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Synthesis, bioactivities, and X-ray structure analysis of 2-cyano-5-methylpyrazolo[1,5-a]pyrimidine

Ming Li,[(1)]* Shuwen Wang,[(1)] Lirong Wen,[(1)] Xiuli Zhang,[(2)] and Ziqin Ke[(3)]

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The title compound crystallizes in the monoclinic space group $P2_1/c$ with unit cell parameters $a = 3.8380(12)$, $b = 11.994(4)$, and $c = 16.245(5)$ Å, $\beta = 90.743(5)^\circ$, $V = 747.7(4)$ Å^3, and $Z = 4$. The final reliability index is 0.0409 for 1088 observed reflections. All the non-hydrogen atoms in the title compound are almost coplanar, the largest deviation from the mean plane being 0.030(2) Å for atom C5. The crystal cohesion is accentuated by C—H···N hydrogen bond. The X-ray crystallography analysis indicates that the methyl group is at the 5-position of the compound **4** rather than at the 7-position of the isomer **4-1**. The preliminary biological test shows that the title compound has moderate herbicidal activity.

KEY WORDS: Pyrazolo[1,5-a]pyrimidine; crystal structure; mechanism; bioactivities.

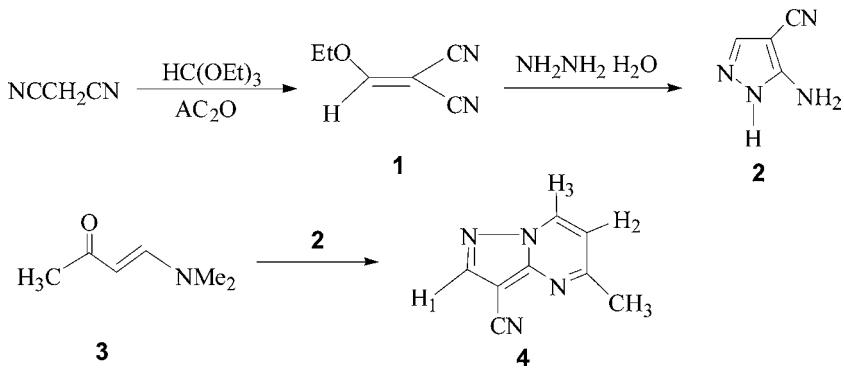
Introduction

Pyrazolo[1,5-a]pyrimidine derivatives have showed various biological activities in the terms of antibacterial, antischistosomal and xanthine oxidase inhibitor.[1–5] The enaminones are highly reactive intermediates and have been extensively used as building block in organic synthesis, especially in the heterocyclic compounds.[6–8] In addition, a great deal of interest has been focused on the synthesis of pyrazolo[1,5-a]pyrimidine through versatile enaminones because of their synthetic and biological potentialities.[9,10]

[(1)] College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P.R. China.
[(2)] Marine Drug and Food Institute, Ocean University of China, No. 5, Yushan Road, Qingdao 266003, P.R. China.
[(3)] Department of Chemistry, Xinjiang Normal University, Urumuqi 830054, P.R. China.
*To whom correspondence should be addressed; e-mail: liming928@263.net.

In continuation of our work on the structure–activity relationship of pyrazolo[1,5-a]-pyrimidine derivatives,[11,12] we have obtained a yellow crystalline compound **4**, which is the product of the reaction of 4-*N*,*N*-dimethylamino-3-butene-2-one and 5-amino-4-cyano-1H-pyrazole. The procedure of syntheses is shown in Scheme 1.

Theoretically, the condensation of enaminones with 5-amino-4-cyano-1H-pyrazole in acetic acid can be generated in two possible ways, as shown in Scheme 2. Path 1 involves the usual condensation between ketones and aminopyrazole to form a Schiff base **A**, the latter then cyclizes to form **4**. Path 2 involves an initial Michael-type addition of the nucleophilic amino group in the aminopyrazole to the enaminones, followed by the elimination of the dimethylamino group to form **B**, which then cyclizes and dehydrates to form **4-1**. IR and ^{1}H NMR studies were insufficient to confirm the structure of the title compound, whether the methyl group is located



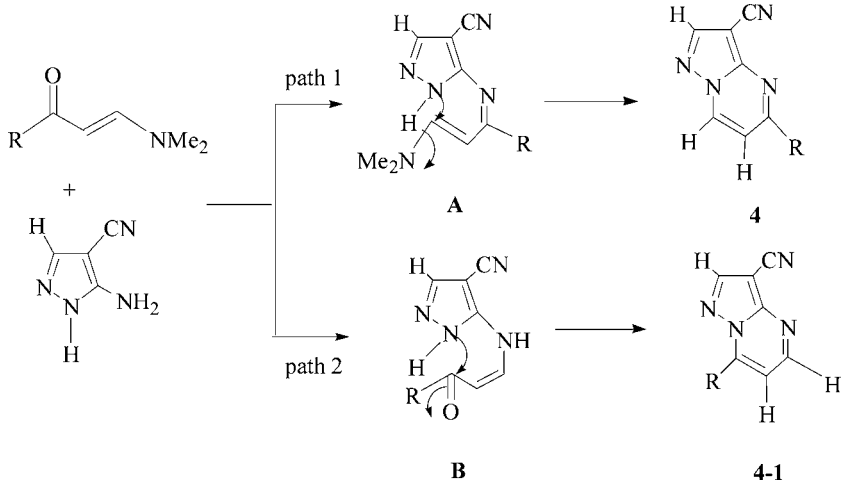
Scheme 1. Route of synthesis.

at the 5- or 7-position of the pyrazolo[1,5-a]pyrimidine skeleton. The structure of **4** was resolved using single-crystal X-ray diffraction.

Compared with the early report,[12] in compound **4**, the methyl group is at 5-position of the pyrazolo[1,5-a]pyrimidine skeleton. This prove that when R is a large group, such as aryl group, the substituent will be probably at 7-position of the pyrazolo[1,5-a]pyrimidine skeleton, while when R is a small group, such as methyl group, the substituent will be at 5-position.

Experimental

Infrared spectra were obtained on a Nicolet 510P FT-IR instrument with the compound in a KBr disc matrix. The ^{1}H NMR spectra were obtained with a Bruker AC-300 instrument. Samples were dissolved in DMSO referenced to TMS. The elemental analysis was performed by Perkin-Elmer 240. Melting point was determined with RK_1 microscopic melting point apparatus and corrected.



Scheme 2. The proposed reaction mechanism.

The intermediates **1**, **2,** and **3** were synthesized according to the references.[13,14] The title compound 3-cyano-5-methylpyrazolo[1,5-a]pyrimidine (**4**) was prepared as follows: Into a 50 mL flask containing 15 mL of glacial acetic acid, 4-*N*,*N*-dimethylamino-3-butene-2-one (**3**) (0.23 g, 2 mmol) and 4-cyano-5-amino-1H-pyrazole (**2**) (0.22 g, 2 mmol) were introduced. It was stirred at room temperature for about 12 h, then dried in vacuum to give a yellow solid (0.26 g, yield 83%) which was recrystallized from ethanol to give yellow needle crystals, melting at 176–178°C. Single crystals of **4** suitable for X-ray diffraction analysis were obtained by slow evaporation from ethanol. Anal. Calcd. (%) for $C_8H_6N_4$: C, 60.74; H, 3.83; N, 35.44. Found: C, 60.62; H, 3.84; N, 35.54. ^{1}H NMR (DMSO-d_6) δ: 2.65 (s, 3H, CH_3), 7.28 (d, 1H, $J = 7.2$ Hz, H-2), 8.74 (s, 1H, H-1), 9.22 (d, 1H, $J = 7.2$ Hz, H-3). IR (KBr) υ: 3100, 2927, 2231, 1633, 1556, 1422, 1383.

A light yellow crystal of the title compound **4** having dimensions of 0.20 mm × 0.16 mm × 0.10 mm was mounted on a glass fiber in a random orientation. The data were collected at 293(2) K on a BRUKER SMART 1000 CCD diffractometer using graphite-monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). A summary of the crystal data is presented in Table 1.

The intensity data were corrected for *Lp* factors and empirical absorption. The structure was solved by direct methods and expanded by using Fourier difference techniques with SHELXS97.[15] Refinements were made by full-matrix least squares on all F^2 data using SHELXL97.[16] All non-hydrogen atoms were anisotropically refined. All hydrogen atoms were added according to the theoretical models.

Table 1. Crystal Data and Structure Refinement

Chemical formula	C_8 H_6 N_4
CCDC deposit no.	254798
Color/shape	Yellow/prism
Formula weight	158.17
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions (Å)	
a	3.8380(12)
b	11.994(4)
c	16.245(5)
β (°)	90.743(5)
Volume (Å^3)	747.7(4)
Z	4
Density (calculated) (mg/m^3)	1.405
Absorption coefficient (mm^{-1})	0.093
θ range for data collection (°)	2.11–26.36
Limiting indices	
	$-4 \leq h \geq 4$ $-9 \leq k \geq 14$ $-17 \leq l \geq 20$
Reflections collected/unique	4246/1523 ($R_{int} = 0.0291$)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.991, 0.957
Data/restraints/parameters	1523/0/110
Goodness-of-fit on F^2	1.030
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0409$, $wR_2 = 0.1017$
R indices (all data)	$R_1 = 0.0654$, $wR_2 = 0.1151$
Largest diff. peak and hole (e.Å^{-3})	0.191, −0.225
F (000)	328

Results and discussion

Precise crystal data and other structure refinement parameters of the title compound are presented in Table 1. Selected bond lengths, bond angles, and torsional angles are summarized in Table 2. General view of the molecule with atomic labeling (thermal ellipsoids drawn at 50% probability) is shown in Fig. 1.

In compound **4**, the interatomic distances for C3—N2 [1.332 Å] and C6—N4 [1.321 Å] are remarkably shorter than the normal carbon–nitrogen single bonds, but close to the typical carbon–nitrogen double bonds,[17] which indicate the electron density of the ring has considerable delocalization. The length of C1—N1 bond is 1.132 Å, indicating that it is a normal triple bond. In addition, the angels of C3—N2—N3, N2—N3—C8, C2—C8—N3, C3—C2—C8 and C8—N4—C6 are much smaller than 120° aquired by sp^2 hybridization, which indicates that the pyrazolopyrimidine ring has strong tensile force. From this result, we assumed that the pyrazolopyrimidine ring might be an important active site of this series of compounds.

Table 2. Select Geometric Parameters (Å and °)

Bond lengths (Å)			
N(1)—C(1)	1.132(2)	C(1)—C(2)	1.423(2)
N(2)—C(3)	1.322(2)	C(2)—C(8)	1.390(2)
N(2)—N(3)	1.3698(19)	C(2)—C(3)	1.400(2)
N(3)—C(4)	1.355(2)	C(4)—C(5)	1.348(2)
N(3)—C(8)	1.3782(19)	C(5)—C(6)	1.417(2)
N(4)—C(6)	1.321(2)	C(6)—C(7)	1.491(2)
N(4)—C(8)	1.347(2)		
Bond angles (°)			
C(3)—N(2)—N(3)	103.63(13)	N(2)—C(3)—C(2)	113.11(16)
C(4)—N(3)—N(2)	125.96(14)	C(4)—C(5)—C(6)	119.99(15)
C(4)—N(3)—C(8)	121.06(14)	N(4)—C(6)—C(5)	122.22(15)
N(2)—N(3)—C(8)	112.98(12)	N(4)—C(6)—C(7)	117.90(15)
C(6)—N(4)—C(8)	116.99(14)	C(5)—C(6)—C(7)	119.87(15)
N(1)—C(1)—C(2)	178.6(2)	N(4)—C(8)—N(3)	122.23(14)
C(8)—C(2)—C(3)	105.38(14)	N(4)—C(8)—C(2)	132.87(14)
C(8)—C(2)—C(1)	126.74(15)	N(3)—C(8)—C(2)	104.90(13)
C(3)—C(2)—C(1)	127.88(16)		
Torsional angles (°)			
C(3)—N(2)—N(3)—C(4)	−179.44(15)	C(4)—C(5)—C(6)—N(4)	−1.3(2)
C(3)—N(2)—N(3)—C(8)	0.09(17)	C(4)—C(5)—C(6)—C(7)	177.74(16)
N(1)—C(1)—C(2)—C(8)	168(8)	C(6)—N(4)—C(8)—N(3)	1.0(2)
N(1)—C(1)—C(2)—C(3)	−11(8)	C(6)—N(4)—C(8)—C(2)	−179.70(16)
N(3)—N(2)—C(3)—C(2)	−0.02(18)	C(4)—N(3)—C(8)—N(4)	−1.1(2)
C(8)—C(2)—C(3)—N(2)	−0.1(2)	N(2)—N(3)—C(8)—N(4)	179.36(13)
C(1)—C(2)—C(3)—N(2)	179.46(16)	C(4)—N(3)—C(8)—C(2)	179.44(14)
N(2)—N(3)—C(4)—C(5)	179.43(15)	N(2)—N(3)—C(8)—C(2)	−0.12(17)
C(8)—N(3)—C(4)—C(5)	−0.1(2)	C(3)—C(2)—C(8)—N(4)	−179.30(16)
N(3)—C(4)—C(5)—C(6)	1.2(2)	C(1)—C(2)—C(8)—N(4)	1.2(3)
C(8)—N(4)—C(6)—C(5)	0.2(2)	C(3)—C(2)—C(8)—N(3)	0.10(17)
C(8)—N(4)—C(6)—C(7)	−178.88(14)	C(1)—C(2)—C(8)—N(3)	−179.42(15)

All the non-hydrogen atoms in compound **4** are coplanar, and the largest deviation from the mean plane is 0.030(2) Å for atom C5. And this planarity is further confirmed by the magnitude of torsion angles (maximum value of torsion for the N1—C1—C2—C3 bond is −11(8)°). This is expected due to the steric hindrance of the cyano group at C2.(Fig. 1)

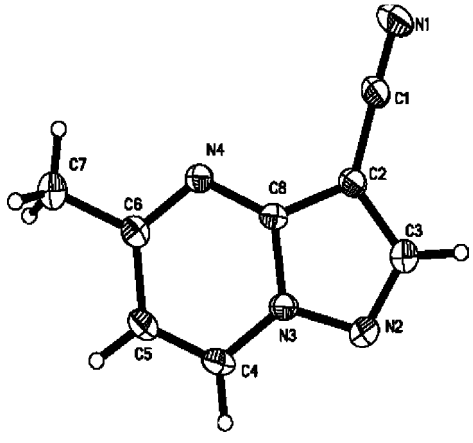


Fig . 1. General view of the molecule with thermal ellipsoids drawn at 50% probability level.

There is a potential weak intermolecular interaction (C—H···N hydrogen bond) in the crystal lattice. N1 atom forms potential weak C—H···N intermolecular interaction with the C4 atom, the donor and the acceptor distance is 3.285(2) Å. The bond angle of the hydrogen bond is 138.7°,with the symmetric codes: $x+1$, $-y+1/2$, $z+1/2$.

The preliminary biological test showed that the title compound exhibits some inhibiting activity against four fungi, *Gibberrella zeave*, *Alternaria solani*, *Phoma asparagi* and *Cercosporsa arachidicola hori*. Its inhibiting rates are 36.4, 45.1, 28.7, 39.6% at 50 μg/mL, respectively. In addition, the preliminary herbicidal activities have been determined at the concentration of 100 and

10 μg/mL using cupplate diffusion method, the inhibiting rate are 65.8 and 40.3%, respectively, which showed moderate inhibitory activities against *Brassica campestris*. Further studies on the structure–activity relationships and structural modifications of these compounds are underway.

Acknowledgments

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Supplementary material CCDC 254798 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223-336033.

References

1. Zoni, F.; Vicini, P. *Arch. Pharm.* **1998**, *331,* 219–223.
2. Li, J.J.; Anderson, D.; Burton, E.G.; Cogburn, J.N. *J. Med. Chem.* **1995**, *38,* 4570–4578.
3. Kirkpatrick, W.E.; Okabe, T.; Hillyard, I.W.; Robins, R.K.; Dren, A.T.; Novinson, T. *J. Med. Chem.* **1977**, *20,* 386.
4. El-Fahham, H.A.; Abdel-Galil, F.M.; Ibrahiem, Y.R.; Elnagdi, M.H. *J. Heterocycl. Chem.* **1983**, *20,* 667.
5. Elnagdi, M.H.; Elmoghayer, M.R.H.; Elgemeie, G.E. *Adv. Heterocycl. Chem.* **1984**, *41,* 319.
6. Hernandez, S.; Sanmantin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2003**, *5*(7), 1095–1098.
7. Li, Y.Z.; Cheng, J.R.; Wang, Q.M.; Guo, X.Y.; Huang, R.Q. *Chin. Chem. Lett.* **2003**, *14*(5), 471–474.
8. Olivera, R.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Tetrahedron Lett.* **2000**, *41,* 4353–4356.
9. Quiroga, J.; Insuasty, B.; Rincon, R.; Larrahondo, M.; Hanold, N.; Meier, H. *J. Heterocycl. Chem.* **1994**, *31,* 1333.
10. Dawood, K.M.; Farag, A.M.; Kandeel, Z.E. *J. Chem. Res. (S)*, **1999**, 88–89.
11. Wen, L.R.; Guo, W.S.; Li, M.; Cao, W.; Hu, F.Z.; Yang, H.Z. *Chinese J. Struct. Chem.* **2005**, *24*(2), 169–173.
12. Wen, L.R.; Wang, S.W.; Xu, H.Z.; Zhang, X.L.; Li, M.; Liu, J.H. *Acta Crystallogr.* **2004**, *E60,* 1294–1295.
13. Zhang, S.Q.; Liu, Y.L.; Wu, D. *Chin. J. Synth. Chem.* **2002**, *2,* 170–172.
14. Vladimir, K.; Marijan, K.; Slovenko, P. *J. Heterocycl. Chem.* **1996**, *33,* 1707–1710.
15. Sheldrick, G.M. *SHELXS97*, *Program for Crystal Structure Solution*; University of Göttingen: Germany, **1997**.
16. Sheldrick, G.M. *SHELXS97*, *Program for Crystal Structure Refinement*; University of Göttingen: Germany, **1997**.
17. Summerton, A.P.; Diamantis, A.A.; Snow, M.R. *Inorg. Chim. Acta* **1978**, *27,* 123.