

Li Ming^{1*}, Wang Shuwen¹, Wen Lirong¹, Yang Huazheng², and Zhang Xiuli³¹College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao, 266042, P. R. China²State Key Laboratory of Elemental Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China³Institute of Marine Drug and Food, Ocean University of China, Qingdao, 266003, P. R. China

Received July 14, 2004

Twelve new 7-aryl-3-cyanopyrazolo[1,5-*a*]pyrimidines (**3a-f**) and ethyl 7-arylpyrazolo[1,5-*a*]pyrimidine-3-carboxylates (**3g-l**) have been conveniently synthesized by the reaction of enaminones with 5-amino-1*H*-pyrazoles in good yields under microwave irradiation. With one substituted enaminone, only one regioisomer was obtained. The structures of new compounds were fully confirmed by elemental analysis, ir, ¹H nmr and X-ray diffraction (XRD) analysis. A plausible reaction mechanism for the synthesis of title compounds is presented. The antifungal activities of some compounds are also reported.

J. Heterocyclic Chem., **42**, 925 (2005).

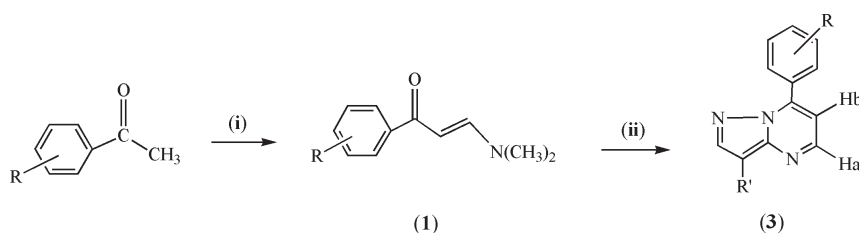
Introduction.

Many fused heterocyclic compounds have showed impressive biological activities in recent reports. Triazolo[1,5-*a*]pyrimidines, developed by DOW Company of America, have been a new-style of acetolactate synthase (ALS) enzyme inhibitors [1-4]. Later, another series of ALS enzyme inhibitors 1,2,4-thiadiazolo[1,5-*a*]pyrimidines were developed by Takeda Chemical Industries Ltd. [5-6]. Inspired by all these satisfactory research results, we then replaced the triazole or thiadiazole, as described above, with a pyrazole ring, in an effort to improve the bioactivities.

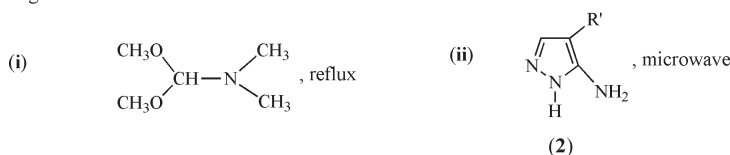
The syntheses of the pyrazolo[1,5-*a*]pyrimidines framework has been mainly based on ring closure reactions of 5-amino-1*H*-pyrazole derivations with β-diketones [7] or

substituted enaminones [8-9] in refluxing glacial acetic acid. More recently, microwave irradiation has broken new grounds in synthetic organic chemistry [10], not only in terms of the reduction of reaction time, but also simplicity of reaction procedures [11]. The combination of microwave irradiation with inorganic solid support further extends the application and scope of microwave [12], thus forming a promising candidate for eco-friendly chemistry. It shows many advantages such as high efficiency, selectivity and ease of separation and purification [13]. All these merits are in good accordance with green chemistry's initiatives of energy saving, high efficiency and environmentally benign procedures [14-17]. Herein we report the synthesis of twelve new pyrazolo[1,5-*a*]pyrimidine derivatives by the reaction 5-amino-1*H*-pyrazoles with a variety

Scheme 1



reagent and conditions:



3a R'=CN, R=H
3b R'=CN, R=*p*-Cl;
3c R'=CN, R=*p*-CH₃;
3d R'=CN, R=*p*-OCH₃;
3e R'=CN, R=*p*-F;
3f R'=CN, R=2,4-dCl

3g R'=COOEt, R=H;
3h R'=COOEt, R=*p*-Cl;
3i R'=COOEt, R=*p*-CH₃;
3j R'=COOEt, R=*p*-OCH₃;
3k R'=COOEt, R=*p*-F;
3l R'=COOEt, R=2,4-dCl

Synthetic route for the synthesis of compounds **3a-l**.

of enaminones under microwave irradiation, which has not been reported before. The antifungal activities of some compounds have also been determined and reported.

Results and Discussion.

The starting enaminones **1** and 5-amino-1*H*-pyrazoles **2** were prepared according to references [18-19]. These compounds and 5 mL glacial acetic acid were irradiated in Smithsynthesized™ to give the corresponding pyrazolo[1,5-*a*]pyrimidines **3a-3l** which were isolated in good yields (Scheme 1).

Replacement of the cyano groups in **2** with the less electron-withdrawing ester group decreased the reaction rate as expected [20]. Accordingly, cyclization of 5-amino-4-ethoxycarbonyl-1*H*-pyrazole with **1** required a higher temperature (140 °C) relative to those of the 5-amino-4-cyano-1*H*-pyrazole (120 °C) with **1**.

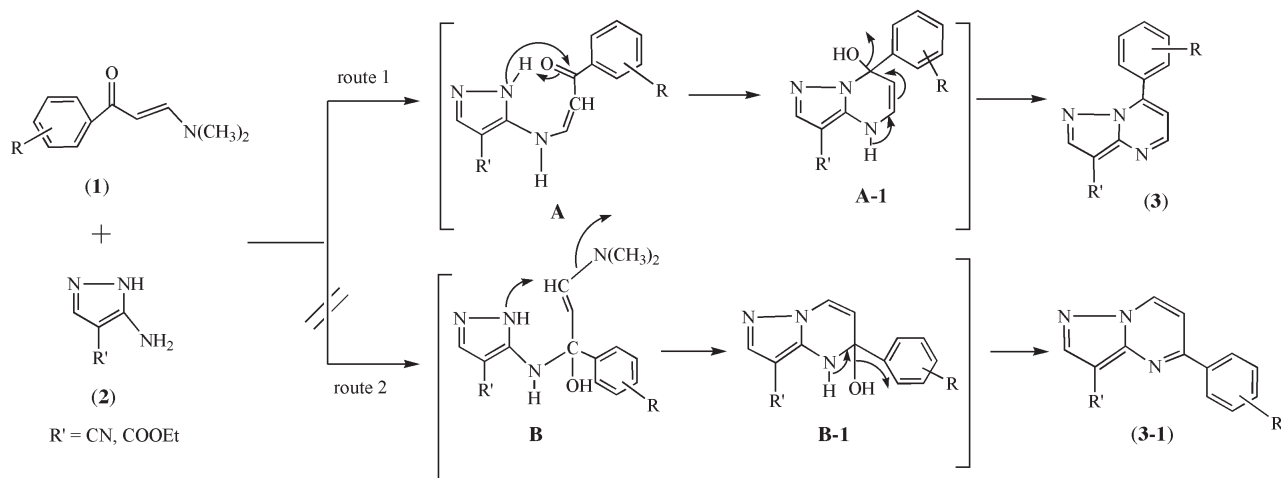
Theoretically, the condensation of 5-amino-1*H*-pyrazoles **2** with enaminones **1** can proceed in two possible ways, as shown in Scheme 2. As for route 1, the nucleophilic amino group attacks the double bond *via* a Michael addition reaction, followed by loss of the dimethylamino group. The intermediate **A** then cyclizes to form **A-1** with subsequent dehydration to give **3**, whose aryl group is at the 7-position. As for route 2, the exocyclic amino group of compound **2** attacks the carbonyl group to generate compound **3-1** *via* intermediate structures **B** and **B-1**, which is the isomer of **3**, with the aryl group located at the 5-position. This regioselectivity has been unambiguously substantiated through X-ray crystallographic analysis of the product **3j** whose aryl group is at the 7-position of the pyrazolo[1,5-*a*]pyrimidine skeleton rather than the 5-position.

Structure characterizations of **3a-3l** were performed on the basis of ir and ¹H nmr spectroscopy. Furthermore, the structure of **3j** was also determined by X-ray diffraction.

Crystallographic Data and Structure Determination of Compound **3j**.

A light yellow crystal of the title compound **3j** with dimensions of 0.30 mm x 0.26 mm x 0.22 mm was mounted on a glass fiber in a random orientation. The data were collected by BRUKER SMART 1000 CCD diffractometer with a graphite monochromated *MoKα* radiation ($\lambda=0.71073 \text{ \AA}$) by using an ω scan mode in the range of $1.46 \leq \theta \leq 25.00^\circ$ at 293(2)K. A total of 7476 reflections were collected with 2577 unique ones ($R_{\text{int}} = 0.0321$), of which 1726 with $I > 2\sigma(I)$ were considered as observed and used in the succeeding refinements. The intensity data were corrected for Lp factors and semi-empirical absorption. The structure was solved by direct methods and expanded by using Fourier difference techniques with SHELXS-97 [21]. All of the non-hydrogen atoms were located with successive difference Fourier syntheses. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were added according to theoretical models. The final refinement gave $R = 0.0608$, $wR = 0.1720$ ($w = 1/[\sigma^2(F_o)^2 + (0.0864P)^2 + 0.2072P]$ where $P = (F_o^2 + 2F_c^2)/3$, $s = 1.14$, $(\Delta/\sigma)_{\text{max}} = 0.000$, $(\Delta\rho)_{\text{max}} = 0.44$ and $(\Delta\rho)_{\text{min}} = -0.34 e/\text{\AA}^3$. A summary of the crystallographic results is listed in Table 1. The final atomic parameters and equivalent isotropic thermal parameters for non-hydrogen atoms are listed in Table 2. The selected bond lengths and bond angles are illustrated in Table 3 and 4 respectively. Figure 1 shows the molecular structure of compound **3j**.

Scheme 2



In compound **3j**, there exist three planes, p1 (pyrazole ring), p2 (pyrimidine ring), p3 (benzene ring). The dihedral angles between p1 and p2, p1 and p3, p2 and p3 are 1.33, 43.84 and 42.57° respectively, which indicates the p1 and p2 are nearly coplanar. In p1 the bond lengths of C (13)–N (1) and C (11)–N (2) (1.321 and 1.394 Å, respectively) are remarkably shorter than the normal C–N bond (1.47 Å), but close to C=N bond (1.33 Å)[22-23], revealing that these two bonds have features of an unsaturated double bond. In p2, the sum of the C (8)–N (2)–N (1), N (1)–N (2)–C (11), C (8)–N (2)–C (11) bond angles is 360.0°, indicating N (2) atom is of sp^2 hybridization [23]. In p3, the phenyl ring does not show any unusual features and the bond lengths and bond angles are within the normal range. The length of C (14)–O (2) bond is 1.232 Å, indicating that it is a normal C=O bond. The dihedral angles between the planes are listed in Table 5.

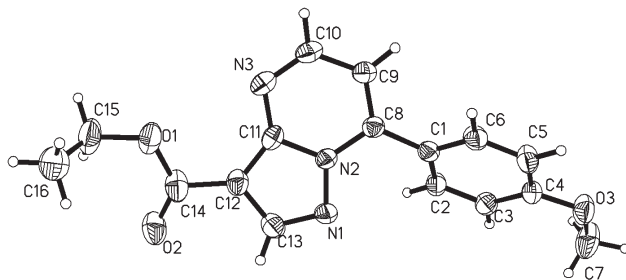


Figure 1. Molecular structure of **3j**

Table 1
Summary of Crystallographic Results for Compound **3j**

Formula	C ₁₆ H ₁₅ N ₃ O ₃
Formula weight	297.31
Crystal system	Monoclinic
Space group	P2(1)/c
<i>a</i> / Å	7.479(2)
<i>b</i> / Å	27.897(8)
<i>c</i> / Å	7.226(2)
α°	90
β°	104.355(5)
γ°	90
<i>V</i> / Å ³	1826(2)
<i>Z</i>	4
<i>D</i> _(calcd.) / g·cm ⁻³	1.352
μ / mm ⁻¹	0.096
Crystal size/mm	0.30x0.26x0.22
Temp. /K	293(2)
θ ranges/°	1.46-25.00
<i>h</i> / <i>k</i> / <i>l</i>	-8,5/-27,33/-8,8
Reflections collected	7476
Independent reflections	2577
Absorption correction	Semi-empirical from equivalents
Data / restraints / parameters	2577/64/238
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> ₁ =0.0608 <i>wR</i> ₂ =0.1433
<i>F</i> (000)	624

The crystallographic data for the compound **3j** has been deposited with the Cambridge Crystallographic Data Center, and the number is 244520.

In conclusion, our results demonstrate that the current reactions are operative under microwave conditions. Moreover, the same high region-selectivity is obtained under microwave conditions as conventional heating.

Table 2

Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$)

Atom	x	y	z	U _{eq}	Atom	x	y	z	U _{eq}
N(1)	356(3)	4874(2)	5726(1)	45(1)	C(6)	2475(3)	6600(2)	3895(2)	43(1)
N(2)	1152(3)	5241(2)	4939(1)	37(1)	C(7)	1863(3)	6445(2)	4755(1)	36(1)
N(3)	1765(3)	4407(2)	3472(1)	46(1)	C(8)	1957(3)	7464(2)	5444(1)	37(1)
N(4)	-517(4)	1074(2)	3941(2)	63(1)	C(9)	2463(4)	7203(2)	6322(2)	44(1)
C(1)	-176(54)	3665(2)	5573(2)	47(1)	C(10)	2606(4)	8202(2)	6929(2)	47(1)
C(2)	251(4)	3226(2)	4712(2)	46(1)	C(11)	2241(4)	9484(2)	6697(2)	44(1)
C(3)	-183(4)	2020(2)	4292(2)	446(1)	C(12)	1738(4)	9728(2)	5823(2)	45(1)
C(4)	1112(3)	4263(2)	4302(2)	39(1)	C(13)	1602(3)	8744(2)	5204(2)	41(1)
C(5)	2399(4)	5571(2)	3287(2)	48(1)	C(14)	2359(4)	10580(2)	7365(2)	60(1)

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

Table 3

Selected Bond lengths [Å]

Bond	Dist.	Bond	Dist.	Bond	Dist.
N(1)–C(1)	1.323(3)	C(1)–C(2)	1.400(3)	C(8)–C(9)	1.392(3)
N(1)–N(2)	1.371(2)	C(2)–C(4)	1.385(3)	C(9)–C(10)	1.375(3)
N(2)–C(7)	1.372(3)	C(2)–C(3)	1.426(3)	C(10)–C(11)	1.389(3)
N(2)–C(4)	1.385(3)	C(5)–C(6)	1.396(3)	C(11)–C(12)	1.382(3)
N(3)–C(5)	1.314(3)	C(6)–C(7)	1.373(3)	C(11)–C(14)	1.509(3)
N(3)–C(4)	1.341(3)	C(7)–C(8)	1.472(3)	C(12)–C(13)	1.375(3)
N(4)–C(3)	1.133(3)	C(8)–C(13)	1.388(3)		

Table 4
Selected Bond Angles [°]

Bond	(°)	Bond	(°)	Bond	(°)
C(1)-N(1)-N(2)	103.72(19)	N(3)-C(4)-N(2)	123.3(2)	C(12)-C(11)-C(10)	117.5(2)
N(1)-N(2)-C(7)	125.87(18)	N(3)-C(4)-C(2)	131.4(2)	C(12)-C(11)-C(14)	120.5(2)
N(1)-N(2)-C(4)	112.46(18)	N(2)-C(4)-C(2)	105.29(19)	C(10)-C(11)-C(14)	122.0(2)
C(7)-N(2)-C(4)	121.62(18)	N(3)-C(5)-C(6)	124.5(2)	C(13)-C(12)-C(11)	121.5(2)
C(5)-N(3)-C(4)	115.1(2)	C(7)-C(6)-C(5)	120.6(2)	C(12)-C(13)-C(8)	120.6(2)
N(1)-C(1)-C(2)	113.3(2)	N(2)-C(7)-C(6)	114.8(2)	C(13)-C(8)-C(9)	118.5(2)
C(4)-C(2)-C(1)	105.3(2)	N(2)-C(7)-C(8)	121.24(19)	C(13)-C(8)-C(7)	118.9(2)
C(4)-C(2)-C(3)	125.2(2)	C(6)-C(7)-C(8)	124.0(2)	C(9)-C(8)-C(7)	122.5(2)
C(1)-C(2)-C(3)	129.4(2)	C(10)-C(9)-C(8)	120.0(2)		
N(4)-C(3)-C(2)	178.5(3)	C(9)-C(10)-C(11)	121.9(2)		

Table 5
The Least-squares Plane Equations and Deviations of the Atoms

Plane 1	7.054 x - 6.06 y + 0.071 z = -1.250					
Atoms	N(1)	N(2)	C(11)	C(12)	C(13)	
Deviations(Å)	-0.004	0.003	-0.001	-0.001	0.003	
Plane 2	6.996 x - 6.56 y + 0.170 z = -1.483					
Atoms	N(2)	N(3)	C(8)	C(9)	C(10)	C(11)
Deviations(Å)	0.003	0.011	0.006	-0.006	-0.002	-0.011
Plane 3	3.369 x - 15.64 y + 4.057 z = -5.016					
Atoms	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
Deviations(Å)	-0.001	-0.004	0.004	0.001	-0.005	0.005
Dihedral angle(°)		p1-p2		p1-p3		p2-p3
		1.33		43.84		42.57

Table 6
Comparison Between Microwave and Conventional Methods

Compound	Microwave Method	Conventional Method	Isolated yield (%)	
			Microwave Method	Conventional Method
3a	120 °C, 20 minutes	Room temperature, 15 hours	81.82	71.2
3b	120 °C, 20 minutes	Room temperature, 18 hours	91.34	65.3
3c	120 °C, 20 minutes	Room temperature, 12 hours	85.47	62.6
3d	120 °C, 20 minutes	Room temperature, 12 hours	81.91	75.1
3e	120 °C, 20 minutes	Room temperature, 18 hours	85.64	72.4
3f	120 °C, 30 minutes	Refluxing, 4 hours	81.41	73.5
3g	140 °C, 20 minutes	Refluxing, 4 hours	92.63	74.4
3h	140 °C, 20 minutes	Refluxing, 4 hours	93.45	75.3
3i	140 °C, 20 minutes	Refluxing, 3 hours	85.42	69.1
3j	140 °C, 20 minutes	Refluxing, 4 hours	87.81	70.2
3k	140 °C, 20 minutes	Refluxing, 3.5 hours	94.56	77.5
3l	140 °C, 30 minutes	Refluxing, 5 hours	82.62	73.6

Table 6 summarizes the comparison between microwave method and conventional method. As can be observed, the yields from the microwave irradiation were slightly improved by 10-20% and the reaction rates were from 10 to 100 times enhanced.

The preliminary biological tests showed that some compounds exhibited inhibiting activity against four fungi, *Gibberrella zeve* (**3d**), *Alternaria solani* (**3b**), *Phoma asparagi* (**3j**) and *Cercospora arachidicola hori* (**3j**), but not remarkably. The inhibiting rates reached up to 38.5%,

33.3%, 26.7%, 26.7% at 50 ppm, respectively. Further studies on other bioactivities are underway.

EXPERIMENTAL

All melting points were determined with a RY-1 apparatus and were uncorrected. Elemental analyses were carried out by Yanaco MT-3 instrument. All ¹H nmr chemical shifts were reported in δ (ppm) downfield from TMS in DMSO-d₆ on a Bruker AC-300 spectrometer. The coupling constants were

expressed in Hz. Ir spectra were recorded on a Nicolet 510 PF-IR spectrometer as KBr pellets. Microwave irradiation was performed on a Smithesynthesized™.

General Procedure for Microwave Assisted Synthesis of 7-Aryl-3-cyanopyrazolo[1,5-*a*]pyrimidines (**3a-3f**).

To the solution of glacial acetic acid (5 mL) were added 5-amino-4-cyano-1*H*-pyrazole (0.108 g, 1 mmol) and enaminones (1 mmol). The mixture was sealed in a 10 mL glass tube with a magnetic stirring bar and irradiated in a Smithesynthesized™ at 120 °C for 20 min under adjustable microwave power range 0-25 W. Completion of the reaction was checked by TLC and the yields were determined by isolation.

3-Cyano-7-phenylpyrazolo[1,5-*a*]pyrimidine (**3a**).

Reaction time was 20 min to give yellow needles, yield 81.82%, mp 235-236 °C; ir: 2231, 1616, 1548, 1494, 755, 890 cm⁻¹; ¹H nmr: δ 7.58 (d, 1H, J = 4.5, pyrimidine-Hb), 7.62~8.10(m, 5H, Ph-H), 8.86 (s, 1H, pyrazole-H), 8.91 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₃H₈N₄: C 70.90, H 3.66, N 25.44. Found: C 70.82, H 3.65, N 25.53.

3-Cyano-7-[4-chlorophenyl]pyrazolo[1,5-*a*]pyrimidine (**3b**).

Reaction time was 20 min to give a yellow solid, yield 91.34%, mp 256-258 °C; ir: 2237, 1614, 1593, 1551, 1495 cm⁻¹; ¹H nmr: δ 7.60 (d, 1H, J = 4.5, pyrimidine-Hb), 7.62~8.16 (m, 4H, Ph-H), 8.87 (s, 1H, pyrazole-H), 8.92 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₃H₇N₄Cl: C 61.31, H 2.77, N 22.00. Found: C 61.45, H 2.76, N 21.94.

3-Cyano-7-[4-methylphenyl]pyrazolo[1,5-*a*]pyrimidine (**3c**).

Reaction time was 20 min to give yellow prisms, yield 85.47%, mp 224-225 °C; ir: 2224, 1610, 1545, 1505 cm⁻¹; ¹H nmr: δ 2.50 (s, 3H, CH₃), 7.45 (d, 1H, J = 4.5, pyrimidine-Hb), 7.56~8.88 (m, 4H, Ph-H), 8.04 (d, 1H, J = 4.5, pyrimidine-Ha), 8.86 (s, 1H, pyrazole-H).

Anal. Calcd. for C₁₄H₁₀N₄: C 71.78, H 4.30, N 23.92. Found: C 71.68, H 4.31, N 24.01.

3-Cyano-7-[4-methoxyphenyl]pyrazolo[1,5-*a*]pyrimidine (**3d**).

Reaction time was 20 min to give yellow needles, yield 81.91%, mp 214-215 °C; ir: 2229, 1613, 1552, 1511 cm⁻¹; ¹H nmr: δ 3.89 (s, 3H, OCH₃), 7.18 (d, 1H, J = 4.5, pyrimidine-Hb), 7.56~8.85 (m, 4H, Ph-H), 8.17 (d, 1H, J = 4.5, pyrimidine-Ha), 8.86 (s, 1H, pyrazole-H).

Anal. Calcd. for C₁₄H₁₀N₄O: C 67.19, H 4.03, N 22.39. Found: C 67.03, H 4.04, N 22.43.

3-Cyano-7-[4-fluorophenyl]pyrazolo[1,5-*a*]pyrimidine (**3e**).

Reaction time was 20 min to give a yellow solid, yield 85.64%, mp 266-268 °C; ir: 2234, 1613, 1550, 1509 cm⁻¹; ¹H nmr: δ 7.60 (d, 1H, J = 4.5, pyrimidine-Hb), 7.47~8.22 (m, 4H, Ph-H), 8.87 (s, 1H, pyrazole-H), 8.90 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₃H₇N₄F: C 65.54, H 2.96, N, 23.52. Found: C 65.38, H 2.97, N 23.61.

3-Cyano-7-[2,4-dichlorophenyl]pyrazolo[1,5-*a*]pyrimidine (**3f**).

Reaction time was 30 min to give a yellow solid, yield 81.41%, mp 168-170 °C; ir: 2232, 1619, 1590, 1555, 1481 cm⁻¹; ¹H nmr: δ 7.56 (d, 1H, J = 4.5, pyrimidine-Hb), 7.70~7.96 (m, 3H, Ph-H),

8.82 (s, 1H, pyrazole-H), 8.99 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₃H₆N₄Cl₂: C 54.01, H 2.09, N 19.38. Found: C 53.87, H 2.08, N 19.42.

General Procedure for Microwave Assisted Synthesis of Ethyl 7-Arylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3g-3l**).

To the solution of glacial acetic acid (5 mL) were added a 5-amino-4-ethoxycarbonyl-1*H*-pyrazole (0.155 g, 1 mmol) and enaminones (1 mmol). The mixture was sealed in a 10 mL glass tube with a magnetic stirring bar and irradiated in a Smithesynthesized™ at 140 °C for 20 min under adjustable microwave power range 14-44 W. Completion of the reaction was checked by TLC and the yields were determined by isolation.

Ethyl 7-Phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3g**).

Reaction time was 20 min to give yellow needles, yield 92.63%, mp 133-134 °C; ir: 1694, 1614, 1549, 1496, 771, 701cm⁻¹; ¹H nmr: δ 1.33 (t, 3H, J = 6.6, CH₂CH₃), 4.34 (q, 2H, J = 6.6, CH₂CH₃), 7.49 (d, 1H, J = 4.5, pyrimidine-Hb), 7.62~8.10 (m, 5H, Ph-H), 8.67 (s, 1H, pyrazole-H), 8.89 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₅H₁₃N₃O₂: C 67.41, H 4.90, N 15.72. Found: C 67.23, H 4.91, N 15.75.

Ethyl 7-[4-Chlorophenyl] pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3h**).

Reaction time was 20 min to give a white solid, yield 93.45%, mp 158.5-160 °C CH₂CH₃), 7.51 (d, 1H, J = 4.5, pyrimidine-Hb), 7.70~8.15 (m, 4H, Ph-H), 8.67 (s, 1H, pyrazole-H), 8.89 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₅H₁₂N₃O₂Cl: C 59.71, H 4.01, N 13.93. Found: C 59.57, H 4.02, N 13.97.

Ethyl 7-[4-Methylphenyl]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3i**).

Reaction time was 20 min to give a yellow solid, yield 85.42%, mp 112-114 °C; ir: 1689, 1609, 1548, 1511cm⁻¹; ¹H nmr: δ 1.33 (t, 3H, J = 6.6, CH₂CH₃), 4.34 (q, 2H, J = 6.6, CH₂CH₃), 2.51 (s, 3H, CH₃), 7.47 (d, 1H, J = 4.5, pyrimidine-Hb), 7.42~8.02 (m, 4H, Ph-H), 8.66 (s, 1H, pyrazole-H), 8.86 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₆H₁₅N₃O₂: C 68.31, H 5.37, N 14.94. Found: C 68.12, H 5.38, N 14.98.

Ethyl 7-[4-Methoxyphenyl]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3j**).

Reaction time was 20 min to give yellow prisms, yield 87.81%, mp 131-133 °C; ir: 1691, 1612, 1551, 1514cm⁻¹; ¹H nmr: δ 1.33 (t, 3H, J = 6.6, CH₂CH₃), 4.33 (q, 2H, J = 6.6, CH₂CH₃), 3.88 (s, 3H, OCH₃), 7.46 (d, 1H, J = 4.5, pyrimidine-Hb), 7.16~8.17 (m, 4H, Ph-H), 8.67 (s, 1H, pyrazole-H), 8.83 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₆H₁₅N₃O₃: C 64.64, H 5.09, N 14.13. Found: C 64.48, H 5.10, N 14.16.

Ethyl 7-[4-Fluorophenyl] pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3k**).

Reaction time was 20 min to give yellow needle, yield 94.56%, mp 172-174 °C; ir: 1716, 1616, 1552, 1506cm⁻¹; ¹H nmr: δ 1.33 (t, 3H, J = 6.6, CH₂CH₃), 4.34 (q, 2H, J = 6.6, CH₂CH₃), 8.17 (d,

¹H, J = 4.5, pyrimidine-Hb), 7.45~8.21 (m, 4H, Ph-H), 8.67 (s, 1H, pyrazole-H), 8.89 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₅H₁₂N₃O₂F: C 63.15, H 4.24, N 14.73. Found: C 62.98, H 4.25, N 14.70.

Ethyl 7-[2,4-Dichlorophenyl] pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**31**).

Reaction time was 30 min to give a yellow solid, yield 82.62%, mp 130-131 °C; ir: 1711, 1619, 1553, 1485cm⁻¹; ¹H nmr: -1.33 (t, 3H, J = 6.6, CH₂CH₃), 4.34 (q, 2H, J = 6.6, CH₂CH₃), 7.45 (d, 1H, J = 4.5, pyrimidine-Hb), 7.71~7.94 (m, 3H, Ph-H), 8.62 (s, 1H, pyrazole-H), 8.96 (d, 1H, J = 4.5, pyrimidine-Ha).

Anal. Calcd. for C₁₅H₁₁N₃O₂Cl₂: C 53.59, H 3.30, N 12.50. Found: C 53.77, H 3.29, N 12.46.

Acknowledgements.

The authors are very grateful to the Natural Science Foundation of Shandong Province (No. Y2003B01) and the National Science Foundation of China (No. 20172031) for financial support.

Also the authors are very grateful to the Key Laboratory of Pesticide & Chemical Biology, Ministry of Education; College of Chemistry, Central China Normal University, Wuhan, 430079, P. R. China for SmithesynthesizedTM.

REFERENCES AND NOTES

- * Correspondence: Li Ming, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao, 266042, P. R. China; Fax: +86-532-4023927; E-mail: liming928@263.net
- [1] R. B. Shankar and R. G. Pews, *J. Heterocyclic Chem.*, **30**, 169 (1993).
 - [2] W. T. Monte, W. A. Kleschick and J. Border, *J. Heterocyclic Chem.*, **36**, 2183 (1999).
 - [3] W. A. Kleschick, M. J. Costales, J. E. Dunbar, R. W. Meikle, W. T. Monte, N. R. Pearson, S. W. Snider and A. P. Vinogradoff, *Pestic. Sci.*, **29**, 341-355 (1990).
 - [4] W. A. Kleschick, C. M. Carson, M. J. Castales, J. J. Doney, B. C. Gerwick, J. B. Hdtwick, R. W. Meikle, W. T. Monte, J. C. Little, N. R. Pearson, S. W. Snider, M. V. Subramanian., J. C. VanHeertum and A. P. Vinogradoff, *Synthesis and Chemistry of Agrochemicals III*, York, PA: Maple Press, 15-25 (1992)
 - [5] N. Okajima, I. Aoki, T. Kuragano and Y. Okada, *Pestic. Sci.*, **32**, 91-104 (1991).
 - [6] N. Okajima, I. Aoki and Y. Okada, *Pestic. Sci.*, **32**, 265 (1991).
 - [7] G. Tenant in "Heterocyclic Chemistry", Vol **40**, P. N. Preston, John Wiley and Sons, Inc., New York, NY, p 257 (1980).
 - [8] S. S. Tseng, J. W. Epstein, H. J. Brabander and G. Francisco, *J. Heterocyclic Chem.*, **24**, 837 (1987).
 - [9] C. Mustazza, M. R. D. Giudice, A. Borioni and F. Gatta, *J. Heterocyclic Chem.*, **38**, 1119-1129 (2001).
 - [10] S. A. Galema, *Chem. Soc. Rev.*, **26**, 233 (1997).
 - [11] J. Jin, Z. Wen, J. Long, Y. M. Wang, T. Matsuura and J. B. Meng, *Synth. Commun.*, **30**, 829 (2000).
 - [12] E. Gutierrez, A. Loupy, G. Bram and E. Ruiz-Hitzky, *Tetrahedron Lett.*, **30**, 945 (1989).
 - [13] S. Caddick, *Tetrahedron*, **51**, 10403 (1995).
 - [14] A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1213 (1998).
 - [15] D. A. Goff and R. N. Zuckermann, *J. Org. Chem.*, **60**, 5744 (1995).
 - [16] J. P. LI, Q. F. Luo, Y. L. Wang and H. Wang, *Synth. Commun.*, **31**, 1793 (2001).
 - [17] P. Abenhaim, C. P. N. Son, A. Loupy and N. B. Hiep, *Synth. Commun.*, **24**, 1199 (1994).
 - [18] F.M.A.A. El-Taweel and M.H. Elnagdi, *J. Heterocyclic Chem.*, **38**, 981 (2001).
 - [19] S. Q. Zhang, Y. L. Liu and D. Wu, *Chin. J. Synth. Chem.*, **2**, 170 (2002).
 - [20] N. Kaval, W. Dehaen, P. Mátyus and E. V. Eycken, *Green Chem.*, **6**, 125 (2004).
 - [21] Y. Sasada, *Molecular and Crystal Structures*. In *Chemistry Handbook*, 3rd ed.; The Chemical Society of Japan, Maruzen, Tokyo (1984).
 - [22] X. J. Zou, L. H. Weng, G. Y. Jin and H. G. Wang, *Chin. J. Struct. Chem.*, **20**, 344 (2001).
 - [23] M. Li, R. Wen L, S. X. Jing, G. L. Zhao and H. Z. Yang, *Chin. J. Struct. Chem.*, **23**, 366 (2004).