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A facile synthesis of 2-aryloxypyrimidine derivatives via a tandem reductive amination/intermolecular S_NAr sequence*

Hai-feng WU[1], Pei-zhi ZHANG[2], Jun WU[†‡1]

([1]*Department of Chemistry, Zhejiang University, Hangzhou 310027, China*)

([2]*School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, Hangzhou 310012, China*)

[†]E-mail: wujunwu@zju.edu.cn

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Abstract: A novel tandem reductive amination/intermolecular nucleophilic aromatic substitution (S_NAr) sequence has been established for the synthesis of amine containing pyrimidine in formation of one carbon-oxygen and one carbon-nitrogen bonds in a one-pot fashion. Treatment of aldehyde with arylamine, 2-methanesulfonyl-4,6-dimethoxypyrimidine and sodium borohydride provides good overall yield. The *p*-toluenesulfonic acid (PTSA) can be used as activator and is generally needed in the reaction. Dioxane is the preferred reaction solvent, but reactions can also be carried out in tetrahydrofuran (THF), MeCN, toluene and dichloromethane. The procedure is carried out effectively in the presence of K_2CO_3. The reaction proceeds smoothly with aromatic aldehydes and arylamines possessing electron-donating or -withdrawing groups. This method can be applied to the synthesis of the oilseed rape herbicide and is superior to the classical one in several aspects: cutting out several purification steps, minimizing solvent use and chemical waste, and saving time. Its advantages such as operational convenience, high-efficient synthesis, and starting material availability make it a desirable method for preparing amines with molecular diversity and biological activity.

Key words: Reductive amination/intermolecular S_NAr, C-O and C-N bonds, Amine, Pyrimidine, Herbicide
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1 Introduction

Reductive amination, where a mixture of an aldehyde (or ketone) and an amine is treated with a reductant, is one of the most useful methods in organic synthesis (Li *et al*., 2009; Tripathi *et al*., 2008; Gomez *et al*., 2002; Abdel-Magid and Mehrman, 2006). The reaction involves the initial formation of an intermediate carbinol amine **1** (Fig. 1), which dehydrates to form an imine (Schiff base) or iminium ion **2**, and the reduction of **2** produces the alkylated amine **3** (Abdel-Magid *et al*., 1996). Because of one-pot reaction, mild reaction conditions, and use of eco-friendly reagents, the reaction is widely used in the preparation of different kinds of amines such as natural products, drugs, and agrochemicals (Guo and O′Doherty, 2008; Küenburg *et al*., 1999; Liu *et al*., 2009; Posner, 1986), and is also ideally suitable for generating molecular diversity since it provides rapid and general access to C-N bond (Dinsmore and Zartman, 2000; Lev *et al*., 1995).

Recently, the development of tandem reductive amination has attracted considerable attention due to steadily increasing academic, economic and ecological interest. For example, Selig *et al*. (2009) developed a three-step reductive amination domino sequence for generation of the central pyrrolidine ring of natural (+)-meloscine. Nöth *et al*. (2008) described a new reductive amination/intramolecular/lactamization sequence to the highly substituted γ-lactams in a single manipulation. Beshore and Dinsmore (2002)

‡ Corresponding author

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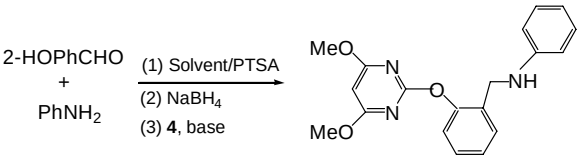
developed a one-pot, tandem reductive amination/transamidation/cyclization reaction to produce substituted piperazin-2-ones in good yields. Bunce *et al*. (2008; 2009) reported a tandem reductive amination-S_NAr cyclization to produce the target heterocycles. These sequential transformations have proved quite efficient for the construction of organic compounds, which form several bonds in a single pot. However, a literature survey shows that there are no reports on a one-pot, tandem reductive amination/intermolecular S_NAr sequence. As a continuation of our interest in improving synthetic efficiency in generating biological molecules, in the present study, we designed a system to explore the feasibility of high-efficient synthesis of amines with a pyrimidine skeleton in a one-pot fashion as shown in Fig. 2.

2 Results and discussion

Initially, our studies began with screening of various solvents for reductive amination/intermolecular S_NAr. The reactions were conducted by adding 2-hydroxybenzaldehyde (5 mmol) to a solution of aniline (5 mmol) and *p*-toluenesulfonic acid (PTSA, 10% mole fraction), then stirred at room temperature for 0.5 h, and followed by addition of $NaBH_4$ (1 equiv.). After being stirred for 0.5 h, the reaction mixture was then directly added with 2-methanesulfonyl-4,6-dimethoxypyrimidine **4** (1 equiv.) and the base (1.5 equivs.), and heated to reflux for 6 h. The results are summarized in Table 1.

Among the solvents tested, ethanol was associated with a lower yield. The reaction gave the product **5a** in only 46% yield (Entry 1) accompanied by the side product 2-ethoxy-4,6-dimethoxypyrimidine in 40% yield due to the occurrence of S_NAr reaction

Table 1 Optimization of the reaction conditions for the reductive amination/intermolecular S_NAr:



5a

Entry	Solvent	Activator	Base	Yield (%)[a]
1	EtOH	None	K_2CO_3	46
2	THF	None	K_2CO_3	0[b]
3	Dioxane	PTSA	K_2CO_3	82
4	THF	PTSA	K_2CO_3	75
5	MeCN	PTSA	K_2CO_3	62
6	Toluene	PTSA	K_2CO_3	60
7	CH_2Cl_2	PTSA	K_2CO_3	50
8	THF	PTSA	Na_2CO_3	70

[a] Isolated yields; [b] The first step proceeded unsuccessfully in the given time, so the following step was not carried on

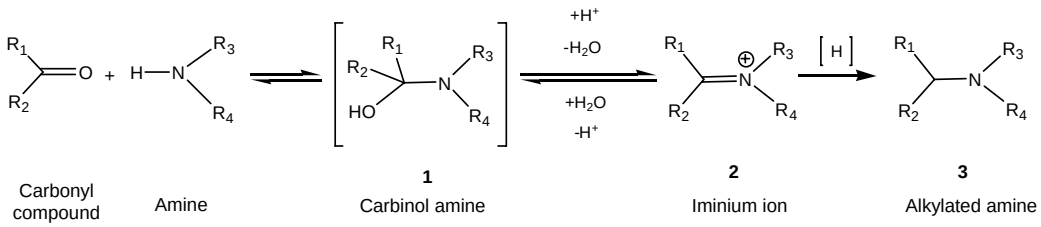


Fig. 1 Scheme of reductive amination

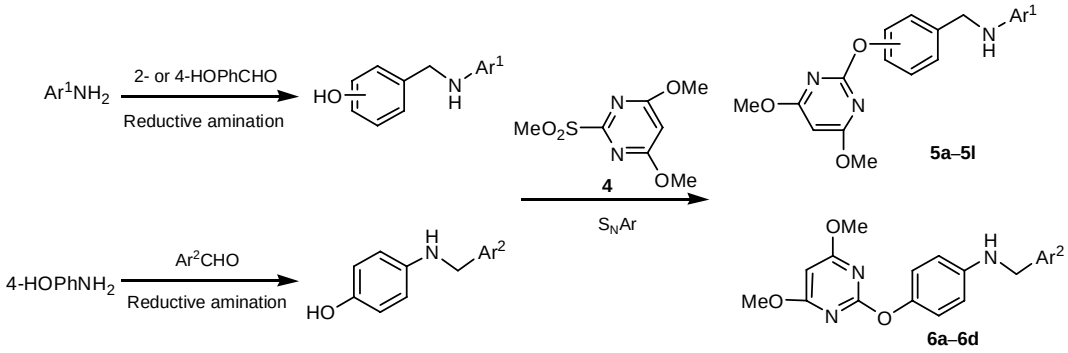


Fig. 2 Scheme of tandem reductive amination/intermolecular S_NAr sequence

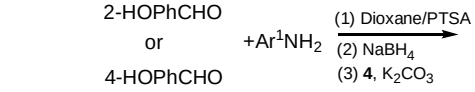
between ethoxide and **4**. This result indicates that ethanol was not a good solvent for reductive amination/intermolecular S_NAr procedure. Unfortunately, the reaction in reductive amination step was sluggish in aprotic solvents such as tetrahydrofuran (THF), and the following S_NAr was not carried on (Entry 2). Next, we investigated the co-effect of solvents and the activator PTSA on the reaction, because PTSA has been proven to be an efficient and mild acid catalyst for formation of imines or iminium ions (Cho and Kang, 2005). Notably, the best yield was achieved with dioxane as the solvent (82%, Entry 3). In addition, other results were obtained by carrying out the reaction in THF (75%, Entry 4), MeCN (62%, Entry 5), toluene (60%, Entry 6), dichloromethane (50%, Entry 7).

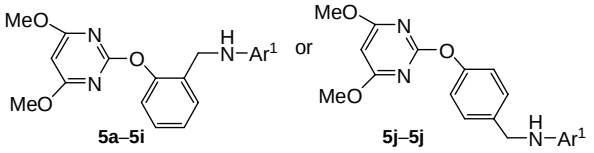
We then investigated the effect of base on the reaction. As shown in Table 1 (Entries 4 and 8), K_2CO_3 was found to be a more appropriate base in the reductive amination/intermolecular S_NAr. Therefore, the optimized conditions employ 1 equiv. of 2-hydroxybenzaldehyde, 1 equiv. of aniline, 1 equiv. of **4**, 1 equiv. of $NaBH_4$, 1.5 equivs. of K_2CO_3, and 10% mole fraction of activator PTSA in dioxane.

With the optimal reaction conditions in hand, we moved on to examine the reductive amination/intermolecular S_NAr of structurally different aldehydes with various arylamines. The reaction of 2-hydroxybenzaldehyde with arylamines proceeded smoothly to give the corresponding amines **5a**–**5i** after recrystallization from ethanol or petroleum ether. Arylamines with electron-donating and -withdrawing groups all gave good overall isolated yields (Table 2, Entries 1–8). Sterically-hindered α-naphthylamine gave **5i** in a slight lower yield (Table 2, Entry 9). Interestingly, 4-hydroxybenzaldehyde reacted well with arylamines, but much longer reaction time (1.5 h) was required in the reductive amination (Table 2, Entries 10–12). It is noteworthy that *p*-chloroaniline and *p*-methylaniline also generated the desired amines **5j**–**5k** in the range of 82%–84% yield, but *m*-methylaniline gave **5l** only 75% (Table 2, Entry 12). Under the same condition, we then explored the reductive amination/intermolecular S_NAr of 4-aminophenol with different arylaldehydes. The results are shown in Table 3. All the reactions provided desired amines **6** in the range of 79%–83% overall yields.

The oilseed rape herbicide **7** is highly active, displaying a novel class of chemistry (Lu *et al*., 2002;

Table 2 Reductive amination/intermolecular S_NAr of 2- or 4-hydroxybenzaldehyde with arylamines and 4 to given *N*-aryl-pyrimidinyloxybenzylamines[a]:

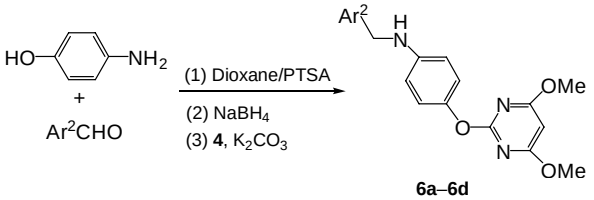




Entry	Aldehyde	Ar^1NH_2	Product	Yield (%)[b]
1	2-HOC_6H_4CHO	C_6H_5	**5a**	82
2	2-HOC_6H_4CHO	3-MeC_6H_4	**5b**	82
3	2-HOC_6H_4CHO	4-MeC_6H_4	**5c**	84
4	2-HOC_6H_4CHO	3-ClC_6H_4	**5d**	80
5	2-HOC_6H_4CHO	4-ClC_6H_4	**5e**	83
6	2-HOC_6H_4CHO	4-FC_6H_4	**5f**	85
7	2-HOC_6H_4CHO	4-BrC_6H_4	**5g**	87
8	2-HOC_6H_4CHO	4-$MeOC_6H_4$	**5h**	82
9	2-HOC_6H_4CHO	1-naphthyl	**5i**	78
10	4-HOC_6H_4CHO	4-ClC_6H_4	**5j**	84[c]
11	4-HOC_6H_4CHO	4-$MeOC_6H_4$	**5k**	82[c]
12	4-HOC_6H_4CHO	3-MeC_6H_4	**5l**	75[c]

[a] Reactions were performed with hydroxybenzaldehyde (5 mmol), arylamines (5 mmol) and *p*-toluenesulfonic acid (PTSA) (0.5 mmol) in dioxane by stirring at room temperature for 30 min, followed by addition of $NaBH_4$ (1 equiv.). After 30 min, **4** (1 equiv.) and K_2CO_3 (1.5 equivs.) were added directly to the vessel. The resultant mixture was heated to reflux for 6 h; [b] Isolated yields; [c] The reductive amination reaction required 1.5 h

Table 3 Reductive amination/intermolecular S_NAr of various arylaldehydes with 4-aminophenol and 4 to given *N*-arylmethyl-4-pyrimidinyloxyanilines[a]:



Entry	Ar^2CHO	Product	Yield (%)[b]
1	C_6H_5	**6a**	80
2	4-$O_2NC_6H_4$	**6b**	83
3	4-ClC_6H_4	**6c**	82
4	2-furanyl	**6d**	79

[a] Reactions were performed using the same stoichiometric proportions and conditions as shown in Table 2. The reductive amination reaction required 1.5 h; [b] Isolated yields

Wu *et al*., 2006). Traditionally, the synthesis of the herbicide **7** was realized by a stepwise procedure. The condensation of salicylaldehyde and 2-bromoaniline formed a carbinolamine, which eliminated H_2O to give the Schiff base. Subsequently, the Schiff base was reduced to the amine, followed by the nucleophilic substitution with **4** to give the herbicide **7** (Wu *et al*., 2006). This multi-step synthetic route suffers from certain drawbacks including tedious experimental procedures and use of multi-solvents, which is unfavorable from the viewpoint of green chemistry (Tietze, 1996). Thus, there is a need for more efficient and simple synthetic methods for creating the herbicide **7**. The one-pot synthesis of herbicide **7** using the tandem reductive amination/intermolecular S_NAr sequence (Fig. 3) further demonstrates the efficiency of this approach (Fig. 3). This new route offers a valuable alternative to the stepwise procedure and is superior to the classical method in several aspects: cutting out several purification steps, minimizing solvent use and chemical waste, and saving time.

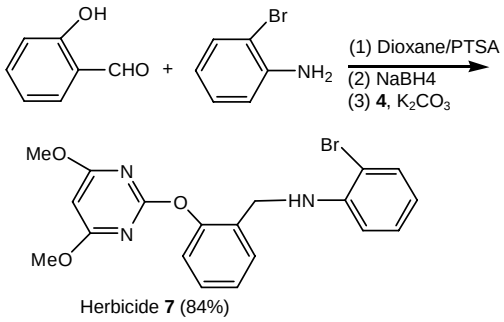


Fig. 3 Scheme of the tandem one-pot synthesis of herbicide 7

3 Conclusion

In summary, we have established a tandem reductive amination/intermolecular S_NAr sequence for the synthesis of amines with a pyrimidine skeleton. The reaction was tolerated with a variety of aromatic aldehydes and arylamines possessing electron-donating or -withdrawing groups. This method can also be applied to the synthesis of the oilseed rape herbicide. The advantages of the method, such as operational convenience, good overall yields, single solvent, high chemoselectivity, and starting material availability, make it a desirable method for preparing different kinds of amines with molecular diversity and biological activity.

4 Experimental section

Solvents and reagents were obtained from commercial sources and used without further purification. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DMX 500 MHz spectrometer or otherwise noted. Mass spectra were recorded with an HP 5989B spectrometer using the electronic ionization (EI) method or on a Bruker Esquire 3000 spectrometer using electrospray ionization (ESI) technique (low-resolution MS). Infrared spectra (IR) were recorded on a Nicolet Nexus 470 FT-IR spectrometer using potassium bromide tablets. Microanalyses were carried out with a Carlo Erba 1110 elemental analyzer. Melting points were taken on an X-4 melting point apparatus and are uncorrected.

4.1 Typical experimental procedures for synthesis of *N*-phenyl-2-(4,6-dimethoxypyrimidin-2-yloxy) benzylamine 5a (Table 2, Entry 1)

In a typical experiment, salicylaldehyde (5 mmol), aniline (5 mmol), and dioxane (35 ml) were mixed into a 100 ml round bottom flask and stirred with a magnetic stir bar. To this, *p*-toluenesulfonic acid (PTSA, 0.5 mmol) was added. Afterwards, the mixture was stirred for 30 min at room temperature, followed by addition of $NaBH_4$ in proportion. After 30 min, the 2-methanesulfonyl-4,6-dimethoxypyrimidine **4** (5 mmol) and K_2CO_3 (7.5 mmol) were added directly to the flask. The resultant mixture was heated to reflux for 6 h, and monitored by thin layer chromatography (TLC). Then, the solid was filtered off, and the filtrate was evaporated. The residue was purified by recrystallization from ethanol.

4.2 *N*-phenyl-2-(4,6-dimethoxypyrimidin-2-yloxy) benzylamine 5a (Table 2, Entry 1)

White solid; m.p. 87–88 °C; IR (KBr): 3399, 3106, 2958, 1600, 1511, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.82 (s, 6H, 2×OCH_3), 4.35 (s, 2H, CH_2), 5.79 (s, 1H, pyrimidine ring), 6.56 (d, J=8.0 Hz, 2H, Ar), 6.69 (m, 1H, Ar), 7.11–7.15 (m, 3H, Ar), 7.16–7.17 (m, 1H, Ar), 7.31 (m, 1H, Ar), 7.47–7.49 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 43.5 (CH_2), 54.4 (OCH_3), 84.8 (CH), 113.0 (CH), 117.6 (CH), 122.8 (CH), 125.9 (CH), 128.3 (CH), 129.1 (CH), 129.3 (CH), 131.8 (C), 148.2 (C), 151.1 (C), 164.5 (C), 173.2 (C); MS (ESI): m/z=338.3 ($[M+H]^+$).

Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.55; H, 5.71; N, 12.52.

4.3 *N*-(3-methylphenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5b (Table 2, Entry 2)

White solid; m.p. 61–62 °C; IR (KBr): 3325, 3039, 2927, 1597, 1482, 1354 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.22 (s, 3H, CH_3), 3.79 (s, 6H, 2×OCH_3), 3.80–4.30 (br s, 1H, NH), 4.31 (s, 2H, CH_2), 5.76 (s, 1H, pyrimidine ring), 6.36 (d, *J*=6.5 Hz, 2H, Ar), 6.49 (d, *J*=8.0 Hz, 1H, Ar), 6.97–7.01 (m, 1H, Ar), 7.12–7.29 (m, 3H, Ar), 7.44–7.46 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.8 (CH_3), 43.6 (CH_2), 54.4 (OCH_3), 84.8 (CH), 110.2 (CH), 113.9 (CH), 118.6 (CH), 122.8 (CH), 125.9 (CH), 128.3 (CH), 129.2 (2×CH), 132.0 (C), 139.1 (C), 148.3 (C), 151.2 (C), 164.5 (C), 173.2 (C); MS (EI): *m*/*z* (%)=351 (M^+, 11), 245 (37), 194 (42), 107 (100). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.34; H, 5.94; N, 11.92.

4.4 *N*-(4-methylphenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5c (Table 2, Entry 3)

White solid; m.p. 65–66 °C; IR (KBr): 3358, 2993, 1589, 1481, 1355, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.20 (s, 3H, CH_3), 3.80 (s, 6H, 2×OCH_3), 3.82–4.29 (br s, 1H, NH), 4.30 (s, 2H, CH_2), 5.76 (s, 1H, pyrimidine ring), 6.47 (d, *J*=8.0 Hz, 2H, Ar), 6.91 (d, *J*=8.0 Hz, 2H, Ar), 7.11–7.28 (m, 3H, Ar), 7.45 (d, *J*=7.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.5 (CH_3), 43.8 (CH_2), 54.4 (OCH_3), 84.8 (CH), 113.2 (CH), 122.8 (CH), 125.9 (CH), 126.8 (C), 128.8 (CH), 129.1 (CH), 129.3 (CH), 132.1 (C), 145.9 (C), 151.1 (C), 164.5 (C), 173.2 (C); MS (EI): *m*/*z* (%)=351 (M^+, 100), 245 (67), 194 (42), 107 (95). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.32; H, 5.96; N, 11.96.

4.5 *N*-(3-chlorophenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5d (Table 2, Entry 4)

Pale yellow solid; m.p. 102–103 °C; IR (KBr): 3309, 2942, 1599, 1482, 1364, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.82 (d, *J*=6.8 Hz, 6H, 2×OCH_3), 3.81–4.31 (br s, 1H, NH), 4.32 (s, 2H, CH_2), 5.79 (s, 1H, pyrimidine ring), 6.39–6.42 (m, 1H, Ar), 6.50–6.51 (m, 1H, Ar), 6.62–6.64 (m, 1H, Ar), 6.98–7.02 (m, 1H, Ar), 7.15–7.34 (m, 3H, Ar), 7.42 (d, *J*=7.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 43.2 (CH_2), 54.2 (OCH_3), 84.6 (CH), 111.1 (CH), 112.4 (CH), 117.2 (CH), 122.7 (CH), 125.7 (CH), 128.3 (CH), 128.8 (CH), 130.0 (CH), 130.9 (C), 134.8 (C), 149.0 (C), 150.9 (C), 164.2 (C), 173.0 (C); MS (EI): *m*/*z* (%)=373 [M^+ (^{37}Cl), 3.6], 371 [M^+ (^{35}Cl), 10.2], 245 (93), 214 (37), 157 (100). Anal. Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.23; H, 4.84; N, 11.49.

4.6 *N*-(4-chlorophenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5e (Table 2, Entry 5)

Pale yellow solid; m.p. 109–110 °C; IR (KBr): 3318, 2926, 1597, 1482, 1365, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.80 (s, 6H, 2×OCH_3), 3.80–4.57 (br s, 1H, NH), 4.30 (s, 2H, CH_2), 5.77 (s, 1H, pyrimidine ring), 6.44–6.46 (m, 2H, Ar), 7.03–7.04 (m, 2H, Ar), 7.12–7.30 (m, 3H, Ar), 7.41 (d, *J*=6.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 43.7 (CH_2), 54.4 (OCH_3), 84.8 (CH), 114.1 (CH), 122.1 (C), 123.0 (CH), 125.9 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 131.3 (C), 146.7 (C), 151.2 (C), 164.5 (C), 173.2 (C); MS (ESI): *m*/*z*=374.3 [$(M+H)^+$ (^{37}Cl)], 372.2 [$(M+H)^+$ (^{35}Cl)]. Anal. Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.47; H, 4.91; N, 11.31.

4.7 *N*-(4-fluorophenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5f (Table 2, Entry 6)

Pale yellow solid; m.p. 93–94 °C; IR (KBr): 3326, 2931, 1597, 1509, 1364, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.79 (s, 6H, 2×OCH_3), 3.80–4.27 (br s, 1H, NH), 4.28 (s, 2H, CH_2), 5.77 (s, 1H , pyrimidine ring), 6.45–6.48 (m, 2H, Ar), 6.80 (t, *J*=9.0 Hz, 2H, Ar), 7.12–7.30 (m, 3H, Ar), 7.42–7.44 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 43.9 (CH_2), 54.1 (OCH_3), 84.5 (CH), 113.6 (d, *J*=8 Hz, CH), 115.4 (d, *J*=22 Hz, CH), 122.6 (CH), 125.7 (CH), 128.1 (CH), 128.8 (CH), 131.4 (C), 144.3 (d, *J*=2 Hz, C), 150.9 (C), 155.8 (d, *J*=230 Hz, C), 164.2 (C), 173.0 (C); MS (EI): *m/z* (%)=355 (M^+, 15), 245 (100), 198 (87), 157 (67). Anal. Calcd for $C_{19}H_{18}FN_3O_3$: C, 64.22; H, 5.11; N, 11.82. Found: C, 64.26; H, 5.05; N, 11.78.

4.8 *N*-(4-bromophenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5g (Table 2, Entry 7)

White solid; m.p. 111–112 °C; IR (KBr): 3316, 2971, 1597, 1481, 1354, 1218 cm^{-1}; ^1H NMR ($CDCl_3$,

500 MHz) δ: 3.81 (d, 6H, J=6.4 Hz, 2×OCH_3), 4.43 (s, 2H, CH_2), 5.78 (s, 1H, pyrimidine ring), 6.52–6.59 (m, 2H, Ar), 7.06–7.44 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 43.3 (CH_2), 54.1 (OCH_3), 84.5 (CH), 108.9 (C), 114.4 (CH), 122.7 (CH), 125.7 (CH), 128.3 (CH), 128.8 (CH), 131.0 (C), 131.7 (CH), 146.8 (C), 150.9 (C), 164.2 (C), 173.0 (C); MS (EI): m/z (%)=417 [M^+ (^{81}Br), 10], 415 [M^+ (^{79}Br), 10], 245 (100), 157 (65). Anal. Calcd for $C_{19}H_{18}BrN_3O_3$: C, 54.82; H, 4.36; N, 10.09. Found: C, 54.91; H, 4.42; N, 10.10.

4.9 *N*-(4-methoxyphenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5h (Table 2, Entry 8)

White solid; m.p. 103–104 °C; IR (KBr): 3359, 2963, 1604, 1518, 1357, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.71 (s, 3H, OCH_3), 3.80 (s, 6H, 2×OCH_3), 4.27 (s, 2H, CH_2), 6.51–6.52 (m, 2H, Ar), 5.76 (s, 1H, pyrimidine ring), 6.70–6.71 (m, 2H, Ar), 7.12–7.28 (m, 3H, Ar), 7.45–7.46 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 44.4 (CH_2), 54.4 (OCH_3), 56.0 (OCH_3), 84.8 (CH), 114.4 (CH), 115.0 (CH), 122.8 (CH), 125.9 (CH), 128.2 (CH), 129.2 (CH), 132.1 (C), 142.4 (C), 151.1 (C), 152.3 (C), 164.5 (C), 173.2 (C); MS (EI): m/z (%)=368 [$(M+H)^+$, 17], 245 (38), 196 (25), 123 (100). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.36; H, 5.88; N, 11.30.

4.10 *N*-(naphthalen-1-yl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5i (Table 2, Entry 9)

White solid; m.p. 113–114 °C; IR (KBr): 3446, 2955, 1602, 1482, 1362, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.78 (s, 6H, 2×OCH_3), 4.53 (s, 2H, CH_2), 4.81 (br s, 1H, NH), 5.68 (s, 1H, pyrimidine ring), 6.57 (d, J=7.5 Hz, 1H, Ar), 7.17–7.26 (m, 4H, Ar), 7.33–7.38 (m, 2H, Ar), 7.43 (m, 1H, Ar), 7.51 (d, J=7.5 Hz, 1H, Ar), 7.69 (d, J=8.5 Hz, 1H, Ar), 7.77 (d, J=8.0 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 43.9 (CH_2), 54.4 (OCH_3), 84.6 (CH), 104.9 (CH), 117.5 (CH), 120.0 (CH), 123.0 (CH), 123.5 (C), 124.7 (CH), 125.8 (CH), 126.0 (CH), 126.7 (CH), 128.6 (CH), 128.8 (CH), 129.5 (CH), 131.4 (C), 134.4 (C), 143.2 (C), 151.4 (C), 164.6 (C), 173.2 (C); MS (ESI): m/z=388.3 ([M+H]$^+$). Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.25; H, 5.41; N, 10.81.

4.11 *N*-(4-chlorophenyl)-4-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5j (Table 2, Entry 10)

White solid; m.p. 67–68 °C; IR (KBr): 3307, 2931, 1585, 1459, 1356, 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.83 (s, 6H, 2×OCH_3), 3.90–4.24 (br s, 1H, NH), 4.30 (s, 2H, CH_2), 5.78 (s, 1H, pyrimidine ring), 6.54 (d, J=8.8 Hz, 2H, Ar), 7.10 (d, J=8.0 Hz, 2H, Ar), 7.18 (d, J=8.4 Hz, 2H, Ar), 7.35 (d, J=8.0 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 47.8 (CH_2), 54.1 (OCH_3), 84.5 (CH), 113.9 (CH), 121.9 (CH), 122.1 (C), 128.2 (CH), 129.0 (CH), 135.5 (C), 146.5 (C), 152.0 (C), 164.1 (C), 172.9 (C); MS (ESI): m/z= 374.3 [$(M+H)^+$ (^{37}Cl)], 372.3 [$(M+H)^+$ (^{35}Cl)]. Anal. Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.33; H, 4.87; N, 11.26.

4.12 *N*-(4-methoxyphenyl)-4-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5k (Table 2, Entry 11)

White solid; m.p. 70–71 °C; IR (KBr): 3350, 2962, 1600, 1509, 1364, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.73 (s, 3H, OCH_3), 3.82 (s, 6H, 2×OCH_3), 4.28 (s, 2H, CH_2), 5.77 (s, 1H, pyrimidine ring), 6.60–6.62 (m, 2H, Ar), 6.76–6.79 (m, 2H, Ar), 7.17–7.18 (m, 2H, Ar), 7.37 (d, J=8.5 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 49.0 (OCH_3), 54.4 (OCH_3), 56.0 (CH_2), 84.8 (CH), 114.4 (CH), 115.1 (CH), 122.1 (CH), 128.5 (CH), 136.5 (C), 142.5 (C), 152.1 (C), 152.5 (C), 164.4 (C), 173.1 (C); MS (ESI): m/z=368.3 ([M+H]$^+$). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.26; H, 5.86; N, 11.40.

4.13 *N*-(3-methylphenyl)-4-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 5l (Table 2, Entry 12)

Brown oily liquid; IR (KBr): 3413, 2934, 1607, 1470, 1363, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.28 (s, 3H, CH_3), 3.85 (s, 6H, 2×OCH_3), 3.97 (br s, 1H, NH), 4.34 (s, 2H, CH_2), 5.79 (s, 1H, pyrimidine ring), 6.49–6.58 (m, 3H, Ar), 7.07–7.08 (m, 1H, Ar), 7.19–7.20 (m, 2H, Ar), 7.39 (d, J=8.5 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.6 (CH_3), 47.8 (CH_2), 54.1 (OCH_3), 84.6 (CH), 110.0 (CH), 113.6 (CH), 118.6 (CH), 121.8 (CH), 128.2 (CH), 129.1 (CH), 136.2 (C), 139.0 (C), 148.1 (C), 151.9 (C), 164.1 (C), 172.9 (C); MS (ESI): m/z=352.3 ([M+H]$^+$).

4.14 Typical experimental procedure for synthesis of *N*-benzyl-4-(4,6-dimethoxypyrimidin-2-yloxy) aniline 6a (Table 3, Entry 1)

In a typical experiment, 4-aminophenol (5 mmol), benzaldehyde (5 mmol) and dioxane (35 ml) were mixed into a 100 ml round bottom flask and stirred with a magnetic stir bar. To this, *p*-toluenesulfonic acid (PTSA, 0.5 mmol) was added. Afterwards, the mixture was stirred for 1 h at room temperature, followed by addition of $NaBH_4$ in proportion. After 30 min, the 2-methanesulfonyl-4,6-dimethoxypyrimidine **4** (5 mmol) and K_2CO_3 (7.5 mmol) were added directly to the flask. The resultant mixture was heated to reflux for 6 h and monitored by TLC. Then, the solid was filtered off, and the filtrate was evaporated. The residue was purified by recrystallization from ethanol.

4.15 *N*-benzyl-4-(4,6-dimethoxypyrimidin-2-yloxy) aniline 6a (Table 3, Entry 1)

White solid; m.p. 65–66 °C; IR (KBr): 3403, 2935, 1604, 1514, 1358, 1222 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.83 (s, 6H, 2×OCH_3), 3.82–4.31 (br s, 1H, NH), 4.31 (s, 2H, CH_2), 5.74 (s, 1H, pyrimidine ring), 6.63 (d, *J*=8.5 Hz, 2H, Ar), 7.02 (d, *J*=8.5 Hz, 2H, Ar), 7.25–7.39 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 49.1 (CH_2), 54.3 (OCH_3), 84.4 (CH), 113.3 (CH), 122.6 (CH), 127.5 (CH), 127.8 (CH), 128.8 (CH), 139.5 (C), 144.7 (C), 145.6 (C), 165.0 (C), 173.1 (C); MS (ESI): *m*/*z*=338.1 ($[M+H]^+$). Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.66; H, 5.70; N, 12.50.

4.16 *N*-(4-nitrobenzyl)-4-(4,6-dimethoxypyrimidin-2-yloxy)aniline 6b (Table 3, Entry 2)

Yellow solid; m.p. 116–117 °C; IR (KBr): 3384, 1597, 1514, 1364, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.83 (s, 6H, 2×OCH_3), 4.10–4.45 (br s, 1H, NH), 4.46 (s, 2H, CH_2), 5.74 (s, 1H, pyrimidine ring), 6.57 (d, *J*=8.5 Hz, 2H, Ar), 7.01–7.02 (m, 2H, Ar), 7.54 (d, *J*=8.5 Hz, 2H, Ar), 8.17–8.19 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 48.3 (CH_2), 54.3 (OCH_3), 84.3 (CH), 113.4 (CH), 122.8 (CH), 124.0 (CH), 128.0 (CH), 144.8 (C), 145.0 (C), 147.4 (C), 147.6 (C), 164.8 (C), 173.1 (C); MS (ESI): *m*/*z*=383.3 ($[M+H]^+$). Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.61; H, 4.75; N, 14.63.

4.17 *N*-(4-chlorobenzyl)-4-(4,6-dimethoxypyrimidin-2-yloxy)aniline 6c (Table 3, Entry 3)

Brown solid; m.p. 100–101 °C; IR (KBr): 3386, 2961, 1597, 1512, 1363, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.82 (s, 6H, 2×OCH_3), 3.84–4.25 (br s, 1H, NH), 4.28 (s, 2H, CH_2), 5.73 (s, 1H, pyrimidine ring), 6.58–6.60 (m, 2H, Ar), 7.09 (d, *J*=9.0 Hz, 2H, Ar), 7.30 (s, 4H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 48.3 (CH_2), 54.3 (OCH_3), 84.4 (CH), 113.3 (CH), 122.7 (CH), 128.9 (CH), 129.0 (CH), 133.1 (C), 138.1 (C), 144.8 (C), 145.3 (C), 165.0 (C), 173.1 (C); MS (ESI): *m*/*z*=374.3 [$(M+H)^+$ (^{37}Cl)], 372.3 [$(M+H)^+$ (^{35}Cl)]. Anal. Calcd for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.27; H, 4.84; N, 11.25.

4.18 *N*-((furan-2-yl)methyl)-4-(4,6-dimethoxypyrimidin-2-yloxy)aniline 6d (Table 3, Entry 4)

White solid; m.p. 68–69 °C; IR (KBr): 3396, 2937, 1605, 1514, 1364, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.82 (s, 6H, 2×OCH_3), 3.82–4.30 (br s, 1H, NH), 4.30 (s, 2H, CH_2), 5.74 (s, 1H, pyrimidine ring), 6.23–6.24 (m, 1H, Ar), 6.31–6.32 (m, 1H, Ar), 6.66 (d, *J*=8.5 Hz, 2H, Ar), 7.03 (d, *J*=9 Hz, 2H, Ar), 7.36 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 42.1 (CH_2), 54.3 (OCH_3), 84.4 (CH), 107.3 (CH), 110.5 (CH), 113.7 (CH), 122.6 (CH), 142.2 (C), 145.0 (CH), 145.1 (C), 152.8 (C), 165.0 (C), 173.1 (C); MS (ESI): *m*/*z*=328.1 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.29; H, 5.22; N, 12.76.

4.19 *N*-(2-bromophenyl)-2-(4,6-dimethoxypyrimidin-2-yloxy)benzylamine 7

White solid; m.p. 95–96 °C; IR (KBr): 3310, 2977, 1597, 1480, 1356, 1219 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.79 (s, 6H, 2×OCH_3), 4.41 (s, 2H, CH_2), 4.66 (br s, 1H, NH), 5.77 (s, 1H, pyrimidine ring), 6.50–6.56 (m, 2H, Ar), 7.04–7.30 (m, 5H, Ar), 7.42 (d, *J*=7.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ: 43.3 (CH_2), 54.4 (OCH_3), 84.9 (CH), 109.7 (CH), 111.8 (CH), 118.0 (CH), 123.0 (CH), 126.0 (CH), 128.5 (2×CH), 128.8 (CH), 131.1 (C), 132.5 (C), 144.8 (C), 151.2 (C), 164.5 (C), 173.2 (C); MS (EI): *m*/*z* (%)=417 [M^+ (^{81}Br), 7], 415 [M^+ (^{79}Br), 7], 245 (100), 180 (30), 157 (48). Anal. Calcd for $C_{19}H_{18}BrN_3O_3$: C, 54.82; H, 4.36; N, 10.09. Found: C, 54.73; H, 4.42; N, 10.14.

4.20 2-ethoxy-4,6-dimethoxypyrimidine

White solid; m.p. 42–43 °C; IR (KBr): 3103, 2982, 1578, 1467, 1375, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.42 (t, J=7.0 Hz, 3H, CH_3), 3.92 (s, 6H, 2×OCH_3), 4.40 (q, J=7.0 Hz, 2H, CH_2), 5.69 (s, 1H, pyrimidine ring); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.6 (CH_3), 54.1 (OCH_3), 63.5 (CH_2), 83.4 (CH), 164.6 (C), 172.9 (C); MS (ESI): m/z=185.3 ($[M+H]^+$). Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.34; H, 6.67; N, 15.36.

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