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Ultrasound-Promoted Synthesis of 4-Pyrimidinols and Their Tosyl Derivatives

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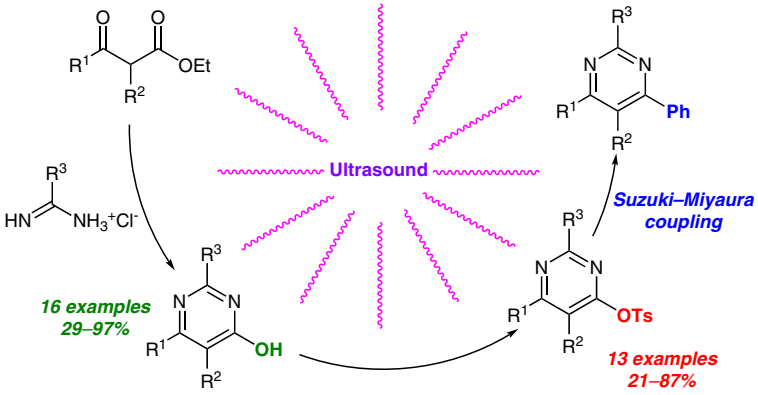

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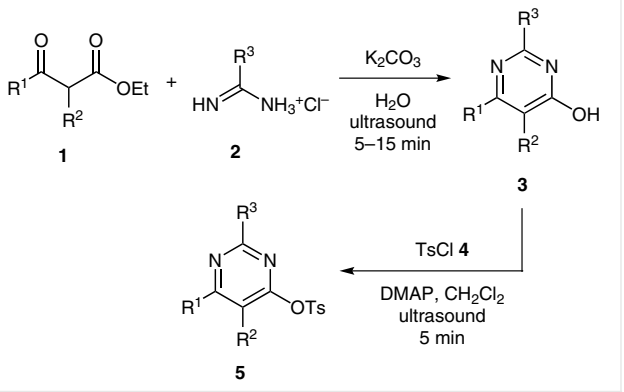
Abstract Ultrasound irradiation promoted the cyclocondensation of β-keto esters and amidines in good to excellent yields to form sixteen highly substituted 4-pyrimidinols. Tosylation of these compounds, in another ultrasound-promoted conversion, formed 4-pyrimidyl tosylates in high yields. The use of the developed protocol as an alternative route to 4-arylpyrimidines was illustrated with three examples of the Suzuki–Miyaura cross-coupling of the prepared tosylates with phenylboronic acid.

Key words condensation, ultrasound, pyrimidinols, tosylation, cross-coupling

The synthesis of azaheterocycles has attracted considerable attention for many years due to their wide range of applications as pharmaceuticals and agrochemicals,[1] and as key intermediates in natural product synthesis[2] and the preparation of new organic materials and new ligands for catalytic processes and optical/magnetic applications.[3] In addition, pyrimidine is a widespread motif found in relevant compounds exhibiting interesting biological properties[1,4] and as a consequence there is a permanent interest in the development of new greener and milder methods for the preparation of its derivatives.

The synthesis of pyrimidines has been carried out traditionally by the condensation between carbonyl derivatives with nitrogen-containing compounds.[5,6] Further functionalization by cross-coupling reactions from pyrimidyl halides has been employed with relative success in these synthesis.[7] Their major drawback are the low yields frequently observed in the halogenation step.[8] Replacement of a halide by another leaving group, such as tosylate, could be a significant improvement. Even though tosylates are less reactive than the corresponding iodides in coupling reactions,[9] the electron-poor pyrimidine system could enhance their reactivity. In fact, electron-poor aryl tosylates are convenient electrophilic coupling partners in Suzuki–Miyaura[10] and Heck–Mizoroki reactions.[11]

In the present report, we describe a successful strategy for the preparation of 4-arylpyrimidines, involving cross-coupling reactions of 4-pyrimidyl tosylates, readily obtained from 4-pyrimidinols (Scheme 1); the use of ultrasound improved both steps considerably.



Scheme 1 Ultrasound-promoted synthesis of highly substituted tosylates **5**

The preparation of the starting 4-pyrimidinols **3** was achieved by condensation of various ethyl β-keto esters **1** with different amidine hydrochlorides **2**. Conditions for the model reaction between ethyl acetoacetate (**1a**, R^1 = Me, R^2 = H) and benzamidine hydrochloride **2a** (R^3 = Ph) were initially studied. Table 1 summarizes the obtained results.

The use of ultrasound irradiation shortened the reaction time considerably. Water proved the best solvent for this reaction, in contrast with previous observation for the synthesis of similar pyrimidines.[12] The fact that yields in-

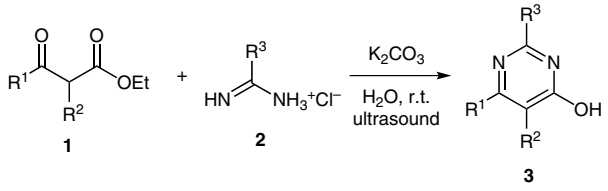
creased with the solvent hydrogen-bond-donor (HBD) strength suggests that solvent participation through hydrogen-bond donation plays an essential role in the process.

Table 1 Solvent Effect on the Condensation Reaction of Ethyl Acetoacetate (**1a**, R^1 = Me, R^2 = H) and Benzamidine Hydrochloride (**2a**, R^3 = Ph)

Entry	Solvent	Conventional heating[a] (60 °C)		Ultrasound[a]	
		Time[b] (h)	Yield[c] (%)	Time[b] (min)	Yield[c] (%)
1	H_2O	24	96	15	89
2	MeOH	24	94	60	94
3	EtOH	24	81	120	23
4	*i*-PrOH	24	57	120	9
5	DMF	24	51	15	20

[a] Reaction conditions: **1a** (2.31 mmol), **2a** (2.54 mmol), K_2CO_3 (5.76 mmol), solvent (5.0 mL).
[b] Reaction times correspond to full conversion as was observed by TLC.
[c] Based on purified compound.

Table 2 Scope of the Ultrasound-Promoted Synthesis of 4-Pyrimidinols **3**



Entry	**3**	R^1	R^2	R^3	Time (min)	Yield[a] (%)
1	**3a**	Me	H	Ph	15	89
2	**3b**	Me	H	4-$O_2NC_6H_4$	5	97
3	**3c**	Me	H	4-ClC_6H_4	10	78
4	**3d**	Me	H	Me	15	29
5	**3e**	Me	H	Et	5	87
6	**3f**	Me	H	*c*-Pr	15	70
7	**3g**	CF_3	H	Ph	15	61
8	**3h**	CF_3	H	4-$O_2NC_6H_4$	15	52
9	**3i**	CF_3	H	*c*-Pr	15	52
10	**3j**	*i*-Pr	H	Ph	15	54
11	**3k**	Et	H	Ph	15	53
12	**3l**	Me	Me	Ph	15	72
13	**3m**	*c*-Pr	H	Et	10	63
14	**3n**	Me	Me	Et	15	71
15	**3o**	Et	H	Et	15	75
16	**3p**	*c*-Pr	H	Ph	15	78

[a] Based on isolated product after purification.

Ultrasound irradiation also improved the purity of the products even at gram scale: ca. 4 g of pure 4-pyrimidinol **3a** could be obtained in 87% yield by sonication in water. DMF was a poor solvent in this conversion, probably due to its decomposition under ultrasound irradiation, confirmed by a TLC analysis of the pure solvent after 15 minutes of sonication.

Table 2 lists the yields of sixteen 4-pyrimidinols **3** obtained by ultrasound irradiation of a mixture of **1** and **2** in water for 5–15 minutes. In general, good to excellent yields were obtained in this short time. The only exception was compound **3d**, with a regular (29%) yield, probably due to its high solubility in water, which reduced the efficiency of the extraction process. Its less hydrophilic analogues **3e** and **3o** could be obtained with much higher yields (87% and 75%, respectively).

The tosylation of the 4-pyrimidinol **3a** with tosyl chloride in anhydrous CH_2Cl_2 for 24 hours, in the presence of DMAP and Et_3N,[13] gave **5a** with a modest 51% yield. When we employed ultrasound irradiation this yield was raised to 75% after five minutes reaction, with DMAP (1.5 equiv) as the best base for this conversion (Table 3).

Under these conditions, thirteen 4-pyrimidyl tosylates **5** were prepared in good to excellent yields (Table 4).

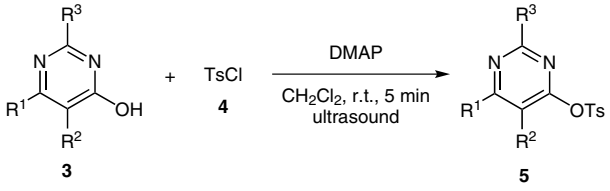
Table 3 Optimization of the Reaction Conditions for the Tosylation of 6-Methyl-2-phenyl-4-pyrimidinol **3a** under Ultrasound Conditions

Entry	TsCl **4** (equiv)	Base (equiv)	Yield[a,b] (%)
1	1.0	DBU (1.0)	44
2	1.0	DBU (1.1)	67
3	1.5	DBU (1.1)	44
4	1.0	Et_3N (1.1)	57
5	1.0	DABCO (1.1)	47
6	1.0	DMAP (1.1)	63
7	1.5	DMAP (1.1)	67
8	2.0	DMAP (1.1)	42
9	1.0	DMAP (1.0)	49
10	1.0	DMAP (1.5)	75
11	1.0	DMAP (2.0)	60
12	1.5	DMAP (1.5)	75

[a] Based on isolated product after purification.
[b] Only the *O*-tosyl derivative was formed during the reaction.

The arylation of 4-pyrimidyl tosylates **5** by Suzuki–Miyaura cross-coupling reaction was illustrated with three different tosylates, which reacted with phenylboronic acid. To our satisfaction, the reaction could be carried out in water by simply heating the reaction mixture for 16 hours at 80 °C. Under these simple conditions, the desired products

Table 4 Scope of the Tosylation of 4-Pyrimidinols **3** under Ultrasound Conditions

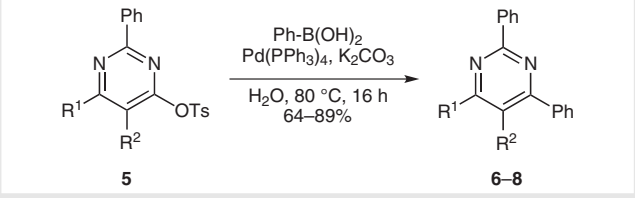


Entry	5	R^1	R^2	R^3	Yield[a] (%)
1	**5a**	Me	H	Ph	75
2	**5b**	Me	H	Me	85
3	**5c**	Me	H	Et	72
4	**5d**	Me	H	*c*-Pr	80
5	**5e**	*i*-Pr	H	Ph	65
6	**5f**	Et	H	Ph	70
7	**5g**	Me	Me	Ph	62
8	**5h**	CF_3	H	*c*-Pr	81
9	**5i**	Me	Me	Et	73
10	**5j**	Et	H	Et	87
11	**5k**	Me	H	4-$O_2NC_6H_4$	54
12	**5l**	Me	H	4-ClC_6H_4	21
13	**5m**	*c*-Pr	H	Ph	85

[a] Based on isolated product after purification.

could be obtained in good yields (64–89%, Scheme 2), making the synthetic protocol described here an attractive alternative for the synthesis of substituted 4-arylpyrimidines.

Application of ultrasound irradiation to the Suzuki–Miyaura reaction of **5a** (R^1 = Me, R^2 = H) with phenylboronic acid at 80 °C led to a shorter reaction time (30 min), but with a lower yield (64%).



Scheme 2 Suzuki–Miyaura cross-coupling reaction of 4-pyrimidyl tosylates **5** with phenylboronic acid, to give 4-arylpyrimidines **6** (R^1 = Me, R^2 = H, 89%), **7** (R^1 = Et, R^2 = H, 87%), and **8** (R^1 = Me, R^2 = Me, 64%).

In conclusion the ultrasound-promoted preparation of substituted 4-pyrimidinols by condensation of amidines with β-keto esters could be achieved in high yields. Tosylation of these 4-pyrimidinols, in another high-yield ultrasound-promoted conversion, allowed access to relatively unknown 4-pyrimidyl tosylates, which underwent Suzuki–Miyaura cross-coupling reactions with phenylboronic acid in good yields. The above route to 4-arylpyrimidines, which employs ultrasound-promoted protocols to achieve high-yielding, inexpensive, and environment-friendly conversions through relatively unexploited pyrimidyl tosylates should find use as an attractive alternative to other methods from less accessible halogenated pyrimidine derivatives.

All reagents were a reagent grade and were used without further purification. TLC analyses were performed on TLC plates (silica gel 60, fluorescence indicator F254, 0.25 mm layer thickness). Products were purified by column chromatography on silica gel 60 (0.063–0.200 mm). NMR spectra were recorded with a Bruker Avance 400 MHz equipment. IR spectra were measured with a Spectrum two FT-IR (ATR) Perkin Elmer spectrophotometer. HRMS analyses were carried out with Varian Ionspec QFT-7 (ESI-FT ICRMS) and Agilent 6210 ESI-TOF instruments. The ultrasound-promoted reactions were carried out in standard oven-dried glassware in a Branson sonicator cup horn working at 19.7–20.0 kHz (75 W). Melting points were recorded with a Microthermal capillary melting point apparatus and are not corrected.

Ultrasound-Promoted Synthesis of 4-Pyrimidinols 3; General Procedure 1

The corresponding amidine hydrochloride (2.54 mmol) and powdered K_2CO_3 (5.76 mmol) were dissolved in water (5.0 mL) in a 20-mL vessel. The β-keto ester (2.31 mmol) was added and the resulting mixture was irradiated for 5–15 min (see Table 2). Upon the end of the reaction (TLC, hexanes/EtOAc, 5:1), the mixture was diluted with sat. aq NH_4Cl (5.0 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (anhyd Na_2SO_4) and filtered. The filtrate was rotary evaporated and the obtained crude product was purified by column chromatography [silica gel, hexane/EtOAc mixtures or recrystallized (EtOH)].

6-Methyl-2-phenyl-4-pyrimidinol (3a)[14]

Colorless solid; yield: 382 mg (89%); mp 212–224 °C (Lit.[14] 220–222 °C); R_f = 0.21 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 6.3 Hz, 2 H, Ph), 7.59–7.44 (m, 3 H, Ph), 6.30 (s, 1 H, C5-H), 2.39 (s, 3 H, CH_3).

6-Methyl-2-(4-nitrophenyl)-4-pyrimidinol (3b)[15]

Light yellow solid; yield: 518 mg (97%); mp 285–287 °C (Lit.[15] 290 °C); R_f = 0.23 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.91–8.50 (m, 2 H, Ph), 8.37 (d, *J* = 8.2 Hz, 2 H, Ph), 6.14 (s, 1 H, C5-H), 2.83 (s, 3 H, CH_3).

2-(4-Chlorophenyl)-6-methyl-4-pyrimidinol (3c)[16]

Colorless solid; yield: 397 mg (78%); mp 228–230 °C (Lit.[16] 233–234 °C); R_f = 0.05 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.14, 7.47 (d, *J* = 8.4 Hz, 2 H each, Ph), 5.92 (s, 1 H, C5-H), 2.17 (s, 3 H, CH_3).

2,6-Dimethyl-4-pyrimidinol (3d)[17]

Colorless solid; yield: 83 mg (29%); mp 191–193 °C (Lit.[17] 190–194 °C); R_f = 0.10 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (s, 1 H, C5-H), 2.39, 2.26 (2 s, 3 H each, C2-CH_3, C6-CH_3).

2-Ethyl-6-methyl-4-pyrimidinol (3e)[18]

Colorless solid; yield: 277 mg (87%); mp 150–151 °C (Lit.[18] 147–149 °C); R_f = 0.10 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17 (s, 1 H, C5-H), 2.70 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.30 (s, 3 H, C6-CH_3), 1.33 (t, *J* = 7.6 Hz, 3 H, CH_3).

2-Cyclopropyl-6-methyl-4-pyrimidinol (3f)

Colorless solid; yield: 243 mg (70%); mp 185–187 °C; R_f = 0.15 (hexane/EtOAc, 1:1).

IR (ATR): 3390, 3080, 2950, 2790, 1645, 1590 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 1 H), 2.21 (s, 3 H), 1.96–1.82 (m, 1 H), 1.23–1.12 (m, 2 H), 1.12–0.98 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.5, 166.2, 162.7, 111.3, 24.1, 11.9, 8.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_{11}N_2O$: 151.0866; found: 151.0871.

2-Phenyl-6-(trifluoromethyl)-4-pyrimidinol (3g)[19]

Colorless solid; yield: 338 mg (61%); mp 218–220 °C (Lit.[19] 219–220 °C); R_f = 0.49 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.14 (d, *J* = 7.1 Hz, 2 H, Ph), 7.57–7.48 (m, 3 H, Ph), 6.75 (s, 1 H, C5-H).

2-(4-Nitrophenyl)-6-(trifluoromethyl)-4-pyrimidinol (3h)

Colorless solid; yield: 343 mg (52%); mp 256–258 °C; R_f = 0.43 (hexane/EtOAc, 1:1).

IR (ATR): 3380, 3060, 2920, 2785, 1640, 1520 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.4 Hz, 2 H), 8.05 (d, *J* = 8.4 Hz, 2 H), 6.15 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.7, 157.7, 153.6, 147.9, 140.8, 128.2, 124.4, 121.6, 107.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_7F_3N_3O_3$: 286.0435; found: 286.0437.

2-Cyclopropyl-6-(trifluoromethyl)-4-pyrimidinol (3i)

Colorless solid; yield: 245 mg (52%); mp 143–145 °C; R_f = 0.45 (hexane/EtOAc, 1:1).

IR (ATR): 3385, 3180, 3020, 2785, 1645, 1575 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.56 (s, 1 H), 2.06–1.84 (m, 1 H), 1.13–1.04 (m, 2 H), 1.01 (dt, *J* = 7.4, 3.8 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.3, 163.4, 153.7, 122.1, 109.6, 13.7, 9.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_8F_3N_2O$: 205.0584; found: 205.0587.

6-Isopropyl-2-phenyl-4-pyrimidinol (3j)[19]

Colorless solid; yield: 267 mg (54%); mp 217–220 °C (Lit.[19] 219–221 °C); R_f = 0.26 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.18, 7.61–7.50 (2 m, 2 H, 3 H, Ph), 6.31 (s, 1 H, C5-H), 3.00–2.74 (m, 1 H, C6-CH), 1.31, 1.29 (2 s, 3 H each, CH_3).

6-Ethyl-2-phenyl-4-pyrimidinol (3k)[14]

Colorless solid; yield: 245 mg (53%); mp 165–167 °C (Lit.[14] 166–168 °C); R_f = 0.26 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31–8.14, 7.62–7.49 (2 m, 2 H, 3 H, Ph), 6.30 (s, 1 H, C5-H), 2.68 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.30 (t, *J* = 7.5 Hz, 3 H, CH_3).

5,6-Dimethyl-2-phenyl-4-pyrimidinol (3l)[14]

Colorless solid; yield: 333 mg (72%); mp 159–161 °C (Lit.[14] 157–160 °C); R_f = 0.35 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.18, 7.61–7.47 (m, 2 H, 3 H, Ph), 2.42 (s, 3 H, C6-CH_3), 2.14 (s, 3 H, C5-CH_3).

6-Cyclopropyl-2-ethyl-4-pyrimidinol (3m)

Colorless solid; yield: 239 mg (63%); mp 95–97 °C; R_f = 0.32 (hexane/EtOAc, 5:1).

IR (ATR): 3380, 3180, 2970, 2780, 1645, 1580 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13 (s, 1 H, C5-H), 2.63 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 1.83–1.70 (m, 1 H, *c*-Pr-CH), 1.26 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.09–1.02 (m, 2 H, *c*-Pr-CH_2), 0.97–0.90 (m, 2 H, *c*-Pr-CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.0, 165.5, 163.1, 107.4, 28.4, 17.3, 11.7, 9.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_9H_{13}N_2O$: 165.1023; found: 165.1028.

2-Ethyl-5,6-dimethyl-4-pyrimidinol (3n)

Colorless solid; yield: 249 mg (71%); mp 144–146 °C; R_f = 0.17 (hexane/EtOAc, 1:1).

IR (ATR): 3360, 3190, 2920, 2790, 1665, 1535 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (q, *J* = 7.6 Hz, 2 H), 2.31 (s, 3 H), 2.04 (s, 3 H), 1.33 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 162.1, 157.6, 118.9, 31.7, 17.4, 13.1, 10.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}N_2O$: 153.1023; found: 153.1030.

2,6-Diethyl-4-pyrimidinol (3o)

Colorless solid; yield: 264 mg (75%); mp 78–80 °C; R_f = 0.23 (hexane/EtOAc, 1:1).

IR (ATR): 3375, 3075, 2970, 2720, 1665, 1600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 1 H), 2.71 (q, *J* = 7.6 Hz, 2 H), 2.57 (q, *J* = 7.5 Hz, 2 H), 1.34 (t, *J* = 7.6 Hz, 3 H), 1.22 (t, *J* = 15.0, 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4, 166.3, 163.1, 107.6, 31.9, 30.2, 13.2, 12.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}N_2O$: 153.1023; found: 153.1025.

6-Cyclopropyl-2-phenyl-4-pyrimidinol (3p)

Colorless solid; yield: 382 mg (78%); mp 83–85 °C; R_f = 0.40 (hexane/EtOAc, 1:1).

IR (ATR): 3390, 3190, 2955, 2785, 1645, 1545 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.79 (m, 2 H, Ph), 7.58–7.49 (m, 3 H. Ph), 6.31 (s, 1 H, H-5), 1.96–1.82 (m, 1 H, *c*-Pr), 1.24–1.13 (m, 2 H, *c*-Pr), 1.07–0.94 (m, 2 H, *c*-Pr).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2, 166.3, 163.2, 136.8, 132.0, 131.1, 129.3, 109.2, 17.2, 9.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2O$: 213.1023; found: 213.1028.

Ultrasound-Promoted Synthesis of 4-Pyrimidyl Tosylates 5; General Procedure 2

The corresponding 4-pyrimidinol (1.07 mmol) and DMAP (1.61 mmol) were dissolved in CH_2Cl_2 (5.0 mL) in a 20-mL vessel, then TsCl (1.07 mmol) was added and the resulting mixture was irradiated for 5 min. The mixture was then diluted with sat. aq $NaHCO_3$ (5.0 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (anhyd Na_2SO_4) and filtered. The filtrate was rotary evaporated and the crude product was purified by column chromatography (silica gel, hexane/EtOAc mixtures).

6-Methyl-2-phenyl-4-pyrimidyl Tosylate (5a)

Colorless solid; yield: 274 mg (75%); mp 132–133 °C; R_f = 0.87 (hexane/EtOAc, 1:1).

IR (ATR): 2925, 2850, 2765, 1680, 1610, 1410, 1185, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 7.8 Hz, 2 H, PhC2-H, C6-H), 7.99 (d, *J* = 8.1 Hz, 2 H, TsC2-H, C6-H), 7.51–7.33 (m, 5 H, Ph, Ts), 6.82 (s, 1 H, C5-H), 2.58, 2.46 (2 s, 3 H each, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 164.69, 164.64, 145.7, 136.5, 134.1, 131.3, 129.9, 128.9, 128.6, 128.5, 108.1, 24.6, 21.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3S$: 341.0955; found: 341.0958.

2,6-Dimethyl-4-pyrimidyl Tosylate (5b)[11]

Colorless solid; yield: 381 mg (85%); mp 96–98 °C (Lit.[11] 97–98 °C); R_f = 0.37 (hexane/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96, 7.36 (2 d, *J* = 7.9 Hz, 2 H each, Ts), 6.77 (s, 1 H, C5-H), 2.57, 2.49, 2.46 (3 s, 3 H each, CH_3).

2-Ethyl-6-methyl-4-pyrimidyl Tosylate (5c)

Yellow oil; yield: 225 mg (72%); R_f = 0.77 (hexane/EtOAc, 1:1).

IR (ATR): 2980, 2930, 2795, 1630, 1550, 1440, 1190, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.7 Hz, 2 H, TsC2-H, C6-H), 7.34 (d, *J* = 7.7 Hz, 2 H, TsC3-H, C5-H), 6.76 (s, 1 H, C5-H), 2.81 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.49 (s, 3 H, C6-CH_3), 2.44 (s, 3 H, TsCH_3), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 170.6, 164.4, 145.8, 133.7, 129.7, 129.1, 107.3, 32.2, 24.2, 21.8, 12.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_3S$: 293.0955; found: 293.0961.

2-Cyclopropyl-6-methyl-4-pyrimidyl Tosylate (5d)

Yellow oil; yield: 261 mg (80%); R_f = 0.76 (hexane/EtOAc, 1:1).

IR (ATR): 3015, 2965, 2780, 1630, 1580, 1435, 1190, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88, 7.33 (2 d, *J* = 8.1 Hz, 2 H each), 6.61 (s, 1 H), 2.43, 2.41 (2 s, 3 H each), 2.11–1.96 (m, 1 H), 0.98–0.89, 0.88–0.80 (2 m, 2 H each).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.6, 170.3, 164.4, 145.6, 134.0, 129.7, 128.7, 106.5, 24.2, 21.8, 18.1, 11.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_3S$: 305.0955; found: 305.0958.

6-Isopropyl-2-phenyl-4-pyrimidyl Tosylate (5e)

Yellow oil; yield: 256 mg (65%); R_f = 0.88 (hexane/EtOAc, 1:1).

IR (ATR): 2925, 2860, 2790, 1625, 1550, 1460, 1095, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 6.6 Hz, 2 H, PhC2-H, C6-H), 8.02 (2 d, *J* = 7.6 Hz, 2 H, TsC2-H, C6-H), 7.64–7.29 (m, 5 H, Ph, Ts), 6.80 (s, 1 H, C5-H), 3.19–2.88 (m, 1 H, *i*-PrC-H), 2.46 (s, 3 H, TsCH_3), 1.34, 1.33 (2 s, 3 H each, *i*-PrCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.0, 164.9, 164.4, 145.7, 136.7, 134.2, 131.2, 129.8, 128.9, 128.6, 128.4, 105.6, 36.3, 21.8, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_3S$: 369.1268; found: 369.1271.

6-Ethyl-2-phenyl-4-pyrimidyl Tosylate (5f)

Yellow oil; yield: 265 mg (70%); R_f = 0.80 (hexane/EtOAc, 1:1).

IR (ATR): 3025, 2925, 2790, 1630, 1545, 1375, 1190, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.15 (m, 2 H, PhC2-H, C6-H), 8.00 (d, *J* = 8.3 Hz, 2 H, TsC2-H, C6-H), 7.51–7.34 (m, 5 H, Ph, Ts), 6.81 (s, 1 H, C5-H), 2.85 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.47 (s, 3 H, TsCH_3), 1.35 (t, *J* = 7.6 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.2, 164.8, 164.6, 145.7, 136.7, 134.2, 131.3, 129.8, 129.1, 128.8, 128.5, 106.8, 31.6, 21.9, 12.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_3S$: 355.1111; found: 355.1116.

5,6-Dimethyl-2-phenyl-4-pyrimidyl Tosylate (5g)

Yellow oil; yield: 235 mg (62%); R_f = 0.71 (hexane/EtOAc, 1:1).

IR (ATR): 3080, 3025, 2785, 1630, 1540, 1405, 1180, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.06 (m, 2 H, PhC2-H, C6-H), 8.01 (d, *J* = 8.3 Hz, 2 H, TsC2-H, C6-H), 7.46–7.34 (m, 5 H, Ph, Ts), 2.57 (s, 3 H, C6-CH_3), 2.49 (s, 3 H, C5-CH_3), 2.30 (s, 3 H, TsCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 162.8, 161.2, 145.5, 136.7, 130.8, 129.8, 129.0, 128.5, 128.2, 117.2, 22.8, 21.9, 11.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_3S$: 355.1111; found: 355.1119.

2-Cyclopropyl-6-(trifluoromethyl)-4-pyrimidyl Tosylate (5h)

Colorless solid; yield: 311 mg (81%); mp 103–105 °C; R_f = 0.36 (hexane/EtOAc, 1:1).

IR (ATR): 3095, 2955, 2790, 1630, 1580, 1430, 1151, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95, 7.40 (2 d, *J* = 8.2 Hz, 2 H each, Ts), 7.04 (s, 1 H, C5-H), 2.48 (s, 3 H, CH_3), 2.27–2.18, 1.15–1.09, 1.05–0.98 (3 m, 1 H, 2 H, 2 H, *c*Pr).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 162.8, 161.4, 138.2, 133.8, 129.9, 129.1, 126.1, 108.3, 24.5, 13.6, 9.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}F_3N_2O_3S$: 359.0672; found: 359.0675.

2-Ethyl-5,6-dimethyl-4-pyrimidyl Tosylate (5i)

Yellow oil; yield: 239 mg (73%); R_f = 0.71 (hexane/EtOAc, 1:1).

IR (ATR): 2970, 2850, 2795, 1630, 1545, 1415, 1175, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99, 7.35 (2 d, *J* = 7.8 Hz, 2 H each, Ts), 2.74 (q, *J* = 7.4 Hz, 2 H, CH_2), 2.45 (s, 6 H, C5-CH_3, C6-CH_3), 2.19 (s, 3 H, Ts-CH_3), 1.16 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 169.0, 162.9, 145.8, 134.7, 129.9, 129.5, 116.1, 32.1, 22.7, 22.1, 12.7, 11.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_3S$: 307.1111; found: 307.1117.

2,6-Diethyl-4-pyrimidyl Tosylate (5j)

Yellow oil; yield: 285 mg (87%); R_f = 0.78 (hexane/EtOAc, 1:1).

IR (ATR): 2975, 2940, 2800, 1630, 1550, 1430, 1180, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96, 7.35 (2 d, *J* = 8.3 Hz, 2 H each), 6.74 (s, 1 H), 2.82, 2.75 (2 q, *J* = 7.6 Hz, 2 H each), 2.45 (s, 3 H, Ts-CH_3), 1.26, 1.20 (2 t, *J* = 7.6 Hz, 3 H each).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.1, 172.8, 164.9, 146.1, 134.1, 130.0, 129.4, 106.2, 32.5, 31.3, 22.2, 13.1, 12.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_3S$: 307.1111; found: 307.1113.

6-Methyl-2-(4-nitrophenyl)-4-pyrimidyl Tosylate (5k)

Colorless solid; yield: 223 mg (54%); mp 126–128 °C; R_f = 0.76 (hexane/EtOAc, 1:1).

IR (ATR): 3055, 2970, 2785, 1625, 1550, 1545, 1420, 1355, 1185, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39, 8.27 (2 d, *J* = 8.9 Hz, 2 H each, Ph), 7.99, 7.41 (2 d, *J* = 8.2 Hz, 2 H each, Ph′), 6.92 (s, 1 H, C5-H), 2.63 (s, 3 H, C6-CH_3), 2.49 (s, 3 H, Ph-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 165.1, 162.7, 149.9, 146.4, 142.5, 134.3, 130.3, 129.8, 129.1, 124.0, 109.6, 24.9, 22.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3O_5S$: 386.0806; found: 386.0811.

2-(4-Chlorophenyl)-6-methyl-4-pyrimidyl Tosylate (5l)

Colorless solid; yield: 84 mg (21%); mp 139–140 °C; R_f = 0.42 (hexane/EtOAc, 1:1).

IR (ATR): 3100, 2890, 2785, 1625, 1550, 1415, 1180, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13, 7.97 (2 d, *J* = 8.3 Hz, 2 H each, Ph), 7.38 (d, *J* = 8.4 Hz, 4 H, Ph′), 6.82 (s, 1 H, C5-H), 2.57 (s, 3 H, C6-CH_3), 2.47 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 165.1, 161.8, 137.8, 133.8, 132.1, 131.7, 130.3, 129.3, 128.1, 125.9, 108.7, 24.6, 21.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}ClN_2O_3S$: 375.0565; found: 375.0568.

6-Cyclopropyl-2-phenyl-4-pyrimidyl Tosylate (5m)

Colorless solid; yield: 333 mg (85%); mp 99–100 °C; R_f = 0.73 (hexane/EtOAc, 1:1).

IR (ATR): 2970, 2905, 2790, 1630, 1575, 1390, 1120, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 7.5 Hz, 2 H), 7.99 (d, *J* = 8.1 Hz, 2 H), 7.50–7.32 (m, 5 H), 6.82 (s, 1 H), 2.46 (s, 3 H), 2.12–1.96 (m, 1 H), 1.31–1.23 (m, 2 H), 1.16–1.08 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.4, 164.7, 164.6, 145.9, 137.0, 134.6, 131.5, 130.1, 129.2, 128.8, 128.7, 106.6, 22.2, 17.9, 12.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_3S$: 367.1111; found: 367.1117.

Suzuki–Miyaura Cross-Coupling Reactions of 4-Pyrimidyl Tosylates 5; General Procedure 3

A 10-mL round-bottom flask was charged with the corresponding 4-pyrimidyl tosylate (0.56 mmol), phenylboronic acid (0.67 mmol), $Pd(PPh_3)_4$ (0.028 mmol), powdered K_2CO_3 (0.56 mmol), and water (2.0 mL). The resulting mixture was stirred for 16 h at 80 °C. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (anhyd Na_2SO_4) and filtered. The filtrate was rotary evaporated and the obtained crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5:1 to 1:1).

4-Methyl-2,6-diphenylpyrimidine (6)[20]

Colorless solid; yield: 129 mg (89%); mp 82–84 °C (Lit.[20] 86–87 °C); R_f = 0.47 (hexane/EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 7.5 Hz, 2 H, PhC2-H, C6-H), 8.29–8.18 (m, 2 H, Ph′C2-H, C6-H), 7.58–7.44 (m, 7 H, Ph, Ph′), 2.66 (s, 3 H, CH_3).

4-Ethyl-2,6-diphenylpyrimidine (7)

Colorless oil; yield: 127 mg (87%); R_f = 0.49 (hexane/EtOAc, 5:1).

IR (ATR): 2970, 2940, 2800, 1630, 1550 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 8.5 Hz, 2 H), 8.22 (d, *J* = 8.7 Hz, 2 H), 7.47–7.55 (m, 7 H), 2.93 (q, 2 H), 1.43 (t, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 164.3, 138.6, 137.9, 131.0, 130.9, 130.1, 129.3, 128.8, 128.7, 127.6, 113.2, 31.7, 13.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2$: 261.1387; found: 261.1392.

4,5-Dimethyl-2,6-diphenylpyrimidine (8)[21]

Colorless solid; yield: 93 mg (64%); mp 125–127 °C (Lit.[21] 125 °C); R_f = 0.52 (hexane/EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54–8.43, 7.69–7.60, 7.55–7.39 (3 m, 2 H, 2 H, 6 H, 2-Ph, 4-Ph), 2.64 (s, 3 H, C6-CH_3), 2.34 (s, 3 H, C5-CH_3).

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Supporting Information

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