-dimethyl-4-bromo-5-(1,2,4-triazol-1-yl)-propione. Their structures were identified by elemental analysis, IR and ^{1}H NMR spectroscopy. The structure of **1** has been determined by X-ray single crystal structure analysis. It crystallizes in monoclinic system with space group $P2_1/c$, a=1.2315(3) nm, b=1.2057(2) nm, c=1.2532(3) nm, β=118.55(3)°, Z=4, V=1.6345(6) nm^3, D_c=1.221 g/cm^3, μ=0.324 mm^{-1}, F(000)=640, final R_1=0.0449. There is obvious potentially weak C—H···N intermolecular interaction in the crystal, which stabilizes the crystal structure. The result of the biological test showed that the two compounds have fungistasis and plant growth regulating activities.

Keywords *N*, *N*-dialkyldithiocarbamate, 1,2,4-triazole, 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 of triazole compounds that contain both triazole group and other active group in a single molecule has rarely been found. Dialkyl-substituted dithiocarbamate salts have also shown interesting biological effects.[4] *N*,*N*-Dialkyldithiocarbamate has been known as broad-range fungicides and having different fungicidal mechanism with triazole compounds.[5] But triazole compounds containing *N*,*N*-dimethyldithiocarbamate moiety have rarely been reported. In order to search for new triazole compounds with higher bioactivity, the two title compounds **1** and **2** (Scheme 1) were synthesized and characterized by IR, elemental analysis, ^{1}H NMR spectroscopy and single crystal X-ray diffraction analysis. The biological activities of the compounds were tested. The synthesis route is described in Scheme 1.

Scheme 1



Experimental

Materials and general methods

All chemicals were obtained from commercial sources and used without further purification. Elemental analyses were performed 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

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melting points were determined on a Yanaco MP-500 melting point apparatus.

Synthesis of the target compounds

The intermediates **I**, **II** and **III** were prepared according to the literatural report.[6-8] The synthesis of the two title compounds **1** and **2** is described below.

To a 100 mL flask 15 mmol of intermediate **III**, 25 mL of acetic acid and 15 mmol of sodium acetate were added. Then 15 mmol of bromine was dropwise added with stirring at 50—55 ℃. 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 40 mL of chloroform were added. Organic layer was successively washed with saturated sodium bicarbonate solution and brine, then dried over sodium sulfate and the chloroform solution containing about 15 mmol of intermediate **IV** was filtrated into a 100 mL flask. Cooled with ice-water, 30 mL acetone solution of intermediate **I** was 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 chromatography (silica gel, using $V_{\text{ethyl ethanoate}}$ ∶ $V_{\text{cyclohexane}}$ =1∶4 as elent) to afford the two target compounds: 2,2-dimethyl-4-*S*-(*N*,*N*-dimethyldithiocabamato)-5-(1,2,4-triazol-1-yl)-propione (**1**) and 2,2-dimethyl-4-*S*-(*N*,*N*-diethyldithiocabamato)-5-(1,2,4-triazol-1-yl)-propione (**2**). Single crystals suitable for X-ray analysis of **1** 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 1

In the determination of the structure of the single crystal, X-ray intensity data were recorded on a Rigaku Raxis-IV diffractometer using graphite monochromated Mo Kα radiation (λ=0.071073 nm). In the range of 1.88°<θ<27.53°, 3130 independent reflections were obtained. Intensities were corrected for Lorentz and polarization effects and empirical absorption, and all data were corrected using SADABS[9] program.

The structure was solved by direct methods using SHELXS-97 program.[10] All the non-hydrogen atoms were refined on F^2 anisotropically by full-matrix least squares method. The hydrogen atoms were located from the difference Fourier map, 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=0.0449, R_w=0.1043 for 2189 reflections with $I>2\sigma(I)$; the weighting scheme, $w=1/[\sigma^2(F_o^2)+(0.0601P)^2]$, where $P=(F_o^2+2F_c^2)/3$. The max and min difference peaks and holes are 235 and −191 e/nm^3, respectively. S=1.017 and $(\Delta/\sigma)_{max}$=0.0100(16). Atomic scattering factors and anomalous dispersion corrections were taken from *International Table for X-ray Crystallography*.[11] The final position parameters of non-hydrogen atoms are given in Table 2.

Results and discussion

Spectral characterization of target compounds 1 and 2

The experimental results with IR and ^{1}H NMR data are shown in Table 3.

Table 1 The physical and elemental analysis data of the two title compounds **1** and **2**

Compound	R	Yield/%	m.p./℃	Elemental analysis (Calcd)/%			Color
				C	H	N	
1	CH_3	39.4	110—112	48.06 (47.97)	6.65 (6.71)	18.61 (18.65)	white
2	C_2H_5	23.1	65—66	50.13 (50.19)	7.32 (7.36)	17.01 (17.06)	white

Table 2 Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (nm^2×10) for the compound **1**

Atom	*x*	*y*	*z*	U_{eq}[a]	Atom	*x*	*y*	*z*	U_{eq}[a]
S(1)	1951(1)	3070(1)	1513(1)	50(1)	C(4)	2115(2)	4390(2)	2262(2)	40(1)
S(2)	2885(1)	2426(1)	4148 (1)	66(1)	C(5)	2633(2)	5184(2)	1657(2)	45(1)
O(1)	1932(2)	5554 (2)	670(2)	62(1)	C(6)	3985(3)	5502(2)	2333(3)	69(1)
N(1)	2103(2)	1054(2)	2283(2)	55(1)	C(7)	4794(3)	4465(3)	2816(4)	117(1)
N(2)	906(2)	5869(2)	2552(2)	47(1)	C(8)	4335(3)	6142(3)	1503(4)	123(2)
N(3)	1408(2)	6074(2)	3759(2)	72(1)	C(9)	4128(3)	6235(3)	3377(4)	128(2)
N(4)	813(3)	7659(2)	2684(3)	81(1)	C(10)	855(2)	4762(2)	2084 (2)	48(1)
C(1)	2368(3)	129(2)	3117(3)	89(1)	C(11)	566(3)	6814(2)	1953(3)	67(1)
C(2)	1589(3)	774(2)	999(3)	81(1)	C(12)	1319(3)	7169(3)	3768(3)	81(1)
C(3)	2316(2)	2091(2)	2702(2)	42(1)					

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

Table 3 The IR and ^{1}H NMR data of the two title compounds **1** and **2**

Compound	IR/cm^{-1}						^{1}H NMR/δ
	C—H	C—H	=C—H	C=O	C=N	C=S	
1	2973 2867	1476 1380	3123	1696	1504	1141	8.04 (s, 1H, Tr-H), 7.87 (s, 1H, Tr-H), 5.57—5.75 (dd, J=4.38, 10.12 Hz, 1H,CH), 4.59—4.88 (dd, J=10.12, 13.18 Hz, 1H, CH_2), 4.26—4.48 (dd, J=4.38, 13.18 Hz, 1H, CH_2), 3.54 (s, 3H, N-CH_3), 3.34 (s, 3H, N-CH_3), 0.95 (s, 9H, Me_3C)
2	2970 2871	1423 1374	3124	1700	1502	1205	8.05 (s, 1H, Tr-H), 7.88 (s, 1H, Tr-H), 5.62—5.75 (dd, J=4.33, 10.02 Hz, 1H, CH), 4.34—4.51 (dd, J=10.02, 12.98 Hz, 1H, CH_2), 4.60—5.01 (dd, J=4.33, 12.98 Hz, 1H, CH_2), 3.67—4.00 (m, 4H, 2N-CH_2), 1.18—1.36 (t, J=7.12 Hz, 6H, 2CH_3), 0.97 (s, 9H, Me_3)

The IR spectra of the two title compounds **1** and **2** show a little difference. The strong sharp absorption peaks at 1141 cm^{-1} for **1** and at 1205 cm^{-1} for **2** are assigned to the C=S stretching vibration. The strong bands at 1696 cm^{-1} in **1** and at 1700 cm^{-1} in **2** are assigned to the stretching vibration of $\nu_{C=O}$ of carbonyl group. The C—H stretching vibrations of alkyl group are 1476, 1380 cm^{-1} for **1** and 1423, 1374 cm^{-1} for **2**, respectively, which suggests the effect on the methyl and ethyl group. The compounds **1** and **2** all exhibit characteristic strong bands at 1502—1504 (C=N) and 679—680 cm^{-1} (ν_{C-H} triazole ring) for the triazole ring and at 2970—2973 and 2867—2871 cm^{-1} for C—H stretching vibration of Me_3C group.

The ^{1}H NMR data for compounds **1** and **2** are as predicted. The chemical shifts for triazole ring protons at δ 8.04 and 8.05 for **1** and **2**, respectively.

Description of the crystal structure of 1

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

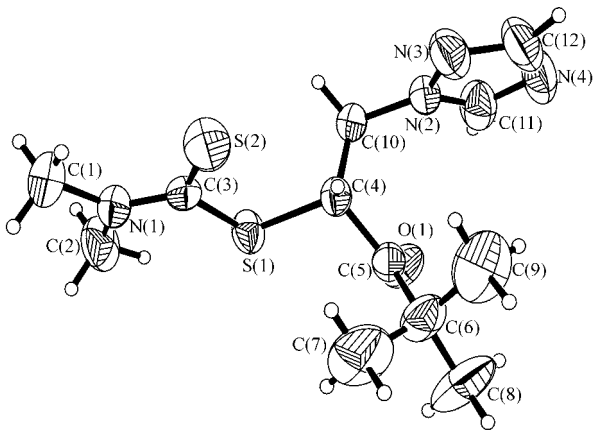

Figure 1 Molecular structure for the title compound **1** with the atomic numbering scheme.

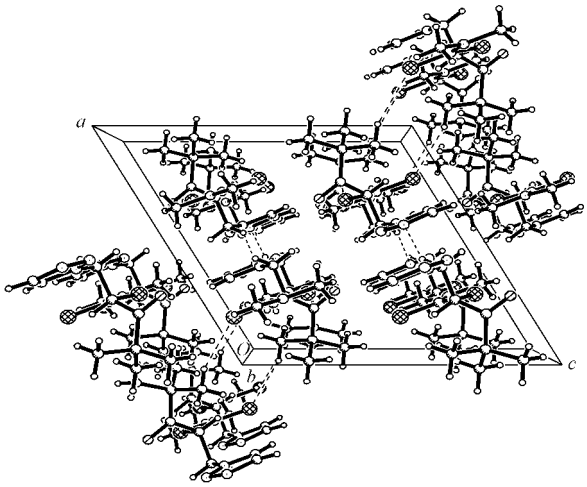

Figure 2 A view of the crystal packing down the *b*-axis for the title compound **1**.

Table 4 Selected bond lengths (nm) and angles (°) for the compound **1**

S(1)—C(3)	0.1780(2)	C(3)-S(1)-C(4)	103.16(10)
S(2)—C(3)	0.1651(2)	N(1)-C(3)-S(1)	111.57(17)
N(1)—C(3)	0.1333(3)	C(10)-C(4)-S(1)	109.17(15)
S(1)—C(4)	0.1810(2)	N(1)-C(3)-S(2)	124.36(18)
O(1)—C(5)	0.1205(3)	S(2)-C(3)-S(1)	124.05(13)

In the compound **1**, bond lengths and angles are generally normal in *tert*-butyl group and triazole ring.[12,13] The bond lengths and angles in *N*,*N*-dimethyldithiocarbamate group are in good agreement with the earlier report.[14] The triazole ring [N(2), N(3), N(4), C(11) and C(12)] and the conjunction carbon atom C(10) are fairly planar, and the deviation from the least squares plane through the ring atoms is all smaller than 0.0022(3) nm. Plane equation: $12.2229x+1.2237y-5.1890z=0.5264$. All atoms in *N*,*N*-dimethyldithiocarbamate group are also quite planar, and the largest deviation from the least squares plane is 0.0014(3) nm. Plane equation: $12.1973x-0.7720y-4.5941z=1.4329$.

The dihedral angle between the plane of *N,N*-dimethyldithiocarbamate group and the plane of triazole is 9.96(2)°.

In the crystal lattice, there is one potentially weak C—H ⋯ N hydrogen bond intermolecular interaction.[15,16] The donor and acceptor distance is C(10)⋯N(4) 0.33635(1) nm (symmetry code: $-x$, $-1/2+y$, $1/2-z$), and bond angle 147.32(2)°. The crystal packing is stabilized by these extensive hydrogen bonds.

Biological activity

Both compounds **1** and **2** show the fungus-inhibiting activity and plant growth regulator activities (See Table 5). The fungus-inhibiting activities of compound **1** and **2** against several tested fungus (*P. Zeae*, *A. Solani*, *P. Piricola* and *C. Arachidicala*) reached 20.0%—35.5% and 24.4%—45.0% at 50 μg/mL, respectively. They all show inhibiting activity towards wheat coleoptile elongation and rape hypocotyledonaey axis. The inhibiting rates for compound **1** and **2** reached 5.9%—7.8% and 11.9%—28.7% at 10 μg/mL, respectively. They all have a remarkable growth-promoting activity on cucumber cotyledon, and the growth-promoting rate for compounds **1** and **2** reached 39.3% and 83.0% at 10 μg/mL, respectively. As far as the relation of structure and activity is concerned, the compound with R being ethyl group has better biological activity than that with R being methyl group.

Table 5 The fungicidal and plant grown regulator activities of compounds **1** and **2**

Coumpound	Fungicidal activities (c=0.005%, inhibition)					Plant growth regulator activities (c=0.0001%)		
	P. zeae	*A solani*	*P. asparagi*	*P. piricola*	*C. arachidicala*	Wheat coleoptile elougation	Rooting of cucumber cotyledon	Pape hypocotyls inhibition
1	20.0	35.5	28.6	20.0	23.5	−7.8	39.3	−5.9
2	45.0	35.5	28.6	24.4	35.3	−28.7	83.0	11.9

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