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Methylation of 5-Amino-3-methylthio-1*H*-pyrazole Derivatives and Two Related Crystal Structures

REN, Xue-Ling(任雪玲)　WU, Chao(吴超)　HU, Fang-Zhong(胡方中)
ZOU, Xiao-Mao(邹小毛)　YANG, Hua-Zheng*(杨华铮)

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

5-Amino-3-methylthio-1*H*-pyrazoles are very important building blocks from which a wide variety of pyrazole derivatives can be prepared. When substituted 5-amino-3-methylthio-1*H*-pyrazole was treated with CH_3I, the methylation occurres at endocyclic two nitrogens at the same time. The ratio of isomers in products was depended upon the nature of 4-position substituent in the pyrazole ring. The products were characterized by X-ray diffraction analysis, and the ratios of isomer were explained by means of the results of *ab inito* calculation.

Keywords methylation, 5-amino-3-methylthio-1*H*-pyrazole, crystal structure, X-ray diffraction, *ab inito* method

Introduction

It has been reported that pyrazoles and their derivatives have biological properties, such as medicinal and pesticidal activity.[1-4] Our group is interested in the synthesis of new pyrazole derivatives in order to look for new herbicidal compounds.

5-Amino-3-methylthio-1*H*-pyrazoles are very important building blocks from which a wide variety of herbicidal pyrazole derivatives can be prepared. It was found that when compound **1** was treated with CH_3I, the methylation occurred at endocyclic two nitrogens of pyrazole ring, and a pair of isomers was generated at the same time (Scheme 1). The ratio of isomers in products was depended upon the nature of other substituents in the pyrazole ring. When 4-position substitute was cyano, the isomer ratio of **2a** and **3a** was 83∶100; while the 4-position substitute was ethoxycarbonyl, the ratio of **2b** and **3b** was changed to 1.13∶100 (**2b** was only shown its existence by GCD).

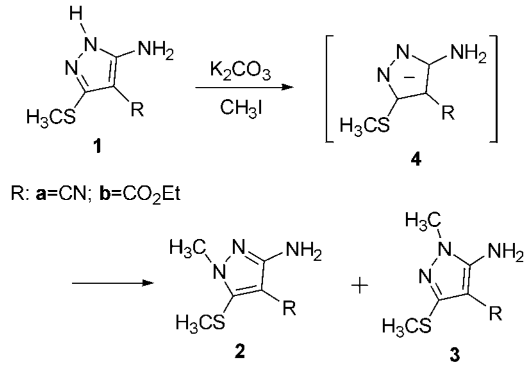
Compounds **2a** and **3b** were characterized by X-ray crystallographic analysis. In an attempt to explain the difference of methylation, *ab inito* method was used to count the electron density of two endocyclic nitrogen atoms of intermediate **4**.

Experimental

General procedure

Melting points were determined in open capillaries and uncorrected. ^1H NMR spectra were recorded on a Bruker AC-P200Q spectrometer with TMS as the internal standard. The ratios of the isomers were measured on GCD (Gas Chromatography Directory, AcqMethod SBX-2001).

Scheme 1



Preparation of compounds 2a and 3a

To a solution of 2 mmol (0.308 g) of 5-amino-4-cyano-3-methylthio-1*H*-pyrazole (**1a**) and 2 mmol (0.276 g) of potassium carbonate in 20 mL of acetone, 2.4 mmol (0.341 g) of CH_3I in 5 mL of acetone was added dropwise at room temperature and the mixture was stirred over night at the same temperature. When the reaction was completed, the solvent was removed *in vacuo* and the residue was washed with water. Crude product 0.324 g (96.3% of theory) was obtained without further purification. ^1H NMR ($CDCl_3$) δ: 2.51 (s, 3H),

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* E-mail: yanghz@public.tpt.tj.cn
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2.56 (s, 3H), 3.60 (s, 3H), 3.71 (s, 3H), 4.43 (NH_2). To separate the isomers, the crude product was purified by silica gel column chromatography [petroleum (60—90 ℃) ∶ ethyl acetate = 3 ∶ 1; *V* ∶ *V*], and the ratio of the isomers was 83 ∶ 100 (**2a** ∶ **3a**). Compound **2a** was characterized by X-ray diffraction analysis. Its yield was 0.146 g (43.81%). m.p. 121—122 ℃; ^1H NMR ($CDCl_3$) δ: 2.53 (s, 3H), 3.70 (s, 3H). Anal. calcd for $C_6H_8N_4S$: C 42.84, H 4.79, N 33.31; found C 42.51, H 4.80, N 33.18.

Preparation of compounds 2b and 3b

When 5-amino-4-ethoxycarbonyl-3-methylthio-1H-pyrazole (**1b**) (0.402 g, 2 mmol) was methyled at the same conditions as above, the crude product was 0.323 g (75.1% of theory) and 0.100 g of start material **1b** was recoverd. The ratio of the isomers was 1.13 ∶ 100 (**2b** ∶ **3b**). The great isomer **3b** was characterized by X-ray diffraction analysis. m.p. 182—183 ℃; ^1H NMR ($CDCl_3$) δ: 1.30 (t, J = 7.10 Hz, 3H), 2.48 (s, 3H), 3.58 (s, 3H), 4.25 (q, J = 7.10 Hz, 2H). Anal. calcd for $C_8H_{13}N_3O_2S$: C 44.64, H 6.09, N 19.52; found C 44.44, H 5.88, N 19.43.

Crystal structure determination

The crystals **2a** and **3b** were mounted at the tops of the glass fibers in a random orientation. The determination of the unit cell and the data collection were performed with Mo Kα (λ = 0.71073 nm) on a BRUKER SMART 1000 diffractometer using ω scan mode. The structure was solved by direct methods using SHELX-97 package at 293(2) K. Most of the non-hydrogen atoms were located from an E-map, the others were determined successively by difference Fourier syntheses. Then, the structures were refined by full-matrix least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were located theoretically and refined with riding model position parameters and fixed isotropic thermal parameters. Data of two crystals were shown in Table 1.

Calculation

The *ab initio* calculations were carried out with the Gaussian 98 software package.[5] The geometries of two intermediates **4** had been fully optimized with density functional theory (DFT) calculations.[6] For the DFT calculations, Becke's three-parameter B3LYP functional was used,[7] and three basis sets 6-31G(d) was used.[9] Hartree-Firk (HF) methods,[8] using three basis set 6-311+G(d,p),[10] had been carried out at the optimized geometries in order to calculate the electron density of two endocyclic nitrogens of intermediates **4**.

Results and discussion

The coordination of atoms for **2a** and **3b** were shown in Tables 2 and 3, and the selected bond lengths and angles in Tables 4 and 5. The molecular structures of **2a** and **3b** and their packing diagram were shown in Figures 1—4, respectively.

Table 1 Crystallographic data for **2a** and **3b**

Crystal data	**2a**	**3b**
Formula	$C_6H_8N_4S$	$C_8H_{13}N_3O_2S$
M_r	168.23	215.27
Crystal system	Triclinic	Monoclinic
Space group	P-1	$P2_1/n$
Unit cell Dimensions	a = 9.376(4) nm, α = 91.965(8)°	a = 7.076(3) nm,
	b = 9.432(4) nm, β = 95.050(8)°	b = 14.260(6) nm, β = 94.734(8)°
	c = 9.453(4) nm, γ = 101.107(7)°	c = 10.420(5) nm
V	816.0(6) nm^3	1047.8(8) nm^3
D_c	1.369 Mg/m^3	1.365 Mg/m^3
Z	2	4
μ (Mo Kα)	0.335 mm^{-1}	0.289 mm^{-1}
F(000)	352	456
Crystal size	0.30 mm × 0.20 mm × 0.15 mm	0.22 mm × 0.22 mm × 0.20 mm
θ_{max}	2.17° ≤ θ ≤ 25.02°	2.43° ≤ θ ≤ 26.44°
Reflections collected/unique	3405/2870	4813/2145
Final R indices [$I > 2\sigma(I)$]	R = 0.0494, wR = 0.0998	R = 0.0455, wR = 0.0756
	$W = 1/[\sigma^2(F_o^2) + (0.0457P)^2 + 0.0587P]$	$W = 1/[\sigma^2(F_o^2) + (0.0302P)^2]$
	$P = (F_o^2 + 2F_c^2)/3$, S = 1.017	$P = (F_o^2 + 2F_c^2)/3$, S = 0.827
Max./min. peak	0.185/−0.192 e • nm^{-3}	0.239/−0.184 e • nm^{-3}

Table 2 Atomic coordinates ($\times 10^4$) and thermal parameters ($nm^2 \times 10^3$) for **2a**

Atom	*x*	*y*	*z*	U_{eq}
S(1)	10373(1)	997(1)	2356(1)	61(1)
S(2)	5440(1)	1033(1)	2853(1)	65(1)
C(1)	9447(3)	2410(3)	2577(3)	46(1)
C(2)	8888(3)	3234(3)	1561(3)	44(1)
C(3)	8243(3)	4212(3)	2315(3)	45(1)
C(4)	9491(4)	2430(4)	5232(3)	67(1)
C(5)	8874(4)	−429(3)	1789(4)	81(1)
C(6)	8918(3)	3094(3)	81(4)	53(1)
C(8)	4500(3)	2446(3)	2591(3)	48(1)
C(9)	3876(3)	3198(3)	3563(3)	47(1)
C(10)	3241(3)	4196(3)	2781(3)	48(1)
C(11)	4688(4)	2601(3)	-32(3)	64(1)
C(12)	3939(4)	−434(4)	2866(5)	92(1)
C(13)	3798(3)	2954(3)	5014(4)	56(1)
N(1)	9145(3)	2910(3)	3828(2)	47(1)
N(2)	8401(3)	4022(2)	3697(3)	49(1)
N(3)	7538(3)	5224(3)	1778(3)	65(1)
N(4)	8919(3)	2981(3)	−1124(3)	77(1)
N(5)	4236(3)	2982(3)	1332(3)	50(1)
N(6)	3454(3)	4073(2)	1419(3)	52(1)
N(7)	2496(3)	5167(3)	3271(3)	67(1)
N(8)	3698(3)	2767(3)	6190(3)	80(1)

Table 3 Atomic coordinates ($\times 10^4$) and thermal parameters ($nm^2 \times 10^3$) for **3b**

Atom	*x*	*y*	*z*	U_{eq}
S(1)	2250(1)	7436(1)	5240(1)	56(1)
N(1)	2536(3)	4753(2)	5287(2)	43(1)
N(2)	2444(3)	5604(2)	4642(2)	44(1)
N(3)	2583(4)	4115(2)	7369(2)	60(1)
C(1)	2522(4)	4850(2)	6561(3)	40(1)
C(2)	2405(4)	5814(2)	6811(3)	38(1)
C(3)	2367(4)	6233(2)	5577(3)	40(1)
C(4)	2655(4)	3898(2)	4542(3)	53(1)
C(5)	2331(4)	6278(2)	8028(3)	42(1)
C(6)	2380(5)	6045(2)	10311(2)	53(1)
C(7)	2503(5)	5228(2)	11222(3)	62(1)
C(8)	2213(5)	7418(2)	3514(3)	69(1)
O(1)	2176(3)	7117(1)	8189(2)	62(1)
O(2)	2434(3)	5666(1)	9022(2)	49(1)

Table 4 Selected bond lengths (nm) and selected angles (°) for **2a**

S(1)—C(1)	1.742(3)	S(1)—C(5)	1.778(3)
C(1)—N(1)	1.331(4)	C(1)—C(2)	1.386(4)
C(3)—N(2)	1.324(3)	C(3)—N(3)	1.350(3)
N(1)—N(2)	1.371(3)	C(6)—N(4)	1.141(4)
S(2)—C(8)	1.746(3)	S(2)—C(12)	1.775(4)
C(2)—C(3)	1.404(4)	C(2)—C(6)	1.404(4)
C(4)—N(1)	1.447(3)		

C(1)-S(1)-C(5)	99.81(15)	C(8)-S(2)-C(12)	99.72(15)
N(1)-C(1)-S(1)	124.4(2)	C(2)-C(1)-S(1)	129.3(2)
C(1)-C(2)-C(6)	127.3(3)	C(3)-C(2)-C(6)	127.0(3)
N(2)-C(3)-C(2)	110.5(2)	N(3)-C(3)-C(2)	127.5(3)
N(5)-C(8)-S(2)	123.9(2)	C(9)-C(8)-S(2)	129.4(2)
C(1)-N(1)-C(4)	128.8(3)	N(2)-N(1)-C(4)	118.8(2)
N(1)-C(1)-C(2)	106.3(2)	N(4)-C(6)-C(2)	178.9(3)
C(1)-C(2)-C(3)	105.7(3)	C(1)-N(1)-N(2)	112.3(2)
N(2)-C(3)-N(3)	121.9(3)	C(3)-N(2)-N(1)	105.1(2)

Table 5 Selected bond lengths (nm) and selected angles (°) for **3b**

S(1)—C(3)	1.751(3)	S(1)—C(8)	1.797(3)
N(1)—C(4)	1.451(3)	N(2)—C(3)	1.329(3)
C(2)—C(3)	1.417(3)	C(2)—C(5)	1.435(3)
C(6)—O(2)	1.451(3)	C(6)—C(7)	1.500(4)
N(1)—C(1)	1.336(3)	N(1)—N(2)	1.387(3)
N(3)—C(1)	1.344(3)	C(1)—C(2)	1.402(3)
C(5)—O(1)	1.214(3)	C(5)—O(2)	1.352(3)

C(3)-S(1)-C(8)	100.54(14)	C(1)-N(1)-N(2)	112.7(2)
N(2)-N(1)-C(4)	118.6(2)	C(3)-N(2)-N(1)	103.9(2)
N(1)-C(1)-C(2)	107.0(2)	N(3)-C(1)-C(2)	130.4(3)
C(1)-C(2)-C(5)	128.5(3)	C(3)-C(2)-C(5)	127.4(2)
N(2)-C(3)-S(1)	121.3(2)	C(2)-C(3)-S(1)	126.3(2)
O(1)-C(5)-C(2)	125.9(3)	O(2)-C(5)-C(2)	112.1(3)
C(5)-O(2)-C(6)	117.7(2)	N(2)-C(3)-C(2)	112.4(2)
C(1)-N(1)-C(4)	128.7(2)	O(1)-C(5)-O(2)	122.0(3)
N(1)-C(1)-N(3)	122.6(2)	O(2)-C(6)-C(7)	107.0(2)
C(1)-C(2)-C(3)	104.0(2)		

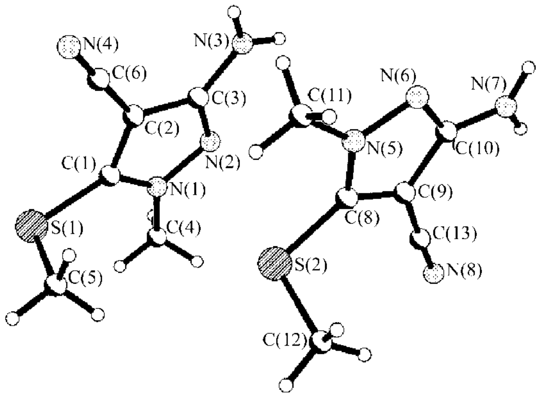


Figure 1 Structure for the asymmetric unit of the compound **2a**.

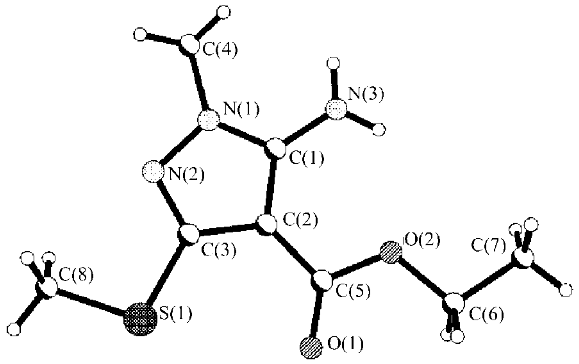


Figure 2 Molecular structure of **3b**.

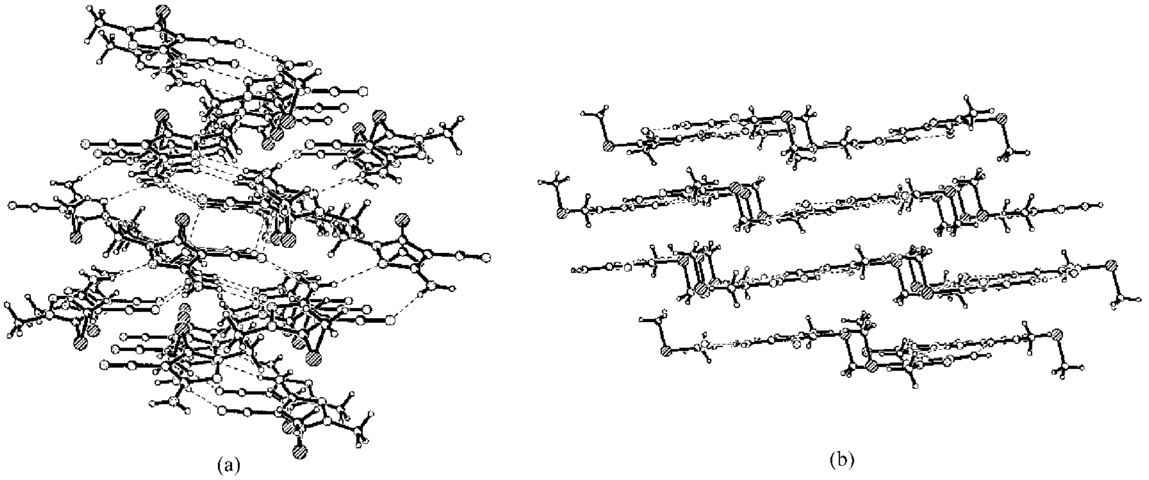
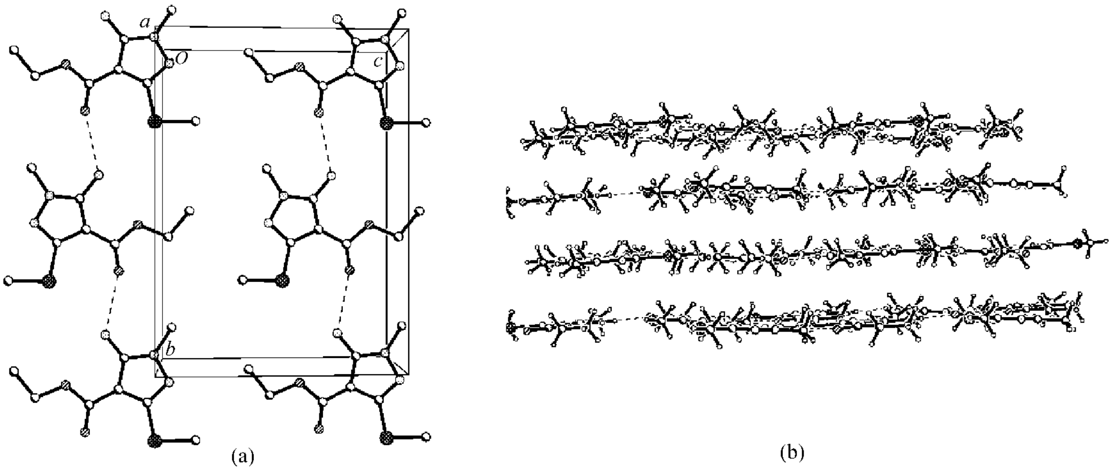

(a) (b)

Figure 3 A view of **2a** along the *b*-axes (a); a view of **2a** along the *c*-axes (b).



(a) (b)

Figure 4 A view of **3b** along the *a*-axes (a); a view of **3b** along the *c*-axes (b).

Compared with the structures of intermediates **4a** and **4b**, there was only a little difference on 4-positions, but why did the isomer ratio of the substitutents effect in the products of methlation happened in 1- and 2-positions a lot? Our group can get the clue from the calculation of the *ab inito* molecular orbital method which was shown in Table 6. Since the substitutent at the 4-position was far from two endocycilc nitrogen atoms, the steric effect of the substitutent could be neglected and the electronic effect might be the first factor to be considered. The electron density for N(1) (−0.015289) and N(2) (−0.301329) of intermediate **4** can explain why the isomer ratio of **2a** and **3a** was 83 ∶ 100 when the substitutent was cyano group, however, if ethoxycarbonyl group instead of cyano, the electron density of N(1) (0.022644) was changed to positive while the density of N(2) (−0.236445) still was negative, thus the N(1) position obviously favored methylation much more, which was the reason the product **3b** was the main one in the case.

The hydrogen interactions in compounds **2a** and **3b** were shown in Table 7. In **2a**, every molecule was connected with three other molecules through hydrogen bonds (Figure 5). As shown in Figure 3 and Figure 4, whole molecules of **2a** and **3b** were interacted through hydrogen-bonding.

In conclusion, methylation of 5-amino-4-cyano-3-methylthio-1*H*-pyrazole and 5-amino-4-ethoxycarbonyl-3-methylthio-1*H*-pyrazole at the same reaction conditions generated endocyclic substituted products at the same time. The ratio of isomers was depended upon the nature of 4-position substituent in the pyrazole ring. From *ab initio* calculation, electronic factor was an important factor to determine the ratio of products. By means of X-ray diffiration analysis, it was indicated that compounds **2a** and **3b** were interacted by hydrogen bonding.

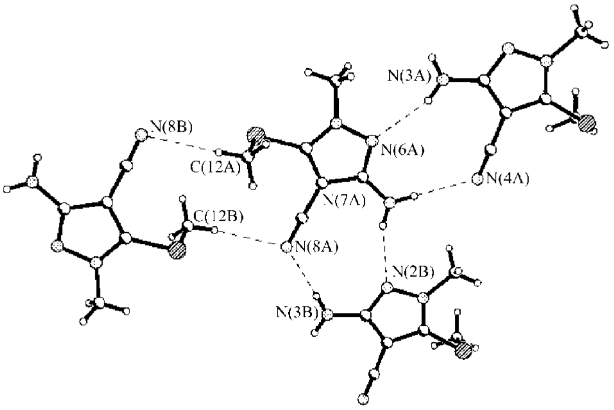


Figure 5 Intermolecular hydrogen bond in **2a**.

Table 6 Electron density of the reaction intermediate

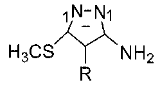
	R	N(1)	N(2)
	CN	−0.015289	−0.301329
	COOEt	0.022644	−0.236445

Table 7 Hydrogen bonds with H···A$<r$(A)+2.000 nm and ∠DHA>110° in compounds **2a** and **3b**

D—H	*d*(D—H)	*d*(H···A)	∠DHA	*d*(D···A)	A
In **2a**					
N(3)—H(3A)	0.860	2.241	178.16	3.101	N(8) [$-x+1,\ -y+1,\ -z+1$]
N(3)—H(3B)	0.860	2.387	161.14	3.213	N(6) [$-x+1,\ -y+1,\ -z$]
N(7)—H(7A)	0.860	2.240	175.00	3.097	N(4) [$-x+1,\ -y+1,\ -z$]
N(7)—H(7B)	0.860	2.343	160.59	3.167	N(2) [$-x+1,\ -y+1,\ -z+1$]
In **3b**					
N(3)—H(3A)	0.860	2.072	166.35	2.915	O(1) [$-x+1/2, y-1/2,\ -z+3/2$]
N(3)—H(3B)	0.860	2.265	121.49	2.811	O(2) [$-x+1/2, y-1/2,\ -z+3/2$]
N(3)—H(3B)	0.860	3.006	114.27	3.450	S(1) [$-x+1/2, y-1/2,\ -z+3/2$]

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