Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient and Benign One-Pot Conversion of N-Tosyl-1,4,5,6-tetrahydropyrimidines to Pyrimidines via Tandem β-Elimination and Aromatization

Tien Ha Trieu [a], Jing Dong [a], Xiao-Xin Shi [a], Xia Lu [a] & Qiang Zhang [a]

[a] Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, Shanghai, China

Accepted author version posted online: 03 Jul 2013.Published online: 04 Sep 2013.

To cite this article: Tien Ha Trieu, Jing Dong, Xiao-Xin Shi, Xia Lu & Qiang Zhang (2013) Efficient and Benign One-Pot Conversion of N-Tosyl-1,4,5,6-tetrahydropyrimidines to Pyrimidines via Tandem β-Elimination and Aromatization, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:23, 3141-3152, DOI: 10.1080/00397911.2013.764433

To link to this article: http://dx.doi.org/10.1080/00397911.2013.764433

Synthetic Communications®, 43: 3141–3152, 2013

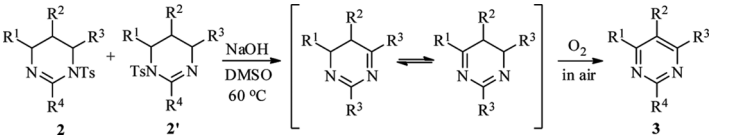
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.764433

EFFICIENT AND BENIGN ONE-POT CONVERSION OF *N*-TOSYL-1,4,5,6-TETRAHYDROPYRIMIDINES TO PYRIMIDINES VIA TANDEM β-ELIMINATION AND AROMATIZATION

Tien Ha Trieu, Jing Dong, Xiao-Xin Shi, Xia Lu, and Qiang Zhang

Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, Shanghai, China

GRAPHICAL ABSTRACT



Abstract *An efficient, mild, benign, and practical method for one-pot conversion of* N-*tosyl-1,4,5,6-tetrahydropyrimidines into pyrimidines is discussed in detail. In this method,* N-*tosyl-1,4,5,6-tetrahydropyrimidines are first prepared via* N-*tosylation of tetrahydropyrimidines with TsCl and then treated with 1.5 equivalents of NaOH in dimethylsulfoxide (DMSO) under air at 60 °C to afford corresponding pyrimidines in 70–95% yields via cascade* β-*elimination and aromatization.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resources: Full experimental and spectral details.]*

Keywords Aromatization; β-elimination; nitrogen-containg heterocycles; pyrimidines; synthetic methods; *N*-tosyl-1,4,5,6-tetrahydropyrimidines

INTRODUCTION

Pyrimidines are important nitrogen-containing heterocyclic aromatic compounds. This kind of compound has found wide applications in many areas. For example, they have exhibited various pharmaceutical properties,[1] and some potencies as pesticides and herbicides;[2] they have also been used as ligands in many organic transformations[3] and as functional molecules in material chemistry.[4] Therefore, development of efficient and practical methods for the synthesis of pyrimidines is of great interest for synthetic chemists.

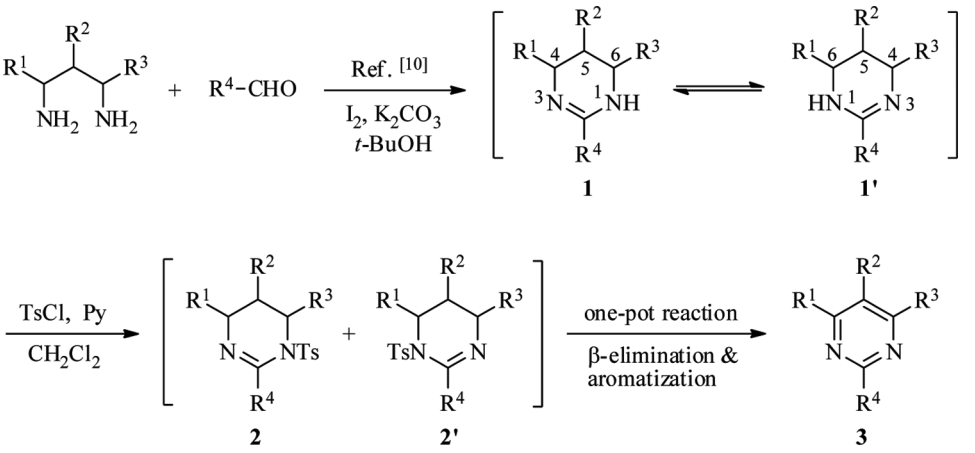
Received October 5, 2012.

Address correspondence to Xiao-Xin Shi, Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, 130 Mei-long Road, Shanghai 200237, China. E-mail: xxshi@ecust.edu.cn

There are two main approaches for the synthesis of various substituted pyrimidines. The first one is direct construction of the pyrimidine ring by two-component[5–7] or three-component[8] cyclizations. The other one is indirect formation of the desired pyrimidines, in which tetrahydro or dihydro-pyrimidines are first prepared, and then these tetrahydro or dihydro intermediates are converted into pyrimidines by aromatization via dehydrogenation or oxidation.[9] Because most aromatization methods suffered from the use of strong oxidants,[9b–9i] noble metal catalyst,[9j] or harsh reaction conditions,[9k] a novel, facile, and practical conversion of tetrahydro or dihydro-pyrimidines into the corresponding pyrimidines without the use of strong oxidants, noble metal catalysts, or harsh conditions would be highly desirable. Herein, we report an efficient, robust, mild, and benign one-pot synthesis of various substituted pyrimidines from the readily available *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines via tandem β-elimination and aromatization.

RESULTS AND DISCUSSION

A novel synthetic route for the synthesis of various substituted pyrimidines is depicted in Scheme 1. Oxidative condensation of 1,3-diamines with aldehydes first produced 1,4,5,6-tetrahydro-pyrimidines **1** according to a known procedure.[10] In this transformation, when symmetric 1,3-diamines ($R^1 = R^3$) were used, pure compounds **1** were obtained, whereas if unsymmetric 1,3-diamines ($R^1 \neq R^3$) were used, tautomeric mixtures of compounds **1** and **1′** would be obtained. Treatment of either pure compounds **1** ($R^1 = R^3$) or the tautomeric mixtures of compounds **1** and **1′** ($R^1 \neq R^3$) with *p*-toluenesulfonyl chloride in the presence of pyridine in dichloromethane would then give *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** ($R^1 = R^3$) or isomeric mixtures of compounds **2** and **2′** ($R^1 \neq R^3$). The compounds **2** ($R^1 = R^3$) or the isomeric mixtures of compounds **2** and **2′** ($R^1 \neq R^3$) were finally converted into the desired pyrimidines **3** via a one-pot procedure via tandem β-elimination and aromatization. Conversion of *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** (or **2** + **2′**)



Scheme 1. Novel synthesis of various substituted pyrimidines from 1,3-diamines and aldehydes.

to pyrimidines **3** is the key step for the whole synthesis. However, a literature search showed this particular conversion is unknown yet, which prompted us to investigate it in detail.

At first, we examined the conversion of *N*-tosyl-2-(3-ethoxy-phenyl)-1,4,5,6-tetrahydropyrimidine **2a** into 2-(3-ethoxyphenyl)-pyrimidine **3a** under various conditions, and results are summarized in Table 1. Seven solvents were tested (Table 1, entries 1–7), and it was found that dimethylsulfoxide (DMSO) was the best solvent for the conversion (entry 7). Other solvents such as ethanol, *iso*-propanol, propanol, *tert*-butanol, butanol, and *N,N*-dimethylformamide (DMF) were not appropriate because the reactions in these five solvents were much slower and gave the desired pyrimidine **3a** only in poor or moderate yields. Strong bases such as NaOH and KOH were necessary for the reaction (entries 7 and 8); weak bases such as sodium carbonate and potassium carbonate only gave trace amounts of the desired product **3a** (entries 9 and 10).

To explore the generality of the conversion, various substituted *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** (or **2** + **2′**) were first prepared as per Scheme 1, and then these *N*-tosyl-tetrahydro intermediates were treated with 1.5 equivalents of powdered sodium hydroxide in DMSO at 60 °C for 3–7 h. A total of 24 *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** (or **2** + **2′**) were tested. All of these intermediates could be smoothly converted into the desired pyrimidines **3a**–**3x** in good to excellent yields (70–95%), and the results are listed in Table 2.

As can be seen from Table 2, either *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** ($R^1 = R^3$, entries 1–18) or the isomeric mixtures of compounds **2** + **2′** ($R^1 \neq R^3$, entries 19–24) could be successfully used as the substrate. Notablely, when substituents R^1 are different from substituents R^3 ($R^1 \neq R^3$), the isomeric mixtures of intermediate compounds **2** and **2′** were directly used as the substrate without isolation for the conversion (Table 2, entries 19–24). Because the subsequent one-pot reactions of both isomeric *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** and **2′** would afford the same desired pyrimidines **3**, isolation of the isomeric intermediate compounds **2** and **2′** was not necessary.

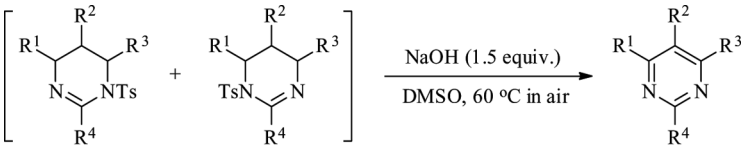
A plausible mechanism for the conversion is proposed in Scheme 2. *N*-Tosyl-1,4,5,6-tetrahydro-pyrimidines **2** and **2′** first underwent β-elimination[11]

Table 1. Conversion of compound **2a** to compound **3a** with various bases under different conditions

Entry	Substrate	Solvent	Base (equiv.)	Temp. (°C)	Time (h)	Product	Yield (%)[a]
1	**2a**	EtOH	NaOH (1.5)	78[b]	20	**3a**	<5
2	**2a**	*i*-PrOH	NaOH (1.5)	82[b]	20	**3a**	38
3	**2a**	*n*-PrOH	NaOH (1.5)	97[b]	20	**3a**	43
4	**2a**	*t*-BuOH	NaOH (1.5)	82[b]	20	**3a**	52
5	**2a**	*n*-BuOH	NaOH (1.5)	118[b]	11	**3a**	62
6	**2a**	DMF	NaOH (1.5)	80	27	**3a**	<5
7	**2a**	DMSO	NaOH (1.5)	60	4	**3a**	80
8	**2a**	DMSO	KOH (1.5)	60	4	**3a**	78
9	**2a**	DMSO	Na_2CO_3 (3)	125	21	**3a**	<5
10	**2a**	DMSO	K_2CO_3 (3)	125	21	**3a**	<5

[a]Isolated yield.
[b]Reflux.

Table 2. One-pot conversion of *N*-tosyl-1,4,5,6-tetrahydropyrimidines (*N*-Ts-THP) **2** (or **2** + **2′**) into the corresponding pyrimidines **3**

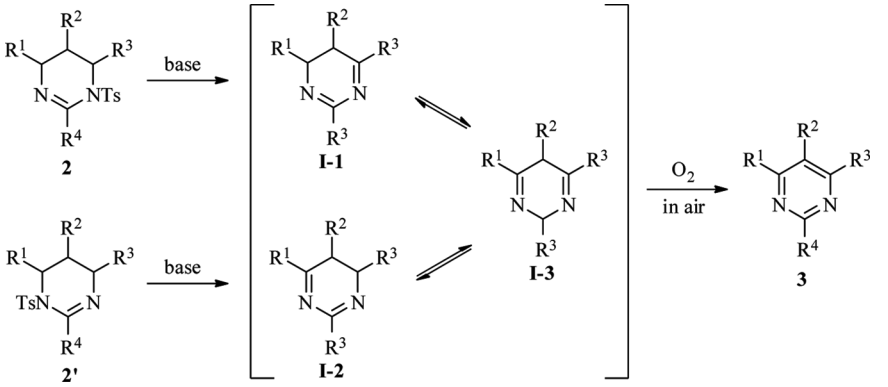


2 **2'** **3**

Entry	*N*-Ts-THP **2** (or **2** + **2′**)	R^1	R^2	R^3	R^4	Time (h)	Product **3**[lit.]	Yield (%)[a]
1	**2a**	H	H	H	3-EtO-Ph	4	**3a**	80
2	**2b**	H	H	H	4-MeO-Ph	4	**3b**[12]	87
3	**2c**	H	H	H	3,4-(CH_2O_2)-Ph	4	**3c**	85
4	**2d**	H	H	H	2-Cl-Ph	4	**3d**	75
5	**2e**	H	H	H	2-Furanyl	3	**3e**[13]	70
6	**2f**	H	H	H	2-EtO-Ph	4	**3f**	80
7	**2g**	H	H	H	3,4,5-$(MeO)_3$-Ph	4	**3g**	88
8	**2h**	H	H	H	3,4-$(MeO)_2$-Ph	4	**3h**[12]	85
9	**2i**	H	H	H	Ph	5	**3i**[12]	81
10	**2j**	Ph	H	Ph	Ph	4	**3j**[14]	92
11	**2k**	Ph	H	Ph	4-MeO-Ph	4	**3k**[15]	94
12	**2l**	Ph	H	Ph	3,4,5-$(MeO)_3$-Ph	4	**3l**	94
13	**2m**	Ph	H	Ph	3,4-(CH_2O_2)-Ph	4	**3m**	95
14	**2n**	Ph	H	Ph	*i*-Pr	7	**3n**	83
15	**2o**	Ph	H	Ph	*n*-Pr	7	**3o**[16]	82
16	**2p**	H	*n*-Bu	H	4-MeO-Ph	6	**3p**	75
17	**2q**	H	*n*-Bu	H	3,4-(CH_2O_2)-Ph	6	**3q**	85
18	**2r**	H	*n*-Bu	H	3,4,5-$(MeO)_3$-Ph	6	**3r**	77
19	**2s** + **2s′**	Ph	H	4-MeO-Ph	3,4,5-$(MeO)_3$-Ph	4	**3s**	95
20	**2t** + **2t′**	Ph	H	4-MeO-Ph	3,4-(CH_2O_2)-Ph	4	**3t**	90
21	**2u** + **2u′**	Ph	H	2-Cl-Ph	4-MeO-Ph	4	**3u**	85
22	**2v** + **2v′**	Ph	H	2-Cl-Ph	3,4-(CH_2O_2)-Ph	4	**3v**	80
23	**2w** + **2w′**	Ph	H	2-Furanyl	4-MeO-Ph	4	**3w**	87
24	**2x** + **2x′**	Ph	H	2-Furanyl	3,4-(CH_2O_2)-Ph	4	**3x**	85

[a]Isolated yield.

under basic conditions to give intermediates **I-1** and **I-2**, respectively. The intermediates **I-1** and **I-2** then rapidly tautomerized into each other via another intermediate **I-3**.[9h] The subsequent in situ oxidation of all these possible dihydro intermediates **I-1**, **I-2**, and **I-3** immediately took place to afford pyrimidines **3**, where molecule oxygen (O_2) in air acted as a mild, benign, and clean oxidant. Unfortunately, although the possible dihydro intermediates **I-1**, **I-2**, and **I-3** could be detected by thin-layer chromatography (TLC) during the reaction, it was hard to isolate any one of these unstable intermediates. The following experiment might support the proposed mechanism. When the reactions were performed in DMSO at 60 °C under an atmosphere of argon, β-elimination happened, and a mixture of dihydro intermediates **I-1**, **I-2**, and **I-3** was formed, but when air was allowed to get into the reaction flask to replace argon, unstable dihydro intermediates **I-1**, **I-2**, and **I-3** rapidly changed to pyrimidines **3**.



Scheme 2. Plausible mechanism for the conversion of **2** (or **2′**) to **3**.

In addition, we have also tried to replace the Ts (tosyl) groups with Ms (mesyl) groups by using methanesulfonyl chloride instead of toluenesulfonyl chloride during the preparation of intermediate compounds **2** (or **2** + **2′**). It was found that one-pot conversion of *N*-mesyl-1,4,5,6-tetrahydro-pyrimidines to pyrimidines **3** also worked well, but herein we recommend the use of Ts groups rather than Ms groups for the described one-pot conversion because of the following two reasons: *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines **2** (or **2** + **2′**) are easier to crystallize than the corresponding *N*-mesyl analogs and toluenesulfonyl chloride is a safer and cheaper reagent than methanesulfonyl chloride.

CONCLUSION

In conclusion, an efficient, mild, benign, and practical method for the synthesis of various substituted pyrimidines is described. As the key step of this novel synthetic method, the one-pot conversion of *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines into pyrimidines has been investigated in detail. Easy preparation of intermediates *N*-tosyl-1,4,5,6-tetrahydro-pyrimidines and some advantages of the key one-pot conversion such as mild reaction conditions, good to excellent yields, ease of manipulation, no need for isolation of isomeric substrates, low cost of all reagents, avoidance of the use of strong oxidant and noble metal catalyst, use of air as a clean oxidant, as well as the wide scope of the reaction, make the described method very useful for the synthesis of pyrimidines.

EXPERIMENTAL

All reagents and solvents were analytically pure and were used as such as received from the chemical suppliers. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM-500 or AM-400 instrument. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on a Nicolet Magna IR-550 spectrometer. Mass spectrometry (MS) spectra were recorded on HP5989A Mass Spectrum

equipment. High-resolution mass spectrometry (HRMS) spectra were recorded on LC/MSD TOF HR-MS equipment. Melting points were determined on a Mel-TEMP II melting-point apparatus. Column chromatography was performed on silica gel (Qingdao Ocean Chemical Factory) to purify the intermediates and final products. 1,4,5,6-Tetrahydro-pyrimidines **1** ($R^1 = R^3$) or the tautomeric mixture of 1,4,5,6-tetrahydro-pyrimidines **1** and **1′** ($R^1 \neq R^3$) were prepared according a literature procedure [10] prior to use.

Typical Procedure for the Preparation of *N*-Tosyl-1,4,5,6-tetrahydro-pyrimidines 2 (or 2 + 2′)

Preparation of compound 2a. A solution of 2-(4-ethoxyphenyl)-1,4,5,6-tetrahydropyrimidine (1.022 g, 5.003 mmol) and pyridine (0.475 g, 6.005 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C with an ice bath, and then a solution of *p*-toluenesulfonyl chloride (0.954 g, 5.004 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. After the addition was finished, the ice bath was removed, and the mixture was further stirred at room temperature for around 3 h. When the reaction was complete (monitored by TLC), an aqueous solution of citric acid (10% w/v, 25 mL) was added. After the stirring was continued for 15 min, the mixture was transferred into a separatory funnel, and the organic phase was separated and washed with an aqueous solution of potassium carbonate (10% w/v, 25 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvent was removed under vacuum to afford compound **2a** (1.756 g, 4.899 mmol) as off-white solid in 98% yield, mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.39$ (t, $J = 7.0$ Hz, 3H), 1.73–1.81 (m, 2H), 2.43 (s, 3H), 3.50–3.55 (m, 2H), 3.77–3.82 (m, 2H), 3.96 (q, $J = 7.0$ Hz, 2H), 6.88–6.96 (m, 2H), 7.04 (d, $J = 7.6$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 8.2$ Hz, 2H), 7.51 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.34$, 152.86, 144.19, 139.22, 136.77, 129.68, 128.70, 127.39, 120.72, 116.48, 113.85, 63.33, 45.88, 44.64, 22.99, 21.60, 14.85. HRMS (ESI) m/z calcd. for $C_{19}H_{23}N_2O_3S$ $[M + H]^+$: 359.1429; found: 359.1420. IR (KBr film): $\nu = 2978$, 2935, 1631, 1598, 1581, 1442, 1355, 1291, 1163, 1108, 1049, 985, 791, 677, 549 cm^{-1}. Anal. calcd. for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.52; H, 6.21; N, 7.75.

Preparation of an isomeric mixture of compounds 2s and 2s′. A solution of 4-(4-methoxyphenyl)-6-phenyl-2-(3,4,5-trimethoxyphenyl)-1,4,5,6-tetrahydropyrimidine (2.163 g, 5.001 mmol) and pyridine (0.475 g, 6.005 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C with an ice bath, and then a solution of *p*-toluenesulfonyl chloride (0.954 g, 5.004 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. After the addition was finished, the ice bath was removed, and the mixture was further stirred at room temperature for around 8 h. When the reaction was complete (minitored by TLC), an aqueous solution of citric acid (10% w/v, 25 mL) was added. After the sitirring was continued for 15 min, the mixture was transferred into a separatory funnel, and the organic phase was separated and washed with an aqueous solution of potassium carbonate (10% w/v, 25 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvent was removed under vacuum to afford an isomeric mixture of compounds **2s** and **2s′** (2.875 g, 4.900 mmol) as

off-white solid in 98% combined yield, which was directly used as such for next step without isolation of the two isomers. Mp 121–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) for one isomer: δ = 2.08–2.18 (m, 2H), 2.36 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 3.85 (s, 6H), 4.59–4.64 (m, 1H), 5.73–5.77 (m, 1H), 6.67 (s, 2H), 6.89 (d, J = 8.2 Hz, 2H), 7.13–7.19 (m, 7H), 7.30–7.37 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) for one isomer: δ = 158.66, 152.51, 151.75, 144.24, 140.02, 137.13, 134.05, 132.95, 129.37, 129.27, 128.96, 127.83, 127.70, 127.41, 127.04, 113.93, 106.22, 60.89, 56.71, 55.82, 55.38, 55.29, 55.21, 36.72, 21.50. ^{1}H NMR (400 MHz, $CDCl_3$) for the other isomer: δ = 2.36 (s, 3H), 2.40–2.49 (m, 2H), 3.71 (s, 3H), 3.83 (s, 3H), 3.85 (s, 6H), 4.65–4.70 (m, 1H), 5.69–5.73 (m, 1H), 6.67 (s, 2H), 6.93 (d, J = 8.2 Hz, 2H), 7.21–7.29 (m, 7H), 7.38–7.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) for the other isomer: δ = 159.18, 152.50, 151.93, 142.14, 139.47, 133.03, 132.00, 129.40, 128.69, 128.53, 128.25, 127.87, 127.66, 127.02, 126.74, 114.31, 106.23, 60.89, 56.26, 55.84, 55.82, 55.73, 55.21, 36.72, 21.49. HRMS (ESI) m/z calcd. for $C_{33}H_{35}N_2O_6S$ $[M+H]^+$: 587.2216; found: 587.2218. IR (KBr film): ν = 2930, 2836, 1612, 1586, 1510, 1456, 1412, 1344, 1248, 1161, 1126, 1065, 1005, 835, 673, 546 cm^{-1}.

Typical Procedure for the One-Pot Conversion of *N*-Tosyl-1,4,5,6-tetrahydropyrimidines 2 (or 2 + 2′) to Pyrimidines 3

Preparation of compound 3a. Compound **2a** (1.434 g, 4.001 mmol) was dissolved in DMSO (10 mL), and powdered sodium hydroxide (0.240 g, 6.000 mmol) was added. The mixture was warmed to around 60 °C, and then stirred at 60 °C for 4 h. When the reaction was complete (monitored by TLC), the mixture was allowed to cool down to room temperature and then was diluted with water (80 mL). The aqueous solution was then extracted twice with ethyl acetate (2 × 60 mL). The extracts were combined and dried with anhydrous $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by flash chromatography to furnish pure 2-(3-ethoxyphenyl)pyrimidine **3a** (0.641 g, 3.201 mmol) in 80% yield as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.0 Hz, 3H), 4.06 (q, J = 7.0 Hz, 2H), 6.92–6.97 (m, 1H), 7.06 (t, J = 4.9 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.90–7.98 (m, 2H), 8.69 (d, J = 4.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.45, 159.35, 157.11, 138.96, 129.57, 120.54, 119.12, 117.83, 113.34, 63.52, 14.85. HRMS (ESI) m/z calcd. for $C_{12}H_{13}N_2O$ $[M+H]^+$: 201.1028; found: 201.1030. IR (neat): ν = 2981, 2936, 1603, 1550, 1452, 1415, 1325, 1220, 1053, 946, 780, 695 cm^{-1}. Anal. calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.11; H, 6.20; N, 13.87.

Preparation of compound 3s. The isomeric mixture of compounds **2s** and **2s′** (2.345 g, 3.997 mmol) was dissolved in DMSO (10 mL), and powdered sodium hydroxide (0.240 g, 6.000 mmol) was added. The mixture was warmed to around 60 °C and then stirred at 60 °C for 4 h. After the reaction was complete (monitored by TLC), the mixture was allowed to cool down to room temperature and then was diluted with water (80 mL). The aqueous solution was then extracted twice with ethyl acetate (2 × 60 mL). The extracts were combined and dried with anhydrous $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by flash chromatography to furnish pure 4-(4-methoxyphenyl)-6-phenyl-2-(3,4,5- trimethoxyphenyl)pyrimidine

3s (1.627 g, 3.797 mmol) in 95% yield as off-white solid. Mp 169–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.28$–8.22 (m, 4H), 8.01 (s, 2H), 7.92 (s, 1H), 7.60–7.52 (m, 3H), 7.08 (d, $J = 8.8$ Hz, 2H), 4.04 (s, 6H), 3.95 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.27$, 164.01, 163.74, 161.93, 153.19, 140.36, 137.59, 133.80, 130.71, 129.76, 128.90, 128.74, 127.22, 114.24, 109.22, 105.58, 61.00, 56.23, 55.43. HRMS (ESI) m/z calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$: 429.1814; found: 429.1815. IR (KBr film): $\nu = 3060$, 3000, 2965, 1605, 1570, 1535, 1505, 1460, 1390, 1365, 1240, 1180, 1125, 1035, 1005, 840, 775 cm^{-1}. Anal. calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.69; H, 5.60; N, 6.62.

SUPPORTING INFORMATION

Characterization data of compounds **3b**–**3r** and **3t**–**3x**; copies of spectra of ^{1}H NMR of compounds **2a**, **2s** + **2s′**, and **3a-3x**; and ^{13}C NMR spectra of compounds **2a**, **2s** + **2s′**, **3a**, **3c**, **3d**, **3f**, **3g**, **3l**, **3m**, **3n**, and **3p**–**3x** are available online.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (No. 20972048) and the Shanghai Educational Development Foundation (Dawn Program No. 03SG27) for the financial support of this work.

REFERENCES

1. (a) Parker, W. B. Enzymology of purine and pyrimidine antimetabolites used in the treatment of cancer. *Chem. Rev.* **2009**, *109*, 2880–2893; (b) Jorgensen, W. L.; Bollini, M.; Thakur, V. V.; Domaoal, R. A.; Spasov, K. A.; Anderson, K. S. Efficient discovery of potent anti-HIV agents targeting the Tyr181Cys variant of HIV reverse transcriptase. *J. Am. Chem. Soc.* **2011**, *133*, 15686–15696; (c) Yaziji, V.; Rodríguez, D.; Gutiérrez-de-Terán, H.; Coelho, A.; Caamaño, O.; García-Mera, X.; Brea, J.; Loza, M. I.; Cadavid, M. I.; Sotelo, E. Pyrimidine derivatives as potent and selective A3 adenosine receptor antagonists. *J. Med. Chem.* **2011**, *54*, 457–471; (d) Al-Abdullah, E. S.; Al-Obaid, A.-R. M.; Al-Deeb, O. A.; Habib, E. E.; El-Emam, A. A. Synthesis of novel 6-phenyl-2,4-disubstituted pyrimidine-5-carbonitriles as potential antimicrobial agents. *Eur. J. Med. Chem.* **2011**, *46*, 4642–4647; (e) Semenov, V. E.; Mikhailov, A. S.; Voloshina, A. D.; Kulik, N. V.; Nikitashina, A. D.; Zobov, V. V.; Kharlamov, S. V.; Latypov, S. K.; Reznik, V. S. Antimicrobial activity of pyrimidinophanes with thiocytosine and uracil moieties. *Eur. J. Med. Chem.* **2011**, *46*, 4715–4724; (f) Mohamed, T.; Yeung, J. C. K.; Rao, P. P. N. Development of 2-substituted-N-(naphth-1-ylmethyl) and N-benzhydrylpyrimidin-4-amines as dual cholinesterase and Ab-aggregation inhibitors: Synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5881–5887; (g) Gu, S.-X.; He, Q.-Q.; Yang, S.-Q.; Ma, X.-D.; Chen, F.-E.; Clercq, E. D.; Balzarini, J.; Pannecouque, C. Synthesis and structure–activity relationship of novel diarylpyrimidines with hydromethyl linker (CH(OH)-DAPYs) as HIV-1 NNRTIs. *Bioorg. Med. Chem.* **2011**, *19*, 5117–5124; (h) Cha, M. Y.; Lee, K.-O.; Kang, S.-J.; Jung, Y. H.; Song, J. Y.; Choi, K. J.; Byun, J. Y.; Lee, H.-J.; Lee, G. S.; Park, S. B.; Kim, M. S. Synthesis and biological evaluation of pyrimidine-based dual inhibitors of human epidermal growth factor receptor 1 (HER-1) and HER-2 tyrosine kinases. *J. Med. Chem.* **2012**, *55*, 2846–2857;

(i) Dowling, J. E.; Chuaqui, C.; Pontz, T. W.; Lyne, P. D.; Larsen, N. A.; Block, M. H.; Chen, H.; Su, N.; Wu, A.; Russell, D.; Pollard, H.; Lee, J. W.; Peng, B.; Thakur, K.; Ye, Q.; Zhang, T.; Brassil, P.; Racicot, V.; Bao, L.; Denz, C. R.; Cooke, E. Potent and selective inhibitors of CK2 kinase identified through structure-guided hybridization. *ACS Med. Chem. Lett.* **2012**, *3*, 278–283; (j) Moreno, E.; Plano, D.; Lamberto, I.; Font, M.; Encío, I.; Palop, J. A.; Sanmartín, C. Sulfur and selenium derivatives of quinazoline and pyrido[2,3-d]pyrimidine: Synthesis and study of their potential cytotoxic activity in vitro. *Eur. J. Med. Chem.* **2012**, *47*, 283–298.

2. (a) Ghanim, M.; Lebedev, G.; Kontsedalov, S.; Ishaaya, I. Flufenerim, a novel insecticide acting on diverse insect pests: Biological mode of action and biochemical aspects. *J. Agric. Food Chem.* **2011**, *59*, 2839–2844; (b) Navarro, S.; Perez, G.; Navarro, G.; Mena, L.; Vela, N. Influence of fungicide residues on the primary fermentation of young lager beer. *J. Agric. Food Chem.* **2007**, *55*, 1295–1300; (c) Sarmah, A. K.; Sabadie, J. Hydrolysis of sulfonylurea herbicides in soils and aqueous solutions: A review. *J. Agric. Food Chem.* **2002**, *50*, 6253–6265; (d) Dec, J.; Haider, K.; Rangaswamy, V.; Schaeffer, A.; Fernandes, E.; Bollag, J.-M. Formation of soil-bound residues of cyprodinil and their plant uptake. *J. Agric. Food Chem.* **1997**, *45*, 514–520; (e) Nezu, Y.; Miyazaki, M.; Sugiyama, K.; Kajiwara, I. Dimethoxypyrimidines as novel herbicides, part 1: Synthesis and herbicidal activity of dimethoxyphenoxyphenoxypyrimidines and analogues. *Pestic. Sci.* **1996**, *47*, 103–113
3. (a) Xu, C.; Dong, X.-M.; Wang, Z.-Q.; Hao, X.-Q.; Li, Z.; Duan, L.-M.; Ji, B.-M.; Song, M.-P. Triphenylphosphine-cyclometallated iridium(III) pyrimidine complexes: Synthesis, crystal structures, and application in α-alkylation of ketones with alcohols. *J. Organomet. Chem.* **2012**, *700*, 214–218; (b) Lippert, B.; Miguel, P. J. S. Metallatriangles and metallasquares: The diversity behind structurally characterized examples and the crucial role of ligand symmetry. *Chem. Soc. Rev.* **2011**, *40*, 4475–4487; (c) Parizel, N.; Ramírez, J.; Burg, C.; Choua, S.; Bernard, M.; Gambarelli, S.; Maurel, V.; Brelot, L.; Lehn, J.-M.; Turek, P.; Stadler, A.-M. Modulation of self-assembly and magnetism of Cu(II) grids in solution. *Chem. Commum.* **2011**, *47*, 10951–10953; (d) Hildebrandt, B.; Reiß, G.; Ganter, C. The first structurally characterized N-heterocyclic carbene complex with a ligand derived from pyrimidine. *J. Organomet. Chem.* **2010**, *695*, 474–477.
4. (a) Xue, W.; Li, L.; Li, Q.; Wu, A. Novel furo[2,3-d] pyrimidine derivative as fluorescent chemosensor for $HSO4^{-}$. *Talanta.* **2012**, *88*, 734–738; (b) Lin, L.-Y.; Tsai, C.-H.; Wong, K.-T.; Huang, T.-W.; Wu, C.-C.; Chou, S.-H.; Lin, F.; Chen, S.-H.; Tsai, A.-I. Efficient organic DSSC sensitizers bearing an electron-deficient pyrimidine as an effective ∏-spacer. *J. Mater. Chem.* **2011**, *21*, 5950–5958; (c) Arrachart, G.; Carcel, C.; Moreau, J. J. E.; Hartmeyer, G.; Alonso, B.; Massiot, D.; Creff, G.; Bantignies, J.-L.; Dieudonne, P.; Man, M. W. C.; Althoff, G.; Babonneau, F.; Bonhomme, C. Organosilicas based on purine–pyrimidine base pair assemblies: A solid state NMR point of view. *J. Mater. Chem.* **2008**, *18*, 392–399; (d) Liu, B.; Zhang, H.-L.; Liu, J.; Zhao, Y.-D.; Luo, Q.-M.; Huang, Z.-L. Novel pyrimidine-based amphiphilic molecules: Synthesis, spectroscopic properties and applications in two-photon fluorescence microscopic imaging. *J. Mater. Chem.* **2007**, *17*, 2921–2929; (e) Wang, C.; Jung, G.-Y.; Batsanov, A. S.; Bryce, M. R.; Petty, M. C. New electron-transporting materials for light-emitting diodes: 1,3,4-Oxadiazole–pyridine and 1,3,4-oxadiazole–pyrimidine hybrids. *J. Mater. Chem.* **2002**, *12*, 173–180; (f) Wang, J.-H.; Shen, Y.-Q.; Si, J.-H. Synthesis and solid-state polymerization of 5-(p-methylthio-o-methyl-pyrimidinyl)-2,4-pentadiyn-1-ol and the third-order optical nonlinearity of its derivatives. *J. Mater. Sci.* **2000**, *35*, 5981–5987.
5. [3 + 3] Two-component cyclization: (a) Burgula, L. N.; Radhakrishnan, K.; Kundu, L. M. Synthesis of modified uracil and cytosine nucleobases using a microwave-assisted method. *Tetrahedron Lett.* **2012**, *53*, 2639–2642; (b) Mokhtar, M.; Saleh, T. S.; Basahel, S. N.

Mg–Al hydrotalcites as efficient catalysts for aza-Michael addition reaction: A green protocol. *J. Mol. Cata A: Chem.* **2012**, *353–354*, 122–131; (c) Portilla, J.; Quiroga, J.; Nogueras, M.; Cobo, J. Regioselective synthesis of fused pyrazolo[1,5-a]pyrimidines by reaction of 5-amino-1*H*-pyrazoles and β-dicarbonyl compounds containing five-membered rings. *Tetrahedron* **2012**, *68*, 988–994; (d) Nayak, M.; Rastogi, N.; Batra, S. Copper-catalyzed cascade reaction of 4-iodopyrazole derivatives with amidines for the synthesis of pyrazolo[4,3-*d*]pyrimidine derivatives. *Eur. J. Org. Chem.* **2012**, 1360–1366; (e) Lin, M.; Chen, Q.-Z.; Zhu, Y.; Chen, X.-L.; Cai, J.-J.; Pan, Y.-M.; Zhan, Z.-P. Copper(II)-catalyzed synthesis of pyrimidines from propargylic alcohols and amidine: A propargylation–cyclization–oxidation tandem reaction. *Synlett* **2011**, 1179–1183; (f) Hu, M.; Wu, J.; Zhang, Y.; Qiu, F.; Yu, Y. Synthesis of polysubstituted 5-aminopyrimidines from α-azidovinyl ketones and amidines. *Tetrahedron* **2011**, *67*, 2676–2680; (g) Anderson, L.; Zhou, M.; Sharma, V.; McLaughlin, J. M.; Santiago, D. N.; Fronczek, F. R.; Guida, W. C.; McLaughlin, M. L. Facile iterative synthesis of 2,5-terpyrimidinylenes as nonpeptidic r-helical mimics. *J. Org. Chem.* **2010**, *75*, 4288–4291; (h) Bannwarth, P.; Grée, D.; Grée, R. Synthesis of new difluoroalkyl propargylic ketones and their use for the preparation of fluorinated heterocycles. *Tetrahedron Lett.* **2010**, *51*, 2413–2415; (i) Sleebs, B. E.; Street, I. P.; Bu, X.; Baell, J. B. De novo synthesis of a potent LIMK1 inhibitor. *Synthesis* **2010**, 1091–1096; (j) Bannwarth, P.; Valleix, A.; Grée, D.; Grée, R. Flexible synthesis of pyrimidines with chiral monofluorinated and difluoromethyl side chains. *J. Org. Chem.* **2009**, *74*, 4646–4649; (k) Kotljarov, A.; Irgashev, R. A.; Iaroshenko, V. O.; Sevenard, D. V.; Sosnovskikh, V. Y. 3-(Polyfluoroacyl)chromones and their hetero analogues as valuable substrates for syntheses of 4-(polyfluoroalkyl)pyrimidines. *Synthesis* **2009**, 3233–3242; (l) Bagley, M. C.; Lin, Z.; Pope, S. J. A. Barium manganate in microwave-assisted oxidation reactions: Synthesis of solvatochromic 2,4,6-triarylpyrimidines. *Tetrahedron Lett.* **2009**, *50*, 6818–6822.

6. [4 + 2] Two-component cyclization: (a) Ahmad, O. K.; Hill, M. D.; Movassaghi, M. Synthesis of densely substituted pyrimidine derivatives. *J. Org. Chem.* **2009**, *74*, 8460–8463; (b) Hill, M. D.; Movassaghi, M. Observations on the use of microwave irradiation in azaheterocycle synthesis. *Tetrahedron Lett.* **2008**, *49*, 4286–4288; (c) Hill, M. D.; Movassaghi, M. Direct synthesis of substituted pyrimidines and quinazolines. *Synthesis* **2008**, 823–827; (d) Robin, A.; Julienne, K.; Meslin, J.-C.; Deniaud, D. Straightforward pyrimidine ring construction: A versatile tool for the synthesis of nucleobase and nucleoside analogues. *Eur. J. Org. Chem.* **2006**, 634–643.
7. [5 + 1] Two-component cyclization: (a) Sasada, T.; Aoki, Y.; Ikeda, R.; Sakai, N.; Konakahara, T. Synthesis of tri- or tetrasubstituted pyrimidine derivatives through the [5 + 1] annulation of enamidines with either N,N-dimethylformamide dialkyl acetals or orthoesters and their application in a ring transformation of pyrimidines to pyrido[2,3-d]pyrimidin-5-one derivatives. *Chem. Eur. J.* **2011**, *17*, 9385–9394; (b) Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Román, R.; Brodsky, B. H.; Sánchez-Roselló, M.; Aceña, J. L.; de Arellano, C. R. New fluorinated 1,3-vinylogous amidines as versatile intermediates: Synthesis of fluorinated pyrimidin-2(1H)-ones. *Tetrahedron* **2006**, *62*, 1444–1451.
8. (a) Esmaeili, A. A.; Zangouei, M.; Fakhari, A. R.; Habibi, A. An efficient regioselective synthesis of highly functionalized 3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidines via an isocyanide-based three-component reaction. *Tetrahedron Lett.* **2012**, *53*, 1351–1353; (b) Bera, M. K.; Reissig, H.-U. A route to alkenyl-substituted 4-hydroxypyridine and pyrimidine derivatives via three-component access to β-alkoxy-β-ketoenamides. *Synthesis* **2010**, 2129–2138; (c) Lechel, T.; Möhl, S.; Reissig, H.-U. A concise synthesis of alkoxy-substituted pyrimidine derivatives based upon a three-component access to functionalized enamides. *Synlett* **2009**, 1059–1062; (d) Sasada, T.; Kobayashi, F.; Sakai, N.;

Konakahara, T. An unprecedented approach to 4,5-disubstituted pyrimidine derivatives by a $ZnCl_2$-catalyzed three-component coupling reaction. *Org. Lett.* **2009**, *11*, 2161–2164; (e) Sheibani, H.; Seifi, M.; Bazgir, A. Three-component synthesis of pyrimidine and pyrimidinone derivatives in the presence of high-surface-area MgO, a highly effective heterogeneous base catalyst. *Synth. Commun.* **2009**, *39*, 1055–1064; (f) Blangetti, M.; Deagostino, A.; Prandi, C.; Zavattaro, C.; Venturello, P. N-Metalated imines by reaction of 1,1-diethoxybut-2-ene with aromatic nitriles, as useful intermediates for the synthesis of substituted pyrimidines and cyclopentenones. *Chem. Commum.* **2008**, 1689–1691.

9. (a) Klimova, E. I.; García, J. J. S.; Klimova, T.; Apan, T. R.; López, E. A. V.; Flores-Alamo, M.; García, M. M. Synthesis and biological evaluation of novel ethyl 2-amino-6-ferrocenyl-1,6-dihydropyrimidine-5-carboxylates and ethyl 2-amino-6-ferrocenylpyrimidine-5-carboxylates. *J. Organomet. Chem.* **2012**, *708–709*, 37–45; (b) Pecchi, S.; Renhowe, P. A.; Taylor, C.; Kaufman, S.; Merritt, H.; Wiesmann, M.; Shoemaker, K. R.; Knapp, M. S.; Ornelas, E.; Hendrickson, T. F.; Fantl, W.; Voliva, C. F. Identification and structure–activity relationship of 2-morpholino 6-(3--hydroxyphenyl) pyrimidines, a class of potent and selective PI3 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6895–6898; (c) Araya, I.; Kanazawa, S.; Akita, H. Process development and large-scale synthesis of NK1 antagonist. *Chem. Pharm. Bull.* **2008**, *56*, 176–180; (d) Hull Jr., J. W., Otterson, K.; Rhubright, D. A new preparation of 5-hydroxypyrimidines derived from carboxylic acids, epichlorohydrin, and ammonia. *J. Org. Chem.* **1993**, *58*, 520–522; (e) Cho, H.; Ohnaka, Y.; Hayashimatsu, M.; Ueda, M.; Shima, K. Synthesis of novel 1,4-, 3,4-, and 4,5-dihydropyrimidines: First successful $POCl_3$ chlorination and regioselective alkoxycarbonylation. *Tetrahedron Lett.* **1986**, *27*, 6377–6380; (f) Lorente, A.; Navio, J. L. G.; Fuentes, L.; Soto, J. L. Synthesis of 6-aryl-5-isopropoxycarbonyl-4-thioxo-3,4-dihydropyrimidines from 3-substituted alkyl 2-cyano-3-thiocarboxamidopropenoates. *Synthesis* **1985**, 86–89; (g) Weis, A.; Frolow, F.; Zamir, D.; Bernstein, M. Acrolein as a synthon for pyrimidinic compounds: Reaction with benzamidine. *Heterocycles* **1984**, *22*, 657–661; (h) Weis, A. L.; Zamir, D. Acrolein as a synthon for 6-hydroxytetrahydropyrimidines, 1,4(1,6)-dihydropyrimidines, and pyrimidines. *J. Org. Chem.* **1987**, *52*, 3421–3425; (i) Solovyev, P. A.; Shutalev, A. D. Synthesis and oxidative aromatization of 5-acetyl-2-cyanoimino-6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidine with manganese dioxide. *Chem. Heterocycl. Compd.* **2009**, *45*, 809–814; (j) Pews, R. G. Synthesis of 2-alkylpyrimidines via 2-alkyl-1,4,5,6-tetrahydropyrimidines. *Heterocycles* **1988**, *27*, 1867–1871; (k) Hitching, G. H.; Russell, P. B.; Whittaker, N. Some 2:6-diamino- and 2-amino-6-hydroxy-derivatives of 5-aryl-4:5-dihydropyrimidines: A new synthesis of 4-alky1–5-arylpyrimidines. *J. Chem. Soc.* **1956**, 1019–1028.
10. Mizuhara, T.; Oishi, S.; Fujii, N.; Ohno, H. Efficient synthesis of pyrimido[1,2-c][1,3]benzothiazin-6-imines and related tricyclic heterocycles by S_NAr-type C-S, C-N, or C-O bond formation with heterocumulenes. *J. Org. Chem.* **2010**, *75*, 265–268.
11. (a) Amos, D. T.; Renslo, A. R.; Danheiser, R. L. Intramolecular [4 + 2] cycloadditions of iminoacetonitriles: A new class of azadienophiles for hetero-Diels–Alder reactions. *J. Am. Chem. Soc.* **2003**, *125*, 4970–4971; (b) Kitahara, K.; Toma, T.; Shimokawa, J.; Fukuyama, T. *O*-TBS-*N*-tosylhydroxylamine: A reagent for facile conversion of alcohols to oximes. *Org. Lett.* **2008**, *10*, 2259–2261; (c) Ishikawa, T.; Manabe, I.; Aikawa, T. Kudo, T.; Saito, S. Intramolecular catalytic Friedel–Crafts reactions with allenyl cations for the synthesis of quinolines and their analogues. *Org. Lett.* **2004**, *6*, 2361–2364; (d) Dong, J.; Shi, X.-X.; Yan, J.-J.; Xing, J.; Zhang, Q.; Xiao, S. Efficient and practical one-pot conversions of *N*-tosyltetrahydroisoquinolines into isoquinolines and of *N*-tosyltetrahydro-β-carbolines into β-carbolines through tandem β-elimination and aromatization. *Eur. J. Org. Chem.* **2010**, 6987–6992.

12. Song, B.; Zheng, X.; Mo, J.; Xu, B. Palladium-catalyzed monoselective halogenation of C-H bonds: Efficient access to halogenated arylpyrimidines using calcium halides. *Adv. Synth. Catal.* **2010**, *352*, 329–335.
13. Molander, G. A.; Canturk, B.; Kennedy, L. E. Scope of the Suzuki–Miyaura cross-coupling reactions of potassium heteroaryltrifluoroborates. *J. Org. Chem.* **2009**, *74*, 973–980.
14. Martinez, A. G.; Herrera, A.; Martinez, R.; Teso, E.; Garcia, A.; Osio, J.; Pargada, L.; Unanue, R.; Subramanian, L. R.; Hanack, M. A new and convenient synthesis of alkyl and aryl pyrimidines. *J. Heterocycl. Chem.* **1988**, *25*, 1237–1241
15. Adib, M.; Mahmoodi, N.; Mahdavi, M.; Bijanzadeh, H. R. Microwave-assisted simple, one-pot, four-component synthesis of 2,4,6-triarylpyrimidines under solvent-free conditions. *Tetrahedron Lett.* **2006**, *47*, 9365–9368.
16. Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Shoar, R. H.; Bamoharram, F. F. A direct oxidative route for the synthesis of pyrimidines using heteropolyacids. *Tetrahedron Lett.* **2009**, *50*, 662–666