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Original article

Direct amination of pyrimidin-2-yl tosylates with aqueous ammonia under metal-free and mild conditions

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ABSTRACT

A metal-free synthesis of pyrimidine functionalized primary amines *via* direct amination of pyrimidin-2-yl tosylate with aqueous ammonia has been developed under mild conditions. The desired products pyrimidin-2-amines can be generated in excellent yields in PEG-400, without any catalysts or other additives.

1. Introduction

Q2 Primary (hetero)aryl amines are widely used in the synthesis of natural products, pharmaceuticals, agrochemicals as well as polymers and materials [1]. The common methods for preparation of primary amines include coupling of aryl halides with ammonia [2], reductive amination of carbonyl compounds [3], and hydroamination of alkenes [4–6]. Recently, ammonia, as one of the most attractive sources of nitrogen, has attracted a lot of attentions due to its great abundance and extremely low cost [7,8]. Very recently, a few methodological advancements for coupling aryl halides with aqueous ammonia to deliver aryl primary amines under mild conditions have been developed [9,10].

Aryl sulfonates that are easily prepared, usually crystalline, and lower toxicity, are with potential values to investigate as better materials to synthesize primary amines. Despite great progress toward the preparation of primary amines has been made, selective synthesis of primary amines from ammonia still encounters challenges, *i.e.* requirement of transition-metal, overreactions of primary amines with ammonia. Hence, further efforts were needed to developing a metal-free, mild method for the selective synthesis of primary amines directly from aqueous ammonia.

3,4-Dihydropyrimidinones and their derivatives have consequently been extensively used as a drug-like scaffold [11] and utilization as important precursors in the synthesis of pyrimidine bases [12]. In continuation of our ongoing interest in the synthesis of 3,4-dihydropyrimidinone derivatives [13], we are recently interesting in the synthesis of 2-aminopyrimidines.

2-Aminopyrimidines show interesting biological activities such as inhibitors of rhoassociated protein kinase [14,15], glycogen synthase kinase 3 (GSK3) [16], and of *N*-type calcium channels [17]. Notably, the 2-amino-4-arylpyrimidine heterocycle is also found in important drugs such as the hypocholesterolemic agent rosuvastatin [18,19] and the potent anticancer drug Gleevec [20].

Usually, 2-aminopyrimidine subunits are constructed by condensation reactions of enones with corresponding guanidine or nitrogen-containing building blocks [21]. In 2007, Kappe et al. [22] have described a three-step procedure to convert Biginelli DHPMs to 2-methylsulfonyl-pyrimidines, which subsequently converted to 2-aminopyrimidine by the substitution of the reactive sulfonyl group with ammonium acetate as substitute for NH_3 (Scheme 1, Method A).

Herein we developed a metal-free approach for the synthesis of 2-aminopyrimidines directly from pyrimidin-2-yl tosylates with aqueous ammonia under mild conditions in PEG medium (Scheme 1, Method B).

2. Experimental

Commercially available reagents were used without further purification unless otherwise stated. Melting points were measured on a XT-4 apparatus and are uncorrected. NMR spectra were

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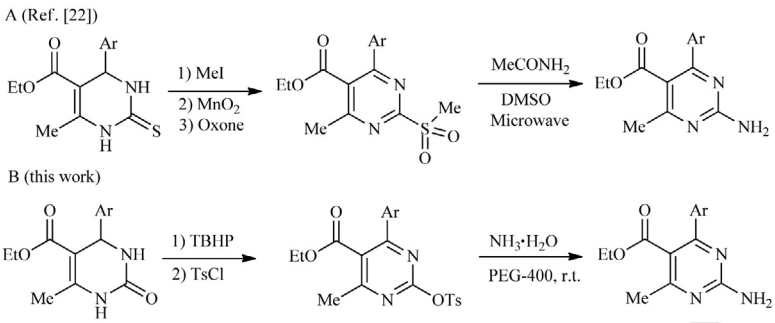

Scheme 1. Synthesis of the 2-aminopyrimidines starting from 3,4-dihydropyrimidinones.

recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEX II 47e mass spectrometer. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were on silica gel GF254 plates.

2.1. General procedure for the synthesis of 2-amino pyrimidines (**2a**–**2n**)

The pyrimidin-2-yl tosylate (**1**, 1.0 mmol), PEG-400 (2 mL) and ammonia water (10 mmol) were added into a test tube. The tube was then sealed with a balloon, and the mixture was stirred at r.t. for 24 h. Then the mixture was poured into water to precipitate the product. Crude product was obtained by means of vacuum filtration, and was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) and (1:1) to give the corresponding products **2a**–**i** and **2j**–**n**, respectively.

Ethyl 2-amino-4-methyl-6-phenylpyrimidine-5-carboxylate (**2a**): White solid, mp 132–133 °C [22]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H), 7.41 (d, 3H, J = 5.2 Hz), 5.82 (s, 2H), 4.05 (q, 2H, J = 7.2 Hz), 2.48 (s, 3H), 0.94 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.31, 167.48, 166.47, 161.98, 138.60, 129.35, 128.15, 127.63, 115.95, 61.00, 22.58, 13.40.

Ethyl 2-amino-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (**2b**): White solid, mp 167–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.49 (m, 2H), 7.08 (t, 2H, J = 8.6 Hz), 5.82 (d, 2H, J = 10.0 Hz), 4.07 (q, 2H, J = 7.2 Hz), 2.48–2.40 (m, 3H), 1.00 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.30, 167.60, 164.98 (d, J = 38.0 Hz), 162.31, 161.92, 134.70, 129.84 (d, J = 8.0 Hz), 116.14, 115.27 (d, J = 22.0 Hz), 61.16, 22.65, 13.58; HRMS: calcd. for $C_{14}H_{15}FN_3O_2$ $[M+H]^+$: 276.1143; found 276.1147.

Ethyl 2-amino-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**2c**): White solid, mp 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 5.74 (s, 2H), 4.08 (q, 2H, J = 7.2 Hz), 2.46 (s, 3H), 1.01 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.11, 167.71, 165.07, 161.83, 137.00, 135.66, 129.16, 128.41, 116.09, 61.17, 22.67, 13.53; HRMS: calcd. for $C_{14}H_{15}ClN_3O_2$ $[M+H]^+$: 293.0847; found 293.0851.

Ethyl 2-amino-4-(4-bromophenyl)-6-methylpyrimidine-5-carboxylate (**2d**): White solid, mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.4 Hz), 5.88 (s, 2H), 4.08–4.03 (m, 2H), 2.43 (s, 3H), 0.98 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.09, 167.78, 165.19, 161.92, 137.49, 131.39, 129.42, 123.95, 116.11, 61.22, 22.70, 13.56; HRMS: calcd. for $C_{14}H_{15}BrN_3O_2$ $[M+H]^+$: 336.0342; found 336.0345.

Ethyl 2-amino-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (**2e**): White solid, mp 151–153 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 2H, J = 7.6 Hz), 7.20 (d, 2H, J = 7.6 Hz), 5.87 (s, 2H), 4.08 (q, 2H, J = 6.8 Hz), 2.45 (s, 3H), 2.37 (s, 3H), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.62, 167.23, 166.30, 161.96, 139.60, 135.66, 128.91, 127.70, 116.12, 61.09, 22.62, 21.27, 13.55; HRMS: calcd. for $C_{15}H_{18}N_3O_2$ $[M+H]^+$: 272.1394; found 272.1400.

Ethyl 2-amino-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (**2f**): White solid, mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, 2H, J = 8.0 Hz), 6.91 (d, 2H, J = 8.0 Hz), 5.95 (d, 2H, J = 29.2 Hz), 4.10 (q, 2H, J = 7.2 Hz), 3.81 (s, 3H), 2.42 (s, 3H), 1.03 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.79, 167.07, 165.56, 161.98, 160.82, 130.88, 129.41, 115.85, 113.65, 61.07, 55.24, 22.53, 13.66; HRMS: calcd. for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1343; found 288.1348.

Ethyl 2-amino-4-methyl-6-(4-nitrophenyl)pyrimidine-5-carboxylate (**2g**): White solid, mp 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.27 (d, 1H, J = 8.0 Hz), 7.84 (d, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 8.0 Hz), 5.75 (s, 2H), 4.11 (q, 2H, J = 7.2 Hz), 2.49 (s, 3H), 1.03 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.45, 167.65, 163.86, 161.94, 140.25, 129.23, 124.11, 123.16, 116.07, 61.43, 22.98, 13.64; HRMS: calcd. for $C_{14}H_{15}N_4O_4$ $[M+H]^+$: 303.1088; found 303.1093.

Ethyl 2-amino-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate (**2h**): White solid, mp 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.28 (d, 1H, J = 8.0 Hz), 7.85 (d, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 8.0 Hz), 5.73 (s, 2H), 4.12 (q, 2H, J = 6.8 Hz), 2.50 (s, 3H), 1.04 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.45, 167.64, 163.85, 161.92, 148.06, 140.25, 133.86, 129.23, 124.11, 123.16, 116.05, 61.42, 22.98, 13.64; HRMS: calcd. for $C_{14}H_{15}N_4O_4$ $[M+H]^+$: 303.1088; found 303.1095.

Methyl 2-amino-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate (**2i**): White solid, mp 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 2H), 7.11 (t, 2H, J = 6.6 Hz), 5.56 (d, 2H, J = 12.4 Hz), 3.62 (s, 3H), 3.13 (s, 1H), 1.25 (t, 6H, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.27, 169.32, 164.78, 164.46, 162.42, 134.65, 129.78 (d, J = 8.0 Hz), 115.51, 115.29, 52.14, 32.82, 21.50; HRMS: calcd. for $C_{15}H_{17}FN_3O_2$ $[M+H]^+$: 290.1299; found 290.1302.

6-Methyl-N^2-phenylpyrimidine-2,4-diamine (**2j**): White solid, mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.52 (d, 2H, J = 7.6 Hz), 7.20 (t, 2H, J = 7.2 Hz), 6.90 (t, 1H, J = 7.4 Hz), 5.70 (s, 1H), 4.77 (s, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.97, 163.81, 159.45, 139.89, 128.64, 121.97, 119.32, 95.48, 23.25; HRMS: calcd. for $C_{11}H_{13}N_4$ $[M+H]^+$: 201.1135; found 201.1139.

6-Methyl-N^2-*o*-tolylpyrimidine-2,4-diamine (**2k**): White solid, mp 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 1H, J = 8.0 Hz), 7.11 (q, 2H, J = 8.0 Hz), 6.90 (t, 1H, J = 7.2 Hz), 6.60 (s, 1H), 5.71 (s, 1H), 4.60 (s, 2H), 2.21 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.73, 163.89, 160.33, 137.96, 130.28, 128.36, 126.34, 122.95, 121.83, 95.47, 23.76, 18.10; HRMS: calcd. for $C_{12}H_{15}N_4$ $[M+H]^+$: 215.1291; found 215.1295.

6-Methyl-N^2-*m*-tolylpyrimidine-2,4-diamine (**2l**): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 3H), 7.09 (t, 1H, J = 7.6 Hz), 6.72 (d, 1H, J = 7.2 Hz), 5.70 (s, 1H), 4.75 (s, 2H), 2.24 (s,

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3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.26, 163.84, 159.72, 139.83, 138.43, 128.52, 122.86, 119.97, 116.57, 95.45, 23.48, 21.51; HRMS: calcd. for $C_{12}H_{15}N_4$ $[M+H]^+$: 215.1291; found 215.1297.

6-Methyl-N^2-*p*-tolylpyrimidine-2,4-diamine (**2m**): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 1H, *J* = 7.2 Hz), 7.35 (d, 2H, *J* = 7.2 Hz), 6.98 (d, 2H, *J* = 7.6 Hz), 5.66 (s, 1H), 4.74 (s, 2H), 2.20 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.38, 163.85, 159.93, 137.30, 131.53, 129.17, 119.79, 95.34, 23.54, 20.69; HRMS: calcd. for $C_{12}H_{15}N_4$ $[M+H]^+$: 215.1291; found 215.1294.

N^2-(4-Chlorophenyl)-6-methylpyrimidine-2,4-diamine (**2n**): White solid, mp 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 1H, *J* = 8.0 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 5.72 (s, 1H), 4.76 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.48, 163.74, 158.89, 138.43, 128.45, 126.60, 120.41, 95.62, 22.86; HRMS: calcd. for $C_{11}H_{12}ClN_4$ $[M+H]^+$: 235.0745; found 235.0758.

4-Nitroaniline: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.64 (s, 2H), 6.59–6.61 (m, 2H), 7.09–7.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 116.15, 123.02, 129.03, 144.88.

3. Results and discussion

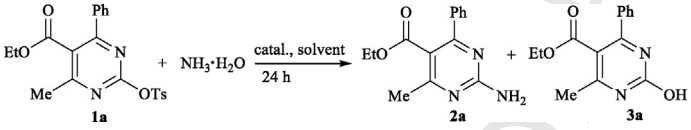
The work was initiated with the optimization of the reaction conditions of the direct amination of pyrimidin-2-yl tosylate **1a** with aqueous ammonia, utilizing 20 equiv. of sodium dodecylbenzenesulfonate (SDBS) as phase-transfer catalyst (PTC) and dioxane as solvent at 100 °C for 12 h (Table 1). As our prediction, the reaction afforded the amination product 2-aminopyrimidine **2a** in a yield of 69% (entry 1), however, hydrolyzed product pyrimidin-2-ol **3a** of **1a** was also isolated in 41% yield. Lowering the temperature to 50 °C resulted in a higher yield of **2a** (entry 2). When the SDBS was changed to hexadecyl trimethyl ammonium bromide (HTAB), cetylpyridinium chloride (CPC) and bromohexadecyl pyridine (CPB), the yield of **2a** increased (84–89%) and trace of **3a** was detected (entries 3–6). In order to find a cheaper PTC, PEG was tested. To our delight, only using PEG-200 without any other solvents, the reaction gave a good yield of **2a** and the hydrolyzation of **1a** was completely inhibited (entries 6 and 7). Further testing implied that PEG-400 was the best one among the PEG-200, PEG-400, PEG-600 and PEG-800 to give **2a** in 86% yield (entries 7–10). Higher temperature slightly enhanced the yield at a shorter time (entries 11 and 12). Therefore, our focus was concentrated on the solvents and reaction conditions. Notably, base can greatly accelerate the translation of **1a** into the byproduct **3a** (82%), with the yields of **2a** tremendously declined (entry 13). Download the amount of aqueous ammonia to 5 equiv. caused lower transformation (entry 14). Thus, the optimal conditions for this reaction were established: using PEG-400 as the reaction medium to perform the reaction at r.t. for 24 h.

Under the optimized conditions, the amination of pyrimidin-2-yl tosylates (**1a**–**i**) with aqueous ammonia was tested in the reaction scope (Scheme 2). In general, good yields of the desired products were obtained. The reaction tolerated a variety of pyrimidin-2-yl tosylates containing the electron-withdrawing group as well as the electron-donating group on the phenyl ring to deliver the products (**2a**–**i**) with good yields. Compared with the previous reports, this non-catalytic approach was proven to be a powerful tool for the amines preparation in mild conditions with the lower-priced ammonia water as ammonia source [22].

Given the operational simplicity and broad generality of this direct amination protocol, we explored to demonstrate the utility of this strategy for the similar amine 2-aminopyrimidines using pyrimidin-4-yl tosylates (**1j**–**n**) as substrates. The desired products (**2j**–**n**) were also obtained in moderate yields under this simple reaction conditions. However, lower yields were observed, which due to the hydrolyzation of the starting materials.

To further demonstrate the versatility of the above described amination protocol, aryl- and pyridinyl tosylates were tested with aqueous ammonia. Unfortunately, only the aryl tosylate with strong electron-withdrawing substituent (NO_2) underwent the amination to afford 4-nitroaniline in 50% yield. However, phenyl tosylate and pyridine-2-yl tosylate did not undergo amination with aqueous ammonia.

Table 1
Optimization of conditions of pyrimidin-2-yl tosylate with $NH_3{\cdot}H_2O$.[a]



Entry	$NH_3{\cdot}H_2O$ (equiv.)	Solvent (PTC)	Temp (°C)	Yield (%)[b]	
				2a	**3a**
1[c]	10	Dioxane/SDBS	50	45	41
2	10	Dioxane/SDBS	r.t.	69	21
3	10	Dioxane/CTAB	r.t.	89	Trace
4	10	Dioxane/CPC	r.t.	84	Trace
5	10	Dioxane/CPB	r.t.	87	Trace
6	10	Dioxane/PEG-200	r.t.	78	Trace
7	10	PEG-200	r.t.	77	Trace
8	10	PEG-400	r.t.	86	Trace
9	10	PEG-600	r.t.	74	Trace
10	10	PEG-800	r.t.	58	Trace
11[c]	10	PEG-400	50	85	Trace
12[c]	10	PEG-400	100	88	Trace
13[d]	10	PEG-400	r.t.	10	82
14	5	PEG-400	r.t.	68	Trace

[a] *Reaction conditions*: pyrimidin-2-yl 4-methylbenzenesulfonates (**1a**) (1.0 mmol), commercial 28% aqueous NH_3 (10 mmol), solvent (2 mL).
[b] Isolated yield.
[c] The reaction time is 12 h.
[d] K_3PO_4 (0.1 mmol) was added.

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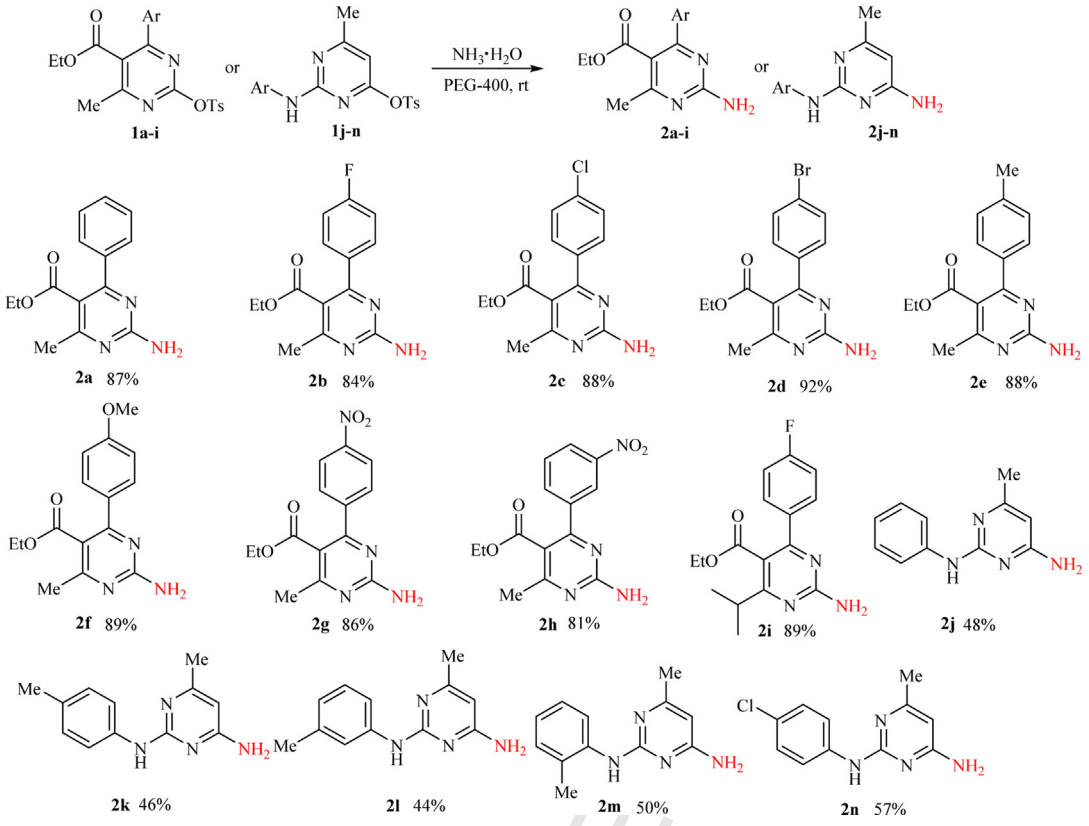

Scheme 2. Scope of the amination of pyrimidin-4-yl tosylates with $NH_3 \cdot H_2O$.

4. Conclusions

In conclusion, we introduced a novel approach for amination of pyrimidinyl-2-tosylates with aqueous ammonia. The desired products 2-aminepyrimidines can be generated in high yields in mild conditions, without any catalysts or other additives. Meanwhile, the similar pyrimidin-4-yl tosylates and aryl tosylates substituted by electron-withdrawing substituents such as $-NO_2$ afforded the desired product under the simple reaction conditions.

Acknowledgments

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