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# $I_2$ 催化 β-酮腈与 1*H*-吡唑-5-胺的环化反应

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**摘要** 开发了一种碘催化的 1*H*-吡唑-5-胺和 β-酮基腈的环化反应, 用来合成吡唑并[1,5-*a*]嘧啶. 该方法提供了获得结构多样的吡唑并[1,5-*a*]嘧啶衍生物的有效途径, 其产率可达到良好至优秀. 该方法具有反应条件简单温和、底物范围广等优点, 并可以克级规模放大反应.

**关键词** $I_2$ 催化; 环化反应; 吡唑并[1,5-*a*]嘧啶

# $I_2$-Catalyzed Cyclization of β-Ketonitrile with 1*H*-Pyrazol-5-amine

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**Abstract** An $I_2$-catalyzed cyclization reaction of 1*H*-pyrazol-5-amine and β-ketonitrile for the synthesis of pyrazolo[1,5-*a*]pyrimidines was developed. This method provides an efficient way to obtain structurally diverse pyrazolo[1,5-*a*]pyrimidine derivatives in good to excellent yields. The method has the advantages of simple operation, mild reaction conditions and a wide range of substrates. It can also be scaled up.

**Keywords** $I_2$-catalyzed; cyclization reaction; pyrazolo[1,5-*a*]pyrimidines

## 1 Introduction

Pyrazolo[1,5-*a*]pyrimidines are an important class of heterocyclic compounds that have been widely used in medicine and agrochemicals,[1] such as the sleeping drugs Indiplon[2] and Zaleplon,[3] the anxiolytic drug Ocinaplon,[4] and the fungicide Pyrazophos[5] (Figure 1).[6-7] Therefore, the construction of pyrazolo[1,5-*a*]pyrimidines has attracted extensive attention in the field of organic synthesis. In 2006, Barsy *et al*.[8] used 5-amino-3-phenylpyrazole and triphenylphosphine as raw materials to obtain 5-(triphenylorthophosphorylimino)-3-phenylpyrazole, and then pyrazolo[1,5-*a*]pyrimidines were produced by the intermolecular Azido-Wittig reaction of 5-(triphenylorthophosphorylimino)-3-phenylpyrazole with β-carbonitrile (Scheme 1a). However, the toxic triphenylphosphine and the organic base triethylamine are necessary for this process. In 2015, Aggarwal's group reported the synthesis of pyrazolo[1,5-*a*]pyrimidines by the reaction of 5-amino-3-hydrazinopyrazole dihydrochloride with β-ketonitrile in the presence of sodium acetate (Scheme 1b).[9] But the substrate 5-amino-3-hydrazinopyrazole dihydrochloride is not readily available. In 2016, Tu's group reported the $I_2$-catalyzed multicomponent bicyclization reaction of β-ketonitrile with aryl sulfonyl hydrazides for the synthesis of pyrazolo-[1,5-*a*]pyrimidin-4-ium sulfonates, which were subsequently converted to pyrazolo[1,5-*a*]pyrimidines in the presence of NaOH (Scheme 1c).[10] However, this reaction is only suitable for the preparation of 2,5-identical diaryl-substituted pyrazolo[1,5-*a*]pyrimidines. On the basis of the above work and our continuous research interests,[11-12] we report herein the iodine-catalyzed reactions of 1*H*-pyrazol-5-amine and β-ketonitriles. A series of novel 2,5-differently diaryl-substituted pyrazolo[1,5-*a*]pyrimidine derivatives (Scheme 1d).

## 2 Results and discussion

Firstly, the reaction conditions for the reaction of 3-phenyl-1*H*-pyrazol-5-amine **1a** with β-ketonitrile **2a** to form 2,5-diphenylpyrazolo[1,5-*a*]pyrimidin-7-amine **3a** (Table 1) were optimized. When using 20 mol% $I_2$ as the catalyst and ethanol as the solvent, the target product **3a** was obtained in 87% yield at a reaction temperature of 80 ℃

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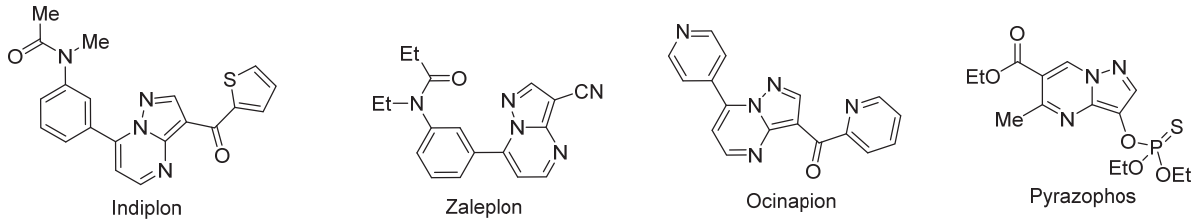
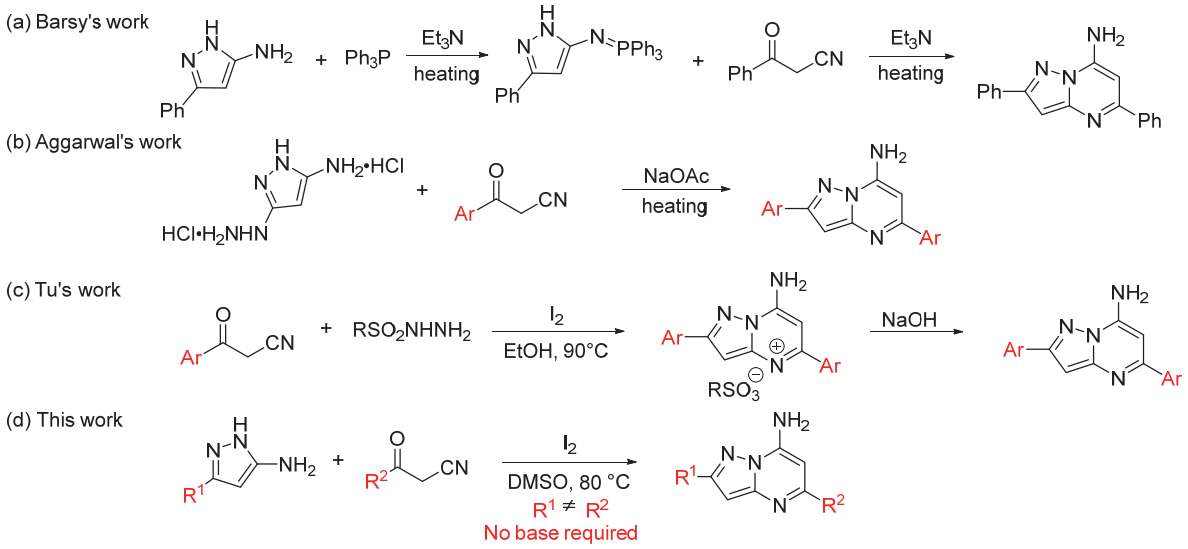
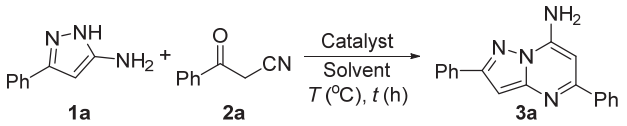



**Figure 1** Some pyrazolo[1,5-*a*]pyrimidine-containing drugs




**Scheme 1** Synthesis of pyrazolo[1,5-*a*]pyrimidines

**Table 1** Optimization of the reaction conditions[a]




| Entry | Catalyst (mol%) | Solvent/mL | *T*/℃ | *t*/h | Yield[b]/% |
|---|---|---|---|---|---|
| 1 | $I_2$ (20) | EtOH | 80 | 12 | 87 |
| 2[c] | $I_2$ (20) | EtOH | 80 | 12 | Trace |
| 3 | $I_2$ (20) | DMSO | 80 | 12 | 94 |
| 4[d] | $I_2$ (20) | EtOH | 80 | 12 | 75 |
| 5 | $I_2$ (20) | DMF | 80 | 12 | 56 |
| 6 | $I_2$ (20) | $CH_3CN$ | 80 | 12 | 28 |
| 7 | TBAI (40) | EtOH | 80 | 12 | 11 |
| 8 | NIS (40) | EtOH | 80 | 12 | 35 |
| 9 | NBS (40) | EtOH | 80 | 12 | 42 |
| 10 | NCS (40) | EtOH | 80 | 12 | 37 |
| 11 | $FeCl_3$ (40) | DMSO | 80 | 12 | 54 |
| 12 | $AlCl_3$ (40) | DMSO | 80 | 12 | 79 |
| 13 | $I_2$ (10) | DMSO | 80 | 12 | 64 |
| 14 | $I_2$ (40) | DMSO | 80 | 12 | 57 |
| 15 | $I_2$ (20) | DMSO | 100 | 12 | 63 |
| 16 | $I_2$ (20) | DMSO | 60 | 12 | 39 |
| 17 | $I_2$ (20) | DMSO | 80 | 8 | 48 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), solvent (2 mL), catalyst (20 mol%), under air. [b] Isolated yield. [c] Additive $K_2CO_3$ (50 mol%). [d] Catalyst DMSO (20 mol%).

(Entry 1). Adding 50 mol% $K_2CO_3$ to the system can only afford a trace amount of the target product **3a** (Entry 2). Then, the reaction solvents such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) and $CH_3CN$ (Entries 3～5) were screened. The experimental results showed that DMSO was the best solvent for the reaction, and the target product **3a** was obtained in 94% yield (Entry 3). Next, the types of catalysts were screened. When the catalyst was changed from $I_2$ to tetrabutylammonium iodide (TBAI) and *N*-iodo-succininide (NIS), the target product **3a** was obtained only in 11% and 35% yields, respectively (Entries 6, 7). *N*-Iodo-succinimide (NIS) and *N*-chloro-succinimide (NCS) as catalysts also failed to obtain satisfactory reaction results, and the target product **3a** was obtained in 42% and 37% yields, respectively (Entries 8, 9). Further adjusting the amount of $I_2$ to 40 or 10 mol%, the target product **3a** was obtained in 63% and 57% yields, respectively (Entries 10, 11). Neither increasing nor decreasing the reaction temperature gave better results (Entries 12, 13). The reduction in time led to a significant decrease in yield (Entry 14).

With the optimal conditions in hand, the scope of 3-phenyl-1*H*-pyrazol-5-amine **1a** and *β*-ketonitrile **2a** was explored. First of all, a variety of different aryl-substituted *β*-ketonitriles containing electron-rich aromatic groups (methyl, *n*-propyl), electron-deficient aromatic groups (fluoride, chloride, bromide) were used, and the reaction

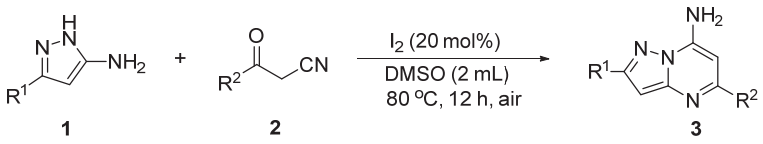
proceeded smoothly, providing the desired products in 50%～94% yields (**3a**～**3f**). Among them, the substitution effect of electron rich group is slightly better than that of electron absorbing group. The yield of 3-*oxo*-3-(*m*-tolyl)-propanenitrile was higher than that of 3-*oxo*-3-(*p*-tolyl)-propanenitrile, and the yield of the target product **3g** was 90% (**3e** vs. **3g**). The 3-*oxo*-3-(3,4,5-trimethoxyphenyl)-propanenitrile substrates were also well suited for this reaction, and the target product **3h** was obtained in 89% yield. 3-Amino-5-(4-chlorophenyl)pyrazole reacted with *β*-ketonitrile to obtain the target product **3i** in 64% yield. Notably, 3-(pyridin-4-yl)-1*H*-pyrazol-5-amine was also suitable for this reaction, and the product **3j** was obtained in 30% yield. Unsubstituted 1*H*-pyrazol-5-amine compounds are also suitable for this reaction. Aryl-substituted *β*-ketonitriles containing electron-deficient aromatic groups (chloride, fluoride, bromide), electron-rich aromatic groups (*n*-pentyl, methoxy, methyl), or hetereoaromatic groups (4-substituted pyridine) smoothly underwent reaction, giving the desired products **3k**～**3r** in 67%～95% yields. The 3-*oxo*-3-(*o*-tolyl)propanenitrile can only obtain the target product **3s** in 42% yield, and the reason for the lower yield may be due to the large steric hindrance of the methyl group. The 3-(3-methoxyphenyl)-3-oxopropanenitrile obtained the target product **3t** in 93% yield. 4,4-Dimethyl-3-oxopentanenitrile was also suitable for this reaction, and the product **3v** was obtained in 28% yield. Finally, *β*-ketonitrile or 1*H*-pyrazol-5-amine bears an alkyl group to participate in the reaction, and both can obtain the target products **3w**～**3z** in good to excellent yields.

The reaction was scaled up with 6 mmol of 3-phenyl-1*H*-pyrazol-5-amine and 9 mmol of *β*-ketonitrile in 20 mL of DMSO to give 1.5567 g of **3a** in 91% yield (Scheme 2a). Under similar conditions, the reaction of 6 mmol of 1*H*-pyrazol-5-amine with 9 mmol of *β*-ketonitrile also gave 1.1359 g of 5-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3k**) in 90% yield (Scheme 2b).

To explore possible reaction mechanism, a number of controlled experiments were performed (Scheme 3a). The model reaction was evaluated under standard conditions without $I_2$ and the yield of the target product was only 14%. It suggests that $I_2$ plays an important role in the reaction. Next, free radical trapping experiments by adding 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were performed, and the product was still able to be obtained in 15% and 82% yields, respectively (Scheme 3b). We speculate that the reaction may not be a free radical process.

Based on the results of controlled experiments and previous reports,[10] a possible mechanism was proposed (Scheme 4). The carbonyl group of *β*-ketonitrile and the amino group of the 1*H*-pyrazol-5-amine first undergo condensation deprotonation to form intermediate **A**. In the presence of the $I_2$ catalyst, intermediate **A** undergoes intramolecular 5-*exo*-dicyclization to form imine intermediate **B**. Finally, the target product **3a** is obtained by [1,3]-H shift of intermediate **B**.[15]

**Table 2** Synthesis of pyrazolo[1,5-*a*]pyrimidines[a]




**3a**, R = H, 94%; **3b**, R = Cl, 69%
**3c**, R = F, 93%; **3d**, R = $^n$Pr, 82%
**3e**, R = Me, 83%; **3f**, R = Br, 50%

**3g**, 90%

**3h**, 89%

**3i**, 64%

**3j**, 52%

**3k**, R = H, 95%
**3l**, R = Cl, 82%
**3m**, R = F, 95%
**3n**, R = Ph, 96%
**3o**, R = *n*-Pentyl, 95%
**3p**, R = OMe, 67%
**3q**, R = Me, 75%
**3r**, R = Br, 90%

**3s**, 42%

**3t**, 93%

**3u**, 95%

**3v**, 28%

**3w**, 99%

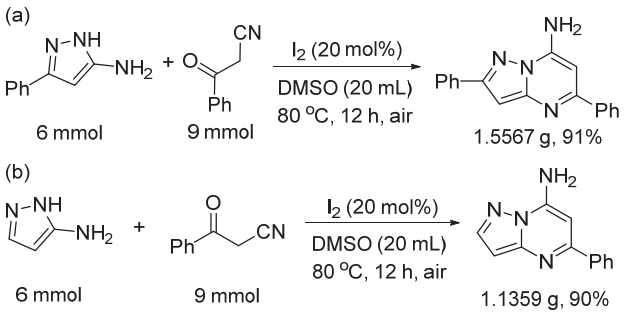
**3x**, 64%

**3y**, 90%

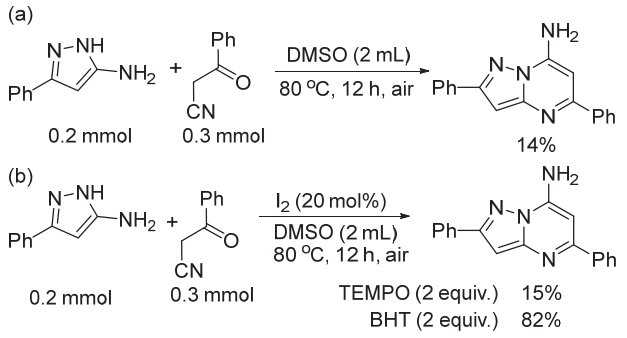
**3z**, 80%

[a] Reaction conditions:**1a** (0.2 mmol), **2a** (0.3 mmol), solvent (2 mL), $I_2$ (20 mol%), 80 ℃, 12 h, under air. [b] Isolated yield.

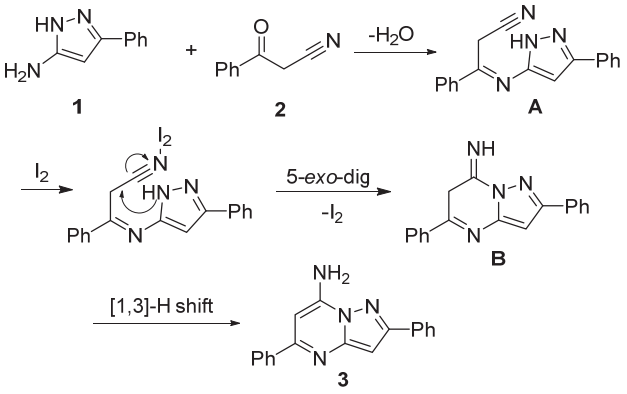
  




**Scheme 2** Gram-scale synthesis of pyrazolo[1,5-*a*]pyrimidines




**Scheme 3** Control experiments under different conditions




**Scheme 4** Proposed mechanism of cyclization reaction between *β*-ketonitrile and 1*H*-pyrazol-5-amine

## 3 Conclusions

In summary, we developed a simple and effective $I_2$-catalyzed cyclization reaction for the synthesis of pyrazollo[1,5-*a*]pyrimidines via the tandem reaction of 1*H*-pyrazol-5-amine and *β*-ketonitriles. The advantages of this approach are simple operation, mild reaction conditions, wide range of substrates and good product yields. In addition, the gram-scale synthesis offers the possibility of a wide range of applications of pyrazolo[1,5-*a*]pyrimidine derivatives in medicinal chemistry and materials science.

## 4 Experimental section

### 4.1 General methods

Unless otherwise noted, all reactions were performed in Schlenk tubes. Melting points were determined with a fusiometer and are not corrected. The materials obtained from commercial suppliers were used without further purification. For chromatography, Qingdao Ocean Chemical 200～300 mesh silica gel was employed. $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer in $CDCl_3$ or DMSO-$d_6$ solution and the chemical shifts are reported relative to the internal standard tetramethylsilane (TMS). High-resolution mass spectrometry (HRMS) was performed on a Thermo Scientific LTQ or bitrap XL mass spectrometer, thermo fisher Q Exactive.

#### 4.1.1 General procedure for $I_2$-catalyzed cyclization reactions of *β*-ketonitriles with 1*H*-pyrazol-5-amine

3-Amino-5-phenylpyrazole **1a** (0.2 mmol) and *β*-ketonitriles **2a** (0.3 mmol) were introduced in a sealed 10 mL reaction tube, and $I_2$ (20 mol%) and DMSO (2 mL) were added. Then, the mixture was stirred at 80 ℃ for 12 h. After completion of the reaction, the reaction mixture was cooled to room temperature. Then, saturated salt solution (10 mL) and sodium thiosulfate solution (10 mL) were used and extracted into ethyl acetate (20 mL×2). The combined organic layers were dried over anhydrous $Na_2SO_4$, and organic solvent was evaporated on a rotatory evaporator. The crude was purified by flash chromatography on silica gel (petroleum ether/EtOAc) to give the corresponding products **3a**.

### 4.2 Characterization data of the products

2,5-Diphenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3a**):[10] 54.0 mg, 94% yield. White solid, m.p. 272.1～273.8 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) *δ*: 8.07 (dd, *J*=16.2, 7.2 Hz, 4H), 7.82 (s, 2H), 7.50 (t, *J*=7.9 Hz, 5H), 7.43 (d, *J*=7.3 Hz, 1H), 6.94 (s, 1H), 6.62 (s, 1H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) *δ*: 156.05, 154.95, 150.62, 148.58, 138.53, 133.47, 130.11, 129.23, 129.17, 129.16, 127.18, 126.63, 91.95, 84.95.

5-(4-Chlorophenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3b**):[13] 44.2 mg, 69% yield. White solid, m.p. 178.1～180.5 ℃; $^1$H NMR (400 MHz, $CDCl_3$) *δ*: 8.05～7.94 (m, 3H), 7.55～7.41 (m, 4H), 6.86 (s, 1H), 6.47 (s, 1H), 5.77 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) *δ*: 156.11, 150.27, 146.60, 136.92, 135.91, 133.03, 128.96, 128.90, 128.76, 128.48, 126.53, 92.86, 85.28.

5-(4-Fluorophenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3c**): 56.4 mg, 93% yield. White solid, m.p. 248.4～250.4 ℃; $^1$H NMR (400 MHz, $CDCl_3$) *δ*: 8.06～7.96 (m, 4H), 7.50～7.38 (m, 3H), 7.16 (t, *J*=8.7 Hz, 2H), 6.86 (s, 1H), 6.46 (s, 1H), 5.77 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) *δ*: 156.38, 156.05, 146.58, 133.07, 129.16, 129.07, 128.93, 128.75, 126.53, 115.77, 115.56, 92.76, 85.29. $^{19}$F NMR (376 MHz, $CDCl_3$) *δ*: −111.80. HRMS (APCI) calcd for $C_{18}H_{14}FN_4$ $[M+H]^+$ 305.1197, found 305.1192.

2-Phenyl-5-(4-propylphenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3d**): 54.0 mg, 82% yield. White solid, m.p. 244.1～246.5 ℃; $^1$H NMR (400 MHz, $CDCl_3$) *δ*: 8.03～7.92 (m, 3H), 7.51～7.23 (m, 5H), 6.86 (s, 1H), 6.50 (s, 1H), 5.76 (s, 2H), 2.84～2.51 (m, 2H), 2.05～1.52 (m, 3H),

0.96 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 157.50, 155.88, 146.57, 144.76, 135.80, 133.19, 128.86, 128.84, 128.73, 127.10, 126.52, 92.57, 85.50, 37.84, 24.42, 13.80. HRMS (APCI) calcd for $C_{21}H_{22}N_4$ $[M+H]^+$ 329.1761, found 329.1756.

2-Phenyl-5-(*p*-tolyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3e**):[13] 49.9 mg, 83% yield. White solid, m.p. 218.5～220.3 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.12～8.04 (m, 2H), 7.94 (d, $J$=8.2 Hz, 2H), 7.72 (s, 2H), 7.49 (d, $J$=7.8 Hz, 2H), 7.42 (d, $J$=7.3 Hz, 1H), 7.32 (d, $J$=8.0 Hz, 2H), 6.90 (s, 1H), 6.59 (s, 1H), 2.37 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 156.05, 154.84, 150.69, 148.48, 139.75, 135.79, 133.50, 129.76, 129.19, 129.15, 127.07, 126.60, 91.81, 84.62, 21.34.

5-(4-Bromophenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3f**):[13] 36.2 mg, 50% yield. White solid, m.p. 198.5～200.3 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.13～8.03 (m, 2H), 8.00 (d, $J$=8.6 Hz, 2H), 7.83 (s, 2H), 7.71 (d, $J$=8.6 Hz, 2H), 7.50 (t, $J$=7.4 Hz, 2H), 7.43 (d, $J$=7.3 Hz, 1H), 6.94 (s, 1H), 6.60 (s, 1H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 155.03, 154.83, 148.60, 137.77, 133.39, 132.13, 129.27, 129.21, 129.17, 126.63, 123.65, 92.09, 84.71.

2-Phenyl-5-(*m*-tolyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3g**): 53.6 mg, 90% yield. White solid, m.p. 208.5～210.9 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.12～8.04 (m, 2H), 7.88 (d, $J$=1.8 Hz, 1H), 7.84～7.79 (m, 1H), 7.75 (s, 2H), 7.50 (dd, $J$=8.2, 6.8 Hz, 2H), 7.40 (q, $J$=7.7 Hz, 2H), 7.29 (d, $J$=7.2 Hz, 1H), 6.93 (s, 1H), 6.61 (s, 1H), 2.41 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 156.21, 154.89, 150.72, 148.49, 138.57, 138.30, 133.49, 130.72, 129.21, 129.15, 129.06, 127.75, 126.61, 124.32, 91.91, 84.96, 21.59. HRMS (APCI) calcd for $C_{19}H_{17}N_4$ $[M+H]^+$ 301.1448, found 301.1442.

2-Phenyl-5-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]-pyrimidin-7-amine (**3h**): 67.0 mg, 89% yield. White solid, m.p. 69.6～72.2 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.06～7.98 (m, 2H), 7.52～7.44 (m, 2H), 7.44～7.34 (m, 1H), 6.86 (s, 1H), 6.47 (s, 1H), 5.89 (s, 2H), 3.96 (s, 6H), 3.91 (s, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 157.18, 155.98, 153.35, 150.23, 146.65, 139.61, 134.21, 133.11, 128.91, 128.76, 126.50, 104.56, 92.59, 85.53, 60.97, 56.29. HRMS (APCI) calcd for $C_{21}H_{21}N_4O_3$ $[M+H]^+$ 377.1608, found 377.1604.

2-(4-Chlorophenyl)-5-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3i**): 41.0 mg, 64% yield. White solid, m.p. 260.5～261.2 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.08 (dd, $J$=22.3, 7.8 Hz, 10H), 7.82 (s, 5H), 7.55 (dd, $J$=23.6, 7.8 Hz, 14H), 6.98 (s, 2H), 6.64 (s, 2H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 156.25, 153.70, 150.82, 148.54, 138.58, 133.77, 132.41, 130.11, 129.23, 129.17, 128.28, 127.17, 92.17, 85.08. HRMS (APCI) calcd for $C_{18}H_{14}ClN_4$ $[M+H]^+$ 321.0902, found 321.0898.

5-Phenyl-2-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3j**): 29.7 mg, 52% yield. White solid, m.p. 212.6～214.7 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.81 (d, $J$=6.0 Hz, 1H), 8.06 (ddd, $J$=15.4, 8.3, 1.5 Hz, 9H), 7.98～7.88 (m, 1H), 7.78 (s, 4H), 7.74 (dd, $J$=7.8, 1.8 Hz, 1H), 7.50 (t, $J$=7.7 Hz, 15H), 6.94 (s, 3H), 6.61 (s, 2H), 1.95 (s, 1H), 1.17 (s, 5H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 150.11, 133.46, 130.11, 129.18, 127.17, 126.62, 91.95. HRMS (APCI) calcd for $C_{17}H_{14}N_5$ $[M+H]^+$ 288.1244, found 288.1257.

5-Phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3k**):[14] 40.0 mg, 95% yield. White solid, m.p. 200.3～205.6 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.08～7.97 (m, 3H), 7.54～7.36 (m, 4H), 6.88 (s, 1H), 6.54 (s, 1H), 5.79 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 157.54, 149.42, 146.75, 144.64, 138.53, 129.77, 128.72, 127.25, 95.91, 85.46.

5-(4-Chlorophenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3l**): 40.1 mg, 82% yield. White solid, m.p. 161.3～166.3 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.10 (d, $J$=2.3 Hz, 1H), 8.08～8.01 (m, 2H), 7.81 (s, 2H), 7.58～7.50 (m, 2H), 6.57 (s, 1H), 6.44 (d, $J$=2.2 Hz, 1H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 159.38, 154.24, 153.62, 149.57, 142.19, 139.55, 133.93, 133.70, 99.82, 89.03. HRMS (APCI) calcd for $C_{12}H_{10}ClN_4$ $[M+H]^+$ 245.0586, found 245.0586.

5-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3m**): 43.4 mg, 95% yield. White solid, m.p. 137.3～142.1 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.30～7.89 (m, 3H), 7.16 (t, $J$=8.6 Hz, 3H), 6.46 (s, 1H), 5.75 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 149.34, 144.72, 129.19, 129.10, 115.78, 115.57, 95.89, 85.12; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$: −111.60. HRMS (APCI) calcd for $C_{12}H_{10}FN_4$ $[M+H]^+$ 229.0884, found 229.0882.

5-([1,1'-Biphenyl]-4-yl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3n**): 55.2 mg, 96% yield. White solid, m.p. 168.7～173.1 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.18～8.07 (m, 3H), 7.87～7.71 (m, 6H), 7.50 (dd, $J$=8.3, 6.9 Hz, 2H), 7.41 (d, $J$=7.3 Hz, 1H), 6.64 (s, 1H), 6.46 (d, $J$=2.2 Hz, 1H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 155.33, 148.88, 144.76, 141.66, 139.84, 129.50, 128.30, 127.79, 127.39, 127.14, 94.91, 84.39. HRMS (APCI) calcd for $C_{18}H_{15}N_4$ $[M+H]^+$ 287.1291, found 287.1287.

5-(4-Pentylphenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3o**): 53.0 mg, 95% yield. White solid, m.p. 183.9～187.5 ℃; 1H NMR (400 MHz, CDCl3) $\delta$: 8.04 (d, $J$=2.3 Hz, 1H), 7.90 (d, $J$=8.2 Hz, 2H), 7.28 (s, 1H), 6.55 (d, $J$=2.3 Hz, 1H), 6.48 (s, 1H), 5.80 (s, 2H), 2.67～2.62 (m, 2H), 1.68～1.60 (m, 2H), 1.33 (dd, $J$=7.3, 3.9 Hz, 5H), 0.91～0.86 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 157.58, 149.39, 146.75, 145.02, 144.55, 135.82, 128.81, 127.15, 95.69, 85.31, 35.73, 31.47, 31.00, 22.55, 14.05. HRMS (APCI) calcd for $C_{17}H_{21}N_4$ $[M+H]^+$ 281.1761, found 281.1756.

5-(4-Methoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3p**): 31.6 mg, 67% yield. White solid, m.p. 188.2～192.8 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.10～7.94 (m, 3H), 7.67 (s, 2H), 7.11～7.00 (m, 2H), 6.53 (s, 1H), 6.38 (d, $J$=2.3 Hz, 1H), 3.82 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 144.65, 129.67, 119.66, 115.89, 112.35, 95.96, 85.59, 77.22, 55.45. HRMS (APCI) calcd for $C_{13}H_{12}N_4O$ $[M+H]^+$ 241.1084, found 241.1080.

5-(*p*-Tolyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3q**): 33.3

mg, 75% yield. White solid, m.p. 143.8～148.7 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.07 (d, $J$=2.3 Hz, 1H), 7.92 (d, $J$=8.2 Hz, 2H), 7.71 (s, 2H), 7.30 (d, $J$=7.5 Hz, 2H), 6.56 (s, 1H), 6.41 (d, $J$=2.2 Hz, 1H), 2.36 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 155.94, 149.64, 148.72, 144.57, 139.65, 135.88, 129.73, 127.08, 94.78, 84.12, 21.32. HRMS (APCI) calcd for $C_{13}H_{13}N_4$ $[M+H]^+$ 225.1135, found 225.1132.

5-(4-Bromophenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3r**): 51.2 mg, 90% yield. White solid, m.p. 187.4～188.9 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.06 (d, $J$=2.3 Hz, 1H), 7.88 (d, $J$=8.6 Hz, 2H), 7.60 (d, $J$=8.6 Hz, 2H), 6.57 (d, $J$=2.3 Hz, 1H), 6.46 (s, 1H), 5.79 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 154.69, 149.48, 148.88, 144.80, 137.80, 132.11, 129.23, 123.60, 95.08, 84.23. HRMS (APCI) calcd for $C_{12}H_{10}BrN_4$ $[M+H]^+$ 289.0083, found 289.0080.

5-(*o*-Tolyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3s**): 19.3 mg, 42% yield. White solid, m.p. 176.2～180.1 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.10 (d, $J$=2.3 Hz, 1H), 7.73 (s, 2H), 7.39 (dd, $J$=7.3, 1.5 Hz, 1H), 7.30 (d, $J$=2.6 Hz, 3H), 6.39 (d, $J$=2.3 Hz, 1H), 6.14 (s, 1H), 2.35 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 159.33, 149.36, 148.23, 144.44, 140.46, 135.63, 131.01, 129.38, 128.77, 126.17, 94.69, 88.40, 20.51. HRMS (APCI) calcd for $C_{13}H_{13}N_4$ $[M+H]^+$ 225.1135, found 225.1133.

5-(3-Methoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3t**): 44.6 mg, 93% yield. White solid, m.p. 181.8～185.8 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.06 (d, $J$=2.3 Hz, 2H), 7.64～7.51 (m, 4H), 7.38 (t, $J$=8.0 Hz, 2H), 7.00 (dd, $J$=7.7, 2.1 Hz, 2H), 6.58 (d, $J$=2.3 Hz, 2H), 6.52 (s, 2H), 5.70 (s, 4H), 3.90 (s, 6H), 2.04 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 144.65, 129.67, 119.66, 115.89, 112.35, 95.96, 85.59, 55.45. HRMS (APCI) calcd for $C_{13}H_{13}N_4O$ $[M+H]^+$ 241.1084, found 241.1082.

5-(Pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3u**): 40.2 mg, 95% yield. White solid, m.p. 210.4～213.4 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.76～8.66 (m, 2H), 8.15 (d, $J$=2.3 Hz, 1H), 8.05～7.81 (m, 4H), 6.66 (s, 1H), 6.52 (d, $J$=2.2 Hz, 1H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 152.90, 150.35, 150.18, 149.08, 148.57, 145.32, 144.52, 120.93, 95.14, 84.18. HRMS (APCI) calcd for $C_{11}H_{10}N_5$ $[M+H]^+$ 212.0931, found 212.0929.

5-(*tert*-Butyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**3v**): 10.5 mg, 28% yield. White solid, m.p. 164.1～167.7 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.00 (d, $J$=2.2 Hz, 1H), 7.49 (s, 2H), 6.29 (d, $J$=2.2 Hz, 1H), 6.14 (s, 1H), 1.28 (s, 9H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 169.21, 149.10, 148.28, 144.10, 93.91, 83.94, 37.79, 30.21. HRMS (APCI) calcd for $C_{10}H_{14}N_4$ $[M+H]^+$ 191.1291, found 191.1291.

5-Methylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3w**): 29.5 mg, 99% yield. White solid, m.p. 135.8～137.8 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.98 (d, $J$=2.2 Hz, 1H), 7.53 (s, 2H), 6.22 (d, $J$=2.2 Hz, 1H), 5.94 (s, 1H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 158.76, 149.51, 147.95, 143.91, 93.45, 87.56, 24.75. HRMS (APCI) calcd for $C_7H_8N_4$ $[M+H]^+$ 149.0822, found 149.0828.

2-Methyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3x**): 59.7 mg, 64% yield. White solid, m.p. 197.0～199.8 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.00 (d, $J$=6.5 Hz, 2H), 7.64 (s, 2H), 7.51～7.42 (m, 3H), 6.51 (s, 1H), 6.23 (s, 1H), 2.41 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 155.67, 153.91, 150.35, 148.24, 138.81, 129.88, 129.09, 127.09, 94.37, 84.12, 14.88. HRMS (APCI) calcd for $C_{13}H_{12}N_4$ $[M+H]^+$ 225.1135, found 225.1144.

2,5-Dimethylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3y**): 29.2 mg, 90% yield. White solid, m.p. 137.5～140.4 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.41 (s, 2H), 6.00 (s, 1H), 5.86 (s, 1H), 2.35 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 158.37, 153.12, 150.17, 147.46, 92.90, 87.26, 24.69, 14.79. HRMS (APCI) calcd for $C_8H_{10}N_4$ $[M+H]^+$ 163.0978, found 163.0983.

5-Methyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (**3z**): 35.9 mg, 80% yield. White solid, m.p. 144.5～147.2 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.03 (d, $J$=7.0 Hz, 2H), 7.54 (s, 2H), 7.47 (t, $J$=7.5 Hz, 2H), 7.39 (t, $J$=7.3 Hz, 1H), 6.71 (s, 1H), 5.97 (s, 1H), 2.34 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$: 159.00, 154.20, 150.62, 147.71, 133.63, 129.09, 129.03, 126.52, 90.59, 88.03, 24.82. HRMS (APCI) calcd for $C_{13}H_{13}N_4$ $[M+H]^+$ 225.1135, found 225.1143.

**Supporting Information** $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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