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# Metal-free cascade synthesis of unsymmetrical 2-aminopyrimidines from imidazolate enaminones†

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A convenient metal-free synthesis of unsymmetrical 2-aminopyrimidines from imidazolate enaminones has been developed. In this procedure, various structural 2-aminopyrimidines, as well as 4,5-dihydroisoxazol-5-ols and pyrazoles were synthesized in moderate to excellent yields. A plausible mechanism was also proposed for the cascade reaction. This method represents an effective strategy towards the synthesis of unsymmetrical 2-aminopyrimidines.

## Introduction

Pyrimidines are important heterocyclic structural motifs, exist in numerous drug molecules and exhibit a wide range of biological activities, such as antineoplastic,[1] antibacterial,[2] anti-HIV,[3] antiviral[4] and antitubercular.[5] As illustrated in Fig. 1, examples of leading commercial drugs based on the pyrimidine scaffold include Imatinib,[6] Pyrimethamine[7] and Rosuvastatin.[8] Moreover, pyrimidines are the essential building blocks in DNA and RNA,[9] and have also found important application in materials chemistry[10] and agricultural chemistry.[11] For these reasons, the development of efficient methodologies for the synthesis of pyrimidines continues to be of great significance.[12]

Conventionally, the most popular approaches to the construction of 2-aminopyrimidine moiety consist of: (a) transition-metal-catalyzed amination of 2-Cl or 2-Br-pyrimidines (Scheme 1a);[13] or (b) condensation of guanidines with 1,3-dicarbonyl compounds or their synthetic equivalents (Scheme 1b).[14] Nevertheless, methodologies based on transition-metal-catalyzed reactions limits their potential application in the pharmaceutical industry owing to the contamination of heavy metals, while routes based on condensation reactions usually require multistep routes to synthesize the unsymmetrical 2-aminopyrimidines, and considerable disadvantages like harsh reaction conditions or poor functional-group tolerance are associated with these processes.[14a–c] Therefore, a practical and efficient method for the synthesis of unsymmetrical 2-aminopyrimidine is still of considerable.

Recently, enaminones[15] have emerged as important building blocks for the construction of versatile 1,2,3-triazoles, pyridines, indoles and pyrroles.[16] However, a method for the synthesis of unsymmetrical 2-aminopyrimidines from enaminones with guanidines has not been reported. Herein, we designed a metal-free strategy for the synthesis of 2-aminopyrimidines from imidazolate enaminones *via* a cascade sequence (Scheme 1c).

## Results and discussion

At the outset of the study, the condensation of 3-(1*H*-imidazol-1-yl)-1,3-diphenylprop-2-en-1-one (*E*/*Z*) **1a** and guanidine

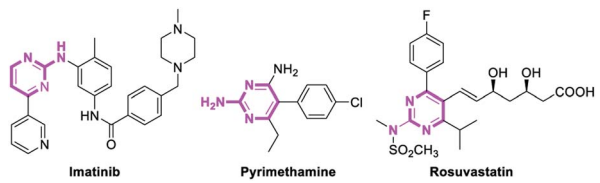
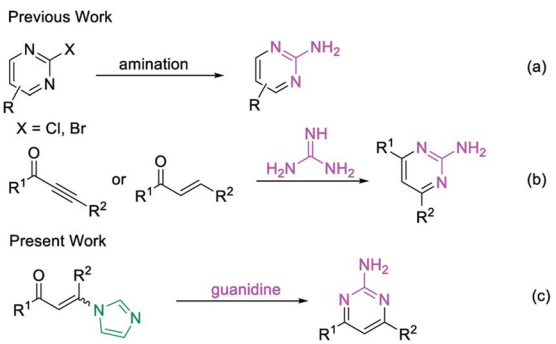



Fig. 1 Selected pyrimidine-containing drugs.




Scheme 1 Strategies for the synthesis of unsymmetrical 2-aminopyrimidine.

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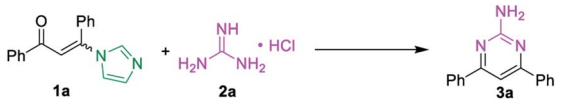
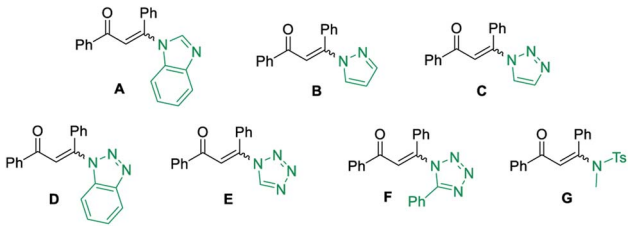
‡ X. Cui and J. Ma contributed equally to this work.

Table 1 Optimization of the reaction conditions[a]




| Entry | Substrate | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **1a** | $K_2CO_3$ | Toluene | 35 |
| 2 | **1a** | $K_2CO_3$ | 1,4-Dioxane | 80 |
| 3 | **1a** | $Cs_2CO_3$ | 1,4-Dioxane | 82 |
| 4 | **1a** | $K_3PO_4$ | 1,4-Dioxane | 78 |
| 5 | **1a** | NaOH | 1,4-Dioxane | 42 |
| 6 | **1a** | NaO$^t$Bu | 1,4-Dioxane | 36 |
| 7 | **1a** | **$K_2CO_3$** | **DMF** | **94** |
| 8 | **1a** | $K_2CO_3$ | DMSO | 92 |
| 9 | **1a** | $K_2CO_3$ | NMP | 89 |
| 10 | **1a** | $K_2CO_3$ | EtOH | 60 |
| 11 | **1a** | $K_2CO_3$ | $CH_3CN$ | 56 |
| 12 | **1a** | $K_2CO_3$ | THF | 42 |
| 13 | **1a** | $K_2CO_3$ | DCE | 38 |
| 14 | **1a** | $K_2CO_3$ | $H_2O$ | n.d.[c] |
| 15 | **A** | $K_2CO_3$ | DMF | 92 |
| 16 | **B** | $K_2CO_3$ | DMF | 89 |
| 17 | **C** | $K_2CO_3$ | DMF | 79 |
| 18 | **D** | $K_2CO_3$ | DMF | 85 |
| 19 | **E** | $K_2CO_3$ | DMF | 83 |
| 20 | **F** | $K_2CO_3$ | DMF | 87 |
| 21 | **G** | $K_2CO_3$ | DMF | 54 |




[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), and base (2.0 mmol) in 3 mL of solvent at 60 °C for 12 h under air. [b] Isolated yield based on **1a**. [c] n.d. = no detected. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl-sulfoxide, NMP = 1-methylpyrrolidin-2-one, DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

hydrochloride **2a** was chosen as a model reaction to screen the reaction parameters (Table 1). To our delight, the desired product **3a** was obtained in 35% yield when the cascade reaction was conducted at 60 °C in the presence of 4.0 equiv. $K_2CO_3$ (based on **1a**) in toluene for 12 h (entry 1). The yield was improved to 80% when the transformation was conducted with 1,4-dioxane instead of toluene (entry 2). Further studies focused on screening of versatile base (entries 3–6). In the presence of a medium-strength base, such as $Cs_2CO_3$ and $K_3PO_4$, the reaction furnished **3a** in 82% and 78%, respectively (entries 3 & 4). Other strong bases, including NaOH and NaO$^t$Bu, provided **3a** in acceptable yields (entries 5 & 6). Further investigation showed that this transformation was highly solvent dependent (entries 7–14). The yield was improved to 94% by switching the solvent 1,4-dioxane to DMF, while no deviations were observed between DMF, DMSO and NMP (entries 7–9).

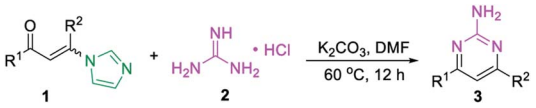
However, other solvents, such as EtOH, $CH_3CN$, THF, DCE and $H_2O$ led to no reaction or lower yield (entries 10–14). When other enaminones **A–G** were subjected to the metal-free cascade reaction, the desired product **3a** could also be successfully attained, albeit in decreased yields (entries 15–21). On the basis of the above results, the optimized conditions for the reaction comprise the base by 4.0 equiv. $K_2CO_3$ at 60 °C in DMF to furnish the single 2-aminopyrimidine **3a** in 94% yield (Table 1, entry 7).

With the optimized reaction conditions in hand, the generality and scope of the metal-free cascade reactions were investigated as illustrated in Table 2. Interestingly, a wide range of substrates were well tolerated under the cascade reaction conditions, affording the corresponding unsymmetrical 2-aminopyrimidines (**3a–3u**) in 58–96% yields. Generally, imidazolate enaminones with electron-donating substituents (–Me, –*n*-Bu & –OMe) (entries 2–9) provided the corresponding products in higher yields than those bearing electron-withdrawing groups (–F, –Cl, –Br, –CN & –COOMe) (entries 10–18). As for regioisomeric substrates, imidazolate enaminones with substituents in Ar-$R^1$ (entries 2, 6, 10 & 15) could be transformed into the corresponding 2-aminopyrimidines products in similar yields as those with substituents in Ar-$R^2$ (entries 3, 7, 11 & 16). A significant influence of steric hindrance on this reaction was observed. For instance, the *ortho*-substituted substrates led to lower yield than the *para*-substituted substrates (entries 2 & 5, 10 & 12). Notably, alkyl enaminones with cyclopropyl or *t*-butyl could also participate in this reaction, albeit giving lower yield of the product (entries 19, 20 & 21). Moreover, imidazolate enaminones possessing thiophenyl and naphthyl ring were also tested (entries 22, 23 & 24). Additionally, other representative guanidine analogues, such as benzimidamide 1,1-dimethylguanidine, were well-tolerated (entries 25 & 26).

Subsequently, hydroxylamine hydrochloride **2b** and hydrazine hydrate **2c** were also tolerated in the cascade reaction system and furnished the product 3,5-diphenyl-4,5-dihydroisoxazol-5-ol **3ab** and 3,5-diphenyl-1*H*-pyrazole **3ac** in 91% and 96% yields, respectively (Scheme 2a and b).[17] However, when imidazolate enaminones **1e′** and **1e** involved to react with hydroxylamine hydrochloride **2b** and phenylhydrazine **2d**, the single products 4,5-dihydroisoxazol-5-ol **3e′b** and pyrazole **3ed** were obtained in 75% and 82% yields, respectively (Scheme 2c and d).[17] It's suggested that the imidazole is replaced by hydroxylamine or hydrazine in the first step of the reaction, while the condensations of hydroxylamine or hydrazine with the carbonyl group do not occurs.

Base on the above results, the mechanistic pathways of this cascade metathesis were proposed and presented in Scheme 3. The initial step of the reaction involved the formation of intermediate **H** from 3-(1*H*-imidazol-1-yl)-1,3-diphenylprop-2-en-1-one (*E*/*Z*) **1a** *via* the substitution procedure followed by the released one molecular of imidazole (path a). Conversely, the condensation of carbonyl group with guanidine was not observed in the first step of the reaction (path b). Then thermally inducing the transformation of intermediate **H** gave the desired unsymmetrical 2-aminopyrimidine **3a**.

Table 2 Scope of substrates[a]



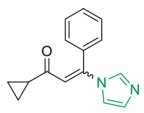
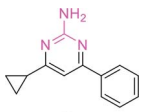
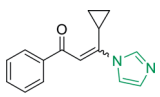
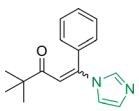
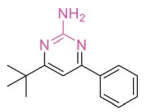
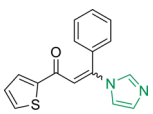
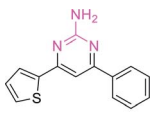
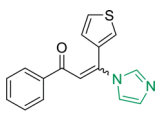
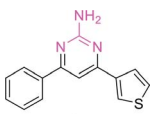
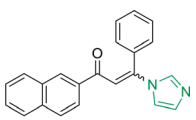
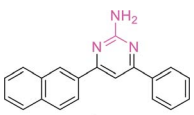
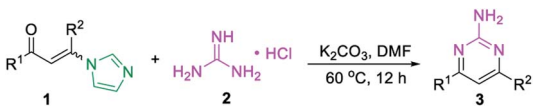
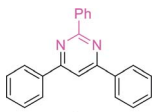
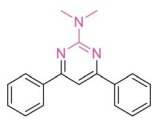
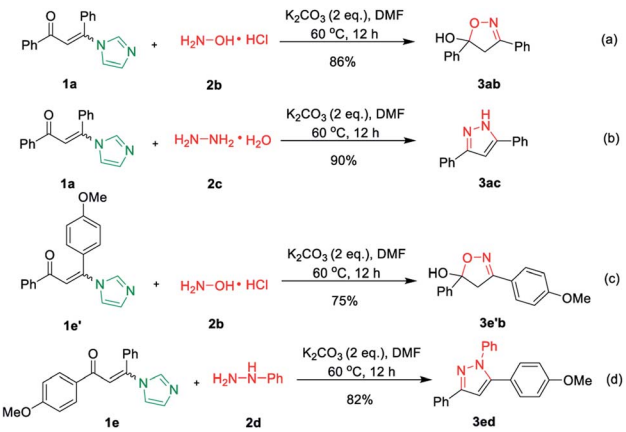

| Entry | | | Yield[b] (%) |
|---|---|---|---|
| 1 | $R^1$ = H, $R^2$ = H, **1a** | **3a** | 94 (90)[c] |
| 2 | $R^1$ = 4-Me, $R^2$ = H, **1b** | **3b** | 95 |
| 3 | $R^1$ = H, $R^2$ = 4-Me, **1b′** | | 92 |
| 4 | $R^1$ = 3-Me, $R^2$ = H, **1c** | **3c** | 90 |
| 5 | $R^1$ = 2-Me, $R^2$ = H, **1d** | **3d** | 80 |
| 6 | $R^1$ = 4-OMe, $R^2$ = H, **1e** | **3e** | 96 |
| 7 | $R^1$ = H, $R^2$ = 4-OMe, **1e′** | | 92 |
| 8 | $R^1$ = 3-OMe, $R^2$ = H, **1f** | **3f** | 88 |
| 9 | $R^1$ = H, $R^2$ = 4-*n*-Bu, **1g** | **3g** | 90 |
| 10 | $R^1$ = 4-F, $R^2$ = H, **1h** | **3h** | 80 |
| 11 | $R^1$ = H, $R^2$ = 4-F, **1h′** | | 78 |
| 12 | $R^1$ = 2-F, $R^2$ = H, **1i** | **3i** | 63 |
| 13 | $R^1$ = 3-Cl, $R^2$ = H, **1j** | **3j** | 81 |
| 14 | $R^1$ = H, $R^2$ = 4-Cl, **1k** | **3k** | 80 |
| 15 | $R^1$ = 4-Br, $R^2$ = H, **1l** | **3l** | 81 |
| 16 | $R^1$ = H, $R^2$ = 4-Br, **1l′** | | 77 |
| 17 | $R^1$ = 4-CN, $R^2$ = H, **1m** | **3m** | 75 |
| 18 | $R^1$ = H, $R^2$ = 4-COOMe, **1n** | **3n** | 72 |
| 19 |  **1o** |  **3o** | 66 |
| 20 |  **1o′** | | 58 |
| 21 |  **1p** |  **3p** | 72 |
| 22 |  **1q** |  **3q** | 65 |
| 23 |  **1r** |  **3r** | 60 |
| 24 |  **1s** |  **3s** | 96 |

Table 2 (*Contd.*)

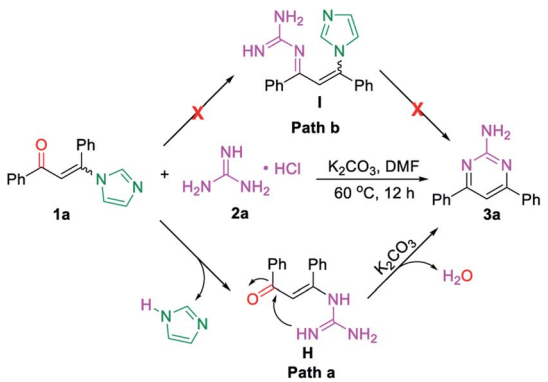



| Entry | | | Yield[b] (%) |
|---|---|---|---|
| 25 | **1a** |  **3t** | 88 |
| 26 | **1a** |  **3u** | 90 |

[a] Under the optimized conditions. [b] Isolated yield. [c] Reaction performed at 10 mmol scale.




Scheme 2 The synthesis of isoxazole and pyrazole.




Scheme 3 Plausible mechanism.

## Conclusions

In conclusion, we have developed a convenient metal-free method for the synthesis of unsymmetrical 2-aminopyrimidines from imidazolate enaminones and guanidine hydrochloride. Imidazolate enaminones with electron-donating and electron-withdrawing groups provided 2-aminopyrimidines in moderate-to-excellent yields. The steric effect on this reaction was also observed. Moreover, the plausible mechanism was proposed base on the synthesis of 5-hydroxy-4,5-dihydroisoxazoles and pyrazoles in the cascade reaction system. This method represents an effective strategy towards the synthesis of unsymmetrical 2-aminopyrimidines.

## Experimental

### General information

Unless otherwise stated, all reagents were used directly without further purification. Silica gel was purchased from Qing Dao Hai Yang Chemical Industry Co. All melting points were determined on a Beijing Science Instrument Dianguang Instrument Factory XT4B melting point apparatus and uncorrected. $^1$H and $^{13}$C NMR spectra were measured on a 400 MHz Bruker spectrometer ($^1$H 400 MHz, $^{13}$C100 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. HRMS-ESI spectra were equipped with an ESI source and a TOF detector. PE is petroleum ether (60–90 °C).

### Typical procedure for the preparation of 4,6-diphenylpyrimidin-2-amine (3a)

A suspension of 3-(1*H*-imidazol-1-yl)-1,3-diphenylprop-2-en-1-one (*E*/*Z*) **1a** (0.5 mmol, 137.0 mg), guanidine hydrochloride **2** (1.0 mmol, 95.5 mg) and $K_2CO_3$ (2.0 mmol, 276.4 mg) in DMF (3 mL) was stirred at 60 °C for 12 h. After **1a** was exhausted completely (monitored by TLC), it was cooled down to room temperature and saturated aqueous brine (10 mL) was added. The mixture was stirred for 10 min and then was extracted by EtOAc (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$. After filtration, removal of the solvent gave a residue, which was purified by a column chromatography (silica gel, PE/EtOAc = 5/1) to afford **3a** as light yellow solid; 116 mg, 94% yield; mp 118–120 °C (lit.[12] 118 °C). IR (KBr) $\nu$ 3307, 3192, 1629, 1365, 763 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 4H), 7.52–7.46 (m, 7H), 5.24 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.2, 163.6, 137.8, 130.4, 128.8, 127.1, 104.3.

### A similar procedure was used for the preparation of products 3b–3t & 3ab–3ed

**4-Phenyl-6-(*p*-tolyl)pyrimidin-2-amine (3b).** 124 mg from **1b**, 95% yield; 120 mg from **1b′**, 92% yield; yellow solid, mp 125–127 °C (lit.[12] 128 °C). IR (KBr) $\nu$ 3314, 3202, 1569, 1365, 770 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 2H), 7.96 (d, $J$ = 8.0 Hz, 2H), 7.49 (m, 3H), 7.45 (s, 1H), 7.30 (d, $J$ = 8.0 Hz, 2H), 5.22 (s, 2H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.1, 166.1, 163.6, 140.8, 137.9, 134.9, 130.4, 129.5, 128.7, 127.1, 127.0, 104.0, 21.4.

**4-Phenyl-6-(*m*-tolyl)pyrimidin-2-amine (3c).** 118 mg, 90% yield; yellow liquid, mp 134–138 °C. IR (KBr) $\nu$ 3309, 3186, 1635, 1366, 768 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 2H), 7.87 (s, 1H), 7.83 (d, $J$ = 8.0 Hz, 1H), 7.49 (m, 3H), 7.44 (s, 1H), 7.38 (t, $J$ = 8.0 Hz, 1H), 7.30 (d, $J$ = 8.0 Hz, 1H), 5.32 (s, 2H), 2.45 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 166.1, 163.6, 138.4, 137.8, 137.7, 131.2, 130.4, 128.7, 128.6, 127.7, 127.1, 124.2, 104.4, 21.5. HRMS *m*/*z* (ESI) calcd for $C_{17}H_{15}N_3$, (M + Na)$^+$ 284.1158; found, 284.1159.

**4-Phenyl-6-(*o*-tolyl)pyrimidin-2-amine (3d).** 105 mg, 80% yield; white solid, mp 134–136 °C. IR (KBr) $\nu$ 3299, 3186, 1629, 1356, 764 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (m, 2H), 7.49–7.43 (m, 4H), 7.36–7.28 (m, 3H), 7.15 (s, 1H), 5.30 (s, 2H), 2.44 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.3, 165.6, 163.2, 138.9, 137.5, 135.7, 130.9, 130.5, 129.1, 128.9, 128.8, 127.1, 126.0, 108.0, 20.2. HRMS *m*/*z* (ESI) calcd for $C_{17}H_{15}N_3$, (M + Na)$^+$ 284.1158; found, 284.1160.

**4-(4-Methoxyphenyl)-6-phenylpyrimidin-2-amine (3e).** 133 mg from **1e**, 96% yield; 127 mg from **1e′**, 92% yield; pink solid, mp 150–152 °C (lit.[12] 152 °C). IR (KBr) $\nu$ 3326, 3196, 1538, 1361, 822 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 8.0 Hz, 4H), 7.49 (m, 3H), 7.41 (s, 1H), 7.00 (d, $J$ = 8.0 Hz, 2H), 5.24 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.0, 165.6, 163.5, 161.6, 137.9, 130.3, 130.1, 128.7, 128.6, 127.1, 114.1, 103.5, 55.4.

**4-(3-Methoxyphenyl)-6-phenylpyrimidin-2-amine (3f).** 122 mg, 88% yield; yellow solid, mp 136–138 °C (lit.[12] 139–140 °C). IR (KBr) $\nu$ 3450, 3314, 1567, 1356, 768 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 2H), 7.62 (m, 2H), 7.53–7.38 (m, 5H), 7.03 (m, 1H), 5.29 (s, 2H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.3, 166.0, 163.6, 160.0, 139.2, 137.7, 130.5, 129.8, 128.8, 127.1, 119.5, 116.4, 112.2, 104.4, 55.4.

**4-(4-Butylphenyl)-6-phenylpyrimidin-2-amine (3g).** 136 mg, 90% yield; yellow solid, mp 90–94 °C. IR (KBr) $\nu$ 2957, 1565, 1531, 1364, 768 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 2H), 7.98 (d, $J$ = 12.0 Hz, 2H), 7.51–7.45 (m, 4H), 7.31 (d, $J$ = 8.0 Hz, 2H), 5.22 (s, 2H), 2.68 (t, $J$ = 8.0 Hz, 2H), 1.64 (m, 2H), 1.38 (m, 2H), 0.94 (t, $J$ = 8.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.3, 166.1, 163.6, 145.8, 137.9, 135.1, 130.4, 128.9, 128.7, 127.1, 127.0, 104.1, 35.5, 33.5, 22.3, 13.9. HRMS *m*/*z* (ESI) calcd for $C_{20}H_{21}N_3$, (M + Na)$^+$ 326.1628; found, 326.1630.

**4-(4-Fluorophenyl)-6-phenylpyrimidin-2-amine (3h).** 106 mg from **1h**, 80% yield; 103 mg from **1h′**, 78% yield; white solid, mp 130–132 °C (lit.[12] 132 °C). IR (KBr) $\nu$ 3333, 3207, 1639, 1228, 768 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09–8.04 (m, 4H), 7.50 (t, $J$ = 4.0 Hz, 3H), 7.42 (s, 1H), 7.18 (t, $J$ = 8.0 Hz, $J$ = 12.0 Hz, 2H), 5.23 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 165.6, 164.4 (d, $J$ = 249.0 Hz), 163.5, 137.6, 133.8 (d, $J$ = 3.0 Hz), 130.5, 129.1 (d, $J$ = 8.0 Hz), 128.8, 127.1, 115.8 (d, $J$ = 1.0 Hz), 103.9.

**4-(2-Fluorophenyl)-6-phenylpyrimidin-2-amine (3i).** 84 mg, 63% yield; yellow solid, mp 123–126 °C. IR (KBr) $\nu$ 3323, 1630, 1358, 759 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 3H), 7.56 (d, $J$ = 4.0 Hz, 1H), 7.50–7.42 (m, 4H), 7.29 (d, $J$ = 8.0 Hz, 1H), 7.19 (dd, $J$ = 8.0 Hz, $J$ = 8.0 Hz, 1H), 5.22 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.1, 163.5, 162.1 (d, $J$ = 2.0 Hz), 161.1 (d, $J$ = 250.0 Hz), 137.6, 131.6 (d, $J$ = 9.0 Hz), 130.6 (d, $J$ = 2.0 Hz),

130.5, 128.8, 127.2, 125.9 (d, $J$ = 11.0 Hz), 124.5 (d, $J$ = 4.0 Hz), 116.4 (d, $J$ = 23.0 Hz), 108.3 (d, $J$ = 11.0 Hz). HRMS $m/z$ (ESI) calcd for $C_{16}H_{12}FN_3$, $(M + Na)^+$ 288.0907; found, 288.0909.

**4-(3-Chlorophenyl)-6-phenylpyrimidin-2-amine (3j).** 114 mg, 81% yield; white solid, mp 118–120 °C (lit.[12] 118 °C). IR (KBr) $\nu$ 3486, 3320, 1638, 1360, 771 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.06–8.01 (m, 3H), 7.92 (d, $J$ = 8.0 Hz, 2H), 7.54–7.38 (m, 6H), 5.54 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.6, 146.7, 163.7, 139.6, 137.6, 134.9, 130.7, 130.4, 130.1, 128.9 (2C), 127.4, 127.2 (2C), 125.3, 104.2.

**4-(4-Chlorophenyl)-6-phenylpyrimidin-2-amine (3k).** 112 mg, 80% yield; yellow solid, mp 158–160 °C (lit.[12] 160 °C). IR (KBr) $\nu$ 3318, 3195, 1634, 1360, 768 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.06–8.00 (m, 4H), 7.51–7.45 (m, 5H), 7.42 (s, 1H), 5.26 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.5, 164.9, 163.6, 137.6, 136.6, 136.1, 130.6, 129.0, 128.8, 128.4, 127.1, 103.9.

**4-(4-Bromophenyl)-6-phenylpyrimidin-2-amine (3l).** 132 mg from **1l**, 81% yield; 126 mg from **1l′**, 77% yield; yellow solid, mp 170–174 °C (lit.[12] 171–172 °C). IR (KBr) $\nu$ 3302, 3192, 1633, 1360, 765 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (m, 2H), 7.95 (d, $J$ = 8.0 Hz, 2H), 7.62 (d, $J$ = 8.0 Hz, 2H), 7.50 (m, 3H), 7.43 (s, 1H), 5.20 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.5, 164.9, 163.6, 137.6, 136.6, 131.9, 130.6, 128.8, 128.6, 127.1, 125.0, 103.9.

**4-(2-Amino-6-phenylpyrimidin-4-yl)benzonitrile (3m).** 102 mg, 75% yield; white solid, mp 184–186 °C. IR (KBr) $\nu$ 3469, 3119, 2322, 1612, 767 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J$ = 8.0 Hz, 2H), 8.06–8.03 (m, 2H), 7.78 (d, $J$ = 8.0 Hz, 2H), 7.53–7.49 (m, 3H), 7.45 (s, 1H), 5.40 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.0, 164.0, 163.8, 142.0, 137.3, 132.6 (2C), 130.9, 129.0 (2C), 127.8 (2C), 127.2 (2C), 118.6, 113.9, 104.5. HRMS $m/z$ (ESI) calcd for $C_{17}H_{12}N_4$, $(M + Na)^+$ 295.0954; found, 295.0951.

**Methyl 4-(2-amino-6-phenylpyrimidin-4-yl)benzoate (3n).** 110 mg, 72% yield; light yellow solid, mp 156–158 °C. IR (KBr) $\nu$ 3386, 3103, 1645, 762 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.16–8.03 (m, 6H), 7.50–7.46 (m, 4H), 5.47 (s, 2H), 3.94 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.8, 165.7, 164.0, 162.8, 140.9, 136.5, 130.7, 129.7, 129.1 (2C), 127.9 (2C), 126.24 (2C), 126.19 (2C), 103.6, 51.4. HRMS $m/z$ (ESI) calcd for $C_{18}H_{15}N_3O_2$, $(M + Na)^+$ 328.1056; found, 328.1058.

**4-Cyclopropyl-6-phenylpyrimidin-2-amine (3o).** 70 mg from **1o**, 66% yield; 61 mg from **1o′**, 58% yield; white solid, mp 122–126 °C. IR (KBr) $\nu$ 2968, 1523, 1510, 1346, 770 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.97–7.94 (m, 2H), 7.45 (t, $J$ = 4.0 Hz, 3H), 6.88 (s, 1H), 5.16 (s, 2H), 1.94–1.88 (m, 1H), 1.12–1.08 (m, 2H), 1.03–0.98 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.5, 164.5, 163.3, 137.7, 130.1, 128.6 (2C), 127.0 (2C), 105.5, 29.6, 17.0, 10.1. HRMS $m/z$ (ESI) calcd for $C_{13}H_{13}N_3$, $(M + Na)^+$ 234.1002; found, 234.1000.

**4-(*tert*-Butyl)-6-phenylpyrimidin-2-amine (3p).** 82 mg, 72% yield; yellow solid, mp 98–102 °C. IR (KBr) $\nu$ 2937, 1545, 1503, 1388, 778 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.98–7.95 (m, 2H), 7.48–7.45 (m, 3H), 7.06 (s, 1H), 5.23 (s, 2H), 1.34 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 179.7, 165.6, 163.1, 138.2, 130.1, 128.6 (2C), 127.0 (2C), 103.4, 37.3, 29.3 (3C). HRMS $m/z$ (ESI) calcd for $C_{13}H_{13}N_3$, $(M + Na)^+$ 250.1315; found, 250.1317.

**4-Phenyl-6-(thiophen-2-yl)pyrimidin-2-amine (3q).** 84 mg, 65% yield; yellow solid, mp 137–140 °C (lit.[12] 208–210 °C). IR (KBr) $\nu$ 3448, 3320, 1580, 1346, 769 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.05–8.00 (m, 2H), 7.78 (d, $J$ = 4.0 Hz, 1H), 7.51–7.47 (m, 4H), 7.36 (s, 1H), 7.15 (t, $J$ = 4.0 Hz, 1H), 5.32 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.2, 163.5, 160.7, 143.2, 137.7, 130.6, 129.3, 128.9 (2C), 128.3, 127.2 (2C), 127.1, 102.6.

**4-Phenyl-6-(thiophen-3-yl)pyrimidin-2-amine (3r).** 76 mg, 60% yield; yellow solid, mp 114–116 °C (lit.[12] 113–115 °C). IR (KBr) $\nu$ 3432, 3347, 1568, 1376, 770 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 4.0 Hz, 1H), 8.05–8.01 (m, 2H), 7.69–7.78 (d, $J$ = 4.0 Hz, 1H), 7.51–7.47 (m, 3H), 7.41 (t, $J$ = 4.0 Hz, 1H), 7.33 (s, 1H), 5.35 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 163.7, 161.7, 140.8, 137.8, 130.6, 128.9 (2C), 127.2 (2C), 126.6, 126.3, 126.3, 104.2.

**4-(Naphthalen-2-yl)-6-phenylpyrimidin-2-amine (3s).** 142 mg, 96% yield; yellow solid, mp 115–118 °C (lit.[12] 113–115 °C). IR (KBr) $\nu$ 3328, 3208, 1645, 805 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.18–8.09 (m, 3H), 7.99–7.88 (m, 3H), 7.59 (s, 1H), 7.55–7.51 (m, 5H), 5.48 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 166.2, 163.8, 137.9, 135.1, 134.5, 133.3, 130.6, 129.0, 128.9 (2C), 128.6, 127.8, 127.3 (2C), 127.2, 126.6, 124.3, 104.6.

**2,4,6-Triphenylpyrimidine (3t).** 136 mg, 88% yield; yellow solid, mp 186–188 °C. IR (KBr) $\nu$ 2858, 1559, 1354, 760 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.75 (d, $J$ = 8.0 Hz, 2H), 8.31 (d, $J$ = 8.0 Hz, 4H), 8.02 (s, 1H), 7.60–7.53 (m, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.7, 164.5, 138.1, 137.5, 130.8, 130.6, 128.9, 128.5, 128.4, 127.3, 110.3.

***N*,*N*-Dimethyl-4,6-diphenylpyrimidin-2-amine (3u).** 124 mg, 90% yield; yellow solid, mp 124–126 °C. IR (KBr) $\nu$ 3325, 1632, 1363, 766 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (m, 4H), 7.52–7.46 (m, 6H), 7.37 (s, 1H), 3.36 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.0, 162.9, 138.5, 130.2, 128.6, 127.1, 101.0, 37.0. HRMS $m/z$ (ESI) calcd for $C_{18}H_{17}N_3$, $(M + Na)^+$ 298.1315; found, 298.1317.

**3,5-Diphenyl-4,5-dihydroisoxazol-5-ol (3ab).** 102 mg, 86% yield; white solid, mp 163–165 °C (lit.[17] 161–163 °C). IR (KBr) $\nu$ 3378, 3298, 1597, 1363, 761 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.71–7.65 (m, 4H), 7.44–7.38 (m, 6H), 3.68 (d, $J$ = 20.0 Hz, 1H), 3.49 (d, $J$ = 16.0 Hz, 1H), 3.20 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.4, 140.7, 130.4, 129.2, 129.0, 128.8, 128.6, 126.8, 125.6, 107.7, 49.0.

**3,5-Diphenyl-1*H*-pyrazole (3ac).** 99 mg, 90% yield; white solid, mp 198–200 °C (lit.[17] 201–203 °C). IR (KBr) $\nu$ 2830, 1461, 685 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 11.35 (s, 1H), 7.72 (d, $J$ = 8.0 Hz, 4H), 7.41–7.37 (m, 4H), 7.35–7.31 (m, 2H), 6.83 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 128.9, 128.2, 125.6, 100.1.

**3-(4-Methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-5-ol (3e′b).** 101 mg, 75% yield; white solid, mp 130–132 °C (lit.[17] 130–132 °C). IR (KBr) $\nu$ 3369, 3300, 1611, 1373, 775 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (m, 4H), 7.39 (m, 3H), 6.92 (d, $J$ = 8.0 Hz, 2H), 3.84 (s, 3H), 3.65 (d, $J$ = 16.0 Hz, 1H), 3.46 (d, $J$ = 16.0 Hz, 1H), 3.26 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.3, 157.0, 140.8, 128.9, 128.5 (2C), 128.3 (2C), 125.6 (2C), 121.8, 114.2 (2C), 107.4, 55.4, 49.2.

**5-(4-Methoxyphenyl)-1,3-diphenyl-1*H*-pyrazole (3ed).** 133 mg, 82% yield; white solid, mp 78–80 °C (lit.[17] 77–79 °C). IR (KBr) $\nu$ 2826, 1458, 676 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 8.0 Hz, 2H), 7.47–7.31 (m, 8H), 7.22 (d, $J$ = 8.0 Hz, 2H),

6.86 (d, $J = 8.0$ Hz, 2H), 6.79 (s, 1H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.5, 151.8, 144.2, 140.2, 133.1, 130.0 (2C), 128.8 (2C), 128.6 (2C), 127.9, 127.3, 125.7 (2C), 125.2 (2C), 122.9, 113.9, 104.6, 55.2.

## Conflicts of interest

There are no conflicts to declare.

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